Translational Brain Rhythmicity

Review Article

Efficacy of EEG neurofeedback in psychiatry: A comprehensive overview and meta-analysis

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Abstract

Background: This article provides a comprehensive overview of studies investigating the efficacy of EEG neurofeedback in the treatment of psychiatric disorders.

Method: Only studies comparing neurofeedback to a control group (passive/semi-active, placebo, or drug treatment) were included. Effect sizes were calculated for individual studies and when possible combined in meta-analysis (Hedges's g).

Results: We retrieved 30 studies including 1171 participants, evaluating neurofeedback for ADHD, autism, OCD, GAD and depression. For ADHD, combining nineteen trials in meta-analysis yielded small to medium effect sizes for symptoms of inattention, hyperactivity and impulsivity. Subgroup analyses showed that neurofeedback was superior to passive/semi-active treatment (medium effects), while efficacy was similar to placebo (only one study) and drug treatment. For ASD, combining five studies resulted in a superior effect of neurofeedback in reducing general symptomatology; subgroup analyses showed that neurofeedback was more effective than passive/semi-active treatment (four studies) and placebo (based on a single study). Three OCD studies showed varying results, depending on the type of control group used. Two GAD studies found neurofeedback to be similar or inferior to EMG biofeedback. One study on depression showed a large effect for neurofeedback when compared to semi-active treatment.

Conclusion: Although 30 studies could be included, our review of the literature reveals serious limitations of the body of research currently performed. Therefore at present, it cannot be concluded that EEG neurofeedback can be regarded as an evidence-based treatment for ADHD, ASD, OCD, GAD and depression. Large, well-designed studies are needed to elucidate whether neurofeedback is a viable treatment option in the field of psychiatry.

Introduction

Neurofeedback was originally described as a method in which specific frequency bands of the electroencephalographam (EEG) are used to train the electrical activity of the brain through biofeedback. This operant conditioning of selected brainwave frequencies is achieved by giving real-time audio and/or visual feedback cues. The general rationale behind neurofeedback is that this conditioning will be related to behavioral improvements.

The interest in EEG neurofeedback over the last 30 years can be understood in the light of accumulating research on the electrophysiological basis of various psychiatric disorders, such as Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), schizophrenia, Obsessive Compulsive Disorder (OCD), anxiety, depression, Tourette syndrome and anorexia nervosa [1]. A voluminous literature describes the robustness of EEG abnormalities found in a high proportion of psychiatric patients and the clinical implications [2], depending on the psychiatric disorder targeted. As the technique is non-invasive and side-effects such as headache or fatigue due to the attentional demands are minimal [3], EEG neurofeedback has been discussed a promising alternative, non-medical treatment option [4].

Moreover, functional magnetic resonance imaging (fMRI) has rapidly emerged as an alternative technique for neurofeedback protocols [5]. Similar to EEG, fMRI provides an indirect measure of neuronal activity, by recording the hemodynamic response in the brain - known as the blood oxygenation level-dependent (BOLD) signal[5]. While the spatial resolution is higher than EEG, the temporal resolution is much lower. Following the development of fMRI-based neurofeedback protocols, the interest in the methodological and clinical aspects of EEG neurofeedback is now renewed [5].

To evaluate whether EEG neurofeedback training constitutes a viable treatment method in the field of psychiatry, this article provides a comprehensive overview of studies that have investigated its therapeutic efficacy by comparing EEG neurofeedback to a control group. Studies are quantitatively summarised and combined in meta-analysis where possible.

Method

Literature search

This quantitative review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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statement (www.prisma-statement.org/ statement.htm). A systematic search for studies published in English, peer-reviewed journals was performed in PubMed, Embase, PsychInfo, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews, using combinations of the following basic search terms: "neurofeedback", "EEG biofeedback", "neurotherapy", "Slow Cortical Potential", "SCP", in addition to psychiatric diagnosis: ADHD, ASD, OCD, Generalized anxiety disorder (GAD), panic disorder, Post-Traumatic Stress Disorder (PTSD), depression, bipolar disorder substance abuse, Tourette syndrome, anorexia nervosa and schizophrenia. Reference lists of retrieved articles and relevant review articles were examined for cross-references. Search cut-off date was January 2nd, 2015.

Articles selected for inclusion met the following criteria:

1) Studies using between-subjects or cross-over design, with a passive or semi-active control group (such as waiting list, EMG biofeedback or cognitive training), a placebo condition (sham treatment), or a drug therapy control group.

2) Included patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III[-R], DSM-IV[R]) [6,7] or the International Classification of Diseases (ICD-9 or -10) [8].

3) Studies reported sufficient information to compute common effect size statistics or authors could supply these data upon request.

4) Pilot studies that were later continued, resulting in another paper with a larger sample size, were excluded to avoid including the same patient more than once.

Calculation of effect sizes

Two reviewers independently extracted data, disagreements were resolved by consensus. Hedges's *g* was used to quantify effect sizes (ES) for the mean difference between change scores (end of treatment minus baseline) of the neurofeedback group versus control group. Change scores were preferred over pre- and post-treatment scores to avoid overestimation of the true effect size because of the pre- and -post-treatment correlation. If not reported, pre- and post-treatment means and standard deviations (*SDs*), or exact *F*, *t* or *p* values were used. Effect sizes were interpreted according to Cohen [9], with an ES of 0.2 indicating a small effect, 0.5 medium, and >0.8 a large effect. When a study compared neurofeedback to both waiting list and a semi-active treatment, the most stringent (i.e. semi-active) control group was used as a reference. Parent ratings were preferred over teacher ratings. Results were combined in meta-analysis when two or more studies were available using similar outcome measures. To differentiate between various methodological designs we also performed subgroup analyses, grouping studies into: (1) those with a passive/semi-active control group, such as waiting list, EMG biofeedback or cognitive training, (2) those with a placebo condition, i.e. sham treatment, and (3) studies comparing neurofeedback to drug therapy.

A random effects model was deemed most appropriate for this research area given the heterogeneity in applied methods [10]. To investigate whether studies could be taken together to share a common population effect size, the homogeneity statistic I^2 was calculated [11]. Ranging from 0 to 100%, I^2 reflects which proportion of the observed variance reflects differences in true effect sizes rather than sampling error. Values of 25%, 50%, and 75% can be interpreted as low, moderate, and high, respectively [11]. Moreover, it is important to investigate potential outlier studies, defined as standardized residual *z*-scores of effect sizes exceeding ± 1.96 (p<0.05, two-tailed). As the number of feedback sessions was expected to vary between studies, random effects meta-regression analyses were conducted to evaluate this as a moderator variable using the unrestricted maximum likelihood model.

