THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry 55:5 (2014), pp 460–472 doi:10.1111/jcpp.12143

Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study

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Background: The number of placebo-controlled randomized studies relating to EEG-neurofeedback and its effect on neurocognition in attention-deficient/hyperactivity disorder (ADHD) is limited. For this reason, a double blind, randomized, placebo-controlled study was designed to assess the effects of EEG-neurofeedback on neurocognitive functioning in children with ADHD, and a systematic review on this topic was performed. **Methods:** Forty-one children (8–15 years) with a DSM-IV-TR diagnosis of ADHD were randomly allocated to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, twice a week. Children were stratified by age, electrophysiological state of arousal, and medication use. Neurocognitive tests of attention, executive functioning, working memory, and time processing were administered before and after treatment. Researchers, teachers, children and their parents, with the exception of the neurofeedback-therapist, were all blind to treatment assignment. Outcome measures were the changes in neurocognitive performance before and after treatment.Clinical trial registration: www.clinicaltrials.gov: NCT00723684. **Results:** No significant treatment effect on any of the neurocognitive variables was found. A systematic review of the current literature also did not find any systematic beneficial effect of EEG-neurofeedback on neurocognitive functioning. **Conclusion:** Overall, the existing literature and this study fail to support any benefit of neurofeedback on neurocognitive functioning in ADHD, possibly due to small sample sizes and other study limitations. **Keywords:** Neurofeedback, attention-deficit/hyperactivity disorder (ADHD), randomized controlled trial (RCT), electroencephalogram (EEG), efficacy, neurocognition, review.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood mental disorders, affecting about 5% of all children worldwide (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007), with an increasing prevalence over the last decade (Getahun et al., 2013). ADHD affects children's personal development substantially and is associated with impairments in social and emotional development, and poor academic and vocational outcomes (Wehmeier, Schacht, & Barkley, 2010). Consequently, the substantial burden on families and society in general is notable (Biederman, 2005; Biederman et al., 2012). Because of the severity and long-term nature of the impairments associated with ADHD, efforts have been made to understand the underlying deficits and identify effective treatments for ADHD.

ADHD & neurocognitive dysfunctions

Neurocognitive models of ADHD have attempted to explain the behavioral symptoms in underlying impairments in executive functions (EFs), attention regulation, reward-related processes, and timing. Associations between ADHD and EFs are found in domains of response inhibition, vigilance, working memory, and planning (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Described ADHD-related attention problems are as weak performances in selective and sustained attention, and attention shifting tasks (Weissman, Chu, Reddy, & Mohlman, 2012). Studies on reward-related processes in ADHD indicate a preference for small immediate rewards over later larger rewards (for review see Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). Finally, timing deficits have consistently been found in subjects with ADHD in three major domains, i.e. motor timing, perceptual timing, and temporal foresight (for review see Noreika, Falter, & Rubia, 2013). Differentiation could be made between timing deficits and delay deficits (Sonuga-Barke,

Conflict of interest statement: See Acknowledgment for disclosures of interest.

Bitsakou, & Thompson, 2010; de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012).

ADHD & EEG-neurofeedback

Concerns about the safety and long-term efficacy of first-line treatment medication in ADHD have led to interest in developing alternative nonpharmacological treatment. EEG-neurofeedback (EEG-NF) is based on the rationale that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies. In other words, by providing continuous real time feedback, i.e. positive reinforcement when changes are made in the desired direction, the self-regulation of ongoing neuronal oscillations in one or more frequency bands can be enhanced (Gevensleben, Rothenberger, Moll, & Heinrich, 2012). Resting state EEG in the majority of children with ADHD is characterized by increased slow-wave activity and decreased fast-wave activity, primarily theta and beta activity, respectively, and higher theta/beta and theta/alpha ratios compared to controls (for review see Barry, Clarke, & Johnstone, 2003), often referred to as an underaroused physiological state. Therefore, most neurofeedback protocols focus on these frequency bands (Monastra, 2005). A minority of children with ADHD has shown increased power of beta activity (Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002), creating a subgroup with an overaroused physiological state.

The placebo-controlled randomized trials published to date, have not found superior effects of EEG-NF compared to placebo-neurofeedback (PL-NF) (Arnold et al., 2012; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013; Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats- Willemse, 2011; Perreau-Linck, Lessard, Lévesque, & Beauregard, 2010). In addition, a systematic review and meta-analysis of randomized controlled trials (RCTs) of nonpharmacological interventions in children with ADHD including EEG-NF studies, reported nonsignificant results for the blind rating of symptoms ($p = .07$) (Sonuga-Barke et al., 2013).

Most studies have focused on behavioral outcome measures. However, it is worthwhile to examine whether EEG-NF is able to improve neurocognitive functioning in ADHD because the persistence of neurocognitive deficits is strongly associated with occupational problems and morbidity (Barkley & Murphy, 2010; Biederman et al., 2012).

The objectives of this article were twofold: (a) to systematically review the existing literature on the effects of two modalities of EEG-NF, namely frequency-NF (F-NF) and Slow Cortical Potential (SCP)-NF on neurocognitive functioning and (b) assess the effect of F-NF on neurocognitive functioning in a double-blind placebo-controlled trial in children with ADHD.

