# Uncovering the Power of Neurofeedback: A Meta-Analysis of its Effectiveness in Treating Major Depressive Disorders

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***Abstract***: Neurofeedback, a non-invasive intervention, has been increasingly used as a potential treatment for major depressive disorders(MDD). However, the effectiveness of neurofeedback in alleviating depressive symptoms remains uncertain. To address this gap, we conducted a comprehensive meta-analysis to evaluate the efficacy of neurofeedback as a treatment for MDD. We conducted a comprehensive meta-analysis of 22 studies investigating the effects of neurofeedback intervention on depression symptoms, neurophysiological outcomes, and neuropsychological function. Our analysis included the calculation of Hedges' g effect sizes and explored various moderators like intervention settings, study designs, and demographics. Our findings revealed that neurofeedback intervention had a significant impact on depression symptoms(Hedges' g = -0.600) and neurophysiological outcomes(Hedges' g = -0.726). We also observed a moderate effect size for neurofeedback intervention on neuropsychological function(Hedges' g = -0.418). As expected, we observed that longer intervention length was associated with better outcomes for depressive symptoms(β = -4.36, $p < .001$) and neuropsychological function(β = -2.89, $p = .003$). Surprisingly, we found that shorter neurofeedback sessions were associated with improvements in neurophysiological outcomes(β = 3.34, $p < .001$). Our meta-analysis provides compelling evidence that neurofeedback holds promising potential as a non-pharmacological intervention option for effectively improving depressive symptoms, neurophysiological outcomes, and neuropsychological function in individuals with MDD.

***Keywords:*** cognitive function, emotional function, meta-analysis, major depressive disorder, neurofeedback.

## 1 Introduction

Major depressive disorder(MDD) is a widespread mental illness that affects people worldwide and is a leading contributor to the global burden of disease(WHO 2017). In addition to pharmacotherapy and psychotherapy, depression is increasingly being treated using non-invasive neuroregulatory techniques, such as neurofeedback. It is a novel intervention that enables individuals to actively regulate their own brain activity in response to real-time feedback of their brain signals, with the goal of improving both neurophysiological function and psychiatric symptoms(Gandara et al. 2020).

Electroencephalogram(EEG) and functional magnetic resonance imaging(fMRI) are two imaging modalities that are commonly used in neurofeedback treatment for MDD(Thibault and Raz 2016). Specifically, EEG-based interventions are commonly employed to target specific frequency bands, including Alpha, Theta, and Beta. One frequently used approach is the assessment of frontal alpha asymmetry(FAA), which examines the relative energy of the Alpha band in the left and right frontal lobes. A substantial body of research has established a significant correlation between FAA and emotional health, with findings suggesting that FAA can serve as a reliable marker of emotional well-being(Alves et al. 2008; Coan and Allen 2003; Davidson 1992; Davidson et al. 1990; Harmon-Jones and Allen 1997). Moreover, evidence has demonstrated that the FAA pattern observed in individuals with depression is associated with reduced motivation and heightened vulnerability to negative emotions, underscoring the potential clinical value of FAA as a tool for evaluating mental health(Hardt 2012).

Additionally, the Theta band energy in the rostral anterior cingulate cortex(rACC) has been identified as a critical factor in regulating the interaction between the default network and central executive system(Leuchter et al. 2012; Pizzagalli 2011; White et al. 2013; Whitton et al. 2019). Studies have demonstrated that resting rACC activity in the theta frequency band could serve as a positive predictor of treatment response across a range of antidepressant classes in individuals with MDD(Korb et al. 2009; Mulert et al. 2007; Schiller 2019).

FMRI-based neurofeedback is a technique that utilizes the blood-oxygenation-level-dependent(BOLD) signal and requires participants to regulate neural activity and/or functional connectivity in specific target regions of the brain. The primary goal of this approach is to improve brain function that are associated with the abnormal affective and cognitive processes of MDD patients. For instance, studies have shown that fMRI-based neurofeedback can be used to enhance attentional bias towards negative stimuli(Mennen et al. 2021), improve the processing of emotional facial expressions(Young et al. 2018a) and decrease recurrent negative thoughts(Takamura et al. 2020; Yu et al. 2020). Moreover, in many studies, subcortical regions such as the amygdala, anterior cingulate gyrus, anterior insula, and the functional connectivity between the dorsolateral prefrontal cortex and amygdala, have been the primary targets for modulation of neural activation or connectivity within the limbic system(Watanabe et al. 2017; Weiskopf 2012; Zhao et al. 2019).

Neurofeedback treatment for MDD patients has been assessed for its effectiveness in three key areas: reduction of depressive symptoms, improvement in

92 neurophysiological outcomes, and enhancement of neuropsychological function. The
93 main reason for focusing on changes in neurophysiological outcomes is to determine
94 if neurofeedback can directly alter activation or functional connectivity of the targeted
95 brain area. This is a common indicator of validity in neurofeedback studies(Kohl et al.
96 2020). This meta-analysis aims to see to what extent neurophysiological function could
97 be modulated which is associated with improvement of depressive symptoms (Jaeckle
98 et al. 2021; Young et al. 2017; Zotev et al. 2020; Zotev et al. 2016). Cognitive and
99 emotional processes are known to be related to the psychopathological mechanism of
100 depression(Crocker et al. 2013; Gotlib and Joormann 2010) and may contribute to the
101 treatment response and prognosis(Cui et al. 2024). Therefore, neuropsychological
102 function is also a major concern in most neurofeedback protocols which hypothesized
103 that improvements in depressive symptoms are achieved by enhancing cognitive and
104 emotional functions. This meta-analysis aimed to explore the neurophysiological and
105 neuropsychological mechanisms underlying the improvement of depressive symptoms
106 and provide a comprehensive view of the efficacy of neurofeedback.

107 Existing research on neurofeedback treatment for individuals with MDD has
108 primarily concentrated on alleviating depressive symptoms. For instance, by utilizing
109 FAA-based neurofeedback, individuals with MDD were instructed to increase their FAA
110 level, which has shown promising short-term effectiveness in alleviating depressive
111 symptoms(Baehr et al. 1997; Choi et al. 2011; Rosenfeld 2000; Wang et al. 2019).
112 Furthermore, fMRI-based neurofeedback interventions have utilized up-regulation
113 strategies to increase the neural activity in the amygdala and dorsolateral prefrontal

cortex(dlPFC) and have demonstrated comparable efficacy in improving depressive symptoms among patients with MDD(Jaeckle et al. 2021; MacDuffie et al. 2018; Mehler et al. 2017; Takamura et al. 2020; Tsuchiyagaito et al. 2021; Young et al. 2018a). However, certain studies employing fMRI-based neurofeedback(Yuan et al. 2014) reported mixed findings, as they did not observe significant improvements in depressive symptoms among MDD patients following a one-session neurofeedback intervention. Therefore, the inconsistent results warrant further investigation and clarification.

Regarding neurophysiological outcomes, there have been frequent observations of inconsistent findings in neurofeedback studies involving individuals with MDD. For example, some studies investigating FAA up-regulation training have reported an increase in FAA scores following neurofeedback(Zotev et al. 2020), while others have not found significant results(Cheon et al. 2016; Wang et al. 2019). Similarly, in fMRI-based neurofeedback studies, the most commonly observed indicator of neurophysiological improvement has been an increase in the activity or functional connectivity of targeted regions. Several studies have reported significant increases in amygdala activation following neurofeedback interventions(Young et al. 2018a; Young et al. 2014; Yuan et al. 2014; Zotev et al. 2016). However, when examining connectivity between specific brain regions, such as the connectivity between the right superior anterior temporal lobe and subgenual frontal cortex, studies have shown nonsignificant improvements in both down-regulation (i.e., reducing the signal level of targeted brain areas) (Taylor et al. 2022)) and up-regulation (i.e., increasing the

signal level of targeted brain areas) (Jaeckle et al. 2021)) scenarios. The complexity of findings has made it challenging to draw definitive conclusions. Therefore, conducting a comprehensive meta-analytic study is essential to address these concerns effectively.

Additionally, recent research has prioritized the improvement of neuropsychological function, particularly emotional function, in patients with MDD. Emphasis has been placed on enhancing emotion regulation skills. Both fMRI- and EEG-based neurofeedback treatments have consistently demonstrated the ability to reduce rumination and self-blaming emotions in individuals with MDD(Takamura et al. 2020; Taylor et al. 2022; Yu et al. 2020). However, there are studies such as Jaeckle et al. (2021) that did not find significant between-group differences in the enhancement of self-blame and self-esteem. Moreover, neurofeedback treatment has also been utilized to improve cognitive function in patients with MDD. Specifically, neurofeedback interventions have shown significant improvements in several domains of executive function, including inhibitory control, attention shift, and working memory(Choi et al. 2010; Escolano et al. 2014; Yu et al. 2020).