When interpreting meta-analytic outcomes, the possibility of an upward bias of the calculated effect sizes due to the omission of unpublished, nonsignificant studies must be taken into account [12]. Potential publication bias was investigated by means of a visual inspection of the funnel plot, with an asymmetrical plot indicating publication bias. Egger's test [13] was evaluated when appropriate (*i.e.*, analysis included a range of study sizes, with at least one of 'medium' size (p<0.05 two-tailed). Moreover, the fail-safe number of studies (N_R) was calculated, providing an estimate of how many unpublished null-findings would be needed to reduce an observed overall significant result to nonsignificance. As a guideline, the fail-safe number should be 5k+10 or higher (k=number of studies in a meta-analysis) to rule out a file drawer problem [12]. All calculations were executed using Comprehensive Meta-Analysis Version 2.0, Biostat [14,15].

Quality check

Evaluating the quality of conducted studies contributes to improved study design, implementation and reporting by researchers. Therefore, randomization procedures, blinded outcome assessments, and indications of sponsoring bias were evaluated. Randomization was qualified as high when all participants were randomly assigned to one of the study groups, and low if (a part of) the participants were not randomly assigned. Furthermore, blinded outcome assessment was qualified as high when raters were blind, compared to a low rating when raters were not blind to treatment allocation. If the acknowledgement section mentioned sponsoring contributions from institutions with connections to neurofeedback materials in general or, in the case of drug-controlled studies, contributions from the pharmacological industry, the qualification was rated as low. If there were no institutions involved that could benefit from the outcome, qualification was rated high.

Results

Thirty studies were identified including a total of 1171 participants, investigating neurofeedback for ADHD [16-34], autism [35-39], OCD [40-42], GAD [43,44] and depression [45] (see Figure 1). For the remaining psychiatric disorders, no studies were retrieved that fulfilled our inclusion criteria. The majority of studies included a passive/semi-active control group, only three placebo-controlled trials were identified and eight studies compared neurofeedback to drug treatment (Figure 1). Twenty-one out of thirty studies used randomization procedures. Eighteen studies were open-label, six used double-blind ratings. Details on methodological design, number of participants, applied neurofeedback protocol, outcome measures and calculated effect sizes for the individual studies are described in Tables 1 to 3.

Attention deficit hyperactivity disorder (ADHD)

Nineteen studies [16-34] were identified for ADHD, including 872 patients (Table 1). Eleven studies compared neurofeedback with passive/semi-active treatment, one with placebo treatment and seven studies used stimulant medication as a reference. Thirteen studies implemented randomization procedures, eleven were open-label and only three trials were double-blind. Six studies could not be included as reported data were insufficient to calculate effect sizes [46-50].

As Arns and colleagues [51] did not find differences among different neurofeedback protocols in a previous meta-analysis, EEG protocols

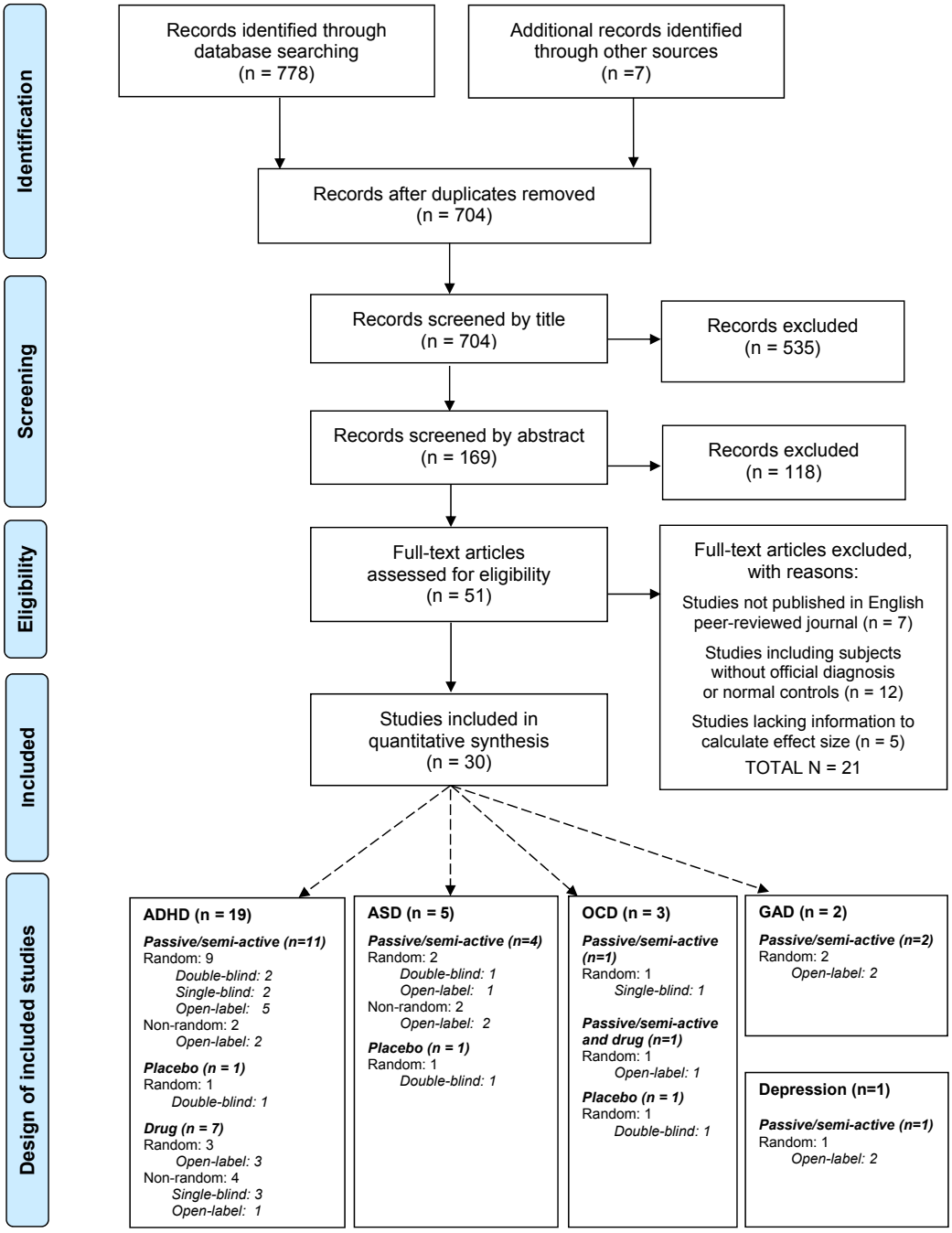

Figure 1. PRISMA Flow Diagram of the performed literature search.

were combined (*i.e.,* sensorimotor rhythm [SMR] enhancement, beta enhancement with theta suppression, training of slow cortical potentials, SMR/theta and beta/theta training, Table 1). Duric *et al.* [32] included two different neurofeedback groups: one receiving neurofeedback, the other combining neurofeedback with drug therapy. Data from the first group (neurofeedback only) were included, as the majority of neurofeedback-receiving participants in the other included studies were unmedicated. Duric [32] did not report exact *SD*s, these were calculated using the 95% confidence intervals ($SD=\sqrt{N}$*[upper limit-lower limit]/3.92).