Review on neurocognitive outcome measures after EEG-NF in children with ADHD

A literature research was carried out in PubMed for the period between January 1994 and May 2012 by combining the following MeSH terms; ("Attention-Deficit Disorder with Hyperactivity"[MeSH]) AND ("Biofeedback, Psychology"[MeSH] OR "Neurofeedback"[MeSH]). A final search was conducted to check for the most recent published trials (February 2013). The database search outlined above was also supplemented by manual searches. The inclusion criteria that were applied to the publications retrieved were (a) study was peer reviewed, (b) diagnosis of ADHD classified by the DSM-III-R (American Psychiatric Association, 1987), DSM-IV (APA, 2000), or the ICD-10 (World Health Organisation, 1992), (c) age 0–18 years, (d) RCT, (e) F-NF and/or SCP-NF was used as treatment modality, (f) neurocognitive data reported in the publication. In total, 10 randomized controlled trials met the inclusion criteria (Arnold et al., 2012; Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Holtmann et al., 2009; Leins et al., 2007; Lévesque, Beauregard, & Mensour, 2006; Linden, Habib, & Radojevic, 1996; Perreau-Linck et al., 2010; Steiner, Sheldrick, Gotthelf, & Perrin, 2011; Wangler et al., 2011). (See online supplementary Figure S1- CONSORT flow diagram)

The 10 selected EEG-NF studies were quite heterogeneous in their design and methodology. The studies included a range of different sample sizes and control conditions (e.g. passive control conditions vs. active control conditions). Investigators were blind to treatment assignment in some studies while in others they were not. The NF-protocol as well as the duration, frequency, and number of sessions varied between studies. Significant differences between the studies were also noted in terms of the participants' characteristics (especially the use of medication), the statistical methods used, and the choice of neurocognitive tasks. The differences in neurocognitive tasks employed also render a meta-analysis impossible. However, areas in which the studies overlapped included the use of predominantly male participants in the same age range (mean round 10 years) as well as a common inclusion criterion that subjects must have a full-scale intelligence quotient (FSIQ) of more than 80 points.

Three of the ten studies reported significant improvement on at least one neurocognitive variable for the NF condition superior to the control condition (Bakhshayesh et al., 2011; Heinrich et al., 2004; Holtmann et al., 2009). More specifically, treatment (i.e. time x group interaction) effects were seen for the variable representing impulsivity on the Stop-signal task (Holtmann et al., 2009) and for all variables representing attention on the Paper-and-Pencil Attention Task (Bakhshayesh et al., 2011). However,

in the Paper-and-Pencil Attention task, the number of errors also increased significantly more in the NF group than in the control group, suggesting that improved speed came at the expense of accuracy. Note that speed-accuracy trade-off calculation was not reported. One study appeared to show a time x group effect on the composite variable of the Kaufman-BRIEF Intelligence Test (K-BIT), a German Intelligence scale. However, this was not explicitly reported (Linden et al., 1996). The study investigating the efficacy of SCP-NF showed a time x group effect for the variable representing impulsivity on a Continuous Performance Task (Heinrich et al., 2004)

Overall, these studies had many methodological limitations (including small sample sizes, increasing the chance for type II errors), and the majority failed to show positive neurocognitive effects of F-NF or SCP-NF. Taken together, these studies suggest that there is no systematic beneficial effect of these two types of NF on neurocognitive functioning.

Methods

Trial design

This study was designed as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs. older than 12 years), electrophysiological state of arousal (hyperarousal vs. hypoarousal), and use of medication (with vs. without medication). After a pilot study (Lansbergen et al., 2011), two adaptations were made: (a) In the F-NF condition, reward thresholds were changed into manual adjustment, resulting in the unblinding of the neurofeedback-therapist (NF-therapist). Participants and raters remained blind, creating a double-blind study. (b) Active learning strategies were implemented, so that children could apply the learned strategies into daily life.

Participants

Children (8–15 years) were included if (a) they had been clinically diagnosed with ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), (b) they had an full-scale IQ (FSIQ) of at least 80, (c) their quantitative electroencephalogram (qEEG) deviated at least 1.5 standard deviations (*SD*) from normative data, (d) they did not use psychopharmaca or used a stable dose of ADHD medication, and (e) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale (0–3) for at least 6 items of the ADHD DSM-IV rating scale (American Psychiatric Association, 2000). Children were excluded if they (a) were involved in psychotherapy, (b) used medication other than ADHD medication, (c) had a comorbid disorder other than oppositional defiant disorder or any anxiety disorder, (d) had a neurological disorder and/or a cardiovascular disease, (e) participated in another clinical trial simultaneously, (f) had received NF in the past, or (g) used alcohol or drugs.

A doctor or psychologist screened potential children via a telephone interview with their parents in which ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999) was used to screen for autism spectrum disorders. The presence of other comorbid disorders was assessed with the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab- Stone, 2000; Steenhuis, Serra, Minderaa, & Hartman, 2009). A positive screening-outcome was followed by diagnostic procedure, including the ADHD and a developmental and psychiatric interview with a child and adolescent psychiatrist. General functioning was measured by the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983), and the severity of ADHD was assessed with the Clinical Global Impression-Severity Scale (CGI-S; Bangs et al., 2008). If an intelligence test had not taken place over the past 1.5 years, two subtests of the Wechsler Intelligence Scale for Children (WISC-III) were administered (i.e. Vocabulary and Block Design) to estimate intelligence (Wechsler, 1991). Finally, 20 min of de-artifacted raw EEG in an eyes-open and eyes-closed condition was acquired to determine deviation from the NeuroGuide database (Thatcher, Walker, Biver, North, & Curtin, 2003).

Recruitment started in August 2008 and ended in May 2012. Children were recruited from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, and from responders to advertisements in the journal of the Dutch Parents Association for Children with Developmental 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 children older than 12 years gave their written informed consent before participation; children younger than 12 year gave oral assent. Travel costs were partially reimbursed. All children received a 10-euro gift certificate and a small present after collecting 30 stickers, given after each session.

