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ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

EEG Neurofeedback for Anxiety Disorders and Post-Traumatic Stress Disorders: A Blueprint for a Promising Brain-Based Therapy

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Abstract

Purpose of Review This review provides an overview of current knowledge and understanding of EEG neurofeedback for anxiety disorders and post-traumatic stress disorders.

Recent Findings The manifestations of anxiety disorders and post-traumatic stress disorders (PTSD) are associated with dysfunctions of neurophysiological stress axes and brain arousal circuits, which are important dimensions of the research domain criteria (RDoC). Even if the pathophysiology of these disorders is complex, one of its defining signatures is behavioral and physiological over-arousal. Interestingly, arousal-related brain activity can be modulated by electroencephalogram-based neurofeedback (EEG NF), a non-pharmacological and non-invasive method that involves neurocognitive training through a brain–computer interface (BCI). EEG NF is characterized by a simultaneous learning process where both patient and computer are involved in modifying neuronal activity or connectivity, thereby improving associated symptoms of anxiety and/or over-arousal.

Summary Positive effects of EEG NF have been described for both anxiety disorders and PTSD, yet due to a number of methodological issues, it remains unclear whether symptom improvement is the direct result of neurophysiological changes targeted by EEG NF. Thus, in this work we sought to bridge current knowledge on brain mechanisms of arousal with past and present EEG NF therapies for anxiety and PTSD. In a nutshell, we discuss the neurophysiological mechanisms underlying the effects of EEG NF in anxiety disorder and PTSD, the methodological strengths/weaknesses of existing EEG NF randomized controlled trials for these disorders, and the neuropsychological factors that may impact NF training success.

Keywords Neurofeedback · Anxiety disorder · Post-traumatic stress disorder · EEG biomarker · Arousal · Learning

Introduction

Anxiety disorders and post-traumatic stress disorders (PTSD) are characterized by excessive fear and anxiety, and associated dysfunctions of neurophysiological stress axes and brain arousal circuits [1]. Even if the pathophysiology of these disorders is complex, one of its defining signatures is behavioral and physiological over-arousal [2, 3]. Arousal is moreover a key dimension of the research domain criteria (RDoC) [4], where it is described as a continuum of sensitivity of the organism to external stimuli. It thus constitutes a critical axis for understanding and treating anxiety disorders or PTSD [5].

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Interestingly, a person's state of arousal is known to be reflected by different electroencephalogram (EEG) patterns. The EEG essentially measures the electrical oscillations of neuronal activities in the cerebral cortex [6]. EEG signals contain oscillatory activity within a number of frequency bands. The first oscillation to be discovered was the alpha rhythm (8–12 Hz), which can be detected from the occipital lobe during relaxed wakefulness, and which increases when eyes are closed [7]. Traditionally, the other frequency bands are delta (1–4 Hz), theta (4–8 Hz), beta (13–30 Hz), and gamma (30–70 Hz). Dominant delta activity can be detected especially during deep sleep, theta activity during deep relaxation states, drowsiness and beginning of sleep, while beta and gamma activities dominate during increasing levels of cognitive load or attention [8]. Oscillations of the sensorimotor rhythms (SMR, 12–15 Hz), and more specifically an increase of their amplitude, can also be detected from the sensorimotor cortex during relaxed wakefulness and reduced motor activity [9, 10].

EEG-based neurofeedback (EEG NF) is a non-pharmacological and non-invasive neuromodulatory tool that can be used to modify arousal-related EEG brain activities. EEG NF has been most extensively studied in ADHD [11]. As can be seen in Fig. 1, EEG NF is characterized by a closed-loop learning process where both patient and computer are simultaneously involved. Here, the patient needs to learn to self-regulate specific brain activities, which are provided—in real time—as visual or auditory feedback by a computer. Thus, following a classification step of the current EEG pattern using machine learning algorithms, the continuous feedback acts to steer patients toward "desired" and away from "undesired" brain states. This enables the subject to develop skills to sustain the targeted activity and, after repeated training sessions, induce long-term neuroplasticity in the brain [12•].

The process of NF learning has recently been elaborated by models that go beyond the basic theory of operant conditioning [13, 14], and it may consequently be considered as a type of adaptive endogenous neuromodulation, in contrast to passive exogenous methods such as transcranial magnetic stimulation or other brain stimulation techniques. EEG NF training has been shown to alter long-term neuronal activity or connectivity and modify associated symptoms of over- or under-arousal (covered in the sections that follow). Although positive effects of EEG NF have been described for anxiety disorders and PTSD, the evidence base is still scarce, particularly from the perspective of neurophysiological mechanisms. Two reviews of the literature on EEG NF treatments for anxiety disorders and PTSD identified few randomized clinical trials (RCTs) [15, 16]. Particularly for anxiety disorders, clinical studies exhibited limited methodological quality in terms of sample sizes, study designs, outcome measures, and extent of reported results. For PTSD, systematic reviews [17–19, 20•] found a number of higher quality RCTs compared to anxiety disorders. Nevertheless, although encouraging, it remains unclear to what extent psychiatric symptom improvement was associated with the specific neuromodulation induced by NF.

Thus, EEG NF has yet to achieve the evidence levels of better validated non-pharmacological treatments, including cognitive behavior therapy (CBT), exposure therapy [21], and eye movement desensitization and reprocessing (EMDR) [22]. Nevertheless, despite a range of treatment options, recovery is rarely completely successful and new therapeutic options need to be explored in order to provide alternative treatments for patients with anxiety disorders and PTSD. Future designs of clinical trials in the field would benefit from taking into account new knowledge of mechanism(s) underlying the modulation of brain arousal [12•, 23], as well as the optimization of closed-loop learning [13, 14, 24••].

