A Randomized Placebo-Controlled Trial of Electroencephalographic (EEG) Neurofeedback in Children With Attention-Deficit/Hyperactivity Disorder

Martine van Dongen-Boomsma, MD; Madelon A. Vollebregt, MSc; Dorine Slaats-Willemse, PhD; and Jan K. Buitelaar, MD, PhD

ABSTRACT

Objective: A double-blind, randomized, placebo-controlled study was designed to assess the efficacy and safety of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder (ADHD). The study started in August 2008 and ended in July 2012 and was conducted at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands.

Method: Forty-one children (aged 8–15 years) with a *DSM-IV-TR* diagnosis of ADHD were randomly assigned to treatment with either EEG neurofeedback (n = 22) or placebo neurofeedback (n = 19) for 30 sessions, given as 2 sessions per week. The children were stratified by age, electrophysiologic state of arousal, and medication use. Everyone involved in the study, except the neurofeedback therapist and the principal investigator, was blinded to treatment assignment. The primary outcome was severity of ADHD symptoms on the ADHD Rating Scale IV, scored at baseline, during treatment, and at study end. Clinical improvement as measured by the Clinical Global Impressions-Improvement scale (CGI-I) was a secondary outcome.

Results: While total ADHD symptoms improved over time in both groups ($F_{1,39} = 26.56$, $P < .001$), there was no significant treatment effect, ie, group × time interaction ($F_{1,39} = 0.36$, $P = .554$); the same was true for clinical improvement as measured by the CGI-I ($P = .092$). No clinically relevant side effects were observed. Among the children and their parents, guessing treatment assignment was not better than chance level ($P = .224$ for children, $P = .643$ for parents).

Conclusion: EEG neurofeedback was not superior to placebo neurofeedback in improving ADHD symptoms in children with ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT00723684

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Corresponding author: *Martine van Dongen-Boomsma, MD, Reinier Postlaan 12, 6525 GC Nijmegen, The Netherlands (m.vandongen-boomsma@karakter.com).*

A substantial proportion of children with attention-deficit/hyperactivity disorder (ADHD) fails to respond favorably to the first-line treatment medication.[1] Indications that long-term use of medication affects growth, neural functioning, and the cardiovascular system[2] and the absence of evidence for long-term efficacy of medication for ADHD[3,4] point to the need for nonpharmacologic treatment options.

Electroencephalographic (EEG) neurofeedback is such an option. With EEG neurofeedback, the hypothesis is that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies via provision of continuous real-time feedback, ie, positive reinforcement when changes are made in the desired direction, through visual and/or acoustic signals representing the brain activity.[5] Most often, the aim of EEG neurofeedback is to increase β activity (or sensorimotor rhythm, 12–15 Hz over the motor cortex), while suppressing θ activity.[6] This goal is based on the observation that slow-wave activity (primarily θ [4–7 Hz]) is increased and fast-wave activity (β [12–30 Hz]) is decreased in most patients with ADHD (see the review by Barry et al[7]). Different EEG neurofeedback treatment protocols are in use. For example, a predetermined protocol (mostly a θ/β protocol) can be used that does not necessarily require pretreatment EEG analysis to assess the individual resting-state EEG. Alternatively, a pretreatment quantitative EEG (qEEG) analysis is performed, and, after comparison of findings with those from a normative database, a personalized treatment protocol focusing on the resting state EEG features of that individual is drawn up. The first method has the advantage that a standardized treatment protocol is used, and the second method has the advantage that treatment is personalized and targeted to the specific EEG deviations of that individual.