The study was registered in the Clinical trial register under 'Project ADHD and EEG-Neurofeedback THERapy'; www.clinicaltrials.gov; NCT00723684.

Interventions

The Neurofeedback Instituut Nederland B.V. (NIN) provided both the F-NF and the PL-NF training. Individualized F-NF protocols based on visual inspection of the raw EEG and qEEG were used for F-NF training.

The F-NF training was intended to normalize power within individually determined frequency bands and electrode sites by receiving feedback on their real-time EEG-signal. In this study, personalized protocols were used to address different EEG abnormalities, i.e. hypoarousal versus hyperarousal, in children with ADHD, consisting of a protocol focusing on the EEG abnormality in that child.

Children watched a film for 20 min in an 'active focusing state' with eyes open. They were instructed to attempt to self-regulate their brain activity. Positive feedback was provided by brightening the computer screen and presentation of auditory tones. Most children in the F-NF group were trained to increase the presence of the sensory motor rhythm (SMR) or low-beta activity while simultaneously suppressing the presence of theta activity, meaning that when the production of SMR remained above threshold, and/or the theta/beta remained below threshold positive feedback was given. Reward threshold levels were manually adjusted to 80% for each training target (i.e. frequency-band and/or location). Therefore, the actual percentage reinforcement depended on the amount of co-occurrence of desirable activity towards training targets (e.g. theta power going downwards at P3 while simultaneously going downwards at P4). Reinforcement was 80% when all training targets were achieved simultaneously only. When assuming no correlation in activity between the different training targets, the reinforcement was 0.8 to the power of the number of training targets (e.g. training theta power downwards and beta power upwards resulted in a rewarding percentage of 64%). In practice, the reinforcement lay between 0.8 and 0.8 to the power of the number of training targets. Thresholds were manually adjusted according to the expertise of the NF-therapist. No specific guideline or protocol was followed. This method was in line with the objective of this study to investigate the efficacy of F-NF as delivered in 'care as usual', in which decisions about adjustments of the threshold are determined by the involved clinical NF-therapist. All of the NF-therapists were BCIA certified (Biofeedback Certification International Alliance, 10200 W 44th Ave, Suite 310, Wheat Ridge CO 80033-2840). An identical procedure was provided in the PL-NF group, except that children in the PL-NF group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG, in accordance with the procedure of an earlier study (Logemann, Lansbergen, van Os, Böcker, & Kenemans, 2010). BrainMaster Atlantis hardware and software provided both training modalities (Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar in experience in an earlier study and in our pilot study (Lansbergen et al., 2011; Logemann et al., 2010). The behavioral effects of this study will be published elsewhere (van Dongen-Boomsma et al., 2013).

Neurocognitive outcomes

All children included in the study underwent a neurocognitive assessment of 1.5 hr before and after treatment. Two versions of the neurocognitive battery controlled for a possible task-order effect. If available, different versions of the tasks were administered before and after the treatment to control for a potential learning effect. Complete task descriptions can be found in the online supporting information 'neurocognitive task descriptions'. Below, the neurocognitive tasks are briefly described.

Sustained attention dots task (SA-DOTS). The Continuous Performance Task from the computerized neurocognitive test battery of the Amsterdamse Neuropsychologische Taken (ANT; de Sonneville, Schmidt, Michel, & Batzler, 1990; de Sonneville, 1999) was used to measure sustained attention. Variables of interest were the number of correct responses, the mean reaction time (RT) in ms on correct responses and its standard deviation, and the number of premature responses (RT < 150 ms). Note there was a trade-off to be made between RT and accuracy. Therefore, the expected (negative) relationship between RT and number of correct trials was addressed by performing similar analyses while controlling for each other.

Visuospatial sequencing (VSS). To measure visuospatial memory, the visuospatial sequencing subtest (VSS) from the ANT (de Sonneville, 1999) was used. The number of correct trials and the number of targets identified in the correct order were determined and used for analyses.

Digit span WISC-III. To measure verbal working memory, the digit span (forward and backward) from the WISC III (Wechsler, 1991; Dutch version: de Kort et al., 2002) was used. The total number of correctly recalled forward digit sequences and backward digit sequences compared to an age-norm was the variable of interest.

The rey auditory-Verbal Learning Test (RAV-LT). Verbal working memory and long-term verbal memory was assessed using the Dutch adaptation of The Rey Auditory-Verbal Learning Test. In the Dutch version Rey's procedure (Rey, 1964) is applied without an interference trial (van den Burg & Kingma, 1999). In this form, the AVLT was administered in the present study. The total number of immediately recalled words over all five presentations and the amount of words recalled 20 min after the last presentation were chosen as the variables of interest.

Instrumental learning task. Instrumental learning tasks are widely used instruments that have their origin in the instrumental/operant learning principle (Thorndike, 1898). A version of this task appropriate

for children was created, derived from two example instrumental learning paradigms (O'Doherty et al., 2004; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). The variables of interest were the total number of choices of high versus low probability actions in reward trials and the trial at which the learning criterion was reached. The learning criterion was defined as eight consecutive high probability actions.

Time production task. To measure precision of time perception, a time reproduction task was constructed based on the task description of van Meel, Oosterlaan, Heslenfeld, and Sergeant (2005). The mean absolute discrepancy and its standard deviation between stimulus length and response length were measured.

Time reproduction task. To measure precision of time reproduction, a task was constructed based on the task description of Rommelse, Oosterlaan, Buitelaar, Faraone, and Sergeant (2007). The mean absolute discrepancy and its standard deviation between stimulus length and response length were measured.