In light of previous EEG NF reviews that mainly concentrated on the sizes of clinical effect [15–19, 20•], more interdisciplinary and mechanistic accounts might be useful to further advance NF applications in this domain. Thus, in this review, we aim to summarize (1) in the first section, the candidate NF mechanism(s) that may be related to targeting states of arousal in anxiety disorders and PTSD; (2) in the second section, the status quo of leading NF RCTs

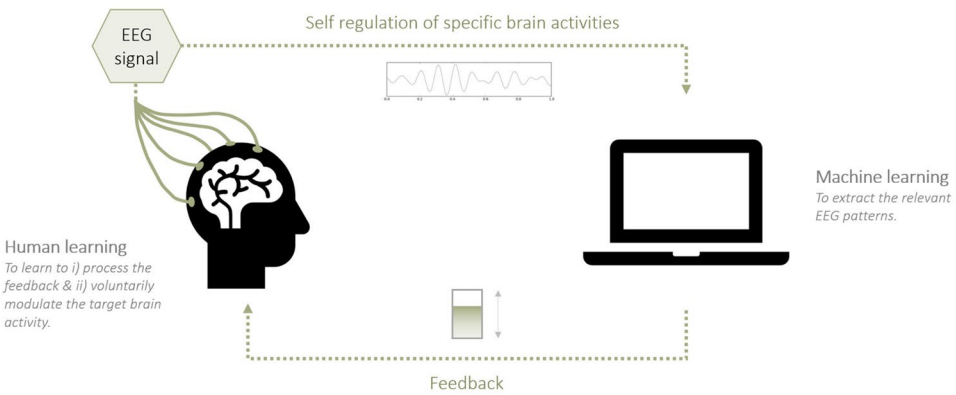

Fig. 1 Principle of EEG NF to obtain endogenous neuromodulation

for anxiety disorders and PTSD; and (3) in the third section, the neuropsychological factors, based on current learning models of EEG NF, that may influence the efficacy of endogenous neuromodulation. Given the fact that NF using functional MRI (fMRI) has been solely used in rare studies on anxiety disorders and PTSD [25–27], and that fMRI NF are related to interdisciplinarity challenge quite different than those of EEG NF [28], this review will focus only on EEG NF.

Mechanisms of Neurofeedback Therapeutic in Anxiety Disorders and PTSD

EEG Biomarkers of Anxiety and Stressor-Related Disorders

There are two major divisions in the human nervous system: the central nervous system (CNS) and the peripheral nervous system. The peripheral nervous system includes the autonomic nervous system (ANS), which is especially linked to negative mental states such as anxiety and stress [29]. The ANS is responsible for breathing, heart rate, digestion, hormone production, and itself consists of two main parts: sympathetic and parasympathetic [30]. The sympathetic and parasympathetic nervous systems act as opposing poles of the "arousal" axis, by initiating stress and relaxation responses, respectively. Naturally, bilateral communication exists between the ANS and the CNS, and the latter usually orchestrates the downstream effects of the ANS based on current information about the state of the environment [31]. Given this bridge, both the ANS and the CNS may be used as "windows" onto the current behavioral state(s) of the organism.

Naturally, the major component of the CNS is the brain, which in more evolved animals has evolved a neocortex. Here, experiments on electrocortical oscillations—measured by the EEG—in humans [32, 33] and animals [34, 35] have found that variations in oscillatory power and frequency are closely related to behavioral arousal. As seen in Fig. 2A, low cortical/behavioral arousal (i.e., activation) is characterized by significant low-frequency oscillations (i.e., delta, theta, and alpha rhythms), whereas high cortical/behavioral arousal is defined by high-frequency oscillations (i.e., beta and gamma rhythms).

Functionally speaking, the alpha rhythm has been established to be an inhibitory oscillation [37], and decreased alpha power has been linked to higher activation in the sensory and motor cortices [38, 39]. This is in line with simultaneous fMRI-EEG studies showing that states of desynchronized (i.e., decreased) alpha rhythm are associated with higher cortical metabolism [40]. Elsewhere, neurophysiological investigations have found that low-frequency oscillations (such as alpha) induce states of lower excitability particularly within visual and sensorimotor cortices [38] by directly reducing neuronal firing [41]. Hence alternating states of low/high alpha power within sensory cortices may be considered as a functional "switch" gating access to information from the external environment [37, 42]. According to this framework, states of lower stress/arousal (i.e., with higher alpha power) would be accompanied with decreased interest in and awareness of environmental stimuli, whereas the opposite would be the case for states of higher stress/arousal (i.e., with lower alpha power). Elsewhere, alpha power has been shown to be inversely correlated with the 1/f slope of the EEG power spectrum, which is a well-established marker of electrocortical activation [33, 43]. Consequently, optimal behavioral performance should theoretically coincide with oscillatory signatures

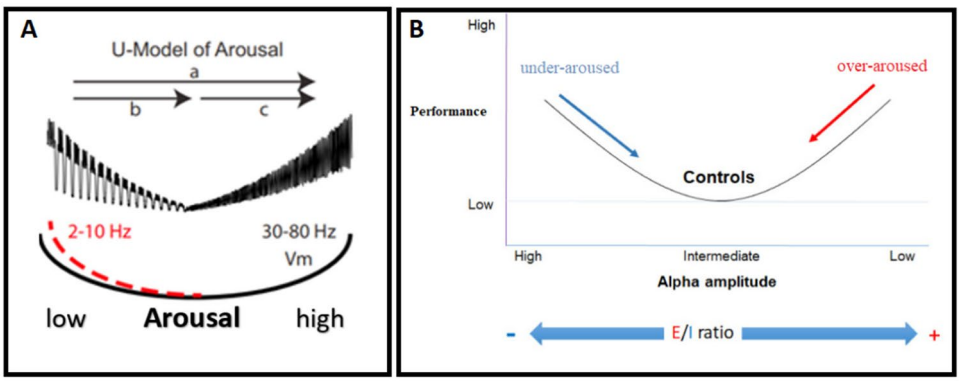

Fig. 2 **A** Linkage between behavioral arousal and spectral content of brain oscillations. Low arousal states are dominated by low-frequency oscillations (i.e., delta, theta, and alpha, 2–10 Hz), while high arousal states are dominated by high frequencies (i.e., beta or gamma, 30–80 Hz). From [35]. **B** "Yerkes–Dodson" relationship between alpha (8–12 Hz) oscillatory power, brain activation/arousal (i.e., excitation/inhibition balance), and performance (adapted from [36])