Several literature reviews have been conducted to summarize the use of neurofeedback in the treatment of MDD(Linden 2014; Melnikov 2021; Sacchet and Gotlib 2016; Trambaiolli et al. 2021). In a recent systematic review by Trambaiolli et al. (2021) that included 24 studies (experimental groups: N = 480; control groups: N = 194), patients with MDD receiving neurofeedback treatment showed superior symptom improvement compared to those in the control groups. While these reviews have provided valuable insight into the use of neurofeedback for improving depressive

158 symptoms, they have not extensively examined the effectiveness of this treatment for
159 other neurophysiological and neuropsychological functions in individuals with MDD.
160 Therefore, there is still a gap in understanding the broader impacts of neurofeedback
161 on these functions in MDD patients. While several meta-analyses have investigated
162 the efficacy of neurofeedback in psychiatric disorders such as attention deficit
163 hyperactivity disorder(Bussalb et al. 2019; Micoulaud-Franchi et al. 2014; Riesco-
164 Matías et al. 2021; Van Doren et al. 2019) and anxiety-spectrum disorders(Russo et al.
165 2022; Steingrimsson et al. 2020; Tolin et al. 2020), there is a lack of comprehensive
166 meta-analyses specifically examining the effectiveness of neurofeedback in improving
167 depressive symptoms, neurophysiological outcomes, and neuropsychological function.
168 In the current study, we aimed to conduct a comprehensive meta-analysis to
169 investigate the efficacy of neurofeedback in improving depressive symptoms,
170 neurophysiological outcomes, and neuropsychological function in individuals with
171 MDD. Additionally, we examined the influence of various moderating factors including
172 intervention variables(e.g., neurofeedback modality, intervention length), study
173 design factors(e.g., control intervention strategies) as well as demographic factors(e.g.,
174 age, sex ratio, duration of illness) on the effectiveness of neurofeedback.

175 Besides, this study compared the efficacy of neurofeedback with repetitive
176 transcranial magnetic stimulation(rTMS) and transcranial direct current
177 stimulation(tDCS) which are two non-invasive brain stimulation therapies widely used
178 to treat depression(Martin et al. 2017; Tateishi et al. 2022; Zhang et al. 2021b). Both
179 rTMS and tDCS make use of external magnetic/electrical stimuli to activate or inhibit

the activation of brain areas so that the participants are passive recipients of the intervention(Trambaiolli et al. 2021) rather than autonomous regulators of their brain activity(Gandara et al. 2020). To further evaluate the superiority of the neurofeedback approach, we compared its efficacy with that of rTMS and tDCS by analyzing the existing results from previous meta-analyses (Begemann et al. 2020; Dalhuisen et al. 2022; Zhang et al. 2021b).

## 2 Materials and Method

### 2.1 Literature search

To identify relevant studies, we systematically searched electronic databases including Web of Science, APA Psycinfo, APA PsycArticles and PubMed from January 2000 to May 2024, using the following search terms:("major depressive disorder" OR "depression" OR "mood disorder" OR "depressive symptom") AND("neurofeedback" OR "self-regulation training") AND("fMRI" OR "EEG" OR "fNIRS"). After removing 163 duplicates, two independent researchers screened 542 articles for eligibility.

### 2.2 Exclusion criteria

We applied several exclusion criteria(see Fig.1) to filter out articles that did not meet our study selection criteria.First, we excluded studies not in English or not peer-reviewed and 319 studies passed the screening. These studies have been checked to see if they have met the exclusion criteria: (1) not utilizing neurofeedback as an intervention, (2) not focusing on patients with depression, (3) without available articles, (4) without quantitative pre-post intervention measurements, and (5) with

only healthy control groups. Ultimately, we included 22 articles in our meta-analysis. It's necessary to acknowledge that our meta-analysis protocol (registration number: CRD42024491789) was registered in PRISMA system in advance and we strictly adhered to the protocol as suggested in the PRISMA requirements during our identification of eligible studies.

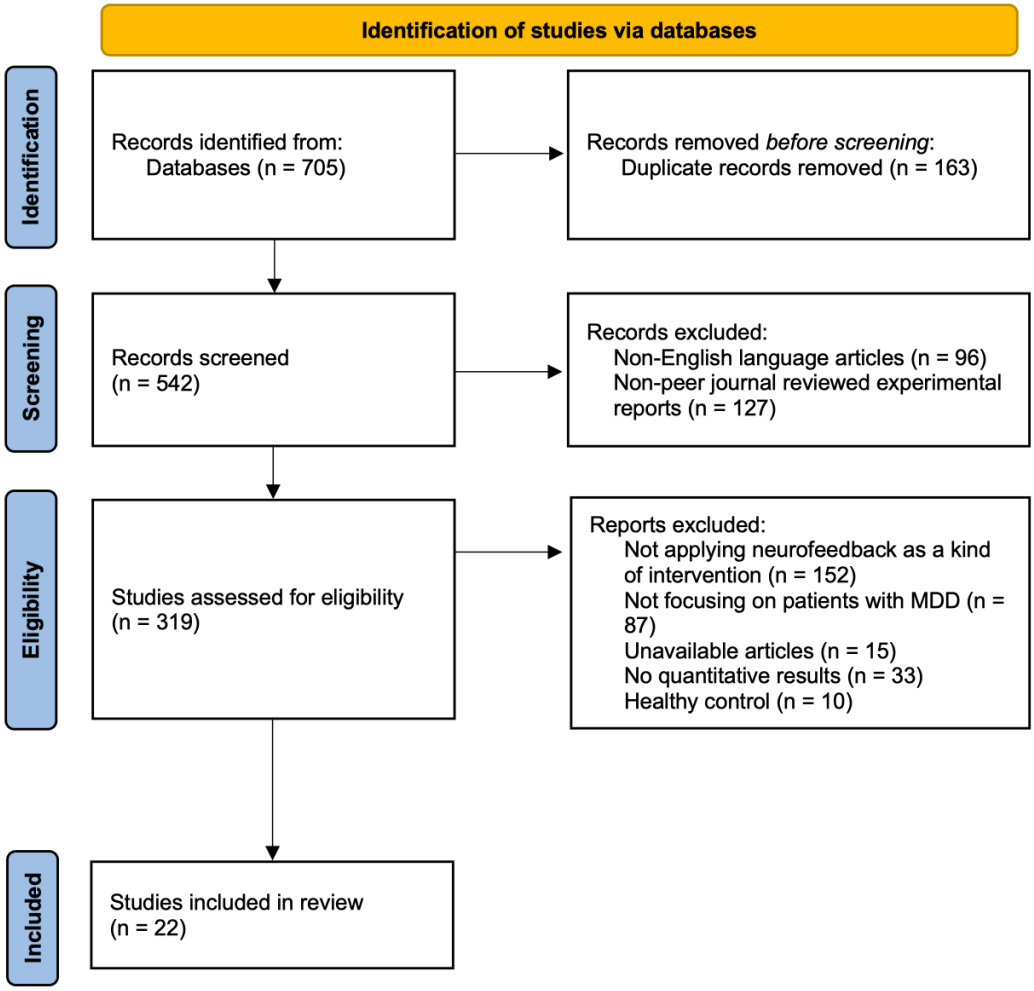


***Fig.1*** Flow diagram according to Preferred Reporting Items for Systematic Reviews

## 2.3 Data coding

To ensure accuracy and consistency in data coding, two independent researchers

recorded major information for each study, including: (1) intervention modality, (2) targeted brain region(cortical/subcortical), (3) intervention goals, (4) ontrol intervention strategies, as described by Trambaiolli(2021), include the following: a) No Control (i.e., participants receive no additional intervention); b) Passive Control (i.e., participants in the control group continue with standard treatment only); c) Active Control (In-Scanner) (i.e., participants perform the same task inside the scanner as those in the experimental group but receive signals from a different participant or from non-targeted brain areas); d) Active Control (Out-of-Scanner) (i.e., participants engage in a similar mental task outside the scanner as those in the experimental group) , (5) participant demographics and clinical characteristics(e.g., age, sex ratio, duration of illness, medication dosage), (6) length and frequency of intervention(e.g., total number of intervention sessions, length of intervention), (7) use of randomized controlled design.

The study assessed three types of outcome variables: depressive symptoms, neurophysiological outcomes, and neuropsychological function. Depressive symptoms were measured using self-report scales(e.g., BDI-II (Beck et al. 1996)) and clinician-administered scales(e.g., HDRS (Hamilton 1960)). Neurophysiological outcomes were primarily evaluated using EEG(e.g., frontal alpha asymmetry) and fMRI imaging(e.g., percentage change of BOLD signal, functional connectivity). The intervention's effect on neuropsychological functions, such as emotional regulation and expression, emotional reactivity, attention bias, and working memory, was also examined. To assess emotional regulation, we included self-report scales such as the Ruminative

Responses Scale(RRS)(Treynor et al. 2003)) and the Thought Control Questionnaire(Wells and Davies 1994). Emotional expression was evaluated through tasks such as the Facial Expression Recognition Task(Young et al. 2018a). Executive functions, which include attention switching and working memory, were measured using the Stroop Color-Word Test(STROOP, (Stroop 1992)) and the Paced Auditory Serial Addition Task(PASAT, (Gronwall 1977)), respectively.