Sample size

Sample size was calculated for the primary outcome and was based on the following considerations. Double blind, placebo-controlled trials have shown an effect size of 0.6 or more for the first-line treatment of ADHD with medication (Faraone & Buitelaar, 2010; Michelson et al., 2002). Pilot open-label studies with EEG-neurofeedback also report an effect size around 0.6 (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). With an alpha error of .05, a sample of 60 children in the EEG- neurofeedback arm and 60 in the placebo-neurofeedback group and a power of 80.0% would enable treatment effects to be detected with an effect size of 0.5.

Randomization

Participating children were stratified and subsequently randomly assigned (1:1 assignment using random block sizes of 2), double blind, to either F-NF or PL-NF. The principal investigator who was not involved in data collection performed this. Randomization by means of minimization was applied, including EEG profile, age, and medication use as factors (Han, Enas, & McEntegart, 2009). The treatment group that would most strongly minimize the imbalance was chosen to allocate the participant.

Blinding

All people involved in the study were blind to treatment assignment, except the NF-therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis.

Statistical methods

The first step was to analyze all neurocognitive variables at group level. Variables of the Instrumental Learning Task, Time Reproduction Task, and Time Production Task were created using MATLAB R2009a (The Math-Works, Inc., Natrick, MA). All statistical analyses were conducted employing the SPSS statistical program (SPSS 20.0). The significance level was set at $p = .05$. Imputation of missing data was used to obtain the most accurate data set (Donders, van der Heijden, Stijnen, & Moons, 2006).

To optimize control for the variance at baseline, baseline was used as a covariate in Analyses of the Covariance (ANCOVA). For each neurocognitive parameter the endpoint measurement was the dependent variable, the baseline measurement a covariate, and group (F-NF vs. PL-NF) the fixed factor.

To reduce within-group error variance and to eliminate confounding additional (ANCOVAs) were performed (Field, 2009, page 396–397). For all main analyses, we also conducted (ANCOVA's) with age, gender, FSIQ, medication use, and electrophysiological arousal as covariates to control for their possible influence.

To confirm the reliable use of ANCOVA, all required assumptions were tested per variable, except the assumption for independence of the sample, which was not expected to be present in this experimental design and the independence of the covariate and treatment effect, which was covered, by randomization and stratification. B-weights, the unstandardized regression coefficients, represent the relationship between the groups and the outcome variable included in the analysis. In this study, a positive value indicates an effect for the F-NF group, a negative value an effect for the PL-NF group. The significance on the ANCOVA's tells whether this relationship is significant.

The next step was to examine whether participants might show significant and reliable individual changes on neurocognitive variables that might be overlooked at group level. The Reliable Change Index (RCI) was to address this issue. The RCI-method, described by Jacobson and Truax (1991) was subsequently applied to a placebo-controlled medication study in children with ADHD (Buitelaar, van der Gaag, Swaab-Barneveld, & Kuiper, 1995). This method was also used by another NF study (Perreau-Linck et al., 2010). The RCI was calculated for individual, *i*, using the following formula:

$$\mathrm{RCI} = \frac{D_i - P_i}{SE}$$

In which D_i is the observed change between pre- and postmeasurement, P_i the mean change score of the placebo group, and *SE* the corresponding standard error. If a child exceeded the critical value of (−)

1.96 (equaling our significance value set at $p = .05$) it was said to reliably change on this measure.

Results

The demographic and clinical characteristics are summarized in Table 1. In sum, 41 children (mean age 10.6 ± 2.3, 83.0% boys, and estimated FSIQ of 105.7 ± 16.7) were included. Of these, 22 children were assigned to the F-NF group (8 of the pilot study, 14 postpilot study) and 19 children to the PL-NF group (no differences made after pilot). Analyses with respect to the neurocognitive results performed on the sample without the pilot NF sample ($N = 33$) and the total sample ($N = 41$), did not yield different results, and therefore data of the total sample will be presented. Furthermore, we tested for blinding of the participants. This test revealed that guessing treatment assignment was not better than at chance level ($p = .224$ for children, $p = .643$ for parents). (For a complete overview of the clinical examination procedure and the administered NF, see online supplementary Data S1- Neurocognitive tasks, and Figure S1.)

Neurocognitive characteristics

All variables were distributed normally within groups, unless specifically stated and dealt with accordingly, (e.g. by removing outliers, defined as 25% of the size of the largest leaf entry in the clustering feature tree, based on the default definition used by SPSS 20.0). All assumptions confirmed permission for using ANCOVA as statistical test method. However, for some variables removing outliers was needed to meet these assumptions. A maximum of 4.9% was removed in favor of creating a normal distribution. Imputation of missing data was used for the SA-DOTS, the VSS, the Instrumental Learning Task, and the Time Reproduction Task with an average of 4.9% and a maximal imputation of 14.6%. Table 2 among others, gives an overview of baseline values and shows that there was no difference between groups at baseline.

Neurocognitive outcomes

All main outcomes are depicted in Table 2 and Figure 1.

Sustained attention dots task (SA-DOTS). Two outliers were detected in the F-NF group and three in the PL-NF group. No treatment effect was found on any of the variables (correct: $t(33) = -0.090$, $p = .928$; RT: $t(33) = 0.868$, $p = .385$; *SD* of RT: $t(33) = 0.109$, $p = .913$). When additionally controlling for the number of correct trials, RT still did not reveal a treatment effect ($t(32) = 0.864$, $p = .387$). Likewise, the number of correct trials did not reveal a treatment effect after additionally controlling for RT ($t(32) = -0.075$, $p = .940$). Making more than 8 premature responses was defined as an outlier. After treatment no difference in premature responses between groups was found (Fisher's Exact Test: $p = 1.000$).