typical of medium excitation-inhibition (E/I) balance and arousal, i.e., medium resting-state EEG power, balanced between high and low frequency activities (see Ros et al. [12•] for an in depth discussion). Accordingly, both high- and low-frequency spectral power extremes are associated with attentional impairment [44]. This is in line with EEG experiments supporting the Yerkes–Dodson law [45, 46] showing a trade-off between arousal and performance accuracy, as well as multiple studies that demonstrate significant EEG power deviations in mental disorders [47].

Interestingly, patients with PTSD display *elevated* relative power of beta rhythms [48], together with *reduced* relative power of alpha rhythms [49, 50••], and may thus be categorized on the right-hand side of the inverted-U in Fig. 2B, toward the cortically "over-activated" end. This is consistent with observations of cardinal symptoms of behavioral hyperarousal in this population. Moreover, patients with PTSD demonstrated significant associations between alpha rhythmicity and hyperarousal [50••] or impulse control [49], while PTSD-related inattention deficits were positively correlated with beta power and negatively correlated with alpha power [51]. A number of other studies are supportive of the notion that elevated relative beta-gamma and/or decreased alpha power coincide with an increased E/I balance of cortical activity and behavioral arousal. Patients with insomnia, whose sleep is frequently interrupted by night-time arousals, exactly demonstrate this pattern [52]. Compatible with this framework, fluctuations of worrying in patients with generalized anxiety disorder (GAD) are tracked by increased high-frequency (gamma) band activities [53]. Persons with alcohol dependence, who are known to display symptoms of anxiety, demonstrate beta power excess [54], while genetic associations were also found between the inhibitory neuromodulator GABA, alcohol dependence, and beta oscillations [55]. Elsewhere, corticotropin-releasing hormone, a hormone involved in the stress response [56], has been associated with resting state alpha oscillations [57]. Moreover, the concept of arousal (and its EEG components) in PTSD and anxiety disorders largely overlap with major depressive disorders and its comorbid forms [58–61]. Thus, even if the EEG biomarkers related to arousal in anxiety disorders and PTSD are hypothesized to be a central dimension, they can lack of specificity according to a categorical nosography, leading to the need for a more dimensional approach of EEG power deviations in mental disorders as suggested by the RDoC project [4].

EEG Modification During Neurofeedback

Alpha or theta training is used in most neurofeedback sessions aimed at reducing anxiety, arousal, and improving relaxation. A study conducted by Nowlis and Kamiya was one of the first to indicate that increasing alpha brain wave levels might increase relaxation (1970) [62]. At the end of their experiment, all individuals were asked what their technique was for turning on and off the EEG NF tone. To maintain the tone, most respondents said that they relaxed, did not focus visually, were aware of inhalations and exhalations, and just letting go. To maintain the tone, they reported being awake and watchful, visually focusing or attempting to get stressed. Subjects who were able to generate alpha rhythms spontaneously reported mental states that reflected relaxation and pleasant feelings. Subsequently, Hardt and Kamiya [63] trained volunteers who scored highest and lowest on the trait anxiety scale to learn to boost and inhibit their Alpha (8–13 Hz) rhythms [63]. Alpha and anxiety levels had statistically strong negative associations, where alpha augmentation decreased both state and trait anxiety selectively in high-trait anxiety participants (Fig. 3).

In addition, relaxation training appears to be useful because it decreases anxiety and improves perceived control over stressful situations [64]. As a result, lowering the stress level of patients with anxiety disorders or PTSD may lead to a decrease in stress-related symptoms (as it will be shown in the second section of this article). "Alpha-theta" was the first EEG NF protocol utilized in an attempt to stress-related symptoms [65]. Here, EEG NF training was designed to train the subjects increase the power spectrum of slower theta (2–6 Hz) and decrease faster (22–36 Hz) beta activity, while simultaneously increasing the power spectrum of mid-range (10–13 Hz starting point) activity. This is based on the fact

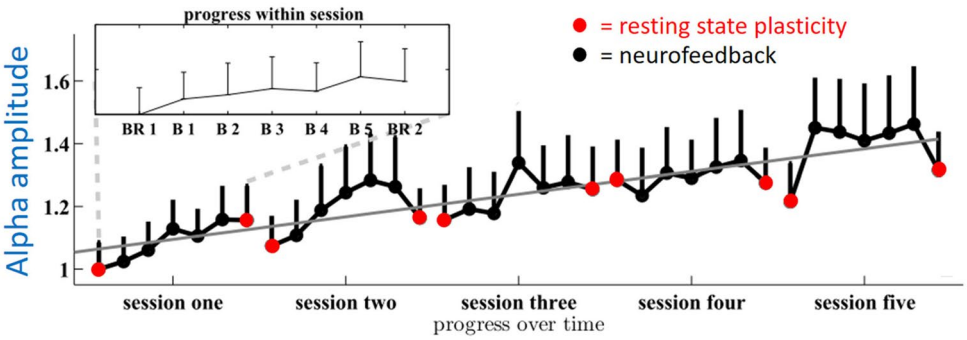

Fig. 3 Impact of EEG NF up-regulation of alpha rhythm on alpha amplitude. The EEG NF protocol enables participants to develop skills to sustain the targeted alpha rhythm activity during neurofeedback, while long-term plasticity mechanisms translate these effects to spontaneous (resting) states (modified from [75])

that theta waves occur during deeper states of relaxation or drowsiness, and which occur during the transition to sleep.