Recent reviews[5,8–10] are reserved about the efficacy of EEG neurofeedback in children with ADHD, despite the finding of medium to large effect sizes, mainly because of methodological shortcomings of the studies. Although the most recent published studies have more robust methodological designs, only 3[11–13] of more than 20 published randomized controlled trials included a placebo condition. A systematic review and meta-analysis[14] of randomized controlled trials of nonpharmacologic interventions in children with ADHD reported nonsignificant results for the blinded rating of symptoms ($P = .07$). Moreover, none of the 3 published placebo-controlled trials[11–13] showed EEG neurofeedback to be superior to placebo neurofeedback. The question of whether EEG neurofeedback is a safe treatment is still to be addressed. As far as we know, our pilot study[12] was the first to systematically monitor safety.

At the time our study was designed and begun, EEG neurofeedback was thought to be a promising treatment for ADHD.

Clinical Points

- The findings of this study are in line with a recent meta-analysis that concluded that EEG neurofeedback does not have proven efficacy as a treatment for children with ADHD.
- Guidance regarding EEG neurofeedback as a treatment for children with ADHD must be in line with these current findings.
- Further research on this topic is needed to determine whether EEG neurofeedback is of clinical relevance in subgroups of children with ADHD.

Therefore, we expected significant improvement of ADHD symptoms after EEG neurofeedback as compared to placebo neurofeedback.

This current study is a valuable addition to the existing literature because of a larger study sample, the use of qualified neurofeedback therapists, the double-blind design, and the inclusion only of participants with a deviant pretreatment EEG. The latter made it possible to apply personalized EEG neurofeedback.

In sum, the present randomized, double-blind, placebo-controlled trial was designed to critically evaluate the efficacy in reducing ADHD symptoms and the safety of EEG neurofeedback in children with ADHD. The study was registered on ClinicalTrials.gov (identifier: NCT00723684).

METHOD

Trial Design

This study started as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs older than 12 years), electrophysiologic state of arousal (hyperarousal vs hypoarousal), and use of medication (with vs without medication). After our pilot study,[12] we made 2 changes: (1) The automatically adjusted reward thresholds in the EEG neurofeedback condition were changed into manually adjusted reward thresholds, with the consequence that the neurofeedback therapist was no longer blinded to treatment assignment; note that the children, their parents and teachers, and the raters were still blinded to treatment assignment. (2) Active learning strategies were introduced, so that children could integrate the learned strategies into daily life.

Children with ADHD were stratified and then randomly assigned in a double-blind manner (1:1 assignment using random block sizes of 2) to either EEG neurofeedback or placebo neurofeedback (treatments to be given twice per week for a total of 30 sessions). The assignment was done by the principal investigator, who was not involved in data collection.

All people involved in the study were blinded to treatment assignment, with the exception of the neurofeedback therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis. Since both participants and raters were still blinded to treatment assignment, this study was labeled as double-blind.

Participants

Children (aged 8–15 years) were included if (1) they had been clinically diagnosed with ADHD according to *DSM-IV-TR* criteria[15]; (2) they had an (estimated) full-scale intelligence quotient (IQ) of at least 80; (3) their qEEG, a technique to produce a visual map of different frequencies and locations of a signal measured from the brain using EEG, deviated at least 1.5 standard deviations (SDs) from normative data; (4) they did not use psychoactive drugs, or they used a stable dose of psychostimulants or atomoxetine; and (5) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale for at least 6 items of the ADHD Rating Scale IV (ADHD-RS-IV).[16] Children were excluded if they (1) were involved in individual or group psychotherapy, (2) used medication other than psychostimulants or atomoxetine, (3) had a comorbid disorder other than oppositional defiant disorder or any anxiety disorder, (4) had a neurologic disorder and/or a cardiovascular disease, (5) participated in another clinical trial at the same time, (6) had received EEG neurofeedback in the past, or (7) used alcohol or drugs.

Psychostimulants or atomoxetine were permitted because the majority of severely affected children with ADHD in The Netherlands use medication. The discontinuation of medication would have been ethically questionable due to the consequence of withholding an evidence-based treatment; moreover, the exclusion of children taking medication would have limited the generalizability of findings.