Visuospatial sequencing (VSS). Two outliers were detected in the F-NF group and excluded from the dataset. The number of correct trials after controlling for baseline score did not show a treatment effect ($t(36) = -0.672$, $p = .502$), neither did the number of

Table 1 Demographic characteristics

Descriptive characteristics	Frequency neurofeedback ($N = 22$)	Placebo-neurofeedback ($N = 19$)	Analysis *T*, χ^2 *p*-value
Age (*M* and *SD*)	10.5 (2.2)	10.7 (2.3)	$p = .734$
Gender (%)			
Male	86.4	78.9	$p = 1.000$
Female	13.6	21.1	
Race (%)			
Caucasian	91	95	$p = 1.000$
Black	9	5	
Full-scale IQ (*M* and *SD*)	108.8 (19.4)	102.1 (12.2)	$p = .205$
Medication for ADHD (%)			
Psychostimulants	50	73.7	$p = .726$
Atomoxetine	4.5	0	
No medication	45.5	26.3	
EEG arousal (%)			
Hypoaroused	86.4	73.7	$p = .513$
Hyperaroused	13.6	26.3	
ADHD subtype (%)			
Combined	77.3	68.4	$p = .543$
Inattentive	18.2	26.3	
Hyperactive/impulsive	4.5	5.3	
Comorbidity (%)			
Oppositional defiant disorder (ODD)	22.7	5.3	$p = .191$
Anxiety disorders	13.6	10.5	$p = 1.000$
Dyslexia	9	15.8	$p = .649$

M, mean; *SD*, standard deviation (in parentheses); EEG, electro-encephalogram; *T*, independent sample *t*-test; χ^2, chi-square test.

Table 2 Baseline and endpoint scores on all neurocognitive parameters. Also depicted is the change scores between baseline and endpoint and the mean individual interaction effect size

	Baseline		Endpoint		Change score		
Neurocognitive parameter (*M* and *SD*)	F-NF ($N \leq 22$)	PL-NF ($N \leq 19$)	F-NF ($N \leq 22$)	PL-NF ($N \leq 19$)	F-NF ($N \leq 22$)	PL-NF ($N \leq 19$)	Effect size[a] (Cohen's *d*)
Sustained attention dots							
Correct trials	551.9 (31.5)	556.6 (29.6)	549.2 (29.7)	555.5 (32.2)	−0.9 (14.9) ↓	−0.8 (25.1) ↓	−0.01
Response time correct trials	3417.2 (873.6)	3434.9 (824.5)	3146.7 (1058.1)	2981.5 (653.5)	−354.5 (571.9)	−511.7 (342.4)	0.34
SD response time correct trials	1533.8 (736.8)	1649.6 (674.5)	1464.9 (891.8)	1504.3 (777.2)	−155.5 (551.9)	−212.5 (336.8)	0.13
Visuospatial Sequencing							
Correct trials	19.6 (2.5)	18.3 (2.9)	19.1 (3.8)	19.4 (3.3)	0.0 (3.7)	1.1 (3.0)	−0.34
Identified in correct order	90.9 (9.7)	86.7 (10.8)	87.6 (16.0)	90.3 (12.0)	−1.5 (15.3) ↓	3.8 (11.2)	−0.42
Digit span WISC-III							
z-Score forward and backward	10.6 (3.2)	10.0 (2.7)	11.5 (3.4)	11.5 (2.4)	0.9 (2.8)	1.5 (2.2)	−0.24
RAVLT							
Direct recall	46.6 (8.4)	44.2 (6.7)	45.5 (9.0)	45.1 (7.0)	−1.1 (7.5) ↓	0.9 (6.0)	−0.30
Delayed recall	9.7 (2.6)	9.6 (2.5)	9.7 (2.5)	9.8 (2.5)	0.0 (2.5)	0.2 (2.2)	0.15
Instrumental learning task							
High probability action	44.8 (3.9)	44.9 (4.1)	42.5 (7.3)	40.2 (7.2)	−2.3 (8.2) ↓	4.8 (7.9)	−0.90
Reach learning criterion	17.3 (2.7)	16.8 (2.0)	17.9 (4.6)	18.0 (4.5)	0.6 (5.8) ↓	1.2 (4.4) ↓	−0.12
Time production task							
MAD from 1 sec (in ms)	205.5 (80.4)	224.9 (74.0)	228.2 (113.7)	230.4 (83.8)	22.7 (83.8) ↓	5.5 (65.0) ↓	0.23
SD from MAD (in ms)	182.5 (76.2)	208.2 (84.4)	338.1 (473.0)	209.7 (102.8)	155.5 (429.5) ↓	1.5 (97.2) ↓	0.50
Time reproduction task							
MAD from trial (in ms)	2043.2 (1254.0)	2694.4 (1740.2)	2672.4 (1604.7)	2388.5 (1556.2)	473.9 (949.3) ↓	310.3 (1258.5) ↓	0.15*
SD from MAD (in ms)	2178.1 (1584.8)	2947.5 (1644.2)	3089.6 (1597.1)	2317.6 (1281.6)	734.1 (1453.1) ↓	619.6 (1412.3) ↓	0.08**

M, mean; *SD*, standard definition (in parentheses); *N*, number of subjects. Note that data were used without using imputed data or outliers. F-NF, frequency-neurofeedback; PL-NF, placebo-neurofeedback; ↓, direction of the change score in opposite direction than direction hypothesized to be improvement. *d*, the difference between groups (PL-NF subtracted from F-NF) for the change scores between endpoint and baseline divided by the pooled standard deviation of the change scores taking into account the sample size; WISC, Wechsler Intelligence Scale; RAVLT, Rey Auditory-Verbal Learning Test; MAD, mean absolute deviation; *SD*, standard deviation.
Independent sample *t*-tests between groups for which $p > 0.20$.
[a]Remaining TIMExGROUP interactions of repeated measures ANOVAs for which $p > 0.10$ unless marked otherwise.
*$p < 0.05$; **$p < 0.01$.