An alternative approach to regulating low-frequency rhythms (e.g., theta or alpha) is to target higher-frequency oscillations such as beta rhythms (i.e., > 15 Hz). In this case, given that faster rhythms have been found to be positively associated with arousal (see Fig. 2), the aim is usually to down-regulate them with neurofeedback. This approach has been used to effectively improve the symptoms of anxiety [66], but also of depression [67]. In both studies, EEG NF was able to significantly decrease beta power relative to the control group, while significant correlations were also found between changes in moods symptoms and the percentage of reduction in high-beta activity [67]. An alternative approach in the field of PTSD was to use EEG NF to target the so-called sensorimotor rhythm (SMR) (12–15 Hz) [68], another low frequency rhythm which is closer to the alpha than the beta rhythms, both in frequency and function. This pilot/exploratory study (without a control group) found interesting results, which lack of study of replicability.

Intriguingly, a more recent neurofeedback protocol, which paradoxically aims to *decrease* alpha power, is also reported to provide clinical benefits in patients with PTSD [50••, 69, 70]. This appears to be the result of a homeostatic "rebalancing" of alpha rhythmicity toward levels exhibited by the healthy population [50••], despite the opposite direction of EEG NF regulation. This approach is reinforced by mechanistic evidence of significant associations between the re-establishment of alpha power and decreases of PTSD-related symptoms of hyperarousal [50••, 71]. Such EEG NF protocols aiming to decrease alpha power have not been used in anxiety disorder. However, an interesting increase of level of arousal with galvanic skin conductance biofeedback (GSR) have been used successfully in patients with stress related epilepsy, leading to similar interesting brain mechanisms related to homeostatic counterintuitive mechanisms [72]. Given these counterintuitive mechanisms, it has been proposed that arousal "flexibility" could be a more interesting target than simply the level of arousal [72, 73]. More alpha "flexible" profiles, e.g., subjects with a balanced arousal, could be related to better capacity to either increase or decrease alpha EEG rhythm. Further studies are needed to evaluate this hypothesis in anxiety disorders and PTSD.

A combined EEG-fMRI study further linked the alpha power "rebound" to the upregulation of the default-mode network [69], which is known to co-activate during "resting" as well as parasympathetic states [74]. Such an approach could help to better understand the mechanism of neurofeedback action in anxiety disorders and PTSD and for stress regulation. Moreover, combined EEG-fMRI studies are also very interesting for identifying new EEG NF targets. The amygdala has a pivotal role in PTSD but fMRI neurofeedback regulation remains an inaccessible procedure. Thus, a novel imaging approach has been developed to monitor of amygdala activity using combined EEG-fMRI. Simultaneous EEG/fMRI investigation enables to find specific EEG biomarkers related to amygdala-blood oxygen level. Such new EEG biomarkers can be implemented in EEG NF and demonstrated that regulation of EEG was associated with regulation of amygdala-blood oxygen level and with reduced amygdala reactivity to stimuli [26]. Such an approach has been used in healthy individuals undergoing a stressful military training program and the results are encouraging to develop EEG NF training targeting EEG biomarkers related to amygdala-blood oxygen level to prevent PTSD [27].

EEG NF Protocols in Anxiety Disorders and PTSD

A number of systematic reviews and meta-analyses already exist on EEG NF for anxiety disorders or PTSD [15–19, 20•]. One systematic review and meta-analysis was of particular interest for PTSD according to the rigorous selection of papers realized and the certainty of evidence evaluation [20•]. Following this preview review, for the sake of rigor we discuss here the Randomized Controlled Trials (RCTs) and mainly their EEG NF protocols (Table 1). All existing RCTs aimed to modify alpha and/or theta rhythms, and one RCT aimed to decrease alpha rhythm in PTSD [71]. There is therefore an evident lack of RCTs targeting alternative EEG markers such as beta [66] or SMR [68] rhythms.

Anxiety Disorders

Rice et al. published the first NF study in the field of generalized anxiety disorders (GAD) [76]. Thirty-eight subjects with GAD were randomized to four groups. Patients received eight sessions of either frontal electromyographic (EMG) biofeedback, EEG NF to increase alpha rhythm ("alpha-up"), EEG NF to decrease alpha rhythm ("alpha-down"), or a "pseudomeditation" control condition. The results demonstrated that all groups exhibited significant reductions in STAI-Trait Anxiety that was maintained at 6 weeks post-treatment. Interestingly, the alpha-up NF group additionally exhibited significant reductions in heart rate reactivity to stressors at a separate psychophysiological testing session. Common to all four groups, the treatment was presented to the subjects as being effective to help subjects to reduce their anxiety. All patients were also told to practice at home on a daily basis what they had learned during the protocol about relaxing. In the biofeedback and neurofeedback group, subjects also received verbal feedback of success from the experimenter, in which their previous score was incremented every 2 min by 2%, leading subjects to believe they were successful at the task.