We conducted a quality assessment of individual studies using the Cochrane Collaboration Risk of Bias tool(Sterne et al. 2019). The tool assessed several domains of criteria, including the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results (See Fig.S1 in the Supplementary materials). Two independent researchers completed it.

**2.4 Meta-analytic approach**

Comprehensive Meta-Analysis Software Version 2.0(Borenstein et al. 2005) was applied to complete the meta-analysis, including the calculation of effect sizes, Jackknife sensitivity analysis, analysis of publication bias, heterogeneity analysis, and moderator analysis.

To derive the main result of our meta-analysis, we utilized Hedges' g, which is a standardized effect size metric. Specifically, we calculated two types of Hedges' g effect sizes: pre-post between-group effect size and within-group effect size. A Hedge's g value of 0.2 signifies a small effect size, 0.5 suggests a medium effect size, and 0.8

indicates a large effect size(Hedges and Olkin 1985). The pre-post between-group effect size indicates the difference in pre-post changes between the intervention group and the control group. For this reason, studies that included a control group with passive, active in, or active out interventions were included in the analysis, while studies without a control group were excluded from the calculation. The within-group effect size reflects the magnitude of change in depressive symptoms, neurophysiological outcomes, and neuropsychological function within the intervention group from pre- to post-treatment. To assess the robustness of our effect size estimates, we conducted Jackknife sensitivity analysis(Miller 1974). Specifically, we systematically removed each study from the meta-analysis and recalculated the effect size to determine whether any one study had a significant influence on the overall treatment effect.

We performed two methods to analyze publication bias. The first method was the classic fail-safe number analysis(Rosenthal 1991), which estimates the number of unpublished studies with null or negative findings needed to be added to the analysis to reduce the overall effect size to a nonsignificant level. The tolerance level was calculated using the formula 5k+10, where $k$ refers to the number of included studies. The second method we used was Egger's regression(Egger et al. 1997), which tests for funnel plot asymmetry. A statistically significant result at the 0.05 level would suggest the presence of publication bias. We conducted a trim-and-fill analysis to adjust effect sizes, accounting for potentially missing studies (Duval and Tweedie 2000).

To evaluate the degree of heterogeneity among the included studies, we

performed Cochran's Q test and calculated Higgins's $I^2$ test statistic. The Cochran's Q test is a non-parametric statistical test employed to assess variations in the effects across different groups. The Q value is calculated by summing the squared differences between the effect size estimates for an individual study and the pooled effect size estimates for all the studies in question, with a p-value less than 0.1 indicating significant heterogeneity. The $I^2$ test statistic estimates the percentage of variation in effect sizes due to heterogeneity, with values over 50% suggesting substantial heterogeneity. Once the Q statistic was below 0.1 or the $I^2$ was more than 50%, we checked if there were outlier value and use random-effects models to estimate effect sizes.

To identify factors that affect the efficacy of neurofeedback, we conducted moderator analysis. We used the pre-post between-group effect size to rule out changes in the typical course of disease and the placebo effect of the therapy itself. We divided neurofeedback modalities into EEG, fMRI, and the combination of EEG and fMRI and targeted brain regions into cortical and subcortical areas. In addition, we included experiment-design and demographic moderators such as control intervention strategies, adoption of randomized controlled design, and medication intake(with or without) in the subgroup analysis. Subgroup analysis was only performed if there were more than 5 studies in each subgroup.

We also conducted meta-regression analysis for the length and frequency of intervention, number of sessions, age, and sex ratio. Regarding duration and Frequency of Neurofeedback Interventions, the optimal duration and frequency of

neurofeedback interventions for depression and other psychiatric disorders are still inconclusive(Arns et al. 2014; Enriquez-Geppert et al. 2017). Additionally, most intervention plans have a single duration setting, making it difficult to assess the impact of length, frequency, and number of sessions from individual studies. This meta-analysis aims to provide insights into the effects of intervention duration on clinical symptoms, neurophysiological function, and neuropsychological function.

For individual characteristic, we also focused on the characteristics of the participants, particularly age and gender. Age is associated with prefrontal lobe atrophy and reduced brain plasticity, which can diminish the effectiveness of neurostimulation therapy(Fregni et al. 2006; Pallanti et al. 2012). This meta-analysis investigated whether neurofeedback has different effects on depression patients of different ages. Gender is another major concern when measuring therapy efficacy. Depressed males and females exhibit distinct characteristics in clinical symptoms and prognosis, influenced by hormonal secretion and social factors(Fernandez-Guasti et al. 2012). For example, the antidepressant effect of repetitive transcranial magnetic stimulation (rTMS) has been found to correlate with the sex ratio of participants, showing better efficacy with a higher proportion of females (Kedzior et al. 2014). This meta-analysis also explored the effect of sex ratio on the efficacy of neurofeedback.

In order to determine the superiority of the neurofeedback approach, we carried out Cochran's Q tests to determine the difference in efficacy between neurofeedback and other neuromodulation therapies, namely rTMS and tDCS.

## 3 Results

### 3.1 Demographic and clinical characteristic of each study

After removing 163 duplicates, we screened 542 articles for eligibility based on pre-defined inclusion and exclusion criteria. Ultimately, we included 22 articles in our meta-analysis with a total sample size of 580 participants. The intervention group consisted of 367 patients (Female: Male = 254 : 113) diagnosed with Major Depressive Disorder (MDD) who received neurofeedback intervention. The comparison group consisted of 213 patients who either received no intervention or a placebo intervention, with 153 female and 60 male patients in this group.

Out of the 22 articles included in the meta-analysis, 14 employed fMRI-based neurofeedback interventions, 7 utilized EEG-based interventions, and only one study utilized a combined modality approach using both fMRI and EEG simultaneously(See Table 1 for details). Nine of these 22 articles are randomized clinical trails.

