Real-time fMRI neurofeedback as a new treatment for psychiatric disorders: a meta-analysis

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Abstract

Neurofeedback using real-time functional MRI (RT-fMRI-NF) is an innovative technique that allows to voluntarily modulate a targeted brain response and its associated behavior. Despite promising results in the current literature, its effectiveness on symptoms management in psychiatric disorders is not yet clearly demonstrated. This meta-analysis aims to evaluate the clinical effectiveness of RT-fMRI-NF in the treatment of psychiatric disorders and to provide methodological suggestions for future studies. Web of Science and PubMed databases were searched using the keywords: neurofeedback AND (fMRI OR “functional magnetic resonance imag*” OR “functional MRI”) AND (“real-time” OR “real time”). Thirty-one clinical trials focusing on psychiatric disorders were included and categorized according to standard diagnostic categories. The RT-fMRI-NF efficacy was assessed by reporting changes in clinical endpoints before vs. after NF training and before or after NF training vs. follow-up. Among the 31 identified studies, 22 consisted of controlled trials, of which only eight showed significant clinical improvement in the experimental vs. control group after the training. Nine studies found an effect at follow-up on ADHD symptoms, emotion dysregulation, facial emotion processing, depressive symptoms, hallucinations, psychotic symptoms, and specific phobia. Within-group meta-analysis revealed large effects of the NF training on depressive symptoms right after the training ($g = 0.84$, $p < 0.01$) and at follow-up ($g = 1.25$, $p < 0.01$), as well as medium effects on anxiety ($g = 0.52$, $p = 0.01$) and emotion regulation ($g = 0.46$, $p = 0.01$). Between-group meta-analysis showed a medium effect on depressive symptoms ($g = 0.46$, $p < 0.01$) and a large effect on anxiety ($g = 0.91$, $p = 0.09$). However, the between-studies heterogeneity is very high. The use of RT-fMRI-NF as a treatment for psychiatric symptoms is promising, however, further double-blind, multicentric, randomized-controlled trials are warranted.

1. Introduction

Psychiatric disorders are a major global health problem because of their high prevalence and burden (1). While the development of pharmacological treatments gradually fades away (1), new stimulation techniques that directly target brain activity are emerging. However, most of these techniques, - such as deep brain stimulation (2), repetitive transcranial magnetic stimulation (3) or transcranial direct current stimulation (4) – require physical interventions. In this context, real-time functional magnetic resonance imaging neurofeedback (RT-fMRI-NF) has recently gained interest in the neuroscientific community as a novel, non-invasive, treatment for psychiatric disorders. Neurofeedback (NF) is a type of biofeedback that aims to measure neural activity in a specific brain region and presents it back to the participants in real-time using a visual, auditory or another symbolic representation (5). Through this feedback, participants can learn to intentionally regulate their brain activity and indirectly the related cognitive processing.

Primarily developed in combination with electroencephalographic (EEG) recordings, neurofeedback opened a new way for the neuroscientific community to tackle neurological and psychiatric disorders (6–8). In the first proof-of-concept, Lubar et Lubar (1984) provided two sessions of EEG neurofeedback training to children with ADHD by targeting the sensorimotor rhythm and the beta activity. All children showed an improvement in academic performance after the NF training (8). Later, Heinrich et al., (2004) demonstrated a reduction of ADHD symptomatology by 25% in 13 children after a slow cortical potential training (6). However, EEG-NF offers only an approximate localization of active brain regions, which is a critical key for successful neurofeedback training, and very limited access to deep subcortical brain areas that are involved in the pathophysiology of many psychiatric disorders (9).

MRI has the advantage of a high spatial resolution, allowing whole-brain activity recordings including subcortical regions. This technique relies on the measure of the hemodynamic response of blood oxygen level-dependent (BOLD signal), which is considered as an indirect measure of neuronal activity (10). Functional MRI-based NF has been used to modulate the behavior by increasing or decreasing the activity in cortical and subcortical region of interest (ROI). The implementation of RT-fMRI provides image processing as fast as image acquisition (11–13), which in turn enables analysis of the entire brain activity within a very short delay and, with an appropriate feedback, to provide guidance to the participants to regulate their own brain activity (13) (see Figure 1).

Figure 1. Symbolic representation of an RT-fMRI-NF experiment with a thermometer display as visual feedback on brain activity

First studies demonstrated the effectiveness of RT-fMRI-NF on the relief of neurological symptoms such as chronic pain (14) or tinnitus (15). In psychiatry, recent advances in neuroscience and neurophysiology allowed to incriminate brain regions and networks that might underlie the pathophysiology of various psychiatric disorders. Normalizing these aberrant activations is therefore a key issue for new treatments aiming at reducing the intensity of the symptoms associated with psychiatric diseases (16).

While more and more studies attempt to use RT-fMRI-NF in the treatment of psychiatric disorders, the clinical effectiveness is not yet clearly demonstrated, especially because of the diversity of the methods, designs, and outcomes measurement. Previous literature reviews that focus on depression demonstrated the efficacy of RT-fMRI-NF with a medium effect size on neural activity during NF training, a large effect size on the transfer run (when the feedback is absent) and small effect sizes on behavioral outcomes (17). They also demonstrated the clinical effectiveness of the technique in the management of depressive symptoms (18). While these studies provide cumulative evidence for the efficacy of neurofeedback in both neural regulation and clinical symptoms improvement in depressive disorders, we still do not know how effective this technique is in other psychiatric disorders or whether the clinical effects observed after training are maintained over time. In this context, the main aims of our meta-analysis are (1) to assess the efficacy of RT-fMRI-NF qualitatively and quantitatively on the improvement of clinical symptoms in various psychiatric disorders, (2) to discuss the methods used in these studies and (3) to provide methodological suggestions for future clinical trials aiming at using RT-fMRI-NF as a therapeutic tool in psychiatric disorders.

2. Methods

2.1. Materials

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (19). Studies were identified until October 19th, 2021 through a search within two databases, PubMed and Web of Science, using the following keywords: neurofeedback AND (fMRI OR “functional magnetic resonance imag*” OR “functional MRI”) AND (“real-time” OR “real time”). To be included in our qualitative synthesis, the articles had to meet the following criteria: 1) focusing on psychiatric disorders as defined by common psychiatric disorders classifications (e.g., DSM-IV (20), DSM-5 (21) or ICD-10 (22) and clinical interviews such as the MINI (23) or the SCID (24)). Only one study did not report the use of common psychiatric classification but directly recruited inpatients admitted for a major depressive episode (25); 2) aiming at improving the clinical symptoms related to a given psychiatric disorder; 3) participants had to regulate their brain activity based on the feedback signal from a given region of interest (ROI) or set of ROIs or the functional connectivity between two or more ROIs, which was recorded in real time with fMRI.

After duplicate removal, we initially identified 508 records. Among them, 293 were excluded based on title and abstract. Precisely, we excluded 65 articles not directly related to RT-fMRI-NF (e.g., performed neurofeedback with a different imaging modality), 137 proceedings, abstracts, or methods articles, 75 reviews, 8 articles published in a language other than English, and 8 secondary analyses of a previously published dataset. We screened the full text of the 215 remaining articles and removed 184 of them because they did not meet our inclusion criteria, mainly because they did not include psychiatric disorders or did not assess symptom severity in the outcomes. We also excluded studies focusing on non-pathological substance abuse (24,26,27). The final sample includes 31 studies (see Figure 2). The summary of this studies can be found in Table 1.

Figure 2. Flow Chart of included studies

INSERT TABLE 1 HERE

2.2. Clinical effectiveness report

Two types of contrasts were evaluated to highlight the effects of NF training in each reviewed study: 1. Training effect describes the clinical effectiveness significance of NF training on the outcome measure between the baseline (i.e., the first session/run) and the primary endpoint (i.e., the last session if it's a multiple-sessions training; or the last run if it's a single-session training). 2. Follow-up effect describes the sustained symptoms improvement beyond the NF training period. For both training effect and follow-up effect, effect sizes of within-group and between-group comparisons were reported with Hedge's g . The between group effect size was based on the differences in clinical outcome between the experimental and control groups. Control groups were either active or no-intervention, depending on design study. Methods and formulas used for the conversion to Hedge's g are reported in Supplementary Materials.

2.3. Meta-analysis of the effect of NF on clinical symptoms

We performed a within-experimental group analysis and a between-group analysis. Papers were included in within-experimental group analysis if they explicitly reported data, T or F values. They were included in between-group analysis only if data were available online. In case, these were not reported or extractable from the reported data in the paper, we reached out to the corresponding authors, requesting this information. If these data were supplied, the paper was included in the final analysis. For all sources that met inclusion criteria, effect sizes, 95% confidence intervals, and their standard errors were calculated using “dmetar” software package in R 2021.09.2+382 ([https://bookdown.org/MathiasHarrer/Doing Meta Analysis in R/](https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/)). For standardization, all effect sizes were transformed in Hedge’s g metric using “esc” software package (<https://CRAN.R-project.org/package=esc>) (28). As we anticipated between-study heterogeneity, a random-effects model was used to pool effect sizes (29,30). The restricted maximum likelihood estimator (31) was used to calculate the heterogeneity variance τ^2 , that quantifies the variance of the true effect sizes underlying our data. We used Knapp-Hartung adjustments (32) to calculate the 95% confidence interval around the pooled effect. The summary statistics of the meta-analysis included several indices. First, overall effect; a weighted mean pooled from all studies included in the analysis. The coefficient weight for each study was calculated based on the confidence interval of the estimated effect, influenced by the study’s sample size. Then, the τ^2 and the I^2 statistic, that accounts for variability in effect sizes that is not due to sampling error (33). To evaluate the heterogeneity, we performed an outlier and influence analyses using “dmetar” package and a leave-one-out method to obtain the influence of each study on the pooled effect, which is recalculated with one study omitted each time. Results of these analyses are reported in Supplementary Results.