Table 1 Principal characteristics of the randomized controlled trials studying the effect of EEG neurofeedback for anxiety disorders or PTSD

First author, year, country	Sample (*n*)	Mental disorders	Symptoms measurement (outcome)	Length of follow-up	Control group	EEG targeted by the neurofeedback protocol	Evaluation of change in the EEG biomarker	Evaluation of association between EEG and symptoms changes
Rice et al. 1993, USA [76]	38	GAD	STAI-Trait Anxiety	6 weeks	EMG biofeedback or pseudo-meditation	Alpha up or Alpha down (8 sessions, 2 times/week)	Yes	No
Agnihotri et al. 2008 & Sandhu et al. 2007, India [77, 78]	45	GAD	CAT	2 weeks	Waiting list or EMG biofeedback	Alpha up (12 sessions, 1 times/day)	Yes	No
Peniston et al. 1991, USA [65]	29	PTSD (veterans)	MMPI	30 months	Standard treatment	Alpha/theta protocol (30 sessions, 5 times/week)	No	No
van der Kolk et al. 2016, USA [81]	52	PTSD (treatment non-responsive)	CAPS	4 weeks	Waiting list	Alpha/theta protocol (24 sessions, 2 times/week)	No	No
Noohi et al. 2017, Iran [82]	30	PTSD	IES-R	0 (at the end of the EEG NF protocol)	No intervention	Alpha/theta protocol (25 sessions, 4 times/week)	No	No
Nicholson et al. 2020, Canada [71]	36	PTSD	CAPS	3 months	Sham neurofeedback	Alpha down (20 sessions, 1 time/week)	Yes	Yes

EEG electroencephalography, *GAD* generalized anxiety disorder, *STAI* State-Trait Anxiety Inventory, *CAT* comprehensive anxiety test, *PTSD* post-traumatic stress disorder, *MMPI* Minnesota Multiphasic Personality Inventory, *IES-R* Impact of Event Scale–Revised, *CAPS* clinician-administered PTSD scale

In 2007 and 2008, the Agnihotri team published two papers [77, 78], where 45 subjects with GAD were randomized to 3 groups (2 active groups and one wait-list control). In active groups, patients received 12 sessions of either EMG biofeedback or EEG NF to increase alpha rhythm. The results showed that the active groups exhibited significant reductions in trait anxiety (Comprehensive Anxiety Test—CAT Questionnaire) that was maintained at 2 weeks posttreatment. Concerning psychophysiological testing, both active groups showed similar changes in terms of blood pressure and galvanic skin response. Subjects of both treatment groups were informed about previous research supporting the effectiveness of biofeedback training in causing relaxation. During the sessions, intermittent positive verbal reinforcement was provided every few minutes by the therapist. All the patients were asked to practice relaxation at home once a day for 25 min. It was strictly determined by the therapist whether each patient regularly practiced at home throughout the treatment period.

Post-Traumatic Stress Disorders

Interest in NF EEG for PTSD was sparked by two historical studies published by Peniston and Kulkosky in the 1990s, and conducted in Vietnam combat veterans at hospitals, with alpha–theta EEG NF [65, 79]. Over the last decade, the traditional alpha–theta protocol of Peniston and Kulkosky were replicated in three independent RCTs [80–82].

Peniston and Kulkosky [65] administered thirty 30-min sessions of training to a group of 15 subjects with PTSD, and compared them at follow-up to a control group of 14 veterans who received treatment as usual (TAU) [65]. At 30-month follow-up, all TAU patients had relapsed, while only 3 of 15 NF training patients had relapsed. Although all patients treated with NF had decreased their medication at follow-up, among TAU patients, only one patient decreased medication, two reported no change, and 10 required more psychiatric medications. Patients' symptoms were measured by the Minnesota Multiphasic Personality Inventory, which is not the more appropriate scale for evaluating PTSD

symptoms. A subsequent study, completed in 1993 [79], randomly selected 20 chronic PTSD subjects with alcohol abuse, and administering the same EEG NF protocol, showed similar results.

In both studies, all subjects were given a brief introduction to EEG NF and were told how to interpret the audio feedback (i.e., beta, alpha.theta) sounds. During neurofeedback training, subjects were instructed to close their eyes and construct visualized scenes of their nightmares and flashbacks. The patients received the following instructions from the investigator: "Now, go back to Vietnam where these traumatic combat events occurred." Then, they were instructed to visualize imageries of increased alpha rhythm amplitude and scenes of the normalization of their personalities. Then, the investigator instructed the subjects to "sink-down" into theta state keeping the mind quiet and alert (but not active), and the body calm. Finally, subjects were instructed by the investigator to initiate the session with a quiet command: "Do it." Prior to the investigator exiting the room, the beta feedback volume control band was turned off; alpha and theta feedback volume control bands were adjusted for a comfortable listening level for each subject.

In the last decade, three RCTs tested the efficacy of the alpha/theta protocol in PTSD patients [80–82]. Different symptom scales were used to measure PTSD symptoms of which all but one [80] were clinically validated (Clinician Administered PTSD Scale CAPS [81]; and Impact of Event Scale–Revised: The IES-R [82]). Treatment length ranged from 4 to 12 weeks. In the study by van der Kolk and colleagues, 52 subjects with PTSD were randomized to 2 groups (neurofeedback or wait-list) [81]. Subjects received 24 training sessions, twice weekly, each lasting up to 30 min. No changes were made to the protocol except adjustments to the reward band frequency. These were made based on rated symptoms of over-arousal (including nightmares; sleep difficulties; hyperactivity; aggressive behavior, anger, anxiety; and self-reports of high arousal including self-harm, suicidal and/or homicidal ideation), and symptoms of under-arousal (including decreased alertness or mental clarity, nausea, depressive symptoms, and decreased energy/fatigue) captured by the Checklist for Changes After Neurofeedback, as well as clinical judgment. If participants reported significant symptoms of over-arousal for at least two training sessions, the reward frequency was lowered by 1 Hz. This procedure was continued until the participant reported no change, positive benefit, or symptoms of under-arousal. If the participant reported symptoms of under-arousal, the reward band was raised by ½ Hz until those symptoms remitted. In the Noohi et al. study, 30 subjects with PTSD (defined by DSM-IV diagnostic criteria) were randomized to 2 groups (neurofeedback or wait-list) [82]. Subjects received 25 training sessions four times a week, each lasting for 30 to 40 min. Follow-up was performed in the final session after 45 days in both experiment and control groups. Subjects were required to recall positive memories during neurofeedback training. Moreover, prior to treatment initiation, participants were instructed to relax through progressive muscle relaxation and diaphragm breathing.

