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ORIGINAL CONTRIBUTION

Behavioral effects of neurofeedback in adolescents with ADHD: a randomized controlled trial

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Abstract Neurofeedback has been proposed as a potentially effective intervention for reducing Attention Deficit Hyperactivity Disorder (ADHD) symptoms. However, it remains unclear whether neurofeedback is of additional value to treatment as usual (TAU) for adolescents with clinical ADHD symptoms. Using a multicenter parallel-randomized controlled trial design, adolescents with ADHD symptoms were randomized to receive either a combination of TAU and neurofeedback (NFB + TAU, $n = 45$) or TAU-only ($n = 26$). Randomization was computer generated and stratified for age group (ages 12 through 16, 16 through 20, 20 through 24). Neurofeedback treatment consisted of approximately 37 sessions of theta/sensorimotor rhythm (SMR)-training on the vertex (Cz). Primary behavioral outcome measures included the ADHD-rating scale, Youth Self Report, and Child Behavior Checklist all assessed pre- and post-intervention. Behavioral problems decreased equally for both groups with medium to large effect sizes, range of partial $\eta 2 = 0.08$–0.31, $p < 0.05$. Hence, the combination of NFB + TAU was not more effective than TAU-only on the behavioral outcome measures. In addition, reported adverse effects were similar for both groups. On behavioral outcome measures, the combination of neurofeedback and TAU was as effective as TAU-only for adolescents with ADHD symptoms. Considering the absence of additional behavioral effects in the current study, in combination with the limited knowledge of specific treatment effects, it is questionable whether theta/SMR neurofeedback for adolescents with ADHD and comorbid disorders in clinical practice should be used. Further research is warranted to

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investigate possible working mechanisms and (long-term) specific treatment effects of neurofeedback.

Keywords Neurofeedback · Theta/SMR-training · ADHD · RCT

Introduction

Adolescents who show a persistent pattern of frequent inattention and/or hyperactivity-impulsivity symptoms—and for whom these symptoms are interfering with developmentally appropriate social, academic, or occupational functioning—are diagnosed with Attention Deficit/Hyperactivity Disorders (ADHD) [1]. This is the most common neurodevelopment disorder with a prevalence of around 5.9–7.1 % [2]. Comorbid disorders like conduct disorders, mood and anxiety disorders are common [3, 4]. Additionally, in youngsters with autism spectrum disorders (ASD) estimations indicate high rates (ranging from 28 up to 78 %) of ADHD comorbidity [5–7].

Currently, best practice in ADHD treatment for adolescents consists of stimulant medication, preferably in combination with behavior therapy [8]. Stimulant medication is effective in reducing ADHD symptoms [9] in 70–80 % of the children suffering from ADHD [10], and in almost half of the children with ASD and comorbid ADHD [11]. Thus, about a quarter of adolescents with ADHD and half of the adolescents with ASD and comorbid ADHD do not benefit (enough) from standard treatment with stimulant medication. Moreover, mild adverse effects of stimulant medication, such as decreased appetite, difficulty falling asleep and headaches are reported relatively often [11, 12]. Therefore, additional ADHD interventions that further increase effectiveness and reduce adverse effects to the standard ADHD treatment are warranted. In this respect, neurofeedback has been suggested as an intervention that is potentially effective in reducing ADHD symptoms by modifying brain activity in youngsters with ADHD [13–15] and ASD with comorbid ADHD [16].

Neurofeedback intends to alter brain activity by giving feedback of electroencephalogram (EEG) activity to patients. Notably, alterations in EEG activity patterns have been related to behavioral problems as seen in ADHD [17, 18]. Increased electroencephalogram (EEG) theta (4–7 Hz) and decreased beta (13–30 Hz) activity in ADHD-children compared to typically developing (TD) children, have been observed across studies [17]. Theta and beta activity can be related to vigilance and attention, respectively [18]. Hence, adaptation of the theta and beta activity in children with ADHD, may lead to improved behavior. Likewise, sensorimotor rhythm (SMR)-activity (13–15 Hz) measured above the central sulcus, is positively related to motor inhibition [19, 20]. Correspondingly, it was reasoned by Lubar and Shouse [21] that training aimed at increasing SMR-activity would improve inhibition in children with ADHD. As a result, the most frequently applied neurofeedback training protocols for ADHD aim to decrease theta (4–7 Hz) activity and increase SMR (12–15 Hz) or beta (12–20 Hz) activity, with electrode placement on the vertex (Cz) [13, 15, 22].