The following outcomes were evaluated (Table 1):

1) *Inattention*: behavioral rating scales, if not available, omission errors/attentional performance on a computer task.

2) *Hyperactivity*: behavioral rating scales.

3) *Impulsivity*: commission/impulsivity errors on a computer task, for Drechsler *et al.* [19] we used rating scale data, as the two groups showed a significant baseline difference on the Go-Nogo task.

ADHD: inattention

Eighteen studies were included, with 850 participants (Table 1). Neurofeedback showed superior efficacy, with a medium ES of 0.38

Table 1. Summary of studies evaluating the efficacy of neurofeedback in ADHD.

Study	Design	Control Group		*N*	Age (yrs)	Treatment	NF site	Mean # sessions	Outcome measure	Instrument	ES Hedges's g (95 % CI)	*p*
NF vs. passive/semi-active control												
Monastra*et al.* 2002 [16]	Not randomized Open label	Waiting List[a]	NF: WL:	51 49	10.0 10.0	Beta/theta+CCC, 51/51 medicated CCC, 49/49 medicated	Cz	43	Inattention Impulsivity	ADDES (PR) TOVA	**2.44 (1.93 to 2.96)** 0.33 (-0.06 to 0.72)	**<.001** .098
Heinrich *et al.* 2004 [17]	Randomized Single blind	Waiting list	NF: WL:	13 9	11.1 10.5	SCP, 6/13 medicated 4/9 medicated	Cz	25	Impulsivity	CPT	**1.26 (0.36 to 2.16)**	**.006**
Beauregard & Levesque 2006 [18]	Randomized Open label	Waiting list	NF: WL:	15 5	10.2 10.2	SMR/theta/beta unmedicated Unmedicated	Cz	40	Inattention Hyperactivity	CPRS-R (PR) CPRS-R (PR)	**1.18** (0.14 to 2.21) 0.73 (-0.27 to 1.72)	**.026** .152
Drechsler*et al.* 2007 [19]	Not randomized Open label	Cognitive Behavioural Therapy	NF: CBT:	17 13	10.5 11.2	SCP, 6/17 medicated 6/13 medicated	Cz	30	Inattention Hyperactivity Impulsivity	FBB-HKS (PR) FBB-HKS (PR) FBB-HKS (PR)	**1.24 (0.47 to 2.01)** 0.49 (-0.23 to 1.20) **0.74 (0.02 to 1.47)**	**.002** .181 **.045**
Gevenslebene*t al.* 2009 [20]	Randomized Open label	Attention skill training	NF: ASK:	59 35	9.10 9.4	Beta/theta/SCP, unmedicated Unmedicated	Cz	36	Inattention	FBB-HKS (PR)	**0.57 (0.15 to 1.00)**	**.008**
Bakhshayesh*et al.* 2011 [21]	Randomized Single blind	EMG	NF: EMG:	18 17	9.6 9.1	Beta/Theta, 4/18 medicated 3/17 medicated	CPz + FCz	30	Inattention Hyperactivity Impulsivity	FBB-HKS (PR) FBB-HKS (PR) CPT	**0.95** (0.26 to 1.63) 0.55 (-0.11 to 1.22) **0.68 (0.01 to 1.35)**	**.007** .100 **.046**
Li *et al.* 2013 [22]	Randomized Double blind	Non-feedback attention training	NF: AT:	32 32	10.8 10.4	Theta/SMR32/32, medicated 32/32 medicated	Not reported	40	Inattention Hyperactivity	ADHD-RS-IV (PR) CPRS (PR)	0.38 (-0.11 to 0.87) **1.06 (0.55 to 1.60)**	.131 **<.001**
Bink *et al.* 2014 [23]	Randomized Open label	Waiting list	NF: WL:	45 26	16.1 16.2	TAU + SMR/ theta/ beta 20/45 medicated TAU 16/26 medicated	Cz	37	Inattention	ADHD-RS (SR)	-0.04 (-0.51 to 0.44)	.886
Christiansen *et al.* 2014 [24]	Randomized Open label	Self-management	NF: SM:	20[b] 22[b]		SCP SM 23% medicated[c]	Cz	30	Inattention	CPRS III (PR)	-0.01 (-0.60 to 0.59)	.986
Maurizio *et al.* 2014 [25]	Randomized Double blind	EMG	NF: EMG:	13 12	10.6 10.0	Theta/beta, 1/13 medicated 1/12 medicated	Anterior cingulate cortex	36	Inattention Hyperactivity	FBB-HKS (PR) SDQ (PR)	0.57 (-0.20 to 1.35) 0.16 (-0.60 to 0.92	.149 .678
Steiner *et al.* 2014 [26]	Randomized Open label	Cognitive training	NF: CT:	34 34	8.4 8.9	Beta/theta, 15/34 medicated 14/34 medicated	Not reported	40	Inattention	Conners 3-P Conners 3-P	0.38 (-0.09 to 0.86) 0.34 (-0.13 to 0.82)	.115 .157
NF vs. placebo												
Van Dongen-Boomsma *et al.* 2013 [27]	Randomized Double blind	Placebo	NF: P:	22 19	10.5 10.7	Individual: SMR/ beta/theta, 11/22 medicated 14/19 medicated	Not reported	30	Inattention	ADHD-RS (IR) ADHD-RS (IR)	-0.12 (-0.72 to 0.48) 0.36 (-0.25 to 0.96)	1.00 .250
NF vs. drug therapy												
Rossiter& La Vaque 1995 [28]	Not randomized Single blind	Drug therapy	NF: DT:	23 23	12.9 12.7	Beta/theta/SRM, 5/23 medicated 23/23 medicated	Cz or Cz/ Fz+Cz/ Pz	20	Inattention Impulsivity	TOVA TOVA	0.27 (-0.30 to 0.84) -0.01 (-0.58 to 0.56)	.355 .977
Fuchs *et al.* 2003 [29]	Not randomized Single blind	Drug therapy	NF: DT:	22 11	9.8 9.6	Beta/theta/SRM, unmedicated 11/11 medicated	C3 or C4	36	Inattention Impulsivity	TOVA TOVA	0.12 (-0.59 to 0.82) -0.14 (-0.85 to 0.57)	.746 .701
Rossiter 2004 [30]	Not randomized Single blind	Drug therapy	NF: DT:	31 31	16.6 16.7	Beta/theta, 6/31 medicated 31/31 medicated	C3 or C4	50	Inattention Impulsivity	TOVA TOVA	0.13 (-0.36 to 0.62) 0.06 (-0.43 to 0.55)	.608 .813
Nazari*et al.* 2011 [31]	Not randomized Open label	Drug therapy	NF: DT:	13 13	9.1 8.8	Beta/theta, unmedicated 13/13 medicated	C3 and C4	24	Inattention	SNAP-IV (PR)	**-1.11 (-1.91 to-0.31)**	**.007**
Duric*et al.* 2012 [32]	Randomized Open label	Drug therapy	NF: DT:	19 22	11.4[d] 10.9[d]	Beta/theta, unmedicated 22/22 medicated	Cz	30	Inattention Hyperactivity	BRSP (PR) BRSP (PR)	0.41 (-0.20 to 1.02) 0.22 (-0.38 to 0.83)	.189 .469
Meisel*et al.* 2013 [33]	Randomized Open label	Drug therapy	NF: DT:	12 11	9.5 8.9	Beta/theta, unmedicated 11/11 medicated	Cz (7-11y) FCz (>11y)	40	Inattention	ADHD-RS-IV (MR)	-0.07 (-0.86 to 0.72)	1.00
Ogrim&Hestad 2013 [34]	Randomized Open label	Drug therapy	NF: DT:	14 15	10.6 11.2	Individual:theta/ beta, SMR, unmedicated 15/15 medicated	Pz, Cz or Fz	30	Inattention	CRS-R (PR)	-0.46 (-0.21 to 0.28)	.220
		NF **Control** **TOTAL**		**473** **399** **872**								