A psychologist or doctor screened potential participants for eligibility by asking their parents a number of questions over the telephone. Current ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Autism Screening Questionnaire (ASQ)[17] was used to screen for autism spectrum disorders. Children who screened positive for ADHD symptoms underwent an extensive diagnostic procedure, including the ADHD-RS-IV and a developmental and psychiatric interview with a child and adolescent psychiatrist, who confirmed the diagnosis on the basis of the findings. The presence of comorbid disorders was assessed with the Diagnostic Interview Schedule for Children, Version IV (DISC-IV).[18,19] General functioning was measured using the Children's Global Assessment Scale (CGAS),[20] and the severity of ADHD was assessed with the Clinical Global Impressions-Severity of Illness scale.[21] If intelligence had not been assessed in the past 1.5 years, 2 subtests of the Wechsler Intelligence Scale for Children 3rd Edition (WISC-III)[22–24] were administered (ie, vocabulary and block design) to estimate intelligence. Finally, a 20-minute EEG was recorded to assess whether the child's qEEG deviated from the NeuroGuide normative database.[25]

As predetermined, the study started in August 2008 and ended in July 2012. Children were recruited from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands, and from responders to advertisements in the magazine of Balans (the Dutch national association of parents with children with learning or behavioral disorders). The study was approved by the Dutch

Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the Declaration of Helsinki. All parents and all children older than 12 years gave their written informed consent before participation; children younger than 12 years gave oral assent. Travel expenses were partially reimbursed. All children received a gift certificate worth €10 and a small present during evaluation.

Sample size was calculated for the primary outcome on the basis of the following considerations. Double-blind, placebo-controlled trials[26,27] have shown an effect size of 0.6 or more for the first-line treatment of ADHD with medication. Pilot open-label studies[28] with EEG neurofeedback also report an effect size of about 0.6. With an α error of .05, we calculated that a sample of 60 children in the EEG neurofeedback arm and 60 in the placebo neurofeedback arm would enable us to detect treatment effects with an effect size of 0.5 and a power of 80.0%.

Interventions

The Neurofeedback Instituut Nederland provided the EEG neurofeedback and placebo neurofeedback training at Karakter Child and Adolescent Psychiatry University Centre. Individualized EEG neurofeedback protocols based on visual inspection of the raw EEG and qEEG were used for EEG neurofeedback training.

To determine whether EEG data deviated from the NeuroGuide database, a minimum of 10 minutes of deartifacted raw EEG per condition (ie, eyes open and eyes closed) was acquired. The aim of the EEG neurofeedback training was to normalize power within individually determined frequency bands and electrode sites by receiving feedback on their real-time EEG signal. During the 45-minute sessions, after preparation, the children watched a film for 20 minutes while sitting quietly on a chair in an "active focusing state" with eyes open. They were instructed to try to self-regulate their brain activity by receiving positive feedback. Positive feedback was provided by brightening the computer screen and by presenting auditory tones. Most children in the EEG neurofeedback group were trained to increase the presence of sensorimotor rhythm or low-β activity while simultaneously suppressing the presence of θ activity, meaning that, when the production of sensorimotor rhythm remained above threshold and/or the θ/β ratio remained below threshold, positive feedback was given. Reward threshold levels were manually adjusted so that the child was rewarded about 80% of the time (ie, received positive feedback). Consequently, the amount of reward remained at about the same level across sessions and across groups. An identical procedure was provided in the placebo neurofeedback group, except that children in the placebo neurofeedback group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG. BrainMaster Atlantis hardware and software were used to provide both training modalities (BrainMaster Technologies; Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar, in experiences in an earlier study[29] and in our pilot study,[12] such that participants did not know whether they had received real or placebo neurofeedback.

At each session, the child was given a sticker, and 30 stickers were rewarded, with a small present given at the last appointment.

Recruitment and assessments were performed at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands.