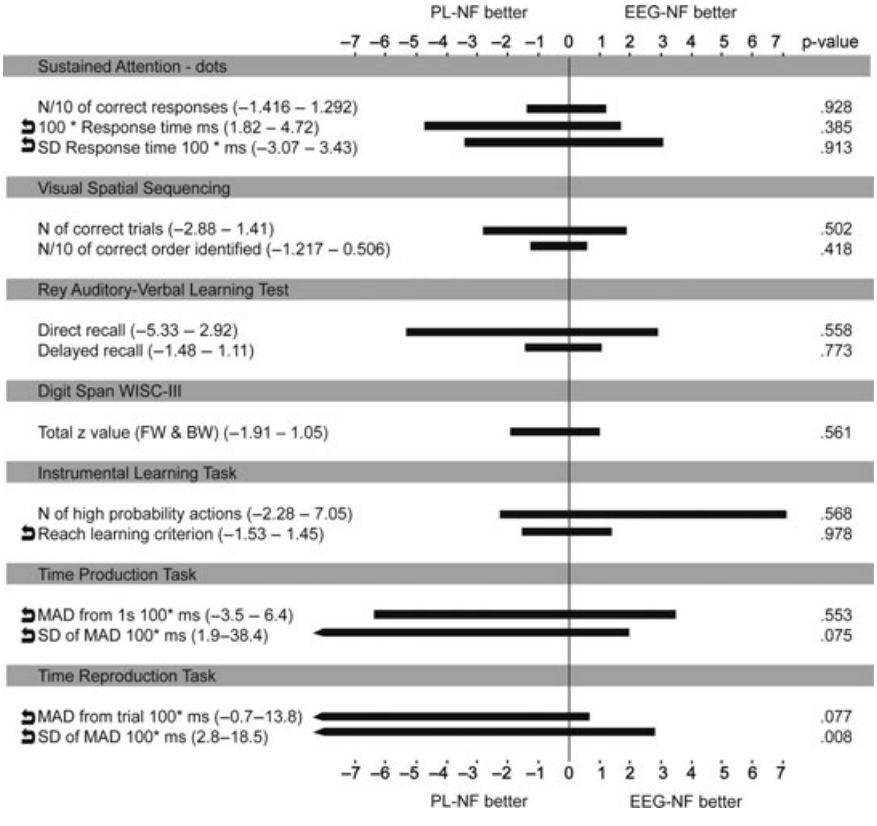

Figure 1 Ninety-five percent confidence intervals for each neurocognitive parameter. Based on B-weights, this figure shows that despite a relatively small sample size and thus limited statistical power, there is no reason to reject the null-hypothesis. A positive value indicates an effect for the EEG-neurofeedback group, a negative value indicates an effect for the placebo-neurofeedback group. Note that values of which lowering is hypothesized to be an improvement are indicated with a preceding arrow and scales are inverted. PL-NF, placebo-group; F-NF, frequency neurofeedback group; *p*-value, probability-value; *N*, number; ms, millisecond *SD*, standard deviation; WISC, Wechsler Intelligence Scale; FW, forward; BW, backward; MAD, mean absolute deviation; s, second

targets identified in correct order ($t(36) = -0.810$, $p = .418$).

Digit span WISC-III. No significant treatment effect was found on the norm-score of forward and backward digit span after controlling for the baseline-score ($t(38) = 0.586$, $p = .561$).

The Rey Auditory-Verbal Learning Test (RAV-LT). No significant treatment effect was found on direct- and delayed recall after controlling for the baseline-score (direct: $t(38) = 0.591$, $p = .558$; delayed: $t(38) = -0.290$, $p = .773$).

Instrumental learning task. Two outliers were detected in the PL-NF group when exploring the data and were excluded from the dataset. No treatment effect was observed on the number of high probability actions ($t(36) = 1.003$, $p = .316$) or on the moment at which the learning criterion of 8 consecutive high probability actions was reached ($t(36) = -0.028$, $p = .978$).

Time production task. Two outliers were detected in the F-NF group and excluded from the dataset. No significant treatment effect was found on the mean absolute deviation (MAD; in ms) from 1 s after controlling for baseline-score ($t(36) = 0.599$, $p = .553$). A trend towards more variance in response length (standard deviation of MAD) in the F-NF than PL-NF group was observed ($t(36) = 1.833$, $p = .075$).

Time reproduction task. No significant treatment effect was found on the MAD from the trial ($t(38) = 1.771$, $p = .077$). A significant treatment effect, the F-NF fluctuating more in response length than the PL-NF, was observed on the *SD* of MAD ($t(38) = 2.674$, $p = .008$).

Covariates analyses

When age, gender, FSIQ, medication, and electrophysiological arousal variables were added as covariates to the main ANCOVA with the neurocognitive parameter as dependent variable, and group as fixed variable. No significant treatment effects were revealed and it also abolished the previous ANCOVA-results that suggested a potential group difference.