Table 1 *Demographic characteristics of the subjects included in the studies*

| Included studies | Modality | Sample size Total (TG:CG) | Diagnosis | Age | Years of education | Sex ratio (female/male) | Medication (TG:CG) | Duration of illness (year) |
|---|---|---|---|---|---|---|---|---|
| Tsuchiyagaito et al., 2023 | fMRI | 39 (20:19) | MDD (DSM-5) | TG = 33.60 ± 10.60<br>CG = 33.42 ± 11.49 | not mentioned | TG = 14/6<br>CG = 14/5 | not mentioned | not mentioned |
| Jaeckle et al., 2021 | fMRI | 43 (22:21) | MDD (DSM-5)<br>early treatment-resistance | TG = 36.74 ± 11.04<br>CG = 37.63 ± 9.74 | TG = 16.95 ± 3.15<br>CG = 18.06 ± 2.52 | TG = 17/5<br>CG = 17/4 | Psychotropic medication (10:10)<br>Antidepressant (9:9)<br>Of which SSRI (6:6) | not mentioned |
| Tsuchiyagaito et al., 2021* | fMRI | 29 (29:0) | MDD (DSM-5) | 29.34 | not mentioned | 17/12 | unmedicated | not mentioned |
| Takamura et al., 2020* | fMRI | 6 (6:0) | MDD | 40.7 | not mentioned | 3/3 | medicated (5:0)<br>unmedicated (1:0) | not mentioned |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Zotev et al., 2020 | fMRI+EEG | 24 (16:8) | MDD | TG = 32 ± 11<br>CG = 34 ± 7 | not mentioned | TG = 13/3<br>CG = 4/4 | unmedicated | not mentioned |
| Wang et al., 2019 | EEG | 70 (24:23:23) | MDD (DSM-5)<br>comorbid anxiety | TG1 = 40.330 ± 14.714<br>TG2 = 42.830 ± 15.816<br>CG = 42.610 ± 13.937 | not mentioned | TG1 = 19/5<br>TG2 = 12/11<br>CG = 16/7 | participants used benzodiazepines, SSRIs, SNRIs, tricyclic antidepressants, other antidepressants, antipsychotics, atypical antipsychotics, and other sedative-hypnotics. | TG1 = 3.783 ± 5.768<br>TG2 = 4.522 ± 6.423<br>CG = 5.826 ± 6.043 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lee et al., 2019 | EEG | 24 (12:12) | TRD (DSM-IV-TR) | TG = 48.25 ± 14.44<br>CG = 54.33 ± 12.67 | TG = 13.58 ± 2.39<br>CG = 12.17 ± 4.13 | TG = 9/3<br>CG = 8/4 | stable medication | not mentioned |
| MacDuffie et al., 2018* | fMRI | 13 (13:0) | MDD | 45 ± 13 | not mentioned | 11/2 | medicated (4:0)<br>unmedicated (9:0) | not mentioned |
| Mehler et al., 2017* | fMRI | 32(16:16) | MDD | TG = 47.19 ± 12.50<br>CG = 46.94 ± 12.74 | not mentioned | TG = 11/5<br>CG = 10/6 | SSRI only (4:7)<br>Non-SSRI antidepressant (6:5)<br>Combination treatment (6:4) | TG = 19 ± 12.39<br>CG = 18.56 ± 14.76 |
| Young et al., 2018a | fMRI | 36 (19:17) | MDD (DSM-IV-TR) | TG = 32<br>CG = 31 | not mentioned | TG = 13/6<br>CG = 13/4 | unmedicated | TG = 2.75<br>CG = 2.58 |
| Young et al., 2018b | fMRI | 36 (19:17) | MDD (DSM-IV-TR) | TG = 32<br>CG = 31 | not mentioned | TG = 13/6<br>CG = 13/4 | unmedicated | TG = 2.75<br>CG = 2.58 |
| Young et al., 2017 | fMRI | 36 (19:17) | MDD (DSM-IV-TR) | TG = 32 ± 12<br>CG = 31 ± 9 | not mentioned | TG = 13/6<br>CG = 13/4 | unmedicated | TG = 2.5 ± 4.67<br>CG = 2.83 ± 4.08 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cheon etal., 2016* | EEG | 20 (20:0) | MDD (DSM-IV-TR) | 43.25 ± 14.29 | 13.6 ± 3.56 | 16/4 | medicated (12:0)<br>unmedicated (8:0) | not mentioned |
| Zotev et al., 2016 | fMRI | 24 (13:11) | MDD (DSM-IV-TR) | TG = 41 ± 9<br>CG = 34 ± 8 | not mentioned | TG = 9/4<br>CG = 9/2 | unmedicated | not mentioned |
| Wang et al., 2016 | EEG | 14 (7:7) | MDD | TG = 49.86 ± 3.98<br>CG = 47.43 ± 13.84 | not mentioned | TG = 5/2<br>CG = 6/1 | Benzodiazepine (6:5)<br>SSRI (1:2)<br>Atypical antidepressants (5:4)<br>Sedative-hypnotic (4:2) | TG = 8.83 ± 2.71<br>CG = 6.68 ± 5.37 |
| Hamilton et al., 2016* | fMRI | 20 (10:10) | MDD(DSM-IV) | TG = 31.2 ± 2.9<br>CG = 34.5 ± 3.7 | TG = 16.4 ± 0.83<br>CG = 17.0 ± 0.75 | TG = 10/0<br>CG = 10/0 | Psychotropic medication (6:4) | not mentioned |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Escolano et al., 2014 | EEG | 60 (40:20) | MDD(DSM-IV) | TG = 53.70 ± 10.87<br>CG = 49.5 ± 10.18 | not mentioned | TG = 25/15<br>CG = 16/4 | medicated (33:15)<br>unmedicated (7:5) | not mentioned |
| Yuan et al., 2014 | fMRI | 27 (14:13) | MDD (DSM-IV-TR) | TG = 38 ± 10<br>CG = 35 ± 8 | not mentioned | TG = 11/3<br>CG = 11/2 | unmedicated | not mentioned |
| Young et al., 2014 | fMRI | 21 (14:7) | MDD (DSM-IV) | TG = 38 ± 10<br>CG = 36 ± 9 | not mentioned | TG = 11/3<br>CG = 7/0 | unmedicated | TG = 4 ± 5<br>CG = 5 ± 5 |
| Peeters et al., 2014* | EEG | 9 (9:0) | MDD (DSM-IV-TR) | 46.6 ± 11.7 | not mentioned | 4/5 | medicated (9:0) | not mentioned |
| Linden et al., 2012* | fMRI | 16（8:8） | MDD (DSM-5) | TG = 48.38<br>CG = 48.5 | not mentioned | TG = 0/8<br>CG = 3/5 | not mentioned | TG = 19.25 ± 5.77<br>CG = 19.125 ± 3.32 |
| Choi et al., 2010 | EEG | 23 (12:11) | MDD (DSM-IV) | TG = 28.46 ± 9.96<br>CG = 28.54 ± 6.84 | TG = 15.83 ± 1.70<br>CG = 14.00 ± 2.00 | TG = 10/2<br>CG = 7/4 | not mentioned | TG = 7.79 ± 11.21<br>CG = 11.00 ± 19.18 |

*Note.* The studies with stars were not included in the pre-post between-group effect size calculation. TG - treatment group; CG - control group; TRD - treatment-resistance depression; SSRI - Selective serotonin reuptake inhibitors; SNRI - Serotonin–norepinephrine reuptake inhibitors.

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We found that 16 of the 22 studies assessed the intervention's impact on depressive symptoms, while 19 studies examined its effect on neurophysiological outcomes, and 10 studies evaluated neuropsychological function. Out of these, 10 studies provided data for the pre-post between-group effect sizes of depressive symptoms, and 10 studies reported data for the pre-post within-group effect sizes. For neurophysiological outcomes, five studies had data for pre-post between-group effect sizes and nine studies for pre-post within-group effect sizes. Moreover, five studies reported data for pre-post between-group effect sizes and five studies for pre-post within-group effect sizes of neuropsychological function (See Table 2). The majority of studies (16 out of 22) demonstrated a relatively low risk of bias in terms of quality control assessment (Please see Fig.1S in Supplementary materials).

Table 2 *Summary of intervention setting and outcomes of the included studies*

| Included studies | Modality | Control intervention strategies | Randomization | Intervention areas | Regulation | Length of entire Intervention | Intervention frequency (session/week) | Intervention effect | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | depressive symptoms | neurophysiological outcome | neuropsychological function |
| Tsuchiyagaito et al., 2023 | fMRI | active control (in) | randomized double-blind | connectivity between PCC and rTPJ | down regulation | 40min*1session | 1 | **MADRS scores:** TIME: TG-pre>post↑ CG-pre>post ↑ GROUP: TG>CG = | **PCC – rTPJ connectivity:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | **Rumination measured by RRS:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ **Self-esteem measured by RSES:** TIME: pre>post ↑ Group: TG>CG = **Self-blame measured by the Brief Implicit Association Test:** |
| Jaeckle et al., 2021 | fMRI | active control (out) | randomized single-blind | connectivity between rSATL and subgenual frontal cortex | up regulation | 15min*3session | 1 | **BDI-II scores:** TIME: pre>post ↑ GROUP: TG>CG = | **rSATL-posterior SC connectivity:** TIME: TG- pre>post = GROUP: TG>CG ↑ | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | TIME: pre>post ↑<br>Group: TG>CG = |
| Tsuchiyagaito et al., 2021* | fMRI | no control | not mentioned | left amygdala | up regulation | 26min*2session | 1 | **MADRS scores:**<br>TIME: pre>post ↑ | The ability to regulate the left amygdala was positively correlated with KynA/QA levels at baseline. | |
| Takamura et al., 2020* | fMRI | no control | not mentioned | left dlPFC | up regulation | 60min*5session | 5 | **BDI-II and HRSD-17 scores:**<br>TIME: pre>post ↑ | The ability to regulate the left dlPFC was positively correlated with the improvement of rumination. | **Rumination measured by RRQ:**<br>TIME: pre>post ↑ |
| Zotev et al., 2020 | fMRI+EEG | active control (in) | not mentioned | left amygdala<br>left rACC<br>frontal alpha/beta asymmetry | up regulation | 52.6min*1session | 1 | **POMS-Depression scores:**<br>TIME:<br>TG-pre>post ↑<br>CG-pre>post =<br>GROUP: TG>CG = | **left amygdala, FAA, FBA:**<br>TIME: pre>post ↑<br>**Functional connections between the left amygdala** | |

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| | | | | | | | | | **and the left rACC:** TIME: pre>post ↑ | |
| Wang et al., 2019 | EEG | passive control | not mentioned | frontal Alpha/Beta band | **Alpha band:** up regulation **Beta band:** down regulation | 25.5min* 10session | 2 | **BDI-II scores:** TIME: pre>post ↑ GROUP: TG>CG = | **Alpha band:** TIME: pre>post = GROUP: TG>CG = **Beta band:** TIME: pre>post ↑ GROUP: TG>CG = | |
| Lee et al., 2019 | EEG | active control (out) | not mentioned | multi-band | up and down regulation | 60min*(12-24) session | 1.5 | **HDRS-17, BDI-II and CGI-S scores:** GROUP: TG>CG ↑ | | |
| MacDuffie et al., 2018* | fMRI | no control | not mentioned | ACC | up regulation | 33min*1session | 1 | | | **CBT strategies:** TIME: pre>post ↑ |
| Mehler et al., 2017* | fMRI | active control (in) | randomized single-blind | limbic and frontal portions of the anterior cerebrum | up regulation | 20min*4session | 1 | **HDRS-17 scores:** TIME: | **Activation of targeted ROIs:** TIME: | The increase in self-efficacy was associated with less depression severity. |