Outcomes

Efficacy measures. The primary end point was efficacy, measured as the difference before and after training of the total severity of inattentive and hyperactive/impulsive symptoms of ADHD according to the ADHD-RS-IV, scored by the investigator in an interview with the parents at baseline; after 6, 10, and 20 sessions; and at study end, using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). Additional analyses were performed for teacher-reported symptoms as assessed with the ADHD-RS-IV at baseline, after 10 and 20 sessions, and at study end. The Clinical Global Impressions-Improvement scale (CGI-I),[21] a widely used scale to evaluate clinical effects in intervention studies, was administered in a final interview by the investigator and was used as an additional outcome measure. The CGI-I consists of a single-item 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Responders were defined as children who were rated as very much improved or much improved. Another outcome measurement was the global improvement in functioning, which was assessed as the difference between baseline and end-of-study scores on the CGAS (scale of 0–100: 0 = most affected global functioning and 100 = best global functioning).

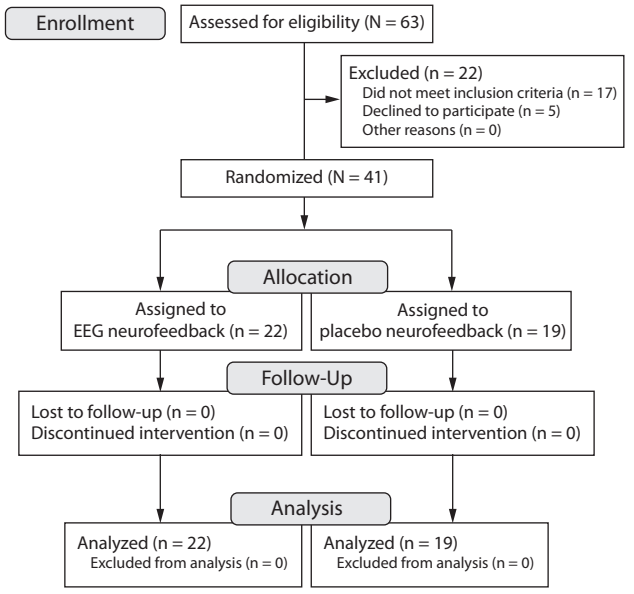
Safety measures. Potential adverse effects of the intervention were measured with the Pittsburgh Side Effects Rating Scale (PSERS), a scale often used in drug treatment studies,[30,31] using the total score for all items (4-point scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe) at baseline; after 6, 10, and 20 sessions; and at study end. For this study, 3 items were added to the original scale, ie, epileptic seizures, nausea, and feeling agitated. Side effects related to sleep quality were assessed by summing the scores of 14 insomnia items on the Dutch version of the Sleep Disorders Questionnaire (SDQ)[32] (5-point scale: 0 = never, 1 = rarely, 2 = sometimes, 3 = usually, 4 = always) at baseline and at study end.

Feasibility outcome. Parents and children were asked about their experience with the training and whether they thought the child had received EEG neurofeedback or placebo neurofeedback training.

Statistical Methods

Statistical analyses were performed with SPSS statistical software, version 20.0 (SPSS Inc; Chicago, Illinois). For each parameter, mean and SD were computed. The significance level was set at $P = .05$ (2-tailed). Repeated-measures analyses

Figure 1. CONSORT Flow Diagram of Study Participants



Abbreviations: CONSORT = Consolidated Standards of Reporting Trials, EEG = electroencephalographic.

of variance, with time as the within-subjects factor and group (EEG neurofeedback vs placebo neurofeedback) as the between-subjects factor, were performed separately for the sum of inattentive symptoms, the sum of hyperactive/impulsive symptoms, the sum of all symptoms on the ADHD-RS-IV, the total sum of adverse events as measured with the PSERS, the total sum of sleep problems as rated by the SDQ, and the CGAS. For the analysis of the ADHD-RS-IV scores, as rated by the investigator, the within-subjects factor *time* had 5 levels (ie, baseline; after 6, 10, and 20 sessions; and at study end). For the analyses of the teacher-rated ADHD-RS-IV, the PSERS, the SDQ, and the CGAS, the within-subjects factor *time* had 2 levels (ie, baseline and study end). Differences between the groups on the CGI-I at study end were tested by a *t* test. Post hoc analysis of covariance was performed with the covariates gender, age, medication, and electrophysiologic state of arousal.