3. Results

3.1. Included studies

We identified 31 articles that evaluated the efficacy of RT-fMRI-NF in psychiatric disorders. Among them, 11 concerned mood disorders (25,34–43), 5 psychotic disorders (44–48), 5 trauma or stress-related disorders (41,49–52), 4 neurodevelopmental disorders (53–56), 3 addiction disorders (57–59), 2 personality disorders (60,61) and 1 anxiety disorders (62). Out of the 31 studies, 22 were controlled studies (see Figure 3A and Table 1).

Figure 3. Distribution of the reviewed studies according to the category of psychiatric disorders (A) and the region of interest (ROI) or the connectivity of interest (COI) selected for the NF training (B). NB: abbreviations used in figure are defined in Table 1's footnote. If an experiment focused on more than one ROI, we included both in the figure (thus, the total number of ROIs exceeds the total number of studies).

Targeting specific ROIs is the most represented strategy (26 out of the 31 studies) all conditions combined (see Figure3B). Most of them focused on modulating the activity of the amygdala (AMY; 12 studies), followed by the insula (4 studies), and the anterior cingulate cortex (ACC; 3 studies). Studies on mood disorders targeted a wide variety of ROIs located in cortical (mainly the prefrontal cortex PFC) (25,34) and subcortical areas (mainly the AMY) involved in depression and emotion processing (37–39,42,43,63), while those focusing on personality disorders only targeted the AMY (60,61). The study on anxiety disorders used a feedback derived from the fronto-insular connectivity (62). Studies on psychotic disorders rather focused on ROIs involved in auditory hallucinations symptoms, such as the superior temporal gyrus (STG) (46,47), the default mode network (DMN) (44), and the ACC (45). Regarding neurodevelopmental disorders, studies that focused on ADHD symptoms targeted hyperactivity and attention via the modulation of the inferior frontal gyrus (IFG) (53) and the ACC activity (55), respectively. In contrast, one study on ASD targeted social processing via the connectivity between the left superior temporal sulcus (STS) and the left somatosensory

cortex (SC) (54). The other targeted the facial emotion expression processing via the right posterior STS activity (56). Trauma and stressor-related disorders studies focused on the modulation of AMY (41,49,50,52) and the ACC (51) because of their implication in emotion dysregulation, a key symptom in PTSD. Addiction studies targeted the PFC (57,58) and salience network (64), which is involved in craving and decision-making (see Figure3B and Figure4).

Figure 4. Symptoms targeted among the category of psychiatric disorders

3.2. Neurofeedback paradigms and clinical efficacy in psychiatric disorders

The reviewed studies employed different types of paradigms, tasks, and self-regulation protocols to train participants to either up- or downregulate the BOLD signal (or connectivity) in brain areas involved in a given disorder. Specific symptoms changes induced by the RT-fMRI-NF training are summarized in Table 2 and Table 3 and detailed for each pathology below.

3.2.1. Mood disorders

The most widely used paradigm in RT-fMRI-NF studies of mood disorder consists of recalling positive autobiographical memories (6 out of 11 studies), in order to increase amygdala activity and thus to treat symptoms related to emotion dysregulation (37,42,63), depression (38,39,43) and anxiety (39,42).

In a first proof-of-concept study of RT-fMRI-NF in MDD, Linden et al. (2012) compared two groups of patients with MDD ($n = 8$ in each group). While the patients with MDD in the active control group performed a mental imagery task involving positive emotions outside the scanner, patients of the experimental neurofeedback group attempted to upregulate regions involved in positive emotions during four three-runs NF-training sessions. Patients in the neurofeedback group showed a significant decrease in depressive symptoms ($g = 1.33$), which was significantly higher than in the control group (34). In one recent study, Mehler et al. (2018) used a larger sample with 16 patients in each group. Patients in the active control group were trained to upregulate regions activated by visual scenes while patients in the experimental group tried to upregulate areas involved in emotion processing during a two six-runs NF-training sessions. Depressive scores were reduced in both groups after the NF training (CG: $g = 2.16$; EG: $g = 2.23$) with a sustained improvement at 1-month follow-up. Similar effects were observed for anxiety levels but only patients in the experimental group showed a sustained improvement in depressive symptoms at follow-up ($g = 1.57$) (35).

In a set of six studies, patients with MDD were trained to upregulate amygdala activity. In the first studies by Young et al. (2014) and Yuan et al. (2014), patients were instructed to recall positive autobiographical memories during a single three-runs NF-training session. Patients with MDD in the active control group received feedback from an unrelated region in the parietal lobe. Participants in the experimental group showed significant decrease in depressive and anxiety scores (37,39) as well as in anger level (37). In Young et al. (2014), the patients also showed increased happiness, as assessed by a happiness visual scale, which was significantly greater than in the control group ($g = 0.36$) (37). Patients with MDD in Zotev et al. (2016) performed the same neurofeedback and self-regulation task during two three-runs sessions of neurofeedback. They also presented less depressive and mood symptoms and a significant increase in happiness. The active experimental group showed a significant decrease in depressive score compared to the control group after the NF training ($g = 0.03$) (63). In a

more recent study (2020), the same authors were able to replicate these results with a greater sample in the experimental group and by targeting the rostro-dorsal ACC. They showed a significant decrease in depression score ($g = -0.59$), and in state anxiety ($g = -0.54$) and a significant increase in happiness ($g = 0.56$) in the experimental group (42). Using the same paradigm, Young et al. (2017) revealed a significant decrease in depressive score in the active experimental group compared to the control group (significant group-by-time interaction) after the training ($g = 1.13$). They also showed a significant sustained decrease in depression score at 1-week follow-up in patients with MDD (within-group analyses: $g = 0.58$ for MADRS; between-group analyses: $g = 1.14$ for MADRS, $g = 0.72$ for BDI-II, $g = 0.90$ for HAM-D) (38). Similarly, Tsuchiyagaito et al. (2020) showed a sustained improvement of depressive symptoms at 2-weeks follow-up ($g = 0.54$) (43).

In a double-blind proof-of-concept study, remitted patients with MDD attempted to upregulate the connectivity between the anterior temporal lobe (ATL) and the subgenual cingulate cortex (SCC) during a single two-run neurofeedback training session by retrieving guilt and indignation/anger-related autobiographical memories. Participants in the experimental group showed increased self-esteem and decreased self-hatred at higher levels than the control group at the end of the training (significant group-by-time interaction) (40). Recently, in Mennen et al. (2021) study, patients underwent an emotional induction task within a three seven-to-nine-runs NF-training sessions of neurofeedback. Authors demonstrated a significant decrease in depressive symptoms after the NF training ($g = 1.28$) with a sustained improvement at 1-month ($g = 1.05$) and 3-month follow-up ($g = 1.30$) (36).

3.2.2. Psychotic disorders

In schizophrenia, authors focused either on the emotion dysregulation (48) or on auditory hallucinations (44–47).

In the first proof-of-concept of RT-fMRI-NF in schizophrenia, Ruiz et al. (2013) taught patients to upregulate the anterior insula in a 12-session neurofeedback training while performing a face emotion recognition task. Patients showed a decrease in negative affect and an increase in positive affect as measured by the PANAS at primary endpoint (48).

In the four other studies, authors focused on the treatment of auditory hallucinations by targeting different cerebral networks. In a pilot study, Dyck et al. (2016) reported various effects of neurofeedback training in three patients who tried to upregulate ACC during three sessions. In most cases, patients reported perceiving fewer negative voices and more positive voices with

a decrease in disturbance by and suffering from voices. Those effects remained constant few days after training. (45). Orlov et al. (2019) trained patients with SZ to downregulate the left superior temporal gyrus during four sessions of neurofeedback. Patients showed a significant decrease in beliefs regarding the origin of voices ($g = 0.59$) and in the intensity of distress perceived ($g = 0.60$) after the NF training. At 1-week follow-up, patients showed a sustained improvement in the beliefs about origins (47). While using the same neurofeedback paradigm, Okano et al. (2020) showed a significant decrease in auditory hallucinations in patients with SZ after the training ($g = 1.72$) (46). Bauer et al. (2020) revealed a significant sustained decreased in the frequency of auditory hallucinations after downregulation of the DMN connectivity at 1-week follow-up ($g = 0.53$) (44).

3.2.3. Trauma- and stressor-related disorders

In the first studies regarding PTSD, patients attempted to downregulate amygdala activity within three sessions of NF-training while hearing trauma-related scripts (49) or watching trauma-related words (50). Gerin et al. (2016) showed a significant decrease in patients' symptomatology at primary endpoint (49). However, Nicholson et al (2017) did not report a difference in PTSD symptoms (50).

In two single-blinded proof-of-concept studies, patients with PTSD in the active control group received feedback from a brain region not related to PTSD symptoms and patients in the experimental group were trained to upregulate the amygdala activity by recalling positive autobiographical memories (52) or by undergoing an happy emotion induction task (41). Both studies showed a significant decrease in PTSD symptoms (Clinician Adminstrated PTSD scale (CAPS) total score : $g = -1.80$ (52) , $g = -1.79$ (41) ; CAPS avoidance symptoms : $g = -1.84$; CAPS hyperarousal symptoms subscale : $g = -1.23$ (41)) and a significant decrease in depressive scores (MADRS : $g = -1.68$ (52) ; HDRS : $g = -2.24$ (41)) in the experimental group at the primary endpoint.

In Zweering et al. 2018, patients with PTSD and healthy participants attempted to upregulate the ACC by performing mental imagery during three sessions of neurofeedback training. The authors showed a significant decrease in intrusion score ($g = 1.64$) and in negative affect, as well as a significant increase in positive affect in the experimental group with a group-by-time interaction at primary endpoint ($g = 1.05$) (51).