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| | | | | | | | | TG-pre>post ↑<br>CG-pre>post ↑<br>GROUP: TG>CG = | TG-pre>post ↑<br>CG-pre>post ↑<br>GROUP: TG>CG = | |
| Young et al., 2018a | fMRI | active control (in) | randomized double-blind | amygdala | up regulation | 45min*2session | 1 | **MADRS scores:**<br>Group(follow-up):<br>TG>CG ↑ | **Amygdala activation:**<br>TIME: TG-pre>post ↑<br>GROUP: TG>CG ↑ | **Positive Information Processing tasks:**<br>TIME: TG-pre>post ↑<br>GROUP: TG>CG ↑ |
| Young et al., 2018b | fMRI | active control (in) | randomized double-blind | amygdala | up regulation | 45min*2session | 1 | **MADRS scores:**<br>Group(follow-up):<br>TG>CG ↑ | **Amygdala connectivity:**<br>TIME: TG-pre>post ↑<br>GROUP: TG>CG ↑ | |
| Young et al., 2017 | fMRI | active control (in) | randomized double-blind | amygdala | up regulation | 45min*2session | 1 | **MARDS, BDI-II and SHAPS scores:**<br>TIME:<br>TG-pre>post ↑<br>CG-pre>post =<br>GROUP: TG>CG ↑ | **Amygdala activation:**<br>TIME: TG-pre>post ↑<br>CG-pre>post =<br>GROUP: TG>CG ↑ | **Positive memory recalls:**<br>TIME: TG-pre>post↑<br>CG-pre>post =<br>GROUP: TG>CG ↑ |

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|---|---|---|---|---|---|---|---|---|---|---|
| Cheon et al., 2016* | EEG | no control | not randomized | left frontal Alpha/Beta/Theta band | up and down regulation | 60min*(16-24) session | 2.5 | **HDRS-17, BDI-II and CGI-S scores:** TIME: pre>post ↑ | **Asymmetry Scores:** TIME: pre>post = | |
| Zotev et al., 2016 | fMRI | active control (in) | not mentioned | left amygdala | up regulation | 45min*1session | 1 | **POMS-Depression scores:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | **Amygdala activation:** TIME: TG-pre>post ↑ GROUP: TG>CG ↑ | |
| Wang et al., 2016 | EEG | passive control | randomized | Alpha asymmetry | up regulation | 60min*6session | 1 | **BDI-II scores:** TG-pre>post ↑ CG-pre>post = | **Asymmetry Scores:** TIME: TG-pre>post ↑ CG-pre>post ↑ | |
| Hamilton et al., 2016* | fMRI | active control (in) | not mentioned | salience network | down regulation | 10.2min*1session | 1 | | **ROI Response:** TIME: TG- pre>post ↑ CG- pre>post = Group: TG>CG = | **Affective response to negative pictures and self-relevance adjectives:** TIME: TG - pre>post ↑ Group: TG>CG ↑ |

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| | | | | | | | | | | **Affective response to positive adjectives:** Group: TG>CG = **Episodic memory tasks:** TIME: pre>post ↑ **Executive function tasks:** TIME: pre>post ↑ |
| Escolano et al., 2014 | EEG | passive control | not randomized | upper alpha power | down regulation | 20min*8session | 2 | | **Power of upper alpha band:** TIME: TG- pre>post ↑ CG- pre-post = | |
| Yuan et al., 2014 | fMRI | active control (in) | randomized double-blind | amygdala | up regulation | 45min*1session | 1 | **HDRS-21 scores:** TIME: TG-pre>post ↑ CG-pre>post ↑ GROUP: TG>CG = **POMS-Depression scores:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG = | **Amygdala connectivity:** TIME: TG-pre>post ↑ CG-pre>post ↑ **left amygdala activation:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | |
| Young et al., 2014 | fMRI | active control (in) | not randomized | amygdala | up regulation | 45min*1session | 1 | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| Peeters et al., 2014* | EEG | no control | not mentioned | frontal Alpha band | up regulation | 24min*30session | 3 | **QIDS-SR$_{16}$ scores:** TIME: pre>post ↑ | **Asymmetry Scores:** TIME: pre>post ↑ | |
| Linden et al., 2012* | fMRI | active control (out) | not mentioned | not fixed | up regulation | 45min*4session | 3 | **HDRS-17 scores:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | **ROIs activation:** TIME: TG- pre>post ↑ | |
| Choi et al., 2010 | EEG | active control (out) | randomized single-blind | right frontal Alpha band | up and down regulation | 24min*10session | 2 | **BDI-II and HDRS scores:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | **Asymmetry Scores:** TIME: TG-pre>post ↑ CG-pre>post = GROUP: TG>CG ↑ | **Executive function tasks:** TIME: TG-pre>post↑ CG-pre>post = GROUP: TG>CG ↑ |

*Note:* The studies with stars were not included in the pre-post between-group effect size calculation. TG - treatment group; CG - control group; BDI-II – Beck Depression Inventory II; rs-FC – resting-state functional connectivity; RRS – Rumination Response Scale; PCC - posterior cingulate cortex; rTPJ - right temporoparietal junction; rSATL - right superior anterior temporal lobe; SC - subgenual cortex; RSES-Rosenberg Self-Esteem Scale; MADRS-Montgomery-Åsberg Depression Rating Scale; HDRS - Hamilton rating scale for depression; RRQ - rumination-reflection questionnaire; POMS - the Profile of Mood States; CRSQ - Chinese response style questionnaire; PAF - peak alpha frequency; QIDS-SR$_{16}$ - Quick Inventory of Depressive Symptoms self-report version; ROI – region of interest; SHAPS - Snaith-Hamilton Pleasure Scale; CGI-S - Clinical Global Impression-Severity scale.

### 3.2 Effect sizes across studies

The meta-analysis of 10 studies that examined the pre-post between-group effect of neurofeedback intervention on depressive symptoms showed a significant and high Hedges' g of -0.600(SE = 0.196, $p$ = .002, 95% CI= [-0.985, -0.215]), as calculated using the random effects model. Among these studies, 6 utilized active-control [in] strategies, resulting in a moderate Hedges' g of -0.383(SE = 0.155, $p$ = .013, 95% CI= [-0.687, -0.080]). Three studies employed active-control [out] strategies, and one study used passive-control strategies. Ten studies were included in the calculation of pre-post within-group effect sizes of depressive symptoms, showing a high Hedges' g of -0.762(SE = 0.111, $p$ < .001, 95% CI= [-0.979, -0.544]).

In terms of neurophysiological outcomes, five studies reported pre-post between-group effects and revealed a high Hedges' g of -0.726(SE = 0.312, $p$ = .020, 95% CI= [-1.338, -0.114]) based on the random effects model, while nine studies reported pre-post within-group effects and showed a moderate-to-large Hedges’ g of -0.505(SE = 0.090, $p$ < .001, 95% CI= [-0.682, -0.328]). Regarding neuropsychological function, five studies reported pre-post between-group effects and yielded a moderate Hedges' g of -0.418(SE = 0.246, $p$ = .089, 95% CI = [-0.900, -0.064]) based on the random effects model, while five studies reported pre-post within-group effects and demonstrated a moderate-to-large Hedges’ g of -0.676(SE = 0.142, $p$ < .001, 95% CI = [-0.954, -0.398])(See Figure 2).