In preliminary analyses, the efficacy and safety of the EEG neurofeedback treatment for the first 8 patients (automatic thresholding, no implementation of active learning strategies) and for another 14 patients (manual thresholding and implementation of active learning strategies) were assessed. As there were no differences in efficacy and safety between these 2 groups, the data for the 2 series of EEG neurofeedback were summed, and results for the whole sample are reported.

RESULTS

Demographic and Clinical Characteristics

In total, 63 children and their parents were eligible for the study and were examined clinically (Figure 1). Twenty-two subjects were excluded. One child withdrew during selection. Four children were included but not enrolled; just before training started, the parents and/or the child decided to withdraw because of difficulty fitting the sessions into their daily schedule. Seventeen children either did not meet the inclusion criteria or did meet the exclusion criteria and were excluded for the following reasons: no room for improvement (n = 6), no deviant EEG (n = 3), epileptic activity on the EEG (n = 1), comorbid Gilles de la Tourette syndrome (n = 1), no ADHD (but rather dysthymic disorder) (n = 1), too great a burden to participate (n = 1), no stable use of ADHD medication (n = 1), and a combination of criteria (n = 3) (above the cutoff score on the ASQ, unstable use of medication, and too great a burden to participate [n = 2]; above the cutoff score on the ASQ and no room for improvement [n = 1]).

Thus, 41 children participated in the study. The mean (SD) age of the sample was 10.62 (2.25) years, and there were 34 boys; 22 children were allocated to the EEG neurofeedback group (8 in the pilot study and 14 post–pilot study), and 19 were allocated to the placebo neurofeedback group. As expected as a result of randomization, no significant differences were found between the 2 groups on baseline characteristics (Table 1). All 41 children completed the training. Two children unintentionally changed the dosage of their medication during the treatment phase (one increased the dosage of the psychostimulant, and the other incidentally introduced drug-free weekends and holidays).

Efficacy Outcome

Table 2 presents detailed statistical results for all study measures by treatment group.

ADHD-RS-IV as rated by the investigator. ADHD symptoms decreased over time ($F_{1,39} = 26.56$, $P < .001$) to a similar extent in both groups, and there was no group × time interaction effect ($F_{1,39} = 0.36$, $P = .554$) (Figure 2). Similar results were observed when the inattentive and hyperactivity/impulsivity scores were analyzed separately.

ADHD-RS-IV as rated by the teacher. As 9 teacher questionnaires were missing for the end-of-study assessment, last-observation-carried-forward data were used, except for 2 end-of-study measurements for which a baseline measurement was the only data present. Teacher-rated ADHD symptoms decreased significantly over time ($F_{1,37} = 13.54$, $P = .001$), without a difference between groups ($F_{1,37} = 0.45$, $P = .509$). Similar results were obtained for the inattentive and hyperactivity/impulsivity scores.

CGI-I. On the CGI-I, 4 of 22 children (18%) in the EEG neurofeedback group were rated as "much improved," 9 of 22 (41%) in the EEG neurofeedback group and 8 of 19 (42%) in the placebo neurofeedback group were rated as "minimally improved," and 9 of 22 (41%) in the EEG neurofeedback group and 11 of 19 (58%) in the placebo neurofeedback group were rated as unchanged at the end of the study. The differences between the groups were not significant ($P = .092$). None of the children deteriorated.