Lastly, in the study of Nicholson et al., aiming to decrease alpha rhythm in PTSD, 36 subjects with PTSD (defined by DSM-IV-TR diagnostic criteria) were randomized to 2 groups (neurofeedback or sham neurofeedback) [71]. Significantly decreased PTSD severity scores (evaluated with the CAPS) in the neurofeedback group only was found. The same EEG NF training protocol as described previously was used [69, 83]. Participants completed EEG NF through interactive gaming. Consistent with a trauma-informed model of treatment and in order to be responsive to personal preference and to keep attention high over the 20-week trial, two visual NFB interfaces (i.e., visual presentation of feedback) were provided to participants. Furthermore, two forms of feedback were used in case one of the interfaces was emotionally triggering for the participant.

RCT and Neurofeedback Procedure

Beside the need for future, rigorously designed RCTs comparing EEG NF with sham or active treatments, our analysis of existing RCTs underlines the importance of taking into account the methods used by experimenters to reinforce NF learning and/or relaxation. This has led some to question the authenticity of NF treatment received by the patients in the Peniston and Kulkosky studies [84]. As a result, it is critical that future RCTs both report and follow methodologies recommended by the NF research-community consensus guidelines and the CRED-nf Check list [85••].

In particular, some important features should be taken into account in the context of anxiety disorders and PTSD. First, although very rarely, EEG NF in PTSD can trigger flashbacks [81, 82]. Unfortunately, the NF data associated with flashbacks were insufficiently collected and/or reported, and the relationship with the NF protocol was not studied. Second, baseline anxiety could be a critical factor in the optimization of NF learning. Yet, these dimensions, which specifically afflict patients with anxiety disorders and PTSD, have not been explicitly considered in the design of recent RCTs. To this end, understanding and modeling the learning strategies during EEG NF in these disorders could be very useful for enhancing its efficacy further.

Learning Strategies in Patients with Anxiety and Stressor-Related Disorders

Of note, Gruzelier and collaborators have shown in a number of RCTs that EEG-NF was efficient for reducing anxiety and consequently increasing performance in different

domains including music [86], ballroom dance [87], singing [88, 89], and medicine [90]. They show that when compared with alternative treatment groups (including physical exercise, mental skill training or other EEG-NF control protocols), only the alpha-theta EEG-NF groups experienced enhancements of real-life performance under stressful conditions. While this research did not target patients with anxiety disorders or PTSD, it reinforces the rationale that EEG NF—notably alpha-theta NF—could be beneficial for managing the specific "dimension" of anxiety, in line with RDoC approaches. Nevertheless, the application of such EEG NF procedures in the context of anxiety disorders and PTSD raises several questions, particularly regarding the learning mechanisms involved [13, 14, 24••].

Indeed, in order to optimize the clinical efficiency of NF training procedures, the targeting of abnormal EEG patterns is of course necessary (as highlighted in previous sections), but may not be sufficient. EEG NF efficiency relies on both *specific* effects, i.e., effects that directly depend on the modulation of the target brain activities, and *non-specific* effects that vary with the patient's cognitive and emotional states [24••]. Patients must indeed be in a general state of performance and learning that enables skill acquisition. Yet, as shown in Fig. 4, their clinical condition that reflects high anxiety levels may make the EEG NF training difficult. While, on the one hand, anxiety can impair learning abilities and thereby EEG NF training efficiency, on the other hand, the EEG NF training procedure may in itself raise patients' anxiety levels. This negative loop affects so-called *non-specific* effects that might in turn be detrimental to (*specific*) NF training efficiency. In this section, we first detail the relationship between anxiety and NF training and how this relationship is mediated by cognitive factors, including self-efficacy and computer anxiety. Then, we show that NF design choices can minimize the counterproductive loop introduced above from having detrimental training effects.

Anxiety and EEG NF Training

Empirical studies suggest that people with high anxiety levels experience difficulties during EEG NF training, and that they obtain lower performances than the ones who are not anxious [91, 92]. According to Brosnan [93], the negative relationship between anxiety and performance in general could be explained by the fact that people with high anxiety levels devote more cognitive resources to "off-task" efforts, including worrying about their performance (so-called performance anxiety), which induces shifts in attention between task and "off-task" processes. When fewer cognitive resources are available to perform the primary task, this results in extended completion times, or in performance drops when the task must be performed in a limited amount of time.

This relationship may also be explained by some cognitive factors that mediate the effect that anxiety and the EEG NF training have on each other.

Indeed, anxiety is associated with low levels of self-efficacy [94]. Self-efficacy refers to one's confidence in the capacity to face up to adverse situations [95]. While this definition suggests that self-efficacy is a general belief, more evidence suggests that patients' self-efficacy beliefs are domain-specific [94]. In our case we should thus focus on the patients' specific beliefs that they are able to complete an EEG NF training and reach high modulation performances. Among the consequences of low levels of self-efficacy is an increase of so-called computer anxiety (CA) that Simsek [96] identifies as being an affective response due to one's beliefs about one's lack of ability to control the technology. CA, also called "Tech-Stress" [97], can be classed as a context-specific anxiety, i.e., a transitory neurotic anxiety ranging between anxiety trait and anxiety state [98]. It is specifically associated with one context: the use of a computer or of a computer-based technology. In turn, CA will have detrimental effects on performance [92, 93].