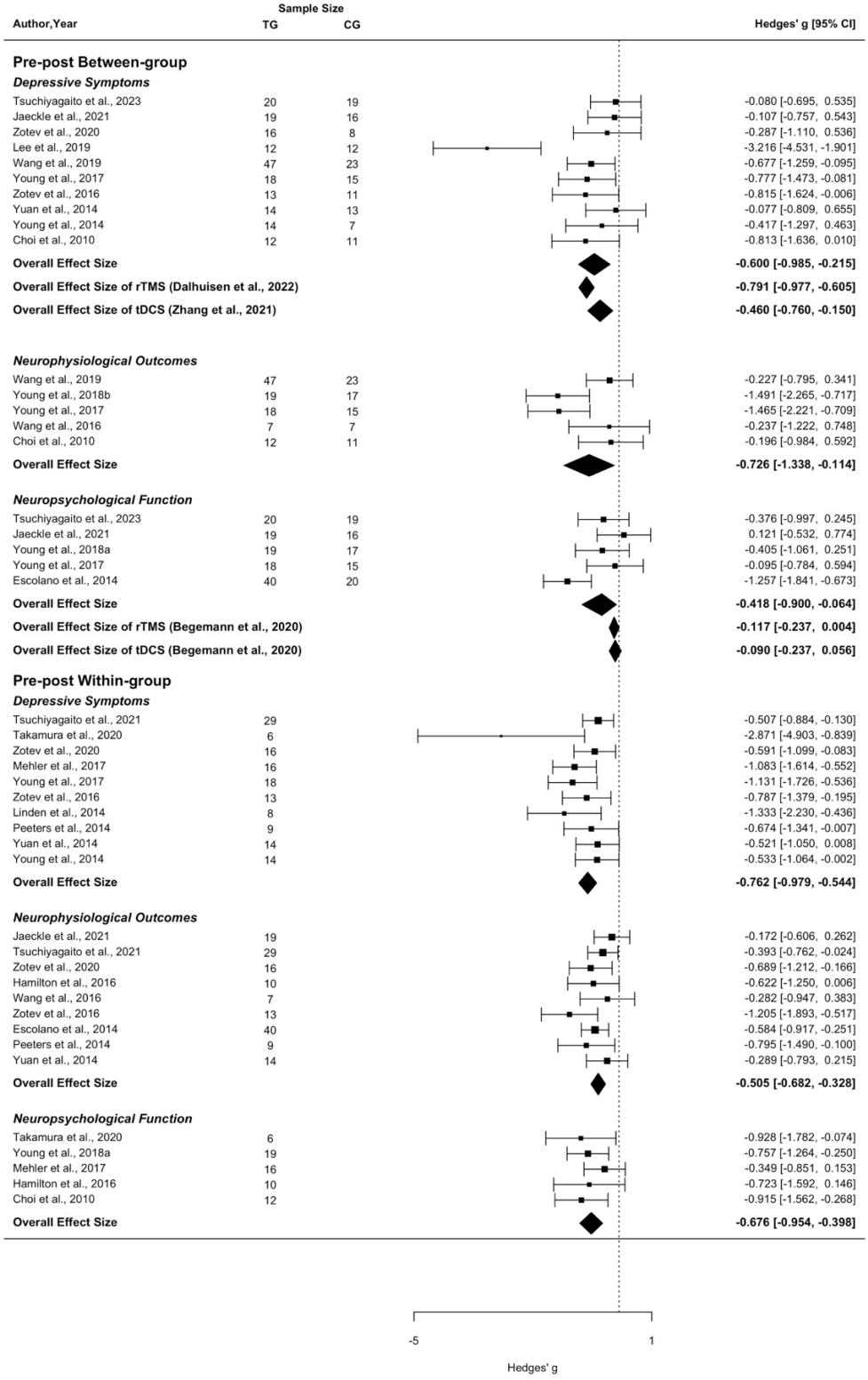



***Fig.2*** Forest plot of the effect sizes and Meta-Analyses

(Note: 'TG' = treatment group; 'CG' = control group; 'CI' = confidence level)

### 3.3 Publication bias

To assess publication bias, Egger's regression intercept was examined for studies included in the pre-post between-group analysis. The intercept was significant for studies of depressive symptoms(Intercept = -5.47, $p$ = .024), indicating some potential for publication bias. However, Egger's regression for studies of neurophysiological function(Intercept = -1.97, $p$ = .726) and neuropsychological function(Intercept = 22.33, $p$ = .070) did not reach significance, suggesting a lower likelihood of publication bias in these areas. After conducting a trim-and-fill analysis to account for potentially missing studies, the adjusted effect size for depressive symptoms remained high, with a Hedges' g of -0.761(95% CI = [-1.141, -0.380]), as shown in Figure 3. The adjusted effect size after trim-and-fill analysis for neuropsychological function also increased to -0.550(95% CI = [-1.017, -0.082]). The calculation of Classic fail-safe numbers indicated that 64 unpublished negative studies may be needed to pull the significant results for the effect of neurofeedback intervention on depressive symptoms towards the null, above the tolerance level of 60.

In the pre-post within-group analysis, Egger's regression intercept was significant for studies of depressive symptoms(Intercept = -2.85, $p$ = .006), indicating potential publication bias. However, for studies of neurophysiological outcome(Intercept = -1.46, $p$ = .314) and neuropsychological function(Intercept = -1.72, $p$ = .342), Egger's regression remained non-significant, suggesting less likelihood of publication bias in

these areas. After accounting for potentially missing studies using a trim-and-fill analysis, the adjusted effect size remained high with a Hedges' g of -0.710(95% CI = [-0.956, -0.464]) for depressive symptoms and a Hedges'g of -0.646(95% CI = [-0.910, -0.381]) for neuropsychological function. The Classic fail-safe numbers for studies in the pre-post within-group analysis were 177, 80, and 59 for depressive symptoms, neurophysiological outcome, and neuropsychological function, respectively.

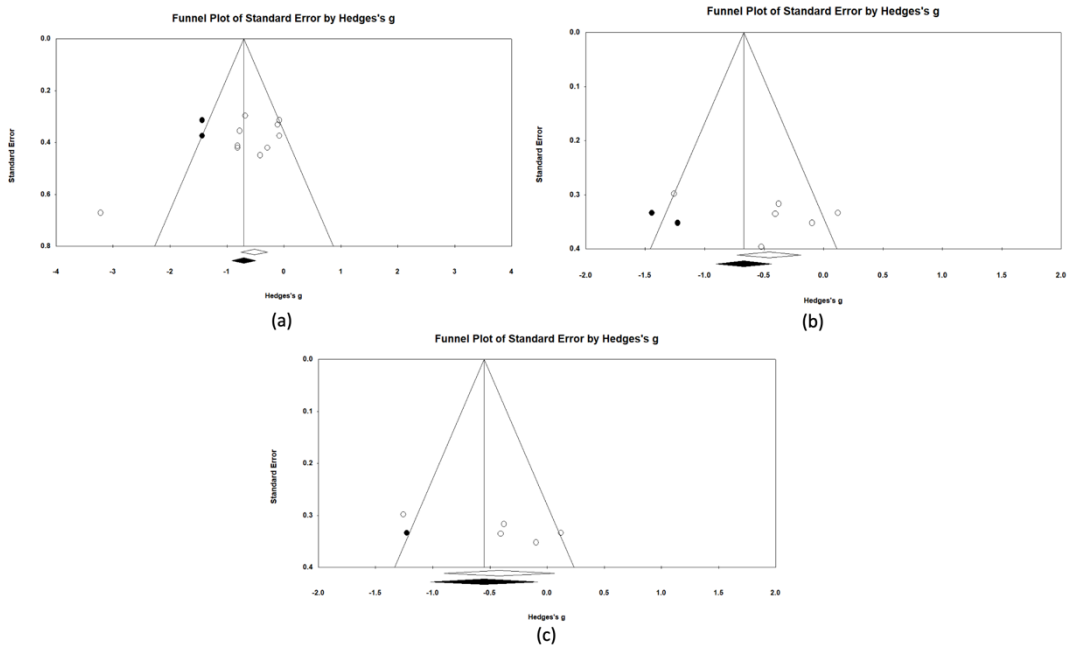
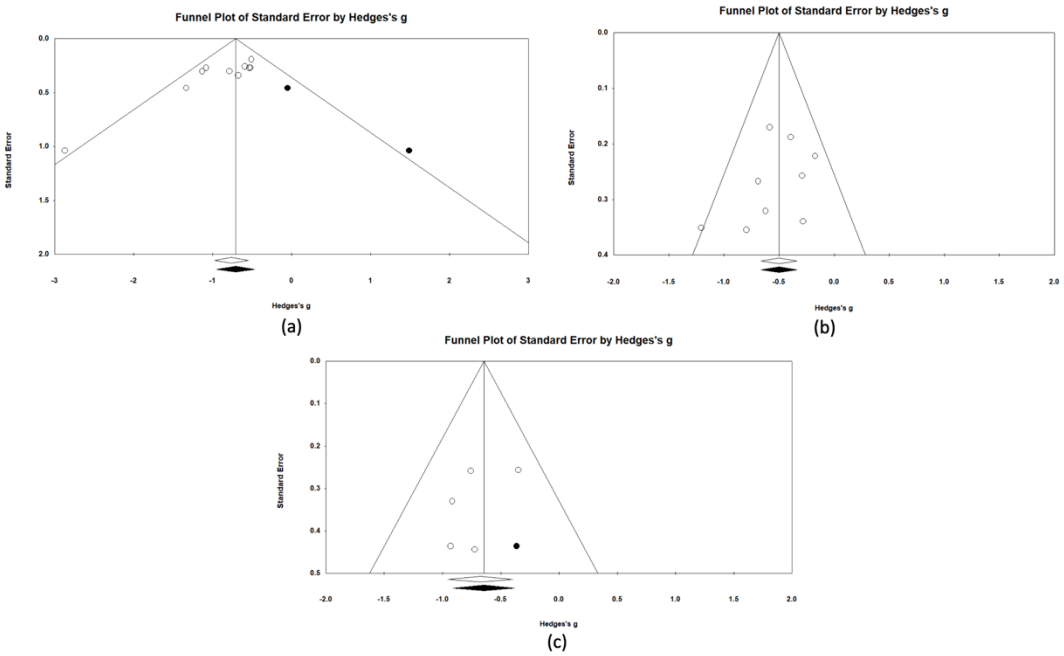



***Fig.3*** Funnel plots of studies included in pre-post between-group analysis. (a) Depressive symptoms; (b) Neurophysiological outcome; (c) Neuropsychological function. Open circles represent original data, while solid circles represent imputed 'missing studies'




405

406 ***Fig.4*** Funnel plots of studies included in pre-post within-group analysis. (a) Depressive

407 symptoms; (b) Neurophysiological outcome; (c) Neuropsychological function. Open

408 circles represent original data, while solid circles represent imputed 'missing studies'.