CGAS. One end-of-study value for the CGAS was missing in the EEG neurofeedback group. The CGAS score

Table 1. Descriptive Baseline Demographic and Clinical Characteristics by Treatment Group (N = 41)

Characteristic	EEG Neurofeedback (n = 22)	Placebo Neurofeedback (n = 19)	*P* Value for *t* or χ^2 Statistic
Age, mean (SD), y	10.5 (2.2)	10.7 (2.3)	.734
Gender, n (%)			1.000
Male	19 (86.4)	15 (78.9)	
Female	3 (13.6)	4 (21.1)	
Race, n (%)			1.000
White	20 (91)	18 (95)	
Black	2 (9)	1 (5)	
Full-scale IQ, mean (SD)	108.8 (19.4)	102.1 (12.2)	.205
Medication for ADHD, n (%)			.726
Psychostimulants	11 (50.0)	14 (73.7)	
Atomoxetine	1 (4.5)	0 (0.0)	
No medication	10 (45.5)	5 (26.3)	
EEG arousal, n (%)			.513
Underaroused	19 (86.4)	14 (73.7)	
Overaroused	3 (13.6)	5 (26.3)	
ADHD subtype, n (%)			.543
Combined	17 (77.3)	13 (68.4)	
Inattentive	4 (18.2)	5 (26.3)	
Hyperactive/impulsive	1 (4.5)	1 (5.3)	
Comorbidity, n (%)			
Oppositional defiant disorder	5 (22.7)	1 (5.3)	.191
Anxiety disorders	3 (13.6)	2 (10.5)	1.000
Dyslexia	2 (9.1)	3 (15.8)	.649
ADHD-RS-IV investigator-rated score, mean (SD)			
Total symptoms	30.6 (7.5)	32.0 (9.6)	.601
Inattention symptoms	17.0 (5.1)	18.2 (3.4)	.369
Hyperactivity/impulsivity symptoms	13.6 (5.5)	13.8 (7.9)	.942
ADHD-RS-IV teacher-rated score, mean (SD)			
Total symptoms	23.6 (14.8)	25.7 (12.8)	.639
Inattention symptoms	13.1 (7.5)	13.9 (6.2)	.712
Hyperactivity/impulsivity symptoms	10.6 (8.4)	11.8 (8.2)	.632
CGI-S score, n (%)			.405
3 (mildly ill)	3 (13.6)	0 (0.0)	
4 (moderately ill)	12 (54.5)	11 (57.9)	
5 (markedly ill)	7 (31.8)	8 (42.1)	
CGAS score, mean (SD)	51.3 (6.6)	51.6 (5.6)	.703

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV = ADHD Rating Scale IV, CGAS = Children's Global Assessment Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, EEG = electroencephalographic, IQ = intelligence quotient, SD = standard deviation.

increased significantly over time ($F_{1,38} = 15.47$, $P < .001$) but increased similarly in the 2 groups ($F_{1,38} = 1.96$, $P = .169$).

Safety Outcomes

Adapted SDQ. Two end-of-study scores for the SDQ were missing in the placebo neurofeedback group. Total sleep problems decreased significantly over time ($F_{1,37} = 5.42$, $P = .025$) but decreased similarly in the 2 groups ($F_{1,37} = 0.05$, $P = .818$).

Adapted PSERS. Two values for the PSERS were missing in the EEG neurofeedback group; the last-observation-carried-forward method was used for the missing data. The total number of adverse events decreased significantly over time ($F_{1,39} = 6.30$, $P = .016$) and decreased similarly in the 2 groups ($F_{1,39} = 0.10$, $P = .754$).

Post hoc analyses. Post hoc analyses with the covariates age, gender, medication use, and state of electrophysiologic arousal revealed no significant treatment effect (ie, group × time interaction) for any outcome. After correction for time, almost all significant results became nonsignificant except for the effect of time on the CGAS, which changed to a marginally significant level ($F_{1,34} = 3.48$, $P = .071$).