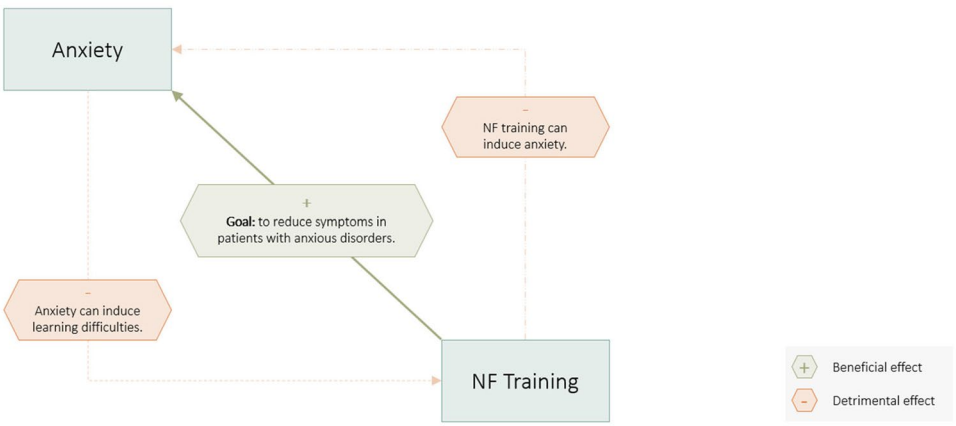

Fig. 4 Factors that can decrease brain EEG NF learning in patients with anxiety disorders or PTSD

On the other hand, when confronted with a new technology (here the EEG NF system), patients are likely to experience anxiety together with a low feeling of agency during their first interaction attempts [92]. These feelings are notably underlain by a fear of the computerized system [99–101] through which the EEG NF training is provided and by a fear of incompetence [100, 102], both having been shown to negatively impact EEG NF performances and learning. This specific apprehension of EEG NF can be defined as CA. High CA levels influence negatively the perceived ease-of-use of the technology [92]. Combined with a lowered feeling of agency (i.e., the fact that participants do not feel agent during the EEG NF training), it will in turn negatively impact the patients' self-efficacy.

Many authors have argued that decreasing CA, and thus increasing self-efficacy, would lead to better skill acquisition—what is more due to the positive correlation between agency and motivation, performance, and general skill acquisition [96–98].

Technologies may thus have both a positive or negative influence on patients' responsiveness to EEG NF. Indeed, as stated by Thibault et al., "neurofeedback demands high engagement and immerses patients in a seemingly cutting-edge technological environment over many recurring sessions, which may represent a powerful form of placebo intervention" [103]. Those authors state that EEG NF efficacy could be increased due to a placebo effect related to the technology. If such a placebo effect exists for some patients, a nocebo effect (due to the computer anxiety phenomenon) may occur for others. Therefore, adapting EEG NF training in order to reduce users' anxiety and optimize their self-efficacy may improve EEG NF performances.

Design Recommendations for Neurofeedback Studies on Anxiety Disorders

The potential detrimental effects of EEG NF training on anxiety can be prevented. Under certain conditions, an EEG NF training procedure can even result in increased self-efficacy beliefs, which may contribute to an increased motivation to use the technology [94] and thereby in lower anxiety and higher performance levels, here in terms of reduction of clinical symptoms of anxiety. EEG NF training can be divided into four main components: the instructions, the training tasks, the feedback, and the training environment [104] (Fig. 5). In the next paragraphs, we suggest guidelines on how to design NF training procedures so that the patients' CA is limited and self-efficacy maximized.

Instructions

EEG NF, and BCIs in general, are being increasingly advertised in the public sector. Mediatization can result in patients being afraid of the technology (e.g., because they think it could read their mind) or having excessive expectations (e.g., think that the training procedure will be effortless). Both will be associated with a lowered engagement of the patients in the EEG NF training, and consequently in a less efficient procedure. Therefore, patients should be fairly informed prior to the EEG NF training, e.g., regarding how the EEG NF system works and the level of therapeutic evidence for anxiety disorders. This will prevent misrepresentations and thereby CA related to the EEG NF use or over-expectations, and thereby favor patients' engagement into the training. In addition, as is the case for any therapeutic procedure, the patients' personality and psychosocial profile

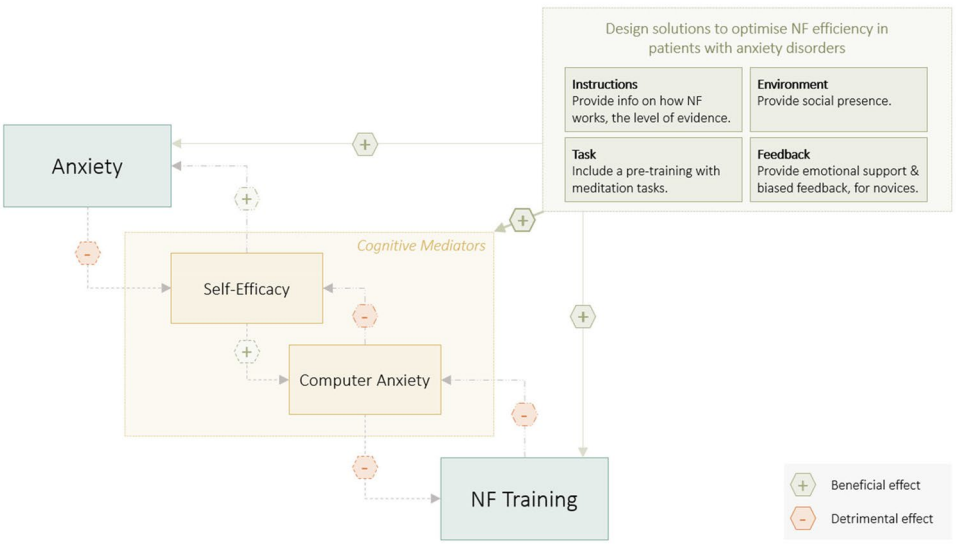

Fig. 5 Factors that should be taken into account to increase brain EEG NF learning in patients with anxiety disorders or PTSD

(including anxiety) will influence the type and precision of instructions that they need [105••].