3.2.4. Neurodevelopmental disorders

In the first single-blinded study assessing the efficacy of RT-fMRI-NF in neurodevelopmental disorders, Ramot et al. (2017) attempted to bring connectivity level between networks, in patients with ASD, closer to those of TD patients. While patients with TD were trained to reinforce the connectivity between the STS and the inferior temporal lobe (two regions as uncorrelated as possible), patients with ASD were trained to upregulate the connectivity between the STS and the SCC during four neurofeedback sessions. All started with a blank screen and were instructed to reveal the picture hidden underneath. This was described as a puzzle task and no further instructions were given. ASD patients showed a significant reduction in autistic traits after NF training (54). Later Direito et al. (2021) showed a significant improvement in fear recognition after the NFB training and at 6-months follow-up in ASD patients after five four-run neurofeedback training sessions while targeting the right posterior STS during an emotion recognition task. They also showed a decrease in depressive score and anger after the primary endpoint (56).

Alegria et al. (2017) compared two groups of adolescents with ADHD during four neurofeedback training sessions. The control group received feedback from the parahippocampal gyrus, a region unrelated to the symptomatology, and the patients in the experimental tried to upregulate the inferior frontal gyrus activity. Authors showed a significant decrease in ADHD scores (ADHD total score: $g = 0.59$; ADHD inattention subscale: $g = 0.65$) and a slight decrease in hyperactivity/impulsivity in the experimental group at primary endpoint ($g = 0.43$). The decrease in ADHD symptoms were significantly maintained at follow-up in the experimental group (ADHD total score: $g = 0.88$; ADHD hyperactivity: $g = 0.87$). Both groups showed a decrease in ADHD severity and only the experimental group control showed significant decrease in ADHD-related difficulties and impairments (53).

In a randomized single-blinded study, Zilverstand et al. (2017) trained the experimental group and the active control group to upregulate the ACC while performing mental calculation during four sessions of neurofeedback training. Patients in the experimental group were the only one to receive continuous feedback from the ACC. Both groups showed a decrease in impulsivity and improved performance in a cognitive interference task. Only the experimental group showed an increase in attention, in response inhibition and in visual working memory after the NF-training (55).

3.2.5. Addiction

Among the three studies concerning addiction, two focused on alcohol use disorder (AUD) and one on nicotine use disorder. Karch et al. (2015) compared two groups of patients with AUD and one group of healthy participants performing an alcohol-cue induced craving task during a single four-run neurofeedback training session. The healthy control group was divided into two groups according to the region of interest used for the feedback calculation: one group received feedback from the PFC (experimental) and one group from the cuneus (control). Authors showed a decrease in subjective craving scores in the experimental group at primary endpoint (58). Later, Subramanian et al. (2021) compared an active control group with “treatment as usual” (TAU) (i.e., psychoeducation, psychological support, and medical management of abstinence) to an experimental group with TAU and six two-run neurofeedback training sessions. They were trained to downregulate the activity of the salience network with an alcohol-cue induced craving. The authors found a significant decrease in alcohol consumption in the experimental group at primary endpoint. At 8-months follow-up, they showed a greater decrease in alcohol consumption in the control group. At 12-month follow-up, the trend was reversed, the patients of the experimental group showed a greater decrease in alcohol consumption in comparison to the control group (59).

Hartwell et al. (2016) assessed the efficacy of the RT-fMRI-NF in nicotine-use disorder with a smoking-cue exposure task. They used a control group composed of patients that did not receive feedback and an experimental group composed of patients who were trained to downregulate the PFC during three three-run neurofeedback training sessions. Patients in the experimental group showed a significant craving decrease ($g = 0.61$), especially regarding the anticipation of the pleasurable outcomes of smoking ($g = 0.65$) at primary endpoint (57).

3.2.6. Personality disorders

Two studies focusing on borderline personality disorder (BPD) were conducted. Both did not include a control group. Patients with BPD were trained to downregulate the activity of the amygdala while watching negative and neutral pictures during four three-runs NF-training sessions (61) and three four-runs NF-training sessions (60). In Paret et al. (2016), the authors showed a significant decrease in emotion dysregulation (Difficulties in Emotion Regulation Scale (DERS) lack of emotional awareness subscale: $g = 1.27$) and in dissociation symptoms ($g = 1.97$) at primary endpoint. Results were sustained 3-days after the training (60). In Zaehrer et al. (2019), patients with BPD showed a significant decrease in symptom severity ($g = 0.63$), which was sustained at 6-weeks follow-up ($g = 0.44$). They also demonstrated a

decrease in alexithymia and affective instability. At follow-up, patients showed a significant decrease in emotion dysregulation ($g = 0.47$), a significant increase in emotional skills ($g = -0.54$) and a decrease in alexithymia (61).

3.2.7. Anxiety disorders

Zilverstand et al. (2015) assessed the anxiety symptoms related to spider phobia. They used an active control group of patients who were told to use an intuitive strategy and an experimental group of patients who were instructed to use reappraisal strategies during an anxiety provocation task. Both groups were trained to upregulate the activity of the dorsolateral PFC and to downregulate the insula during four single-run NF-training sessions. Authors showed significant decrease in anxiety levels in both groups with lower average anxiety in the experimental group, as well as a significant group-by-time interaction ($g = 2.59$) at primary endpoint. At follow-up, both groups showed a decrease in spider phobia (62).

INSERT TABLE 4 HERE

3.3. Meta-analysis of clinical improvement in the experimental groups

Seventeen studies were included in this meta-analysis (see Table 5). Within-experimental group analysis was performed for depressive symptoms, anxiety symptoms and emotion regulation improvement at the end of NF training. Only depressive symptom's improvement was evaluated at follow-up. Between-group analysis was conducted only in controlled studies assessing the depressive symptoms and the anxiety symptoms.

3.3.1. Within-experimental group analysis

The results of within-experimental group analysis showed a significant effect, with a large effect size for the depressive symptoms improvement after NF training measured by within-experimental-group differences in depressive score between the baseline and the primary endpoint across 13 studies ($g = 0.84$ 95%-CI [0.52; 1.16], $T = 5.42$, $p < 0.01$) (see Figure 5 top). A large effect size for the depressive score is also observed between the baseline and the follow-up across 4 studies ($g = 1.25$, 95%-CI [0.6216; 1.8698], $T = 5.54$, $p < 0.01$) (see Figure 6). The anxiety improvement and emotion regulation improvement after NF training yielded a medium

effect size (respectively: $g = 0.52$, 95%-CI [0.19-0.85], $T = 4.43$, $p = 0.01$; $g = 0.46$, 95%-CI [0.17-0.76], $T = 4$, $p = 0.01$) across 5 studies each (see Figure 5 middle and bottom).

The between-study heterogeneity variance was estimated at $\tau^2 = 0.07$ (95%-CI [0; 0.7020]), with a heterogeneity factor I^2 value of 42,5% (95%-CI [0%; 70%], $p = 0.05$), revealing a significant between-study variance for the depressive symptom meta-analysis. The between-study variance did not reached a significant level for the anxiety symptom ($\tau^2 = 0$, 95%-CI [0.0000; 0.5143]; $I^2 = 0$, 95%-CI [0.0%; 79.2%], $p = 0.76$) and for the emotion regulation analyses ($\tau^2 = 0$, 95%-CI [0.0000; 0.3250]; $I^2 = 0$, 95%-CI [0.0%; 74.6%], $p = 0.53$) (see Figure 5), and depressive score at follow-up ($\tau^2 < 0.0001$, 95%-CI [0.0000; 6.8479]; $I^2 = 38.6\%$, 95%-CI [0.0%; 77.2%], $p = 0.16$ (see Figure 6).

To explore what causes this between-study heterogeneity when assessing depressive score and to evaluate the robustness of our pooled results, we conducted an outlier and influence analyses (65) using a leave-one-out method (see Supplementary results). Importantly, theses analyses revealed a possible overestimation of the pooled effect size of studies assessing depressive scores. By removing one study (the outlier) (35), the pooled effect of $g = 0.73$ is smaller than our initial estimate $g = 0.84$, but still within the same orders of magnitude. The heterogeneity I^2 also decreased from 42,5% (95%-CI 0%-70%) to 0% (95%-CI 0%-58%) (see Figure S2 and Table S3). Our subgroup analyses indicated an influence of the outcome measurement used to evaluate the clinical symptoms (see Table S1 in Supplementary Materials), of the number of sessions (see Table S2) and the number of runs (see Table S3) on the between-study heterogeneity (see Supplementary results).

3.3.2. Between-group analysis

The between-group analysis showed a medium effect size at the primary endpoint within 10 studies assessing depressive score improvement ($g = 0.46$ 95%CI [0.75-0.78], $T = 3.36$, $p < 0.01$). A large-effect size was found across 5 studies evaluating anxiety's improvement ($g = 0.91$ 95%CI [-0.20 2.02], $T=2.27$, $p = 0.09$).

The between-study heterogeneity variance did not reach significant level for the depressive symptom ($\tau^2 < 0.0001$ 95%-CI [0.0000; 0.5858], $I^2 = 11\%$ 95%-CI [0.0%; 51.9%], $p = 0.34$). However, the between-study heterogeneity was estimated at $\tau^2 = 0.34$ (95%-CI [0.0388; 7.4947]), with a heterogeneity factor I^2 value of 69% (95%-CI [19.3%; 87.8%], $p = 0.01$),

revealing a significant between-study variance for the anxiety symptom meta-analysis (see Figure 7).

To better understand the between study heterogeneity observed in anxiety's analyses, we conducted an outlier and influence analyses using leave-one-out method. These analyses revealed a possible overestimation of the pooled effect size and an increase of the heterogeneity value. By removing one study (62), the pooled effect decreased from $g = 0.91$ to $g = 0.57$. The heterogeneity value I^2 also decreased from 69% (95%-CI [19.3%; 87.8%]), to 24% (95%-CI [0.0%; 88.3%]) (see Figure S3 and Table S7). Our subgroup analyses indicated an influence of the outcome measurement used in one study (62) which tend to overestimate the effect size of between-group analyses assessing anxiety symptoms. This is consistent with our leave-one-out analyses.