Feasibility Examination

Among the children, 10 of 41 (24%) correctly guessed which treatment they had received, 13 of 41 (32%) guessed incorrectly, and 10 of 41 (24%) did not know; data were missing for 8 of 41 children (20%). Among the parents, 14 of 41 (34%) guessed the treatment assignment correctly, 19 of 41 (46%) guessed incorrectly, and 6 of 41 (15%) did not know; data were missing for 2 of 41 parents (5%). Fisher exact tests showed that the children and their parents did not guess treatment assignment significantly better than chance level ($P = .224$ for children, $P = .643$ for parents).

DISCUSSION

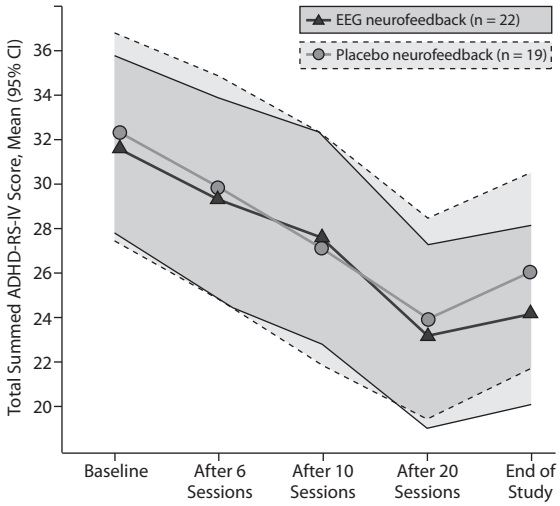
This study examined the safety and efficacy of EEG neurofeedback treatment for core symptoms in children with ADHD using a randomized, double-blind, placebo-controlled design with blinded participants and raters. Treatment

Table 2. Results for All Study Outcomes by Treatment Group (N = 41)

Measure	EEG Neurofeedback (n = 22)		Placebo Neurofeedback (n = 19)		Statistical Analysis					
					Time Effect			Group × Time Effect		
	Baseline, Mean (SD)	End of Study, Mean (SD)	Baseline, Mean (SD)	End of Study, Mean (SD)	*F*	*df*	*P* Value	*F*	*df*	*P* Value
ADHD-RS-IV investigator-rated score										
Total symptoms	30.6 (7.5)	23.4 (9.5)	32.0 (9.6)	26.3 (7.2)	26.56	1,39	< .001	0.36	1,39	.554
Inattention symptoms	17.0 (5.1)	13.2 (6.0)	18.2 (3.4)	13.8 (3.1)	27.17	1,39	< .001	0.17	1,39	.682
Hyperactivity/impulsivity symptoms	13.6 (5.5)	10.2 (5.3)	13.8 (7.9)	12.5 (6.3)	10.80	1,39	.002	2.26	1,39	.141
ADHD-RS-IV teacher-rated score										
Total symptoms	23.6 (14.8)	19.3 (11.4)	25.2 (12.5)	18.9 (10.2)	13.54	1,37	.001	0.45	1,37	.509
Inattention symptoms	13.1 (7.5)	11.3 (5.7)	13.4 (5.9)	11.0 (4.8)	7.63	1,37	.009	0.25	1,37	.624
Hyperactivity/impulsivity symptoms	10.6 (8.4)	8.0 (7.0)	11.8 (8.3)	8.0 (6.6)	15.74	1,37	< .001	0.53	1,37	.473
CGI-I score[a]		3.2 (0.8)		3.6 (0.5)						.092
CGAS score[a]	51.3 (6.6)	58.1 (9.1)	51.6 (5.6)	54.8 (4.5)	15.47	1,38	< .001	1.96	1,38	.169
SDQ score	25.3 (8.3)	24.0 (7.0)	26.3 (6.3)	24.9 (9.2)	5.42	1,37	.025	0.05	1,37	.818
PSERS score	5.5 (5.5)	4.1 (4.3)	5.6 (4.9)	3.9 (4.2)	6.30	1,39	.016	0.10	1,39	.754

[a]Reduced scores reflect improvement, except for the CGI-I and the CGAS.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV = ADHD Rating Scale IV, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impressions-Improvement scale, EEG = electroencephalographic, PSERS = Pittsburgh Side Effects Rating Scale, SD = standard deviation, SDQ = Sleep Disorders Questionnaire.