Training Environment

The presence of a clinician during the EEG NF training can be perceived either as supportive and reassuring, or as a judgment/evaluation. In the first case it will enable reducing the patient's CA while in the second it might increase it. In the same vein, a playful training environment may be perceived either positively, the challenge increasing some patients' engagement and perceived self-efficacy, or negatively, the same challenge being overwhelming for others. As suggested by Roc et al. (2021), the training environment, in terms of playfulness and social presence notably, should therefore be thought and organized based on each patient's preferences [105••].

Training Tasks

The efficacy of mindfulness-based interventions to reduce anxiety has been repeatedly shown, both in healthy individuals and in patients with anxiety disorders [106, 107]. As suggested by Evans et al., patients could be trained to meditate before they start their NF training [108]. Mindfulness meditation has actually already been shown to improve EEG NF performances in a paradigm targeting the modulation of sensorimotor rhythms [109]. Meditation is also known to improve attentional abilities [110]. Yet, learning to self-regulate brain activities is a complex task that is resource consuming and requires good attention abilities. These attention abilities have moreover been defined as major predictors of EEG NF/BCI performance and learning [92]. As such, training users to meditate before NF training might be a task-unspecific way of improving their subsequent performances through the reduction of CA.

Feedback

The feedback is a core element of EEG NF training procedures. The optimal form of a feedback has not been defined yet and will, once more, certainly depend on the patient's profile. In a general way, a transparent feedback, i.e., feedback that is consistent with the cognitive task performed to self-regulate the targeted brain activities [111], will favor the patients' sense of agency and thereby their feeling of self-efficacy. Several reviews of studies performed on healthy individuals have shown that a positively biased feedback was beneficial for novice EEG NF users [92, 105••]. Positive biases would enable reducing performance anxiety and increasing the perceived agency and self-efficacy. It should be noted that such biases could however be detrimental for more experienced persons as they would engender inconsistencies between the expected and actual outcomes of their actions [92].

The efficiency of this approach should be specifically tested, particularly with regards to the study of Khdour et al. [112]. The authors compared learning performances of healthy individuals and patients with different anxiety disorders when provided with different types of feedback: either positive or negative. They show that patients with GAD and those with social anxiety disorder (SAD) obtain lower performances than the control group (healthy individuals) and patients with panic anxiety disorders when they are provided with positive feedback, while it is not the case when they receive negative feedback. This result suggests that (1) the feedback provided should be adapted to the patient's diagnosis, and (2) that patients with GAD and SAD are more sensitive to negative feedback. Finally, beyond performance-related cognitive feedback, we can also provide emotional feedback.

Pillette et al. have designed a learning companion that provided NF users with emotional feedback (e.g., greetings, encouragements) depending on their performance and progression [113]. They show that the learning companion positively impacted the performances of users with low self-reliance levels while it had a detrimental effect on those who were the most self-reliant. One hypothesis is that the emotional feedback provided helps the users who are the most in need to reduce their CA levels and raise their perceived self-efficacy, while it can be annoying/frustrating for the most self-reliant participants who prefer learning in autonomy.

For a complete review of EEG NF (and, more generally, BCI) protocol design and reporting guidelines, please refer to [85••, 105••]. Indeed, beyond the need to rigorously design EEG NF training procedures in order to optimize both specific (self-regulation of the targeted brain patterns) and non-specific (self-efficacy, motivation) EEG NF effects, we also need to report rigorously the NF training procedures. Only thorough reporting will enable rigorous meta-analyses to be performed and reliable conclusions to be made regarding the efficiency of NF training procedures to reduce clinical symptoms, notably in patients with GAD and PTSD.

Conclusion

In this review on EEG NF for anxiety disorders and PTSD, we proposed an interdisciplinary approach in order to consider more carefully both the neural and psychological elements that could influence NF therapeutic success. Looking back, future research would certainly benefit from more rigorous methodological designs, including double-blind RCTs, with larger sample sizes, a neurofeedback sham group, and longitudinal follow-up results to increase the credibility of findings. Technically, EEG NF is a next-generation treatment

based on the concept of closed-loop control of a brain computer interface [13, 114], offering a very interesting way to treat patients with psychiatric disorders on the basis of their specific neurophysiological signatures [115•], in line with the RDoC approach [116•]. Based on the fact that arousal is a core RDoC dimension, we have shown that modulating this dimension via its associated EEG signatures may be a fruitful approach for treating anxiety disorders and PTSD. Based on the literature on learning models of NF, we also discussed how levels of experienced anxiety during NF could undermine training efficacy. Recently proposed learning models from NF and BCI experiments in healthy subjects suggest that techniques that aim to modulate individual arousal and motivation could be improved in order to enhance NF skill acquisition. Finally, we recommend that Hebbian as well as homeostatic plasticity mechanisms should be more deeply investigated in future studies of NF for anxiety disorders and PTSD, as well as other disorders such as depression.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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