Figure 5. Forest plot with overall effect of NF training after the primary endpoint on depressive score (top panel), anxiety symptoms (middle panel) and emotion regulation (bottom panel) symptoms. CI = confidence interval, g = Hedge's effect size, SE = standard error

Figure 6. Forest plot with overall effect of NF training at follow-up on depressive score. CI = confidence interval, FU = follow-up, g = Hedge's effect size, SE = standard error

Figure 7. Forest plot of between-group analysis with overall effect of NF training at primary endpoint on depressive score (top) and on anxiety score (bottom). CI = confidence interval, g = Hedge's effect size, SE = standard error

4. Discussion

Since the emergence of RT-fMRI-NF, the interest in its use is still growing in the scientific community. This technique allows participants to self-regulate the activity of region(s) in their brain, through real-time feedback. As this technique can be used in combination with pharmaceutical treatments, many studies attempt to integrate RT-fMRI-NF in the health care pathway of patients with psychiatric conditions. Because the clinical effectiveness is not clearly established, we conducted a systematic review and meta-analysis to evaluate the efficacy of RT-fMRI-NF in the improvement of clinical symptoms in various psychiatric disorders. Thirty studies assessed the effectiveness of RT-fMRI-NF on the improvement of psychiatric clinical symptoms. Out of the 31 studies, 20 reported significant clinical improvement in the experimental group after NF training with eight of them with a sustained improvement at follow-up, 8 slight symptoms improvement in the experimental group after the training while two reported also a sustained improvement at follow-up, one reported improvement in both the experimental and the control group, one reported sustained improvement at follow-up (post-NF training results not available) and one reported no difference in symptoms enhancement in the experimental group after the NF-training. We found only two double-blind randomized controlled trials that showed clinical symptoms improvement in mood disorders after the training. In general, studies on mood disorders showed a large effect on depressive symptoms when targeting the amygdala with a greater effect in the experimental group compared to the control group after the training. The variety of paradigms and methodologies used is wide and the heterogeneity of the results very high.

The meta-analysis of RT-fMRI-NF studies pointed a significant clinical improvement in depressive, anxiety symptoms and emotion regulation in the experimental groups between baseline and the end of the NF training and showed a clinical improvement in anxiety symptoms in the experimental group compared with sham control groups. This suggests that the clinical improvement following NF training cannot be attributed simply to the general processes involved in the training such as expectations, participant's exposure or reward processing (discussed below) (66). The clinical improvement in depressive score is maintained beyond the NF training with a large effect size. The present meta-analyses should be interpreted with caution since there is heterogeneity in effect sizes between studies, particularly in those assessing depressive score. This is indicated by the I^2 parameter and τ^2 (33), illustrating that a large proportion of the total variation in the described sample remains to be explained.

Interestingly, we tested the influence of certain design parameters (i.e., the outcome measure, the number of session and the number of run). We found a statistical significance, indicating that the parameters alone could explain the variability in modulation effect size. This suggests that heterogeneity across studies may arise from several variables, and perhaps from an interaction between design choices that will be discussed in the subsequent discussion.

For successful clinical trials in the neurofeedback studies, the choice of the control condition is a critical challenge to prove the efficacy of the technique, and to dissociate the changes relying on the neurofeedback training itself from other factors (e.g., mental strategy, the attention, the motivation) that comes through participation in neurofeedback training (67,68). The design of the study can either involve a passive control group (e.g., continuing the treatment as usual (TAU) vs. TAU and neurofeedback training) (59), or researchers can choose to employ an active control group (e.g., performing the same task as the experimental group but receiving the signal from another participant in the experimental group) (69). There is no consensus yet as to which control conditions is the most optimal (66,70). Some studies have shown that participants who believe they are receiving the true feedback (even if they did not) show significant changes in attention (53) and depressive symptoms (35). This highlights the importance of conducting rigorous randomized double-blind placebo-controlled NF studies, which is considered as the gold standard in clinical trials. However, many studies identified in our systematic review lack adequate control. Only 22 studies out of 31 reviewed studies included a control group. Eleven were included in the meta-analysis. Several studies used as a control condition, a region not involved in the targeted cognitive process (i.e., sham feedback; 12 out of 22 controlled studies). As an example, Young et al. (2014) used the signal from the intraparietal sulcus as sham feedback for the control group and from the amygdala for the experimental group. They showed a significant increase in happiness in depressed patients in the experimental group. This enables to control for the level of motivation and belief of those receiving the real NF (66,71), but it is difficult to identify regions not involved in a cognitive process and participants may become discouraged because the visual feedback may not follow their attempts to achieve regulation. Other studies decided not to provide feedback on brain activity to the control group but to give them the same cognitive task as the experimental group (55,57,62), which allowed the authors to prove that the observed effects were not due to the participants' exposure to the training, but to the cognitive consequences induced by the feedback on their brain activity. We can then conclude that, ideally, both a sham-control group and a no-feedback group should be used in clinical trials (72). However, the inclusion of two control

conditions would be considerably expensive and time consuming (66,71). Sorger et al. (2019) argue that the type of control condition depends on the purpose of the neurofeedback study. To determine clinical efficacy, sham neurofeedback groups might be more appropriate because participants in both experimental and control groups are engaged in the same experimental procedure.

As the gold standard in clinical trials, double-blinded trials allow to prevent behavioral changes resulting from NF training to be attributed to experimental biases, such as the involuntary transmission of hypotheses or knowledge of which group the participants is assigned to, which may influence the participant's and investigator's motivation (73). In addition, randomization is an important aspect of the control of the experimental bias, to allow an equivalence and a fair comparison between the experimental and the control groups. Such well-controlled double-blind randomized placebo-controlled clinical trials in NF-fMRI studies are so far quite rare (71,74). Only two out of the 22 controlled-studies reviewed used double-blind randomized controlled procedures (38,40). Therefore, more rigorous, double-blind RCTs are needed in order to prove the clinical efficacy of RT-fMRI-NF training in the treatment of psychiatric disorders (72,75).

The primary outcome for all studies was to evaluate the progression of the symptomatology after the NF training. In order to demonstrate the clinical efficacy of the RT-fMRI-NF training, studies have to show (1) an additional improvement in the experimental group in comparison to the control group (i.e. between-group comparisons) ; (2) the transferability of RT-fMRI-NF to situations where the feedback is absent (i.e. during the transfer run) and (3) the sustainable effect over time as measured by follow-up visits (71). Between-group comparisons after the training and ideally an interaction between Groups (experimental vs. control) and Time (pre vs. post training) are required to conclude as to the efficacy of the NF training vs. placebo or retest effect. Young et al. (2017) provided a good example. They found that left amygdala neurofeedback training reduced depressive symptoms right after the training and at 1-week follow up with a transfer effect post-NF training. The optimal duration of the follow-up is not yet well established. Some studies reported a sustained improvement after RT-fMRI-NF training for a month (35,36,53,56,59,61,62), while others only after one week (38,43,44,47). Despite the importance of these measures, only 10 studies out of the 30 reviewed collected and reported follow-up data. This leads to a reduction of the clinical relevance of this technique and may lead to an underestimation of the size of the NF effect. We would recommend future studies

to systematically assess the evolution of the symptoms post-NF training for at least three months after the training.

The efficacy of neurofeedback can be dependent on the number of runs and sessions of NF training. Indeed, the number and the length of each training session and runs varies considerably across different studies. We reported a high variability in the number of sessions in studies included in this systematic review (range = 1-12). The number of sessions chosen in each study seems somewhat arbitrary as the ideal number of sessions for optimal training response is not yet well established (70,71). Young et al. (2017) reported lower depressive scores after two NF training sessions (with three runs each). Similarly, Bauer et al. (2020) showed an improvement in auditory hallucinations after two NF training sessions (with four runs each). As suggested by Zahn et al. (2019), the ability of a single session of RT-fMRI-NF training to produce lasting changes in neural processes and the related symptomatology appears to be somewhat lacking in credibility. Indeed, they did not report score differences in depressive symptoms in patients with remitted MDD whilst retrieving guilt and indignation/anger-related autobiographical memories, after a single NF training session by targeting the ATL-SCC connectivity. Further research needs to be done to identify the optimal number of sessions and runs required in RT-fMRI-NF experiments for clinical efficacy (72) by considering contextual and individual factors that can affect the optimal training (motivation, the time of day when participants are tested, age, participant sleep time, physical condition, menstrual cycle).

One of the most challenging issues encountered in RT-fMRI-NF research is undoubtedly the choice of target region(s). The question is whether fMRI-based NF should focus on localized activity (i.e., BOLD response) in a target specific region (defined a priori with standard atlases or through a subject specific localizer), or rather on network related parameters. If only one target region is chosen to be modulated by NF training, it is important to ask whether the primary purpose of the training is to regulate the activation of a disrupted region (e.g., amygdala in emotion regulation (39,42,52,61); or the prefrontal cortex in addictions (57,58)). Most studies reviewed here (26 out of the 31) used a single-ROI approach. The amygdala, the medial and lateral prefrontal regions, including the ACC and limbic regions are the regions most used as ROIs. These regions are relevant targets for RT-fMRI-NF studies because of their role in self-regulation, emotion regulation and reward processes. Salience network areas, such as the insula, were used in some studies because of the role in the regulation of emotion (fear, sadness). The ROI-based approach is based on the hypothesis that specific regions might be

critical in the pathophysiology in a given disorder or symptom (72,76) without considering that cerebral regions are widely interconnected and a specific region could be considered as a hub. A growing number of RT-fMRI-NF studies target functional connections rather than a single-ROI (72). There is some evidence that connectivity-based signals are more effective than ROI-based approaches. In Kim et al. (2015), researchers showed that the connectivity feedback was more efficient than the ROI feedback in cigarette craving regulation in healthy individuals (26). In contrast to studies using a single ROI-based approach, five studies here reviewed adopted a connectivity-based approach (36,40,44,54,59). It consists of returning functional connectivity measurements, i.e., the measure synchronization or desynchronization of brain activity between different brain regions (71,72). For example, Ramot et al. (2017) used a connectivity-based approach to target the connectivity between the STS and the SCC in patients with ASD. They showed an increase in STS-SCC connectivity during resting-state and showed a reduction in autistic traits in the experimental group after the training.