NF: Neurofeedback; WL: Waiting List; CBT: Cognitive Behavioral Therapy; ASK: Attention Skill Training; EMG: Electromyographic Biofeedback; AT: Attention Training; SM: Self-management; CT: Cognitive Training; P: Placebo; DT: Drug Therapy; CCC: Comprehensive Clinical Care; PR: Parent-Rated; IR: Investigator-Rated; MR: Mother-Rated; ADDES: Attention Deficit Disorders Evaluation Scale; TOVA: Test Of Variables of Attention; CPT: Continuous Performance Task; CPRS-R: Connors' Parent Rating Scale-Revised; FBB-HKS: Fremdbeurteilungsbogen Für Hyperkinetische Störungen (German rating scale); ADHD-RS: Attention Deficit Hyperactivity Disorder Rating Scale; SDQ: Strengths and Difficulties Questionnaire; Conners 3-P: Conners 3-Parent Assessment Report; SNAP-IV: Swanson, Nolan and Pelham (SNAP) Questionnaire; BRSP: Barkley Rating Scale for Parents CRS-R: Conners' Rating Scale-Revised; ES: Effect Size; 95%CI: 95% Confidence Interval

[a]Comprehensive Clinical Care and Ritalin as additional therapy for both groups; [b]Based on additional data provided by author; [c]23% of 58 children that completed the diagnostic study procedure were medicated; study is in progress, therefore not all have completed end-of-treatment assessments; [d]Based on number of patient at baseline (including drop-outs during study)
Significant effect sizes are indicated in bold type.

Table 2. Summary of studies evaluating the efficacy of neurofeedback in autism spectrum disorder.

Study	Design	Control group		*N*	Age (yrs)	Treatment	NF site	Mean # sessions	Outcome measure	Instrument	ES Hedges's g (95%CI)	*p*
NF vs. passive/semi-active control												
Coben & Padolsky 2007 [35]	Not randomized Open label	Waiting list	NF: WL:	37 12	8.9 8.2	Reducing hyperconnectivity, 15/37 medicated No treatment, 4/12 medicated	Individualized	20	General symptoms	ATEC (PR)	**1.40 (0.70 to 2.01)**	**<.001**
Kouijzer *et al.* 2009 [36]	Not randomized Open label	Waiting list	NF: WL:	7 7	9.6 10.6	Theta/beta, unmedicated No treatment, Unmedicated	C3/C4	40	General symptoms	CCC-2 (PR)	0.14 (-0.84 to 1.12)	.781
Kouijzer *et al.* 2010 [37]	Randomized Open label	Waiting list	NF: WL:	10 10	9.4 9.1	Theta, unmedicated Unmedicated	individualized	40	General symptoms	SCQ (PR)	**1.38 (0.44 to 2.33)**	**.004**
Kouijzer *et al.* 2013 [38]	Randomized Double blind	Skin conductance	NF: SC:	7[a] 8[a]	15.3[b] 14.5[b]	Individualized[c] SC biofeedback[c]	Cz or FCz	40	General symptoms	SCQ (PR)	0.11 (-0.84 to1.07)	.814
NF vs. placebo												
Pineda *et al.* 2008-2 [39]	Randomized Double blind	Placebo	NF: P:	9 10	9.4 10.1	Mu + EMG[c] Artificial mu + EMG[c]	C4	30	General symptoms	ATEC (PR)	**0.96 (0.05 to 1.88)**	**.039**
		NF Control TOTAL		**70 47 117**								

NF: Neurofeedback; WL: Waiting List; SC: Skin Conductance; P: Placebo; PR: Parent-Rated; ATEC: Autism Treatment Evaluation Checklist; CCC: Children's Communication Checklist; SCQ: Social Communication Questionnaire; TMT: Trail Making Test (part C-part B); TOL: Tower Of London; TOSSA: Test of Sustained Selective Attention; ES: Effect Size; 95%CI: 95% Confidence Interval

[a]Indicating the number of regulators: regulators were distinguished from non-regulators in the EEG- and SC-biofeedback groups (regulators: negative correlation between mean amplitude of EEG [EEG-biofeedback group] or SC [SC-biofeedback group] signal during sessions and number of sessions)

[b]Based on number of patients at baseline (including drop-outs during study)

[c]Not reported how many patients were taking medication. For Kouijzer *et al.* 2013, medication was not reported specifically for the regulators

Significant effect sizes are indicated in bold type.

Table 3. Summary of studies evaluating the efficacy of neurofeedback in OCD, GAD and depression.