Figure 2. Mean Total Summed Scores and 95% Confidence Intervals for the ADHD Rating Scale IV (ADHD-RS-IV) Over Time As Rated by the Investigator and Shown by Treatment Group



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, EEG = electroencephalographic.

assignment was not guessed better than chance level. EEG neurofeedback was not superior to placebo neurofeedback in affecting ADHD symptoms or other secondary efficacy outcomes. The intervention was safe as no adverse effects were reported. Post hoc analyses with the covariates age, gender, medication, and electrophysiologic state of arousal did not lead to any significant results compared to the main analyses. These findings are in line with those of our previous feasibility pilot study[12] and 2 recently published placebo-controlled EEG neurofeedback studies.[11,13] Moreover, a recent systematic review and meta-analysis[14] of randomized controlled trials of nonpharmacologic interventions in children with ADHD concluded that the significant effect size of unblinded ratings could not have been replicated if blinded ratings were used (meta-analysis[14] of 7 open-label studies and 1 triple-blind EEG neurofeedback study). Thus, it seems that methodologically sound studies do not confirm the efficacy of EEG neurofeedback in children with ADHD.

Changing from automatic to manual thresholds did not result in larger effects for EEG neurofeedback, nor did the addition of active learning strategies. Making passive learning active by adopting learning strategies is hypothesized to be an important aspect of the working mechanism of EEG neurofeedback.[5] Our findings did not support this hypothesis.

Unfortunately, we were unable to recruit a sufficient number of participants to meet our planned sample size. Post hoc, our sample had 80% power to detect a treatment effect of 0.90. However, since there was virtually no difference between the effect of EEG neurofeedback and placebo neurofeedback in the smaller sample, it is unlikely that our negative results were due to limited statistical power.

The study was carefully designed to tackle the methodological shortcomings of previous studies, resulting in a randomized placebo-controlled trial with blinded participants and raters, an extended selection procedure, and several behavior and safety evaluations of both interventions. Conducting such a study has drawbacks. First, the 50% chance of receiving placebo neurofeedback treatment probably adversely influenced recruitment. During our entire clinical trial, patients with ADHD had access to EEG neurofeedback in the general clinical practice without the risk of being assigned to placebo neurofeedback, and treatment costs were fully reimbursed by health insurance companies. Another potential limitation is the change from a triple-blind to a double-blind design (which means that the neurofeedback therapist was no longer blinded); however, participants and raters were still blinded to treatment assignment. The use of medication by most participants may have influenced the ability to detect a significant effect of EEG neurofeedback. At this time, follow-up data are not yet available; we plan

to reassess all participants after 6 months and will describe these findings in a separate report. Last, because most children were white, the generalizability of findings to other races cannot readily be assumed.

In conclusion, our results seriously question the claims that EEG neurofeedback is an effective treatment for children with ADHD. Further research with more participants is needed to determine whether this traditional form of neurofeedback is effective in particular patient subgroups.

Drug names: atomoxetine (Strattera).

Author affiliations: Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands (all authors); and Department of Cognitive Neuroscience (Drs van Dongen-Boomsma and Buitelaar and Ms Vollebregt) and Department of Psychiatry (Dr Slaats-Willemse), Radboud University Nijmegen Medical Centre and Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.

Author contributions: Drs Slaats-Willemse and Buitelaar are joint last authors.

Potential conflicts of interest: In the past 3 years, **Dr Buitelaar** has been a consultant to, a member of the advisory boards of, and/or a member of the speakers bureaus for Janssen-Cilag, Eli Lilly, Bristol-Myers Squibb, Schering-Plough, UCB, Shire, Novartis, and Servier. **Drs van Dongen-Boomsma** and **Slaats-Willemse** and **Ms Vollebregt** have no financial disclosure or potential conflicts of interest to declare.

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