The selection of specific regions is very important, especially in children and adolescents. Indeed, one could ask whether it is more adequate to train a young patient to regulate brain regions involved in a cognitive function at a specific developmental state or whether they should be trained to directly regulate the brain networks that support that ability in a mature adult brain (68). Only one study in this review trained adolescents and adults with ASD to regulate the STS-SCC functional connectivity (54). However, they did not consider the age of the participants and the putative cerebral anatomical differences. Indeed, it is important for future RT-fMRI-NF to consider that during brain development, cognitive functions are not always supported by the same brain networks as in adulthood (68).

The development of multivariate approaches or “multivariate pattern analysis” (MVPA) in the neuroimaging field also offers promising applications for neurofeedback training. Classifier-based MVPA aims to classify brain activity associated with the to-be-discriminated cognitive states and then provide feedback based on proximity to the desired brain state (77,78). Methods such as Decoded Neurofeedback (or DecNef) aim at discovering a pattern of brain activity that might be related to different brain states, and to target these patterns in NF training (79). The purpose of this technique is to train participants to regulate ongoing brain activity related to a specific behavior (66,73). The advantage of this procedure is that it incorporates data from the entire brain (multivariate per se) and compensatory processes outside the expected ROIs or networks (66). To date, only one study has been conducted using DecNef to reduce

subsyndromal phobia to spiders, with promising results (80). DecNef method seems to be highly relevant to target the complexity of the neuropathophysiology of psychiatric disorders. We suggest that future studies should consider the growing understanding of the importance of functional connectivity and multiple brain regions involved in complex behaviors and patients' symptomatology.

Another source of variability in the studies referenced in the current review concerns the evaluation of the symptoms. Different scales can be used to evaluate the intensity of a given symptom. For example, to assess the intensity of the depressive symptoms, the MADRS and the HDRS are the most common clinical scales used. Although both scales assess the severity of depression, they differ according to the number of items (10 for the MADRS and 21 for the HDRS) and their scoring (i.e., all items are used to measure depression severity with the MADRS, while with the HDRS only the first 17 items are used). This heterogeneity in clinical scales used makes meta-analyses either difficult or impossible to perform. In our meta-analyses, the subgroup analyses showed a statistical significance for the heterogeneity in studies using HDRS-17 in studies assessing depressive score. Standardization of the clinical rating scales for each symptom could help bypass these difficulties.

In this review, we did not include EEG-NF studies. However, EEG and fMRI are two complementary techniques. EEG has a high temporal resolution. However, its spatial resolution is limited by the number of electrodes. Importantly, EEG does not allow a good source localization for deep brain structures. In contrast, fMRI has a higher spatial resolution and allows a whole-brain exploration. However, its temporal resolution is constrained by the delay of the hemodynamic response. The major motivation for the combination of both techniques is the possibility of linking the precise anatomical localization and precise temporal evolution of brain activation signals for real-time feedback (12,72,81). Machine learning algorithms are a great tool to help the reconstruction of the EEG signal source to have a fine temporal resolution of a deep brain area. In Zotev et al. (2014), participants underwent a RT-fMRI-EEG-NF protocol in depression. The EEG-NF was used for regulation of frontal asymmetry in the high-beta band (21-30 Hz) and the fMRI-NF was used for the regulation of the activity of the left amygdala. They applied RT-fMRI-EEG-NF to emotional self-regulation training in healthy subjects performing a positive emotion induction task based on the retrieval of happy autobiographical memories. Participants were able to regulate both their BOLD fMRI activation in the left amygdala and frontal power asymmetry in the high-beta band. In this

review, three studies used RT-fMRI-EEG-NF in major depressive disorders (42,63) and in PTSD (41). Zotev et al. (2016) showed an improvement in depression scores after the RT-fMRI-EEG-NF training. They used a simultaneous EEG recording during RT-fMRI-NF paradigm, allowing to identify electrophysiological correlates of the RT-fMRI-NF training (63). With this paradigm, EEG correlates of fMRI-NF could be used as potential targets for EEG-NF or EEG-fMRI-NF for more efficient and/or more portable neurotherapies. Keynan et al., (2019) reported promising results with an RT-fMRI-EEG-NF study in alexithymia by targeting the amygdala activity in healthy participants. Although this technique is promising, there is very few RT-fMRI-EEG-NF research applied to psychiatric disorders. Indeed, it is an expensive and complicated technique to set up because of the EEG/MRI compatibility issues and the heaviness of the protocol for the participants. Further research must be done to overcome those technical issues and lead to advances in the non-pharmacological treatment of psychiatric pathologies.

5. Conclusion

RT-fMRI-NF provides patients to access, beyond mental states, to their own brain activity. The possibilities offered by this technique are multiple for the management of certain clinical psychiatric symptoms. Our review showed that, indeed, many studies found significant clinical improvements after NF training, especially in mood disorders. Although the use of RT-fMRI-NF in psychiatry is appealing, the level of evidence given by recent clinical trials remains moderate. Most studies face methodological issues both in the design and the report of the results of the performed trials. Considered as the gold-standard in clinical research, conducting double-blind randomized-controlled trials is still a major challenge for future RT-fMRI-NF studies. Innovative techniques, such as NF experiments based on functional connectivity or using a multivariate approach, offer new perspectives that could help to target the complex pathophysiology of psychiatric disorders and to ultimately relieve symptoms of patients suffering from psychiatric disorders.

Authors contribution

PP conducted the review and wrote the first draft of the manuscript along with PF. PF and JH conceptualized this review. All authors contributed to and have approved the final manuscript.

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Conflict of Interest

All authors declare no conflict of interest.

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Table 1. Overview of the reviewed studies

Disorder	Study	Population	Concomitant Treatment (EG/CG)	Training target in experimental group (N subjects in final sample)	Training target in control group (N subjects in final sample)	Clinical outcome measures	NF training session number / runs number	Transfer run	Follow-up (duration/ N sujets)	Feedback (type / task)
ADHD	Alegria et al. 2017	Adolescents	Psychostimulant (15 / 9)	↑ right IFG (N = 18)	<u>Active control group (N = 13)</u> : feedback from an unrelated control region (PHG)	ADHD - RS	Nsession = 4 / Nruns = 3- 4	Yes	Yes (11 months / EG = 13, CG = 11)	Continuous / Mental imagery
	Zilverstand et al. 2017	Adult	Psychostimulant (3 / 3)	↑ dorsal ACC (N = 7)	<u>Active control group:</u> (N = 6): no continuous feedback from ACC	ADHD-RS	Nsession = 4 / Nruns = 3	Yes	No	Continuous only for EG / Mental calculation
Anxiety	Zilverstand et al. 2015	Adult	No	↑ DLPFC + ↓ insula (N = 9)	<u>Active control group (N = 9)</u> : different strategy (reappraisal strategy in EG vs strategy based on intuition in CG)	Likert scale + SBQ + FSQ	Nsession = 1 / Nruns = 4	No	Yes (2 weeks + 3 months)	Intermittent / Anxiety provocation
ASD	Direito et al. 2021	Adult	ASD-related symptomatology (N = 8)	↑ STS	No control group	FEEST	Nsession = 5/ Nruns = 4	No	Yes (6 months)	Intermittent/ Emotion recognition task
ASD	Ramot et al. 2013	Adolescents - Adult	No	↑ left STS - SCC connectivity	<u>Healthy control group (N=10)</u> : feedback from other regions (STS - IPL connectivity)	SRS	Nsession = 4 / Nrun = 4	No	Yes (5 - 56 weeks / EG = 15)	Continuous/ Puzzle task
Alcohol use disorder	Karch et al. 2015	Adult	Not clearly reported	↓ DLPFC (N = 13)	<u>Healthy control group:</u> one group received feedback from PFC (N = 14) and one group received feedback from cuneus (N = 5)	OCDS	Nsession = 4 / Nrun = 1	No	No	Continuous / Alcohol-cue induced craving

Disorder	Study	Population	Concomitant Treatment (EG/CG)	Training target in experimental group (N subjects in final sample)	Training target in control group (N subjects in final sample)	Clinical outcome measures	NF training session number / runs number	Transfer run	Follow-up (duration/ N sujets)	Feedback (type / task)
Borderline personality disorder					<u>Active control group</u> (N = 2) : feedback from an unrelated control region (cuneus)					
	Subramanian et al. 2021	Adult	Yes (psycho- education, psychological support, and medical management of abstinence)	↓ salience network (N = 20)	<u>Passive control group</u> (N = 27); treatment as usual	Alcohol timeline followback	Nsession = 6 / Nruns = 2	No	Yes (8-month and 12-month, EG =	Continuous / Alcohol-cue induced craving
	Paret et al. 2016	Adult	SSRI (5) + other antidepressant (5) + neuroleptics (2) + methylphenidate, mood stabilizer or opioid receptor antagonist (1)	↓ amygdala (N = 8)	No control group	DERS + DSS	Nsession = 4 / Nruns = 3	Yes	Yes (3 days / EG = 8)	Continuous / watching negative vs. Neutral pictures
MDD	Zaehring et al. 2019	Adult	Psychotropic medication (N = 26)	↓ amygdala (N = 26)	No control group	ZAN-BPD + DERS + SEK-27	Nsession = 3 / Nruns = 4	No	Yes (6 weeks / EG = 24)	Intermittent / Watching negative vs. Neutral pictures
	Linden et al. 2012	Adult	Antidepressant medication (N = 8)	↑ regions involved in the generation of positive emotions (VLPFC and insula) (N = 8)	<u>Active control group</u> (out): Patients performing mental imagery of positive emotions outside the scanner (N = 8)	HDRS	Nsession = 4 / Nruns = 3	No	No	Continuous / positive mental imagery
	Mehler et al. 2018	Adult	Antidepressant medication (N = 32)	↑ emotion areas (N = 16)	<u>Active control group</u> : ↑ control region activated by visual scenes (N = 16)	HDRS	Nsessions = 5 / Nruns = 6	Yes	Yes (1 month / EG = 13, CG = 13)	Continuous / positive mental imagery