	Study	Design	Control group		*N*	Age (yrs)	Treatment	NF site	Mean # sessions	Outcome measure	Instrument	ES Hedges's g (95% CI)	*p*
OCD	Barzegary *et al.* 2011 [40]	Randomized Open-label	Waiting list Drug therapy	NF: WL: DT:	4 4 4	28.3 28.3 31.8	qEEG guided,unmedicated Unmedicated 4/4 medicated	Individualized	30	Obsessions Compulsions	Padua inventory (SR) *NF vs. WL* *NF vs. DT* Padua Inventory (SR) *NF vs. WL* *NF vs. DT*	 **1.91 (0.38 to 3.43)** -0.09 (-1.30 to 1.11) **1.45 (0.05 to 2.84)** -0.89 (-2.17 to 0.40)	**.014** .881 **.043** .176
	Kopřivová *et al.* 2013 [41]	Randomized Double-blind	Placebo	NF: P:	8 10	24.5 28	CBT+individualized NF, 6/8 medicated CBT + placebo, 7/10 medicated	Individualized	25	Obsessions Compulsions	Y-BOCS (IR) Y-BOCS (IR)	-0.08 (-0.97 to 0.81) **1.23 (0.26 to 2.20)**	.861 **.013**
	Deng *et al.* 2014 [42]	Randomized Single-blind	Waiting list	NF: WL:	37 35	26.7[a] 26.6[a]	CBT + medication + alpha/beta/SMR NF CBT + medication	Not reported	40	General symptoms	Y-BOCS (IR)	**0.74 (0.27 to 1.21)**	**.002**
GAD	Rice *et al.* 1993 [43]	Randomized Open-label	EMG	NF A+: NF A-: EMG:	9 9 9	Total: 27.4	Alpha enhancement[b] Alpha suppression[b] Eye+eyebrowtension[b]	Oz+right mastoid	8	Trait anxiety	STAI-T (SR) *NF A+ vs. EMG* *NF A- vs. EMG*	 -0.14 (-1.02 to 0.74) -0.27 (-1.15 to 0.62)	 .752 .554
	Agnihotri *et al.* 2007 [44]	Randomized Open-label	EMG	NF: EMG:	15 15	Total: 18-30	Alpha enhancement[c] Frontalis muscle tension[c]	Not reported	12	Trait anxiety State anxiety	STAI-T (SR) STAI-S (SR)	0.02 (-0.68 to 0.71) **-2.44 (-3.37 to -1.51)**	.961 **<.001**
DEP	Choi *et al.* 2011 [45]	Randomized Open-label	Psychotherapy placebo training	NF: PPT:	12 11	28.5 28.5	Alpha (asymmetry)[c] PPT[c]	F3/F4 (Cz)	10	Depressive symptoms	HAM-D (IR)	**0.92 (0.09 to 1.76)**	**.030**

OCD: Obsessive Compulsive Disorder; GAD: General Anxiety Disorder; DEP: Depression; NF: Neurofeedback; WL: Waiting List; DT: Drug Treatment; P: Placebo; NF A+: Alpha Enhancement Neurofeedback; NF A-: Alpha Suppression Neurofeedback; EMG: Electromyographic Biofeedback; PPT: Psychotherapy Training; CBT: Cognitive-Behavioral Therapy; SR: Self-Rated; IR: Investigator-Rated; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; STAI: State-Trait Anxiety Inventory (-T: trait anxiety,-S: state anxiety); HAM-D: Hamilton Depression Inventory; ES: Effect Size; 95%CI: 95% Confidence Interval.

[a]Based on number of patient at baseline (including drop-outs during study)

[b]38 participants officially diagnosed with GAD (DSM-III); 7 subjects had subclinical GAD (: positive in 2 of 4 categories, rather than 3 of 4 as required by DSM-III)

[c]Not reported how many patients were taking medication

Significant effect sizes are indicated in bold type

(p=.031, 95%CI=0.04 to 0.73), Figure 2. Pooling of studies yielded high heterogeneity however (I^2=83%), supporting the inconsistency of effect sizes in this domain. The funnel plot and Egger's test (t=0.51, p=.61) did not indicate publication bias. The number of missing null studies to render this positive result tot nonsignificance was 120. Similarly to a previous meta-analysis by Arns *et al.* [51], the exceptionally large effect size of 2.44 by Monastra *et al.* [16], was identified as an outlier (z=2.94, p=.003). Without this study, the overall effect size reduced to 0.25 while remaining significant (p=.030, 95%CI=0.02 to 0.47). N_R decreased to 32, heterogeneity was moderate (I^2=56%).

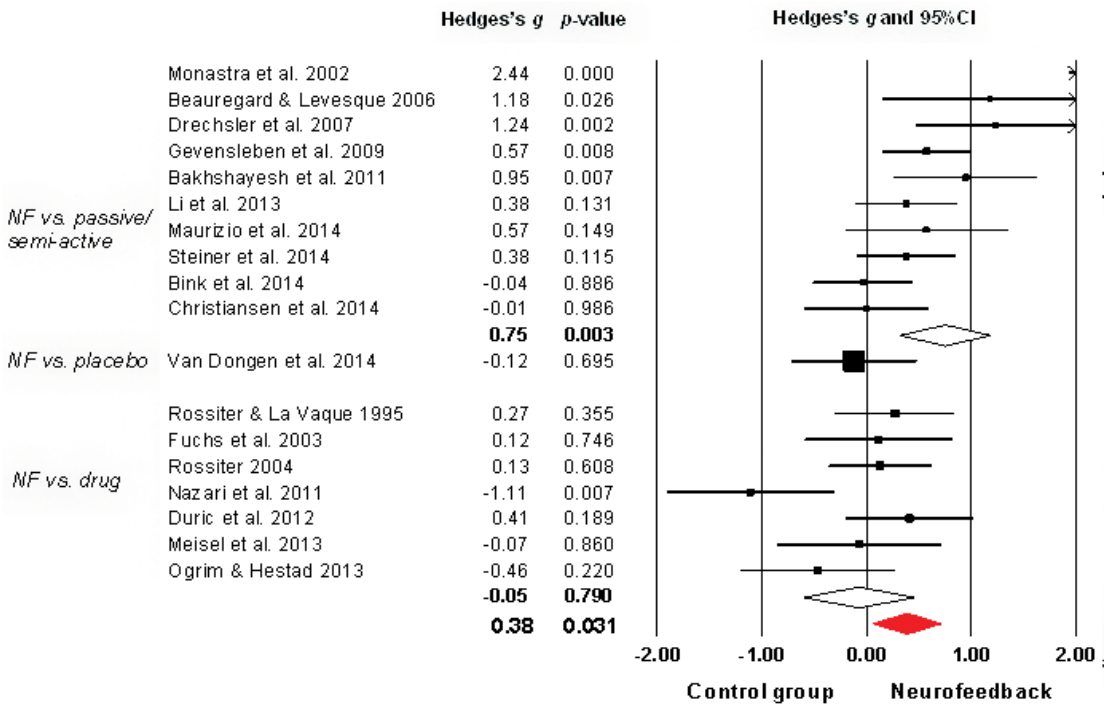

Figure 2. Meta-analysis of NF treatment for symptoms of inattention in ADHD.