Reliable change index

Similar to results of Perreau-Linck et al. (2010), each participant improved on at least one measure, however, each participant also deteriorated on at least one measure. Figure 2 displays the percentage chil-

dren that showed improvement and deterioration per group for each variable. These results did not yield a different conclusion than group analysis did; i.e. F-NF was not superior to PL-NF in improvement on the neurocognitive measures. When focusing on the few children that showed a significant behavioral improvement (i.e. a clinical response) (see van Dongen-Boomsma et al., 2013), each of these children showed improvement on some neurocognitive measures but deterioration on others.

Post-hoc analyses of the F-NF training

EEG-data during the sessions were available for 10 children (8 children were part of the pilot group in which EEG recordings were not saved and for four additional children, data were missing). Mean power was calculated per trained frequency-band and electrode for the first, 10th, 20th, and last session. Seven children showed a change in power towards one of the training targets. However, the variability between sessions was great and no children showed such a desired change in more than one frequency-band. Moreover, all children additionally showed a change in power away from a training target. Clinical responders showed an EEG change in the desired as well as nondesired direction also.

Discussion

This study evaluated whether or not F-NF had beneficial effects on neurocognitive functioning in

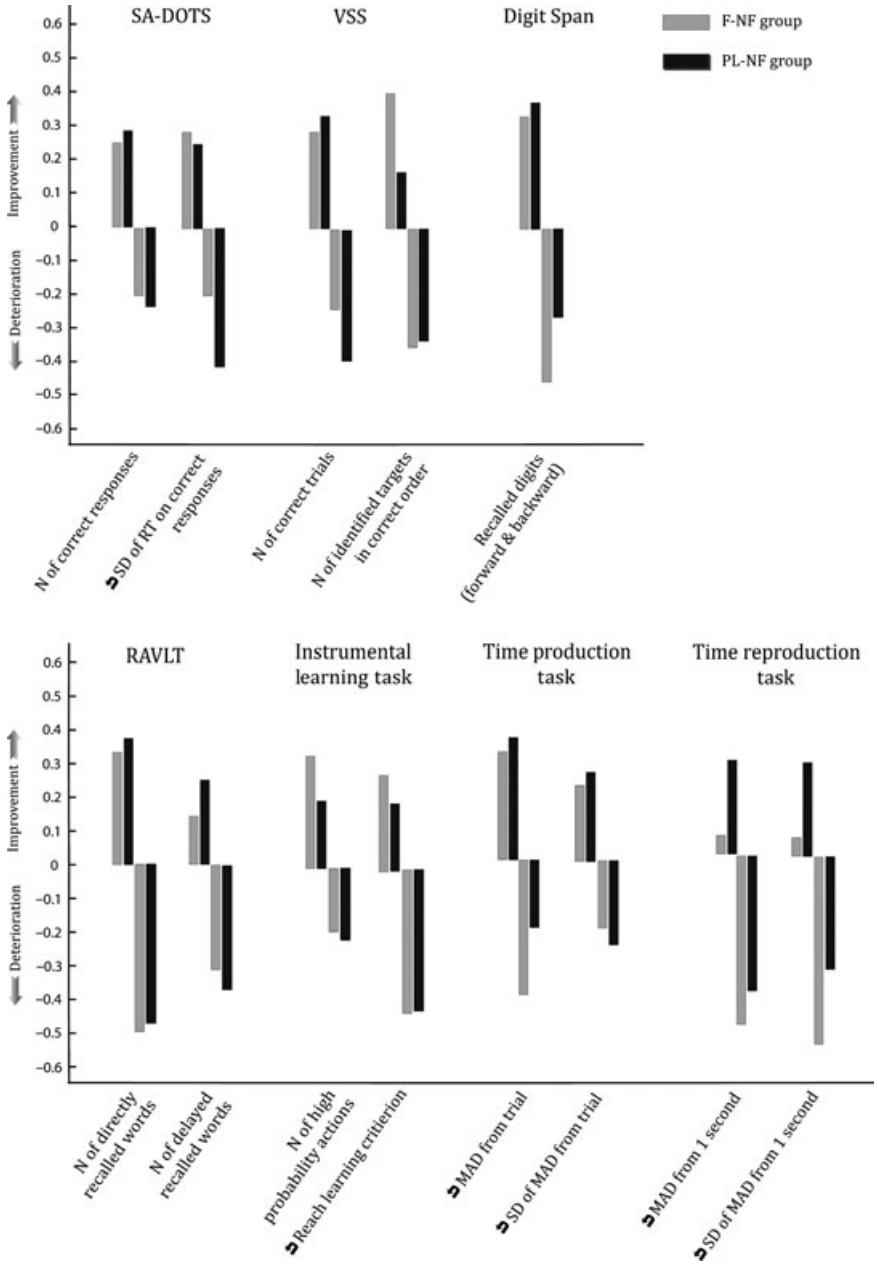

Figure 2 Proportion of children that shows improvement or deterioration on the Reliable Change Index per group for each variable. The preceding arrow indicates an inverted scale; value of which lowering is hypothesized to be an improvement. *SD*, standard deviation; RT, reaction time; WISC, Wechsler Intelligence Scale; RAVLT, Rey Auditory-Verbal Learning Test; MAD, mean absolute deviation; F-NF, frequency neurofeedback group; PL-NF, placebo-group

children with ADHD, based on the results of our placebo-controlled double-blind design, and on a review of the existing literature.