Disorder	Study	Population	Concomitant Treatment (EG/CG)	Training target in experimental group (N subjects in final sample)	Training target in control group (N subjects in final sample)	Clinical outcome measures	NF training session number / runs number	Transfer run	Follow-up (duration/ N sujets)	Feedback (type / task)
	Mennen et al. 2021	Adult	Not clearly reported	Whole-brain ROI (N=15)	<u>Healthy control group</u> (N=12) : whole brain ROI	MADRS	Nsessions = 3/Nruns = 7-9	No	Yes (1 month EG = 14 / 3 months EG = 13)	Intermittent / Visual negative images
	Young et al. 2014	Adult	No	↑ amygdala (N=14)	<u>Active control group (N = 7)</u> : Patients receiving feedback from an unrelated region (HIPS)	POMS + VAS	Nsession = 1 / Nruns = 3	Yes	No	Continuous / Recall positive autobiographical memories
	Young et al. 2017	Adult	No	↑ amygdala (N=19)	<u>Active control group (N = 17)</u> : Patients receiving feedback from an unrelated region (HIPS)	MADRS	Nsession = 2 / Nruns = 3	Yes	Yes (1 week/ EG = 18 EG, CG = 15)	Intermittent / Recall positive autobiographical memories
	Yuan et al. 2014	Adult	No	↑ amygdala (N=14)	<u>Healthy control group (N = 27)</u> : Feedback from the ROI <u>Active control (N = 13)</u> : Patients receiving feedback from an unrelated region (HIPS)	HDRS + HAM-A	Nsession = 1 / Nruns = 3	Yes	No	Continuous / Recall positive autobiographical memories
	Zhan et al. 2019	Adult	No	↑ ATL-SCC correlations (N = 14)	<u>Active control group (N=14)</u> : remitted patients received a feedback which stabilized the preceding degree of correlation	BDI + IQG + RSES	Nsession = 1 / Nruns = 2	No	No	Intermittent / Retrieving guilt and indignation/anger-related autobiographical memories
	Zotev et al. 2016	Adult	No	↑ amygdala (N=13)	<u>Active control group (N=11)</u> : feedback from an unrelated region (HIPS)	POMS + VAS	Nsession = 2 / Nruns = 3	Yes	No	Continuous / Recall positive autobiographical memories

Disorder	Study	Population	Concomitant Treatment (EG/CG)	Training target in experimental group (N subjects in final sample)	Training target in control group (N subjects in final sample)	Clinical outcome measures	NF training session number / runs number	Transfer run	Follow-up (duration/ N sujets)	Feedback (type / task)
	Zotev et al. 2020	Adult	No	↑ amygdala (N=16)	<u>Active control group (N=8)</u> : feedback received from an unrelated region (rostrom-dorsal ACC)	POMS + VAS + STAI	Nsession = 1 / Nruns = 3	Yes	No	Continuous / Recall positive autobiographical memories
	Takamura et al. 2020	Adult	Yes (N =5). Type not reported	↑ DLPFC (N =6)	No control group	BDI + HDRS + RRQ	Nsession = 5/ Nruns = 1 -5	No	No	Intermittent/Mental imagery
	Tsuchiyagaito et al. 2021	Adult	No	↑ amygdala (N=29)	No control group	MADRS	Nsession = 2 / Nruns = 3	Yes	Yes (2weeks / N=29)	Intermittent / Recall positive autobiographical memories
Nicotine use disorder	Hartwell et al. 2016	Adult	No	↓ PFC (N = 21)	<u>Active control group (N=23)</u> : patients receiving no feedback	QSU-B	Nsession = 3 / Nruns = 3	No	Yes (1 week / EG = 17, CG = 19)	Intermittent/ Smoking-cue exposure task
	Gerin et al. 2016	Adult	No	↓ amygdala (N = 3)	No control group	CAPS + PCL-M	Nsession = 3 / Nruns = 4	No	No	Continuous/Hearing of trauma-related scripts
	Misaki et al. 2021	Adult	Not clearly reported	↑ amygdala (N = 20)	<u>Active control group (N = 9)</u> : feedback received from an unrelated region (HIPS)	CAPS + MADRS	Nsession = 7/ Nruns = 4	Yes	No	Continuous/ recall a positive autobiographical memory
PTSD	Nicholson et al. 2017	Adult	No	↓ amygdala (N = 10)	No control group	RSDI	Nsession = 3 / Nruns = 4	Yes	No	Intermittent/ Watching trauma-related vs neutral words
	Zweering et al. 2018	Adult	Not clearly reported	↑ ACC (N = 9)	<u>Healthy control group (N=9)</u> : feedback from the ROI	IES-R + PANAS-X	Nsession = 3 / Nruns = 1	Yes	No	Continuous/ Mental imagery
	Zotev et al. 2018	Adult	No	↑ amygdala (N = 20)	<u>Active control group (N = 11)</u> : feedback received from an unrelated region (HIPS)	CAPS + HDRS	Nsession = 3 / Nruns = 3	Yes	No	Continuous / Happy emotion induction

Disorder	Study	Population	Concomitant Treatment (EG/CG)	Training target in experimental group (N subjects in final sample)	Training target in control group (N subjects in final sample)	Clinical outcome measures	NF training session number / runs number	Transfer run	Follow-up (duration/ N sujets)	Feedback (type / task)
SCZ	Bauer et al. 2020	Adult	Antipsychotic	↓ DMN connectivity (N = 11) + SMC connectivity (control region)	No control group	AHRS	Nsession = 2 / Nruns = 4	Yes	Yes (1 week/ EG = 11)	Continuous/Mental noting task
	Dyck et al. 2016	Adult	Antipsychotic (N=2)	↑ ACC (N = 3)	No control group	AVHRS + PANAS	Nsession = 3 / Nruns = 1	Yes	No	Continuous/ Mental imagery
	Okano et al. 2020	Adult	Antipsychotic	↓ STG (N = 10) + SCC (control region)	No control group	AHRS	Nsession = 2/ Nruns = 6	Yes	Yes (1 week / EG =10)	Continuous/ Hearing AVH - provoking stimuli
	Orlov et al. 2019	Adult	Antipsychotic	↓ STG (N = 11)	No control group	Psyrrats	Nsession = 4/ Nruns = 1-6	Yes	Yes (1 week/ EG = 11)	Continuous / Voice perception task
	Ruiz et al. 2013	Adult	Antipsychotic	↑ anterior insula (N = 9)	No control group	PANAS	Nsession = 12 / Nrun = 1	Yes	No	Continuous/ Face emotion recognition

↑ = upregulation; ↓ = downregulation; N = sample size; EG = Experimental group; CG = Control group

Note: ACC = anterior cingulate cortex, ADHD = Attention Deficit Hyperactivity Disorder, ADHD-RS = ADHD rating scale, ATL = anterior temporal lobe, A(V)HRS = Auditory (vocal) hallucination rating scale, ASD = Autism Spectrum Disorder, BDI = Beck Depression Inventory, BPD = Borderline Personality Disorder, CAPS = Clinician-Administered PTSD scale, CEN = Control – executive network, DERS = Difficulties in Emotion Regulation Scale, DLPFC = Dorso Lateral Prefrontal Cortex, DMN = Default Mode Network, DSS = Dissociation tension Scale – Short version, FEEST = Facial Expressions of Emotion—Stimuli and Tests, FSQ = Fear Spider Questionnaire, HDRS = Hamilton Depression Rating Scale, HIPS = Horizontal segment of the Intraparietal Sulcus, IES-R = The German Version of the Impact of Event-scale – revised, IPL = Inferior Parietal lobe, IFG = inferior frontal gyrus, IGQ = Interpersonal Guilt Questionnaire, MADRS = Montgomery - Åsberg Depression Rating Scale, MDD = Major Depressive Disorder, OCDS = Obsessive-compulsive drinking scale, PANAS = Positive and Negative Affect Scale, PANAS-X = The German version of the extended PANAS, PCL –M = PTSD Checklist – Military Version, PFC = Prefrontal cortex, PHG = Parahippocampal gyrus, POMS = Profile of Mood States, Psyrrats = Psychotic Rating Syndrome Scale, PTSD = Post-traumatic syndrome disorder, QSU-B = Questionnaire of Smoking-Urges – Brief, RRQ = Rumination-reflection questionnaire, RSDI = Response to Script Driven Imagery, RSES = Rosenberg self-esteem scale, SBQ = Spider Belief questionnaire, SCC = subgenual cingulate cortex, SSC = Somatosensory cortex, SCZ = Schizophrenia, SEk-27 = The German version of the Emotion Regulation Skills Questionnaire, SMC = Somatosensory Motor Cortex, SRS = Social Responsiveness Scale, STAI = The State-Trait Anxiety Inventory, STG = Superior Temporal Gyrus, STS = Superior temporal sulcus, VAS = Visual Analogue Scale, VLPFC = Ventro Lateral Prefrontal Cortex, ZAN-BPD = The Zanarini rating scale for borderline personality disorders

Table 2. Clinical improvement in primary outcomes measures post-NF and at follow-up