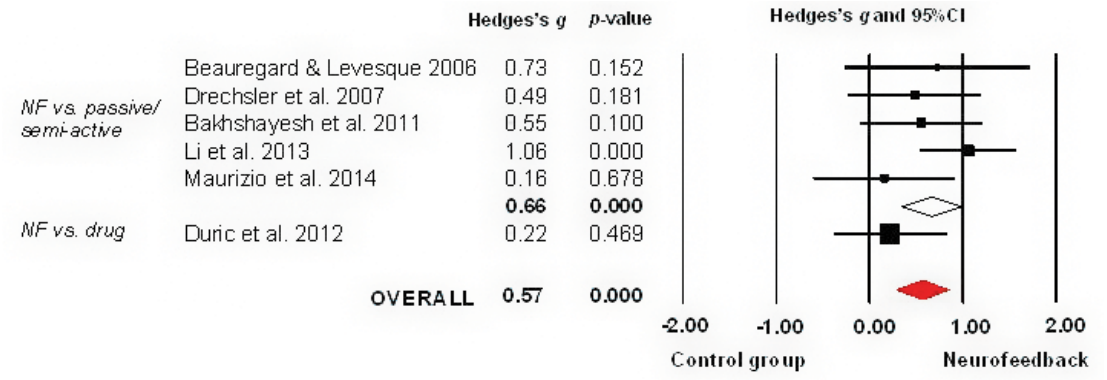

Figure 3. Meta-analysis of NF treatment for symptoms of hyperactivity in ADHD.

NF *vs.* passive/semi-active control: Combining eight studies showed superior efficacy for neurofeedback, with a medium ES of 0.75 (p=.003, 95%CI=0.26 to 1.24, N_R=146). However, heterogeneity was high (I^2=86%). Without the outlier study by Monastra [16] (z=2.32, p=.021), overall effect size reduced to 0.49 (p<.001, 95%CI=0.22 to 0.76, N_R=51). Heterogeneity was moderate (I^2=46%).

NF *vs.* placebo: The only randomized, double-blind, placebo-controlled study by Van Dongen-Boomsma [27], found no difference between neurofeedback and placebo treatment (ES -0.12, p=1.00).

NF *vs.* drug therapy: Combined results of seven studies indicated that neurofeedback has similar effects as drug therapy (ES -0.05, p=.790, 95%CI=-0.40 to 0.30), with moderate heterogeneity (I^2=49%).

ADHD: hyperactivity

Six studies combined (N=215, Table 1) showed a medium effect for neurofeedback (ES 0.57, p<.001, 95%CI=0.27 to 0.87, I^2=15.85%), Figure 3. No publication bias was indicated (Egger's test=0.86, p=.44). However, the fail-safe number of studies was only 18, indicating a potential file drawer problem.

NF *vs.* passive/semi-active treatment: Five trials combined showed a medium superior effect for neuro-feedback over passive/semi-active treatment (ES 0.66, p<.001, 95%CI=0.35 to 0.98, N_R=16, I^2=6%).

NF *vs.* drug therapy: Duric *et al.* [32] found no difference between neurofeedback and stimulant medication therapy (ES 0.22, p=.469).

ADHD: impulsivity

Combining seven studies (N=328, Table 1) showed a significant small to medium effect for neurofeedback (ES=0.34, p=.026, 95%CI=0.04 to 0.65, Figure 4). Heterogeneity was moderate (I^2=43%), no publication bias was indicated (t=1.87, p=.29). However, fail-safe N_R was only 11.

NF *vs.* passive/semi-active treatment: Combining four studies showed a medium effect for neurofeed-back (ES 0.62, p=.001, 95%CI=0.26 to 0.97, I^2=25%), although fail-safe N_R of 15 was relatively small.

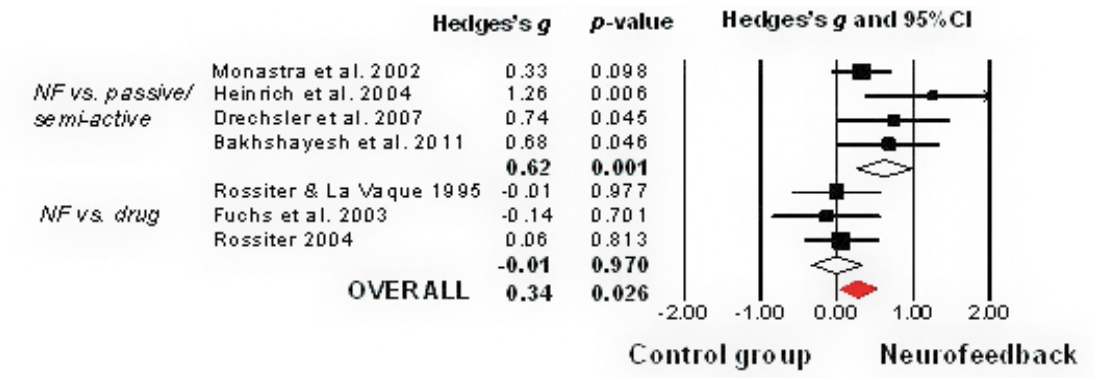

Figure 4. Meta-analysis of NF treatment for symptoms of impulsivity in ADHD.

NF *vs.* drug therapy: Three studies showed no difference between neurofeedback and stimulant medication (ES -0.01, p=.97, 95%CI=-0.34 to 0.32, I^2=0%).

Autism spectrum disorders (ASD)

Five studies [35-39] were retrieved for ASD, including 130 patients (Table 2). Three studies were open-label, only one randomized double-blind placebo-controlled trial could be included. Although neurofeedback protocols differed greatly between studies, meta-analyses were conducted to provide overall effect sizes. Effects on general symptomatology were evaluated (Table 2), as rated on a behavioral rating scale. Data from the Auti-R as reported by Kouijzer *et al.* 2009 [36] were insufficient, therefore the Children's Communication Checklist (CCC-2) was used - total scores were calculated by averaging the ten subscales (each consisting of seven items, $SD=\Sigma SD/\sqrt{}$number of subscales).

ASD: general symptomatology

Neurofeedback showed a large superior effect of 0.85 (p=.003, 95% *CI*=0.29 to 1.40). Heterogeneity was moderate (I^2=49%), publication bias was not indicated (t=1.64, p=.20) although fail-safe N_R was only 18.

NF *vs.* passive/semi-active treatment: Four studies combined showed a large superior effect for neurofeedback compared to waiting list or skin conductance therapy (ES 0.80, p=.029, 95%CI=0.08 to 1.52). However, heterogeneity was moderate to high (I^2=62%), fail-safe N_R was only 11.

NF vs. placebo: Pineda *et al.* [39] found a large superior effect of neurofeedback over placebo treatment (ES 0.96, p=.039).

Obsessive compulsive disorder (OCD)

Three studies [40-42] were included on OCD, with 102 patients (Table 3). The randomized single blind study by Deng *et al.* [42] investigated neurofeedback combined with medication and cognitive behavioral therapy (CBT), compared to treatment with medication and CBT only. Barzegary *et al.* [40] compared neurofeedback with waiting list as well as a medication treatment group, in a randomized open-label study. Kopřivová *et al.* [41] was the only randomized double-blind placebo-controlled study. Effects of neurofeedback on general symptomatology, and obsessions and compulsions separately, were evaluated using behavioral rating scales.

OCD: general symptomatology

NF *vs.* passive control: Deng *et al.* [42] found a medium to large effect of neurofeedback treatment (ES 0.74, p=.002).