No significant improvement of neurocognitive functioning after F-NF compared to PL-NF was found, which is in line with previous analyses of behavioral effects on the same dataset (van Dongen-Boomsma et al., 2013). Participants who showed positive behavioral responses to F-NF did not show any sign of neurocognitive improvement. In addition, Reliable Change Indices assessing individual changes in neurocognitive measures for each participant yielded essentially the same results. Furthermore, the only significant interaction effect found was in favor of the PL-NF.

The systematic review suggests that neurocognitive improvements occur over time, but when compared with the control conditions, only two out of the nine RCT's reported a treatment effect of F-NF on some neurocognitive variables (i.e. impulsivity and attention). The findings of these two RCT's are likely based on chance as the family wise error rate is large when conducting such a high number of statistical tests. Also, the few papers that report neurocognitive improvements had significant methodological limitations.

The most likely explanation why we did not find improvement of neurocognitive functioning after F-NF is that F-NF is not an effective treatment in ADHD. This conclusion is in line with three recently published placebo-controlled F-NF studies reporting no superior effect on the core behavior symptoms of ADHD (Arnold et al., 2012; van Dongen-Boomsma et al., 2013; Lansbergen et al., 2011; Perreau-Linck et al., 2010). Yet another explanation is that neurocognitive improvement takes longer to manifest and may only be detectable at later time periods after end of the study. Furthermore, the results are based on a selected battery of neurocognitive tests, reflecting neurocognitive functions hypothesized to be impaired in ADHD (Nigg, 2005). The battery focussed more on attentional processes, as these have been shown to be most sensitive to EEG-NF on behavioral level (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). However, not all hypothesized impaired neurocognitive functions were (fully) represented by the chosen test battery, as is the case for conflict resolution and inhibition. The current study was conducted with care, especially with respect to study design and implementation of a comprehensive neurocognitive test-battery. Due to the requirement of a deviant pretreatment EEG, this study enabled the child to train specific EEG deviations, in line with the hypothesis that EEG-NF improves or even normalizes deviant pretreatment brain activity. This requirement did not lead to generalizability problems, because 95% of the participating children did have a deviant pretreatment EEG.

Nevertheless, this study has some limitations. First, children with all subtypes of ADHD and with an FSIQ of at least 80 points were included in this study. Thus, clear findings of improvements in subgroups of ADHD or children with a significant lower IQ cannot be made. Second, the current cohort is smaller in size than planned, due to recruitment difficulties. Especially the F-NF post-pilot group, which could have shown improvement driven by implemented learning strategies, was small ($N = 14$). However, all 95%-CI's of the B-weights, the unstandardized regression coefficients (Figure 1) are centered around zero, which suggests that the marginal effects that were found for three parameters were possibly based on chance. Type II errors due to a lack of power are therefore less likely than if the 95%-CI's had not been centered around zero. The RCI analyses also suggest that power was not the most likely explanation of the failure to find an effect. Third, the NF-therapist was not blind, allowing for the possibility of a different attitude or bias towards the child, depending on group assignment. Fourth, to arrive at a normal distribution, up to 4.9% of the data was removed and to deal with missing data, imputation was used for an average of 4.9%, up to 14.6% of the data. Although these procedures were necessary to perform analyses in the most valid way, these procedures are still regarded as limitations of the study. It should also be noted that, the current findings are based on a Caucasian sample and thus should not be presumed to be applicable to other races. Finally, this study aimed to investigate neurofeedback training delivered in 'care as usual'. Applying 80% positive feedback per condition leaded to a relatively low amount of reward in the more complex protocols. This decision was made in congruency with 'care as usual', but adds a limitation to this study-design. Furthermore, EEG-data from children in the F-NF group (after the two protocol adaptations) recorded during the sessions, showed that not all desired training directions were met. Significant improvement on group level can only solidly be interpreted if all training conditions hypothesized to improve ADHD (either on behavioral or neurocognitive level) are actually improved in the desired direction. In 'care as usual', decisions about adjustments of the threshold were determined by the involved clinical NF-therapist. Future research should therefore focus on different ways to deliver neurofeedback. In addition, the influence of F-NF on neurocognitive domains not covered by the current study therapy should be investigated.

Conclusion

This study was unable to establish positive treatment effects on neurocognitive functioning after F-NF compared to PL-NF. This finding is in line with a systematic review of the current literature, but maybe influenced by the existing study limitations.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 CONSORT flow diagram.

Data S1 Neurocognitive task descriptions.

Acknowledgments

This study was supported by BrainGain Smart mix program, a Dutch initiative of the Netherlands Organization for Scientific Research (NWO) to support applied research.

This study was written with equal contribution of M.A.V. and M.v.D.-B. J.K.B. has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis, and Servier, in the past three years; he is neither an employee nor a stock shareholder of any of these companies; he has no other financial or material support (e.g. expert testimony, patents or royalties). All of the other authors have declared that they have no competing or potential conflicts of interest.

The authors would like to thank the participating children and their parents and teachers, and appreciate the invaluable support of Mrs. Nadine Schalk, research management assistant (Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, the Netherlands) and Dr. M. Lansbergen (former senior researcher at the Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Psychiatry, Nijmegen, the Netherlands).

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Key points

- This double-blind randomized placebo-controlled study could not demonstrate superior effects of EEG-NF on neurocognitive functioning.
- A systematic review of the existing literature on this topic also was unable to find a firm indication of superior neurocognitive improvement after EEG-NF compared to control conditions.
- The systematic review as well as this small study does not support significant benefits of F-NF in its current form on neurocognitive functioning of children with ADHD, however this finding is probably influenced by methodological limitations.

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Accepted for publication: 5 August 2013
Published online: 30 October 2013