Disorder	Study	Clinical Improvement			
		Baseline vs primary endpoint		Baseline vs follow-up	
		Within-group	Between-group	Within-group	Between-group
ADHD	Alegria et al. 2017	↓ ADHD-RS total score (g = 0,59)*		↓ ADHD-RS total score (g = 0,88)*	
		↓ ADHD-RS inattention subscale (g = 0,65)*	No significant group x time interaction	↓ ADHD-RS inattention subscale (g = 0,81)	No significant group x time interaction in primary endpoint
		↓ ADHD-RS hyperactivity-impulsivity subscale (g = 0,43)		↓ ADHD-RS hyperactivity - impulsivity subscale (g = 0,87)*	
	Zilverstand et al. 2017	↓ ADHD attention and impulsivity score in EG	Not reported	Not applicable	Not applicable
		↓ ADHD impulsivity score in CG	Not reported	Not applicable	Not applicable
Anxiety	Zilverstand et al. 2015	↓ anxiety levels in both group with lower average anxiety in EG	Group x time interaction *	↓ spider fear in both group	Not reported
ASD	Direito et al. 2021	↑ fear recognition*	Not reported	↑ fear recognition*	
	Ramot et al. 2017	↓ SRS scores in EG*	Not reported	Not reported	Not reported
Alcohol use disorder	Karch et al. 2015	↓ subjective craving scores in EG	No significant group x time interaction	Not applicable	Not applicable
	Subramanian et al. 2021			CG > EG : ↓ alcohol consumption 8 months after training	
		↓ alcohol consumption in EG	Not reported	EG > CG : ↓ alcohol consumptions 12 months after training	Not reported
Borderline Personality Disorder	Paret et al. 2016	↓ DERS "lack of emotional awareness subscale" (g = 1,27)*	Not applicable	Stability of the effect observed in post-NF	Not applicable
		↓ dissociation (g = 1,97)*			
		↓ DSS aversive tension subscale			
	Zaehring et al. 2019	↓ BPD symptoms (g = 0,63)*	Not applicable	↓ BPD symptoms (g= 0,44)*	Not applicable

Disorder	Study	Clinical Improvement			
		Baseline vs primary endpoint		Baseline vs follow-up	
		Within-group	Between-group	Within-group	Between-group
		Non-significant ↓ Emotion dysregulation		↓ Emotion dysregulation (g= 0,47)*	
				↑ Emotional skills (g = -0,54)*	
MDD	Linden et al. 2012	↓ depressive symptoms in experimental group (g = 1.33)*	Group x time interaction for HDRS *	Not applicable	Not applicable
	Mehler et al. 2018	↓ HDRS in both groups (CG: g = 2.16; EG: g = 2.23)* ↓ anxiety levels and depressive levels in both groups	No significant group x time interaction	↓ HDRS in experimental group (g = 1,57)* ↓ anxiety levels and depressive levels in both groups	No significant effects
	Mennen et al. 2021	↓ depressive ratings (g=1.28)*	Not reported	↓ depressive ratings at 1-month (g=1.05) and 3-months follow-up (g=1.30)	Not reported
	Young et al. 2014	↓ POMS depression subscale and anger subscale in EG (g = 0.50)* ↑ VAS hapiness rating ↓ VAS restlessness, anxiety and irritated subscale ↓ VAS sadness subscale in CG	EG > control group: ↑ VAS happiness (g = 0.36)*	Not applicable	Not applicable
	Young et al. 2017	↓ Depressive symptoms in EG (g=1.17)*	EG > CG: Group x time interaction for MADRS (g=1.13)*	↓ MADRS (g= 0,58)*	EG > CG : ↓ MADRS (g=1.14)*, BDI-II (g = 0.72)*, HAM-D (g=0.90)*
	Yuan et al. 2014	↓ HARS (g = 0.66) and HDRS (g = 0.61) scores in EG and active control group	Not reported	Not applicable	Not applicable
	Zahn et al. 2019	↓ self-hate and ↑ self-esteem in EG	Group x time interaction for RSES*	Not applicable	Not applicable
	Zotев et al. 2016	↓ POMS depressive scores, mood disturbance scores and ↑ VAS hapiness*	EG > CG : ↓ POMS depressive scores (g = 0.03)*	Not applicable	Not applicable

Disorder	Study	Clinical Improvement		Baseline vs follow-up	
		Baseline vs primary endpoint			
		Within-group	Between-group	Within-group	Between-group
	Zotев et al. 2020	↓ POMS depression ($g = -0.59$)*, confusion ($g = -0.69$)*, total mood disturbance ($g = -0.57$)*, STAI state anxiety ($g = -0.54$)*, and ↑ VAS happiness ($g = 0.56$)*	No differences between groups	Not applicable	Not applicable
	Takamura et al. 2020	↓ BDI-II ($g = 1.19$)*, HDRS ($g = 4.74$)*, RRQ-rumination ($g = 0.93$)*	Not applicable	Not applicable	Not applicable
	Tsuchiyagaito et al. 2021	↓ MADRS scores ($g = 0.47$)*	Not applicable	↓ MADRS ($g = 0.54$)*	Not applicable
Nicotine use disorder	Hartwell et al. 2016	Not reported	EG > CG : ↓ QSU total score ($g = 0.61$)* and QSU Factor 1 ($g = 0.65$)*	Not reported	Not reported
			No group x time interaction		
PTSD	Gerin et al. 2016	↓ PTSD symptoms as assessed by CAPS total score* and ↓ in PCL-M scores for 2 patients*	Not reported	Not applicable	Not applicable
	Misaki et al. 2021	↓ CAPS scores ($g = -1.80$)* and MADRS scores ($g = -1.68$)*	Not reported	Not applicable	Not applicable
		↓ symptoms in CG			
	Nicholson et al. 2017	No difference in RSDI scores	Not reported	Not applicable	Not applicable
	Zweering et al. 2018	↓ intrusion score ($g = 1.64$)* and ↓ avoidance and sum score of the IES in EG	Group x time interaction for positive affect ($g = 1.05$)*	Not applicable	Not applicable
		↑ positive affect and ↓ negative affect in EG*			
	Zotев et al. 2018	↓ HDRS total score ($g = 0.96$)*, CAPS total score ($g = 0.64$)*, avoidance symptoms ($g = -1.84$)*, hyperarousal symptoms ($g = -1.23$)* in EG	No between-group differences	Not applicable	Not applicable

Disorder	Study	Clinical Improvement			
		Baseline vs primary endpoint		Baseline vs follow-up	
		Within-group	Between-group	Within-group	Between-group
SCZ	Bauer et al. 2020	Not reported	Not applicable	↓ AH scores (g = 0.53)*	Not applicable
	Dyck et al. 2016	<u>Patient 1</u> : ↓ negative voices intensity, ↓ disturbance ↓ in suffering, ↑ positive mood and negative mood but remained constant on 2 last days <u>Patient 2</u> : ↑ voices negativty, ↓ perceived control, ↓ number of voices, ↑ positive mood, ↓ negative mood for the 2 first days, ↓ positive mood on last day <u>Patient 3</u> : ↓ presence and negativity of the voices, ↓ of suffering and disturbance by voice, ↓ in the number of voices heard, ↑ positive mood, ↓ negative mood on 2 first day, ↓ positive mood on last day and strong ↑ in negative mood on last day	Not applicable	Not applicable	Not applicable
	Okano et al. 2020	↓ auditory hallucinations (g = 1.72)*	Not reported	Not reported	Not reported
	Orlov et al. 2019	↓ Beliefs about origins subscale of Psyrats (g = 0.59)* and ↓ intensity about distress (g = 0.60)*	Not applicable	↓ Beliefs about origins subscale of Psyrats	Not applicable
	Ruiz et al. 2013	↓ PANAS in the negative affects scales and stabilization of PANAS in the positive affects scales	Not applicable	Not applicable	Not applicable

*= significant results; ↑ = upregulation; ↓ = downregulation; NF = neurofeedback; EG = Experimental group; CG = Control group

Note: ADHD-RS = ADHD rating scale, A(V)HRS = Auditory (vocal) hallucination rating scale, AAUD = Alcohol Use Disorder, BDI = Beck Depression Inventory, BPD = Borderline Personality Disorder, CAPS = Clinician-Administered PTSD scale, DERS = Difficulties in Emotion Regulation Scale, DMN = Default Mode Network, DSS = Dissociation tension Scale – Short version, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, HIPS = Horizontal segment of the Intraparietal Sulcus, IES-R = The German Version of the Impact of Event-scale – revised, MADRS = Montgomery - Åsberg Depression Rating Scale, MDD = Major Depressive Disorder, PANAS = Positive and Negative Affect Scale, PCL –M = PTSD Checklist – Military Version, POMS = Profile of Mood States, Psyrats = Psychotic Rating Syndrome Scale, PTSD = Post-traumatic syndrome disorder, QSU-B = Questionnaire of Smoking-Urges – Brief, RRQ = Rumination-reflection questionnaire, RSDI = Response to Script Driven Imagery, RSES = Rosenberg self-esteem scale, SCZ = Schizophrenia, SRS = Social Responsiveness Scale, STAI = The State-Trait Anxiety Inventory, VAS = Visual Analogue Scale, ZAN-BPD = The Zanarini rating scale for borderline personality disorder

Table 3. Clinical improvement in secondary outcome measures

Disorder	Study	Other significant outcomes		Follow-up (compared to baseline)	
		Post- NF (compared to baseline)		Within-group	Between-group
		Within-group	Between-group		
ADHD	Alegria et al. 2017	↓ ADHD severity (measured with CPRS) in both groups	No significant time x group interaction	Not reported	Not reported
		<u>Control group</u> : ↓ ADHD-related difficulties and functional impairments *	No significant time x group interaction	Not reported	Not reported
	Zilverstand et al. 2017	↑ cognitive interference task in both group	Not reported	Not applicable	Not applicable
		<u>Experimental group</u> : ↑ response inhibition and ↑ in visual working memory	Not reported	Not applicable	Not applicable
ASD	Ramot et al., 2017	↓ depressive score + ↓ POMS tension + ↓ POMS anger	Not reported	Not reported	Not reported
AUD	Karch et al. 2015	No changes in BRIEF	Not reported	Not reported	Not reported
	Subramanian et al. 2021	Not reported	Not reported	Not applicable	Not applicable
		EG > CG : ↓ alcohol craving	Not reported	Not reported	Not reported
BPD	Zaehring et al. 2019	CG > EG : ↓ alcohol stroop interference	No significant group x time interaction	Not applicable	Not applicable
		↓ Alexithymia symptoms	Not reported	CG > EG : ↓ alcohol consumption 8 months after training	Not reported
			Not reported	↓ Alexithymia symptoms	Not reported
MDD	Linden et al. 2012	↓ affective instability	Group x Time interaction for POMS*	EG > CG : ↓ alcohol consumptions 12 months after training	Not applicable
			Not applicable	Stability of the effect observed in post-NF	Not applicable
		↑ current mood as assessed by POMS	No significant time x group interaction in POMS	Not applicable	Not applicable