OCD: obsessions

NF *vs.* passive control: Barzegary *et al.* [40] 2011 found a large superior effect of neurofeedback compared to waiting list (ES 1.91, p=.014).

NF *vs.* placebo: Kopřivová *et al.* [41] showed the effects of neurofeedback training to be similar to sham feedback (ES -0.08, p=.861).

NF *vs.* drug therapy: Barzegary *et al.* [40] (2011) found that neurofeedback was similar to medication therapy (ES -0.09, p=.881).

OCD: compulsions

NF *vs.* passive control: Barzegary *et al.* [40] showed a large effect for neurofeedback compared to waiting list (ES 1.45, p=.043).

NF *vs.* placebo: Kopřivová *et al.* [41] found a large effect for neurofeedback over sham feedback (ES 1.23, p=.013).

NF *vs.* drug therapy: Barzegary *et al.* [40] found no differences in efficacy between neurofeedback and drug therapy (ES -0.89, p=.176).

Generalized anxiety disorder (GAD)

Two randomized open-label studies [43-44] were identified, comparing neurofeedback to EMG biofeedback (see Table 3).

GAD: trait anxiety

NF *vs.* semi-active treatment: Combining the two studies showed that EEG alpha-enhancement was similar to EMG biofeedback (ES -0.04, p=.874, 95%CI=-0.59 to 0.502, I^2=0%). Rice *et al.* 1993 [43] also found a non-significant result for alpha-suppression training (ES -0.27, p=.554).

GAD: state anxiety

NF *vs.* semi-active treatment: Agnihotri *et al.* 2007 [44] found alpha-enhancement neurofeedback to be inferior to EMG biofeedback in reducing state anxiety, with a large negative effect size of -2.44 (p<.001).

Depression

Only one study [45] was retrieved for depression (Table 3). Choi *et al.* 2011 [45] randomly assigned participants to neurofeedback (N=12) or a semi-active control group (N=11), patients and investigators were not blind to treatment allocation. Neurofeedback was superior to psychotherapy training, with a large effect size of 0.92 (p=.030).

Meta-Regression

When combining studies for ADHD and autism, significant heterogeneity was detected. A priori, it was assumed that inter-study differences in the number of feedback sessions could possibly explain observed variance between studies. Indeed, number of applied neurofeedback sessions differed greatly, ranging from 20 to 50 sessions. However, meta-regressions conducted for ADHD (inattention, hyperactivity and impulsivity) did not show a significant association between the number of feedback sessions and obtained effect sizes, nor in the subgroup analyses where studies were divided into the different types of control groups. Similarly for autism, meta-regressions did not show significant associations between the number of sessions and calculated effect sizes.

Quality check

Assessment of the methodological quality of the included studies can be found in Table 4. Six of the nineteen trials on ADHD did not randomize participants to the different conditions. In only nine studies, raters assessing symptom severity were blind to the subjects' treatment allocation. There were no indications for sponsoring bias in the majority of trials. For the study by Li *et al.* [22], two authors had competing interests as they had received funding from profit organizations. Three articles did not report acknowledgements.

When evaluating the five studies on autism, three studies were randomized, raters were blind to treatment allocation in two studies. Four articles acknowledged that neurofeedback equipment was donated or shared by an external company, one study did not include an acknowledgement section. All studies on OCD, GAD and depression were randomized, while raters were blind to treatment allocation in only two studies. Quality with regard to sponsoring bias was rated high for three trials, while the remaining articles did not include an acknowledgements section.

Table 4. Quality check of the included studies
CT: computer task; RS: rating scale

Study	Random-ization	Blinded outcome assessment	Quality regarding sponsoring bias
ADHD			
Rossiter& La Vaque 1995	Low	High	Not reported
Monastra *et al.* 2002	Low	Moderate (CT: high; RS: low, raters not blind)	High
Fuchs *et al.* 2003	Low	High	High
Heinrich *et al.* 2004	High	High	High
Rossiter 2004	Low	High	Not reported
Beauregard & Levesque 2006	High	High	High
Drechsler *et al.* 2007	Low	Low	High
Gevensleben *et al.* 2009	High	Low	High
Bakshshayesh *et al.* 2011	High	High	High
Nazari *et al.* 2011	Low	Moderate (CT: high; RS: low, raters not blind)	High
Duric*et al.* 2012	High	Low	High
Li *et al.* 2013	High	High	Low
Bink *et al.* 2014	High	Low	High
Christiansen *et al.* 2014	High	Low	Not reported
Meisel *et al.* 2013	High	Low	High
Ogrim & Hestad 2013	High	Low	High
Van Dongen-Boomsma *et al.* 2013	High	High	High
Maurizio *et al.* 2014	High	High	High
Steiner *et al.* 2014	High	Low	High
Autism			
Coben & Padolsky 2007	Low	Low	Not reported
Pineda *et al.* 2008-2	High	High	Moderate
Kouijzer *et al.* 2009a	Low	Moderate (CT: high; RS: low, raters not blind)	Moderate
Kouijzer *et al.* 2010	High	Moderate (CT: high; RS: low, raters not blind)	Moderate
Kouijzer *et al.* 2012	High	High	Moderate
OCD			
Barzegary et. al 2011	High	Low	Not reported
Koprivova et. al 2013	High	High	High
Deng *et al.* 2014	High	High	High
GAD			
Rice *et. al* 1993	High	Low	Not reported
Agnihotri *et al.* 2007	High	Low	Not reported
Depression			
Choi *et. al* 2011	High	Low	High

Discussion

We included 30 studies with 1171 participants in total, evaluating neurofeedback as a treatment method for ADHD [16-34], autism [35-39], OCD [40-42], GAD [43,44] and depression [45]. Our review of the literature reveals serious limitations of the body of research currently performed on this topic. The large majority of neurofeedback studies have at least one major methodological limitation such as lack of randomization, non-blind designs and use of waiting list control conditions, as evidenced in our quality check. Studies including a sham EEG feedback control group, accounting for the non-specific effects of EEG neurofeedback training, were sparse. Also, sample sizes were too small. To detect a medium effect size of 0.5, a minimal sample size of 64 per group is needed (alpha error 0.05, power of 80%). This criterion was not met by any of the included studies, with median group size being 15 subjects (ranging from 4 to 51 patients). Underpowered studies carry the risk of both false positive and negative findings, and are more likely to be affected by publication bias, selective data analysis and selective reporting of outcomes [52]. These important shortcomings pose a limitation to the results of published studies in this field, making it impossible to draw any conclusions regarding the efficacy of neurofeedback based on the current literature. The results should therefore be interpreted with caution.