409

410 **3.4 Sensitivity analysis**

411 To assess the robustness of the findings, Jackknife sensitivity analysis was

412 conducted by removing each study in turn. The results indicated that the overall effect

413 size of studies included in the pre-post between-group analysis was stable and

414 remained significant for depressive symptoms, neurophysiological outcomes, and

415 neuropsychological function(depressive symptoms: [-0.673, -0.431];

416 neurophysiological outcomes: [-0.877, -0.535]; neuropsychological function: [-0.196, -

417 0.552]). However, when the study by Lee et al. (2019) was removed from the analysis

418 of depressive symptoms , the overall Hedges' g dropped to a lower effect size of -

419 0.431(95% CI= [-0.669, -0.193]). Additionally, removing the study by Escolano et al.

(2014) led to a decrease in the overall Hedges' g for neuropsychological function to a low effect size of -0.196(95% CI= [-0.523, 0.131]). Nevertheless, the summary effect of studies in the pre-post within-group analysis remained robust(depressive symptoms: [-0.979, -0.544]; neurophysiological outcomes: [-0.682, -0.328]; neuropsychological function: [-0.954, -0.398]).

### 3.5 Heterogeneity analysis

In the pre-post between-group analysis, moderate heterogeneity was observed in studies of depressive symptoms(Q = 23.223, $p$ = .006; $I^2$ = 61.246%). Similarly, moderate-to-large heterogeneity was found in studies of neurophysiological outcomes(Q = 12.992, $p$ = .011; $I^2$ = 69.213) and neuropsychological function(Q = 11.355, $p$ = .023; $I^2$ = 64.774%), according to the Cochran's Q test and Higgins's $I^2$ test statistic. Conversely, the pre-post within-group analysis showed little heterogeneity across studies of depressive symptoms(Q = 12.240, $p$ = .200; $I^2$ = 26.472%), neurophysiological outcomes(Q = 9.203, $p$ = .325; $I^2$ = 13.068%), and neuropsychological function(Q = 2.597, $p$ = .627; $I^2$ < .001%).

### 3.6 Moderator analysis

We performed moderator analyses primarily on the studies included in the pre-post between-group analysis. Due to the limited number of studies in each group, the subgroup analysis of intervention- and experiment-related moderators(such as intervention modality, targeted brain regions, and control intervention strategies) was

not conducted in the current study.

### 3.6.1 Intervention Length, Sessions, and Frequency

Longer interventions were significantly associated with greater improvements in depressive symptoms(β = -4.36, $p$ < .001) and neuropsychological function(β = -2.89, $p$ = .003). Contrary to expectations, longer interventions were found to be associated with smaller improvements in neurophysiological outcomes in individuals with MDD (β = 3.34, $p$ < .001, See Figure 5a, 5d and 5g).

Furthermore, intervention session number had a significant moderating effect on the improvement of depressive symptoms(β = -3.41, $p$ <.001), neurophysiological outcomes(β = 3.42, $p$ < .001) and neuropsychological function(β = -2.76, $p$ = .006) in patients with MDD. Interestingly, while an increase in the number of intervention sessions was associated with greater improvement in depressive symptoms and neuropsychological function, it was also found to be linked to a decrease in the efficacy of neurofeedback on neurophysiological outcomes (See Fig. 5b, 5e and 5h).

Finally, our findings revealed a significant moderating effect of intervention frequency on the efficacy of neurofeedback for neurophysiological outcomes in depressed participants(β = 2.15, $p$ = .032) and neuropsychological function(β = -3.11, $p$ = .002). More frequent intervention was related with better outcome of neuropsychological function. However, higher intervention frequency was surprisingly associated with less improvement in neurophysiological outcomes(Fig. 5f and 5i).

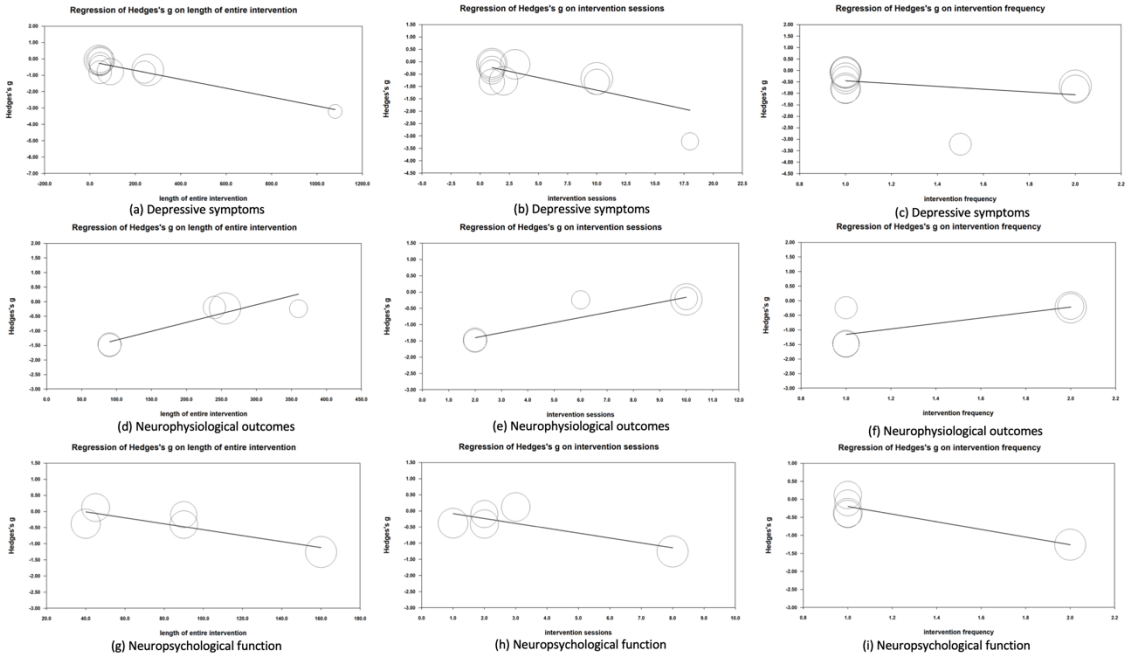



***Fig.5*** Moderating effects of the length of entire intervention, intervention sessions and intervention frequency. Panels (a) ,(b) and (c) represent depressive symptoms, panels (d), (e), and (f) represents neurophysiological outcomes, and panels (g) ,(h) and (i) represent neuropsychological function.

### 3.6.2 Demographic moderators

We focused on investigating the potential moderating effects of two factors: the mean age and sex ratio (Female %) of the experiment group. However, our analysis revealed that neither of these moderators had a significant influence on the effect size of neurofeedback on the depressive symptoms(age: β = -1.51, *p* = .130; sex ratio: β = 0.50, *p* = .614), neurophysiological outcome(age: β = 0.04, *p* = 0.34; sex ratio: β = 4.67, *p* = .350). But we found a significant effect of mean age on neuropsychological function(β = -2.87, *p* = .004) with older age coorelated with greater improvement of neuropsychological function. A marginally significant moderating effect of sex ratio

was also detected(β = -1.91, $p$ = .056), reflecting a tendency of higher ratio of female participants being associated with better outcomes of neuropsychological function.

### 3.7 Comparison with other neuromodulation therapies

In comparison to neurofeedback, other neuromodulation therapies such as tDCS and rTMS have reported moderate effect sizes of 0.460(Razza et al. 2020; Zhang et al. 2021a) and 0.791(Dalhuisen et al. 2022) for improving depressive symptoms (see Figure 2). Interestingly, our analysis found no significant difference in efficacy between tDCS, rTMS, and neurofeedback(Q = 2.121, $p$ = .346) , based on data from studies by Zhang et al. (2021a) and Dalhuisen et al. (2022). Additionally, to compare the efficacy of rTMS, tDCS, and neurofeedback on cognitive improvement in MDD patients, a Cochran's Q test was conducted using data extracted from the meta-analysis of Begemann et al. (2020). The results revealed that neurofeedback outperformed both rTMS and tDCS in enhancing cognitive function in MDD patients(Q = 21.337, $p$ < .001).