Disorder	Study	Other significant outcomes			
		Post- NF (compared to baseline)		Follow-up (compared to baseline)	
		Within-group	Between-group	Within-group	Between-group
	Young et al. 2014	↓ negative affect in EG	State Anxiety were significantly ↓ in EG (compared to CG) *	Not applicable	Not applicable
	Young et al. 2017	↓ STAI State subscale and Trait subscale in EG*	State Anxiety were significantly ↓ in EG (comapred to CG)*	Not applicable	Not applicable
		EG: ↓ BDI-II (d=1.09)*, HAM-A (d=1.04)*, SHAPS (d=0.54)*	EG > CG: ↓ BDI-II (d=0.71)*, HAM-D (d=0.66)*	↓ HAM-A (d= 0,86)*, HAM-D (d= 1.19)*, BDI-II (d = 1.09)*, SHAPS (d=0.83)*	EG > CG : ↓ SHAPS (d=0.54)*
	Zahn et al. 2019	CG: ↓HAM-A (d=0.89)*	EG > CG: ↓BDI-II (d=0.71)*, HAM-D (d=0.66)*	↓ Emotion dysregulation (d= 0,49)*	Not applicable
	Zotev et al. 2020	↑ ATL-SCC correlation in EG for guilt vs. Indignation	↑ ATL-SCC correlation in the EG post-training (vs. Pre-training) compared to CG for guilt vs. Indignation	Not applicable	Not applicable

↑ = upregulation; ↓ = downregulation, NF = neurofeedback, EG = experimental group, CG = control group, NF = neurofeedback

Note: ADHD = Attention Deficit Hyperactivity Disorder, ATL = Anterior Temporal Lobule; AUD = Alcohol Use Disorder, BDI = Beck Depression Inventory, BPD = Borderline Personality Disorder, BRIEF = Behavior rating inventory of executive function; CAPS = Clinician-Administered PTSD scale, CPRS = Conners' Parent Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MDD = Major Depressive Disorder, POMS = Profile of Mood States; PTSD = Post-traumatic syndrome disorder; SCC = Somatosensory cortex, SCZ = Schizophrenia; SHAPS = Snaith-Hamilton Pleasure Scale, STAI = The State-Trait Anxiety Inventory,

Table 4. Robustness of included studies

Disorder	Study	Type of blinded studies	Randomization	Number of NF training session	Number of NF training runs	Control (Y/N)	Type of control
ADHD	Alegria et al. 2017	Single-blinded	Y	4	3 or 4	Y	Contingent sham
	Zilverstand et al. 2017	Single-blinded	Y	4	3	Y	No feedback
Anxiety	Zilverstand et al. 2015	Single-blinded	Y	1	4	Y	No feedback
ASD	Ramot et al. 2017	Single-blinded	N	4	4	Y	Contingent sham
AUD	Karch et al. 2015	N	N	4	1	Y	Healthy control and contingent sham
	Subramanian et al. 2021	N	Y	6	2	Y	Passive control TAU
BPD	Paret et al. 2016	N	N	4	3	N	-
	Zaehringer et al. 2019	N	N	3	4	N	-
MDD	Linden et al. 2012	N	N	4	3	Y	Imagery control
	Mehler et al. 2018	Single-blinded	Y	2	6	Y	Contingent sham
	Mennen et al. 2021	N	N	3	7 to 9	Y	Healthy control
	Young et al. 2014	Double-blinded	N	1	3	Y	Contingent sham
	Young et al. 2017	Double-blinded	Y	2	3	Y	Contingent sham
	Yuan et al. 2014	Double-blinded	N	1	3	Y	Healthy control and contingent sham
	Zahn et al. 2019	Double-blinded	Y	1	2	Y	Stabilization as control intervention
	Zotev et al. 2016	N	N	2	3	Y	Contingent sham
	Zotev et al. 2020	N	N	1	3	Y	Contingent sham
	Takamura et al. 2020	N	N	5	1 to 3	N	-
	Tsuchiyagaito et al. 2021	N	N	2	3	Y	No control group
NUD	Hartwell et al. 2016	N	Y	3	3	Y	No feedback
PTSD	Gerin et al. 2016	N	N	3	4	N	-

	Misaki et al., 2021	Single-blinded	Y	7	4	Y	Contingent
	Nicholson et al. 2017	N	N	3	4	N	-
	Zotев et al. 2018	N	Y	3	3	Y	Contingent sham
	Zweerings et al. 2018	N	N	3	1	Y	Healthy control
SCZ	Bauer et al. 2020	N	N	2	4	Y	Cross over
	Dyck et al.	N	N	3	1	N	-
	Okano et al. 2020	N	N	2	6	Y	Contingent sham
	Orlov et al.	N	N	4	1 to 6	N	-
	Ruiz et al. 2013	N	N	12	1	N	-

NB: ADHD = Attention Deficit Hyperactivity disorder, ASD = Autism Spectrum Disorder, AUD = Alcohol use disorder, BPD = Borderline Personality Disorder, MDD = Major Depressive Disorder, NUD = Nicotine Use disorder, PTSD = post-traumatic syndrome disorder, SCZ = Schizophrenia

Table 5. Studies included in the meta-analysis

Study	Disorder	Within-experimental group	Between-group	Follow-up	Type of control
Zilverstand et al. 2015	Anxiety	↓ anxiety level ($g = 0.95$)	Group* time interaction ($g = 2.59$)	↓ spider fear in both group ($g = 1.22$)	Active
Paret et al. 2015	BPD	↓ DERS "lack of emotional awareness subscale" ($g = 1.27$)* ↓ dissociation ($g = 1.97$)* ↓ DSS aversive tension subscale	Not applicable	Stability of the effect observed in post-NF	No control group
Zaehring et al. 2019	BPD	↓ BPD symptoms ($g = 0.63$)* No-significant ↓ Emotion dysregulation	Not applicable	↓ BPD symptoms ($g = 0.44$)* ↓ Emotion dysregulation ($g = 0.47$)* ↑ Emotional skills ($g = -0.54$)*	Active
Linden et al. 2012	MDD	↓ depressive symptoms in experimental group ($g = 1.33$)*	Group* time interaction ($g = 1.51$)	Not applicable	Active
Mehler et al. 2018	MDD	↓ HDRS in both groups (CG: $g = 2.16$; EG: $g = 2.23$)* ↓ anxiety levels and depressive levels in both groups	No significant group x time interaction	↓ HDRS in experimental group ($g = 1.57$)* ↓ anxiety levels and depressive levels in both groups	Active
Mennen et al. 2021	MDD	↓ depressive ratings ($g = 1.28$)*	Not reported	↓ depressive ratings at 1-month ($g = 1.05$) and 3-months follow-up ($g = 1.30$)	Active
Young et al. 2014	MDD	↓ POMS depression subscale and anger subscale in EG ($g = 0.50$)* ↑ VAS happiness rating ↓ VAS restlessness, anxiety and irritated subscale	EG > control group: ↑ VAS happiness ($g = 0.36$)*	Not applicable	Active

Study	Disorder	Within-experimental group	Between-group	Follow-up	Type of control
		↓ VAS sadness subscale in CG			
Young et al. 2017	MDD	↓ Depressive symptoms in EG (g=1.17)*	EG > CG: Group x time interaction for MADRS (g=1.13)*	↓ MADRS (g= 0,58)*	Active
Yuan et al. 2014	MDD	↓ HARS (g = 0.66) and HDRS scores (g = 0.61) in EG and active control group	No significant group x time interaction in HARS and HDRS	Not applicable	Not applicable
Zahn et al. 2019	MDD	No significant BDI improvement (g = 0)	No group*time interaction in BDI	Not applicable	Active
Zotev et al. 2016	MDD	↓ POMS depressive scores (g= 0.51)	EG > CG : ↓ POMS depressive scores* (g = 0.03)	Not applicable	Active
Zotev et al. 2020	MDD	↓ POMS depression (g = -0.59)*, confusion (g=-0.69)*, total mood disturbance (g=-0.57)*, STAI state anxiety (g=-0.54)*, and ↑ VAS happiness (g=0.56)*	No group*time interaction in POMS	Not applicable	Active
Takamura et al. 2020	MDD	↓ BDI-II (g=1.19)*	Not applicable	Not applicable	No control group
Tsuchiyagaito et al. 2021	MDD	↓ MADRS scores (g=0.47)*	Not applicable	↓ MADRS (g= 0,54)*	No control group
Misaki et al. 2021	PTSD	↓ MADRS scores (g=-1.68)*	No group*time interaction in MADRS	Not applicable	Active
Zweering et al. 2018	PTSD	↑ positive affect (g= 0.67) and ↓ negative affect in EG (g = 0.27)*	Group* time interaction for positive affect (g = 1.05)*	Not applicable	Active
Zotev et al. 2018	PTSD	↓ HDRS total score (g = 0.96)	No group*time interaction in HDRS	Not applicable	Active

↑ = upregulation; ↓ = downregulation; CG = Control Group EG = Experimental Group

Note: BDI = Beck Depression Inventory, BPD = Borderline Personality Disorder, CAPS = Clinician-Administered PTSD scale, HARS = Hamilton Anxiety Rating Scale, MDD = Major Depressive Disorder, POMS = Profile of Mood States; PTSD = post-traumatic syndrome disorder; STAI = The State-Trait Anxiety Inventory, VAS = Visual Analogue Scale