ADHD

Nineteen studies were retrieved for ADHD, including 872 patients. Neurofeedback showed small to medium effects on inattention, hyperactivity and impulsivity. Subgroup analyses showed that neurofeedback training was superior to waiting list/semi-active treatment for all symptoms evaluated (medium effect). However, the only placebo-controlled study by Van Dongen-Boomsma and colleagues [27] showed that the effects of neurofeedback on ratings of inattention did not differ from sham treatment, nor for combined ratings of hyperactivity/impulsivity symptoms (not included in current meta-analysis: ES 0.36, p=.25). Effects of neurofeedback training were similar to drug therapy, currently the gold standard in ADHD treatment. Given the methodological shortcomings of most included studies however, these findings must be interpreted with great caution.

First, as stressed in a recent meta-analysis by Micoulaud-Franchi and colleagues [53] (updating Sonuga-Barke *et al.*) [54], the evidence supporting EEG neurofeedback for ADHD is influenced by the (probable) blinded status of the assessor. They only included

randomized controlled trials and while positive effects were found on symptoms of inattention in both probably unblinded (parents) and probably blinded (teacher) ratings, the superior effect of neurofeedback on hyperactivity/impulsivity was only significant in the probably unblinded parent assessments. Furthermore, we could retrieve only one randomized double-blind trial [27] that actually included a sham EEG feedback control group, showing no difference between EEG neurofeedback and sham treatment. The other methodologically sound study by Arnold *et al.* [50] was not included as reported data were insufficient to calculate ES, but this RCT also failed to show superior effects of neurofeedback. A study by Logemann *et al.* [55] found similar placebo effects when evaluating ADHD symptoms in a student population. Finally, it must be pointed out that not all of our calculated significant effect sizes were confirmed by a large fail-safe number of studies. According to Rosenthal [12], fail-safe N_R should be $5k+10$ or higher (k=number of included studies). While the effect of neurofeedback treatment on inattention was accompanied by a large fail-safe N_R of 124), this number was substantially smaller after removal of one outlier study (N_R=35). Fail-safe N_R was also small for the positive effect of neurofeedback on hyperactivity and impulsivity (18 and 11, respectively). Overall, given the major methodological limitations of most included studies in addition to the possible mediating role of non-specific (*i.e.,* placebo) effects, our findings currently cannot confirm the clinical efficacy of neurofeedback for ADHD.

ASD

Five studies including 130 patients showed a large significant effect on general symptomatology. Importantly however, fail-safe N_R was only 18. Neurofeedback was superior to passive/semi-active treatment (four studies, although N_R was only 11). The single sham-controlled study [39] also showed a large superior effect. However, the same limitations as noted for the ADHD literature apply to studies on ASD, with the added remark that median sample size was even smaller in this field (10). Our meta-analyses primarily relied on comparison of neurofeedback to waiting list, which is more susceptible to placebo effects and only two studies were conducted in a randomized double-blind fashion. We therefore conclude that the efficacy of neurofeedback in the treatment of ASD is not sufficiently supported by the trials conducted till now.

Other psychiatric disorders

The few studies on OCD, GAD and depression had very small sample sizes, ranging from 4 to 37 participants per treatment condition. Results for the three studies on OCD depended on type of treatment used as comparison. Neurofeedback was superior to waiting list in reducing general symptomatology (one study). When rating obsessions and compulsions separately, neurofeedback was superior to waiting list but similar to drug therapy (one open-label study). The only placebo-controlled trial found a large effect for neurofeedback in reducing compulsions but not obsessions. For GAD, alpha-enhancement (two studies) and alpha-suppression training (one study) were similar to EMG biofeedback (two studies) in reducing trait anxiety. Moreover, alpha-enhancement training was inferior to EMG biofeedback when evaluating state anxiety (one study) size. For depression, the only randomized open-label study included showed a large effect for neurofeedback compared to psychotherapy training.

Taken together, few studies have evaluated the efficacy of neurofeedback in the treatment of OCD, GAD and depression, with very small sample sizes. Only one randomized double-blind study was included. As the found results are inconclusive, future trials are needed to assess the clinical utility of neurofeedback training in the treatment of these three disorders.

Limitations

Although pioneer studies investigating EEG neurofeedback as a treatment for psychiatric disorders were already conducted over 25 years ago, the majority of studies published so far have important methodological shortcomings. The lack of standardization amongst neurofeedback trials is problematic, as also highlighted by Schoenberg & David 2014 [56], with very few trials aiming to replicate previous results. We found that type of control group differed greatly between studies. Generally, neurofeedback was superior to waiting list or a semi-active control group, while efficacy did not differ from sham treatment (although only two placebo-controlled trials could be included). Therapeutic effects were mainly similar to medication therapy. Although the number of applied neurofeedback sessions also varied greatly between studies (ranging from 20 to 50 sessions), meta-regressions did not show significant associations. Studies also used different outcome measures including interviews, rating scales or computerised tests. Furthermore, surprisingly few articles reported the number of responders and non-responders, i.e. which participants gain control over their brain activity and which do not. This information is essential when trying to relate improvements in self-regulated brain activity to clinical outcome [57]. As suggested by Zuberer *et al.* [57], the treatment process and learning of EEG self-regulation should be carefully analysed when investigating the efficacy and specificity of neurofeedback. Moreover, Arns *et al.* [58] found that clinical outcome was improved when personalizing neurofeedback training to the individual qEEG. Implementation of this technique as a treatment method for psychiatric symptoms therefore requires good clinical practice, and careful implementation and evaluation of neurofeedback training during treatment sessions is essential.

The large number of studies not meeting our relatively lenient inclusion criteria stresses the fact that systematic, well-designed intervention studies are lacking. Given its mild side effect profile, neurofeedback is widely used to treat psychiatric disorders, in particular children with ADHD or ASD. Although neurofeedback is non-invasive and side-effects such as headache or fatigue due to the attentional demands are indeed minimal [3], individuals can experience somatic complaints such as nausea, muscle twitches, sleep disturbances, OCD like symptoms, agitation, or even seizure [59]. Children may skip school hours to attend neurofeedback sessions. In this light, the risks of subjecting individuals to a treatment method that is not yet evidence based can be more than only a waste of time and finances, as it may also extend the time until effective treatment is started. As recently noted by Holtmann *et al.* [60], placebo-controlled trials could provide strong evidence for the efficacy of neurofeedback treatment. Although several issues have been raised about the use of sham treatment, including ethical concerns and feasibility problems, large studies comparing neurofeedback to an adequate control condition are needed to assess whether EEG neurofeedback is solely responsible for observed positive effects on symptomatology and cannot be attributed to non-specific factors associated with placebo effects.

Conclusion

In sum, the lack of methodologically sound studies prevents evidence-based conclusions on the efficacy of EEG neurofeedback in the treatment of ADHD, ASD, OCD, GAD and depressive disorder. It is paramount that future studies are carefully planned and executed,

including power calculations to establish required sample sizes, randomization, blinding and adequate control conditions. Only then can we assess whether neurofeedback is a viable treatment option in the field of psychiatry.

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