## 4 Discussion

This meta-analysis provides strong evidence supporting the potential of neurofeedback as a promising intervention for enhancing depressive symptoms, neurophysiological, and neuropsychological functions in individuals with MDD. The findings suggest that various intervention settings, including the length and frequency of the intervention and targeted brain regions, may significantly influence the efficacy of neurofeedback.

### 4.1 The efficacy of neurofeedback in MDD patients

The findings from the pre-post between-group analysis indicated moderate-to-large effect sizes in studies assessing the effectiveness of neurofeedback on depressive symptoms and neurophysiological outcomes, while a moderate effect size was observed in studies focusing on neuropsychological function. Furthermore, the pre-post within-group analysis also revealed moderate-to-large effect sizes for all three outcome variables.

The studies using EEG as the intervention mode targeted the physiological indicators related to the emotional function of patients, such as FAA, beta and theta band(Cheon et al. 2016; Choi et al. 2010; Wang et al. 2019). Meanwhile, the main targeted brain regions of fMRI-based neurofeedback were also related to the abnormal emotional function of patients(Jaeckle et al. 2021; MacDuffie et al. 2018; Mehler et al. 2017; Takamura et al. 2020; Tsuchiyagaito et al. 2021). Both EEG- and fMRI- based neurofeedback involved in the dopamine system, which may be the reason why neurofeedback has a moderate effect size in patients with depression.

Our findings indicate that neurofeedback demonstrates promising efficacy in alleviating depressive symptoms, and its effectiveness is comparable to that of tDCS and rTMS. Additionally, neurofeedback intervention appears to have a relatively superior impact on neuropsychological function compared to tDCS and rTMS. In contrast to passive interventions that rely on external electrical or magnetic stimulation to modulate brain activity, such as tDCS and rTMS(Trambaiolli et al. 2021),

neurofeedback involves active participation from individuals who learn to regulate their own brain activity using cognitive strategies. The acquisition of self-regulation skills during neurofeedback interventions may lead to lasting effects on both clinical symptoms and cognitive function. The durability of neurofeedback effects has been demonstrated in interventions for ADHD(Dobrakowski and Łebecka 2020; Loriette et al. 2021; Van Doren et al. 2019) and anxiety(Abbasi et al. 2018; Scheinost et al. 2013) , highlighting the promising potential of neurofeedback.

### 4.2 Moderating Effects of Intervention Length, Sessions, and Frequency

Our meta-regression analysis revealed that the duration and frequency of neurofeedback sessions were positively correlated with the effectiveness of the intervention in improving depressive symptoms and neuropsychological function in MDD patients. However, we also found that longer neurofeedback interventions(measured in minutes) or those with a higher frequency(sessions per week) had an aversive effect on neurophysiological outcomes in these patients.

The optimal length, sessions, and frequency of neurofeedback intervention for different disorders are still a matter of debate. For instance, some studies suggest that at least 20 sessions of EEG-based neurofeedback are needed to improve clinical symptoms of ADHD(Arns et al. 2014; Vernon et al. 2004). However, other studies caution against "overtraining" and recommend avoiding excessive neurofeedback sessions to prevent a decrease in efficacy(Enriquez-Geppert et al. 2017; Matthews 2008). A similar concern has been raised for fMRI-based neurofeedback, suggesting

that additional sessions after trainees learn to modulate target brain signals may lead to decreased efficacy(Sulzer et al. 2013).

Increasing the duration and frequency of neurofeedback sessions has shown potential to enhance the amelioration of depressive symptoms and neuropsychological function. However, excessively lengthy interventions or high-frequency sessions might induce neurophysiological fatigue, necessitating further empirical research to substantiate these claims. The current body of meta-analysis studies is relatively limited, warranting more robust evidence. Moreover, striking a balance between central nervous system benefits and symptom/function improvement is imperative. We advocate for preliminary experiments to establish optimal intervention parameters, optimizing efficacy while mitigating trainee fatigue.

The notable influence of the quantity and intensity of neurofeedback in moderating the efficacy of depressive symptoms and neurophysiological outcomes suggests that the relationship between depressive symptoms and targeted brain areas or frequency bands is not straightforward. Emerging evidence consistently indicates that MDD is characterized by dysfunction at the large-scale system level in the brain rather than isolated regional dysfunction(Kaiser et al. 2015; Peng et al. 2021). Therefore, improvements in depressive symptoms may be linked to neurophysiological enhancements in the large-scale system, which may not be accurately reflected by regional indicators alone. As mentioned earlier, targeting specific regions involved in the dopaminergic pathway can alter dopamine concentrations, thereby influencing the functioning of the reward circuit and potentially alleviating depressive symptoms

(Martin-Soelch 2009; Zhang et al. 2019).

### 4.3 Generalization of neurofeedback techniques

Our findings indicate that demographic and clinical factors, such as sex ratio, age, and medication dosage, did not significantly moderate the effects of neurofeedback on depressive symptoms, neurophysiological outcomes, and neuropsychological function in MDD patients. These results suggest that neurofeedback can be effectively applied to a broad range of MDD patients, irrespective of their gender, age, or medication status. Similar to our findings, it is worth mentioning that Yu et al. (2020) focused on subclinical depressive individuals and reported moderate effect sizes for the efficacy of neurofeedback in improving depressive symptoms (effect size = -0.506) and neuropsychological function (effect size = -0.523). Recent meta-analyses that specifically examined the efficacy of neurofeedback in treating ADHD (Van Doren et al. 2019), anxiety (Russo et al. 2022) and obsessive-compulsive disorder (Zafarmand et al. 2022) have also confirmed its promising results in the treatment of other psychiatric illnesses. Thus, these findings highlight the intervention effects of neurofeedback regardless of clinical conditions and status.

Moreover, the placebo effect observed in our study was relatively small, which can be attributed to the active nature of neurofeedback. Unlike passive interventions, neurofeedback involves active regulation of brain activity (Trambaiolli et al. 2021), which may help minimize placebo effects and enhance the generalizability of neurofeedback across diverse patient populations. In summary, our findings strongly

suggest that neurofeedback holds promise as an intervention for MDD patients and can be widely and effectively applied across different demographic and clinical groups. These results provide further support for the potential of neurofeedback as a personalized and targeted treatment approach for depression and subclinical groups.

### 4.4 Gaps and future challenges

Despite the promising findings obtained in this meta-analysis, it is important to acknowledge the limitations that remain and the unanswered questions they raise. Firstly, the effectiveness of neurofeedback across different stages of depression and its potential preventive effects require further investigation. More empirical research is needed to determine whether neurofeedback can effectively prevent the onset or recurrence of depressive episodes.

Secondly, the influence of medication on the effectiveness of neurofeedback is still unclear due to limited reporting on participants' drug use in the included studies. Understanding how medication may interact with neurofeedback is crucial for optimizing treatment outcomes and tailoring interventions for individuals taking different medications (Lee et al. 2019; Tsuchiyagaito et al. 2021).

Thirdly, the majority of existing studies have primarily focused on the regional regulation of brain activity, while major depressive disorder (MDD) is characterized by network dysfunction that involves multiple brain regions and their interconnections (Drevets et al. 2008; Hamilton et al. 2013; Mayberg 1997; Mulders et al. 2015). To gain a more comprehensive understanding of the effects of neurofeedback, future studies

should give more attention to the regulation of functional connectivity and brain network dynamics in individuals with MDD.

Fourthly, the sustained effects of neurofeedback in the treatment of MDD have been limitedly investigated. Only one study included in this meta-analysis assessed the efficacy of neurofeedback on depressive symptoms in MDD patients after a follow-up period of 8-10 days (Yuan et al. 2014). It is important to determine the extent to which the effects of neurofeedback can be maintained over a longer period of time.

Last but not least, the effect sizes of outcomes measured by objective tasks or self-report scales were not compared due to the limited number of studies. It will be more comprehensive and reliable for future studies to apply both subjective and objective measurements when evaluating the efficacy of neurofeedback.

In conclusion, this meta-analysis offers compelling evidence supporting the potential of neurofeedback as a therapy for enhancing depressive symptoms, neurophysiological outcomes, and neuropsychological function in individuals with MDD. The active nature of neurofeedback, which involves the regulation of brain activity, allows it to be effectively applied to MDD patients regardless of their age, sex, and medication dosage. Furthermore, the minimal placebo effects and side effects associated with neurofeedback make it a favorable treatment option in the near future.

**Acknowledgments**

This study was supported by grants from the Natural Science Foundation of Shanghai [grant number 21ZR1421000], the National Natural Science Foundation of China [grant number 32171084], Shanghai Health Commission Clinical Research Fund Project (202140007) ,the University Health Joint Fund (2022JKXYD09003) and the Open Fund of Key Laboratory of Philosophy and Social Science of Anhui Province on Adolescent Mental Health and Crisis Intelligence Intervention (SYS2024A09). These funding agents had no role in the study design; collection, analysis, and interpretation of the data; or writing of the manuscript.

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