Based on previous reviews, claims on the effectiveness of neurofeedback for ADHD symptoms range from possibly effective [13–15] to 'efficacious and specific' [23]. The estimated effect sizes varied between medium and large for the ADHD symptoms hyperactivity, impulsivity and attention [23]. However, several methodological shortcomings have hampered many of the included studies: the majority of the studies were not randomized, sample sizes were small, and/or non-specific treatment effects were not controlled for. The more recently published reviews, using more rigorous inclusion criteria, report more conservative estimations of effects [13–15, 22] and results even dropped to non-significant levels when only studies were included with probably blinded assessments [24]. In addition, a review pertaining to neurofeedback training in children with ASD concluded that neurofeedback was not effective for autism symptoms but possibly effective for comorbid ADHD symptoms [16]. All in all, neurofeedback seems potentially effective though previous shortcomings in study design and unknown (negative) side effects preclude strong conclusions. To address these shortcomings, more controlled research is necessary to see which specific patients will profit from which specific neurofeedback training protocol [13, 14]. Furthermore, research is needed to see whether neurofeedback can be of additional value to multimodal treatment protocols [14].

Therefore, the aim of the current study was to investigate the additional value of neurofeedback on behavior over treatment as usual (TAU) for adolescents diagnosed with ADHD and comorbid disorders, with a multicenter parallel-randomized controlled trial design. It was expected that behavioral measures of attention would improve more in the group that received neurofeedback (in addition to TAU) than the group that received TAU-only. In addition, to address non-specific treatment effects and side effects of neurofeedback, indices of experienced improvement on non-standardized behavioral measures, headaches and sleep problems, as well as effects on autism symptoms were analyzed.

Method

Participants

Eligible participants were male adolescents with Dutch as their native language, between 12 and 24 years old, with

a clinical DSM-IV-TR primary diagnosis of ADHD and a full-scale total intelligence quotient (TIQ) >80 on the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) [25, 26]. Adolescents diagnosed with ASD (including: Autism, Asperger disorder and PDD-NOS) with notification of clinical ADHD symptoms equal to a full ADHD diagnosis were also included. ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults [27] and the Mini International Neuropsychiatric Interview [MINI; [28, 29]]. Exclusion criteria were neurological disorders, schizophrenia and other psychotic disorders. There are indications that there might be sex differences in EEG power spectra, with elevated global theta power in male adolescents [30] and adults [31] with ADHD compared to controls, whereas this global theta difference seems not present in females with ADHD compared to sex matched controls. Because the intervention is primarily based on the idea that a decrease in theta by neurofeedback training will result in improved behavior in ADHD patients, female patients were not included in this study.

Initially, a total of 90 adolescents were randomized over the interventions: combined neurofeedback and TAU (NFB + TAU; $n = 59$) or TAU ($n = 31$). The drop-out and exclusion rate did not differ for NFB + TAU, $n = 14$ (23.7 %) and TAU, $n = 5$ (16.1 %), $p = 0.778$ two-tailed Fisher exact test. At direct post-intervention analysis, NFB + TAU and TAU comprised $n = 45$ and $n = 26$ adolescents, respectively. Drop-out reasons included motivational and/or organizational reasons NFB + TAU = 9; TAU = 5) and transfer to another region (NFB + TAU = 2). Three adolescents were excluded from analyses because of occurrence of psychotic symptoms (NFB + TAU = 2) and borderline disorder (NFB + TAU = 1) and hence these data were considered not reliable. A participant flow diagram is presented elsewhere [32].

Medication use and presence of comorbid disorders were allowed. Comorbid disorders included: depressive disorders (4), anxiety disorders (2), substance related disorders (4), conduct disorders (4), learning disorders (6), communication disorders (1), tic disorders (1) elimination disorders (1), adjustment disorders (1), reactive attachment disorder (1). The final group characteristics are listed in Table 1.

Trial Design

This was a multicenter parallel-group study, stratified for age (12 through 16, 16 through 20, 20 through 24 years of age) and with imbalanced randomization [2:1] for NFB + TAU versus TAU-only. Randomization was generated using an online automatic random number generator [33]. The block lengths were 3, 6, 9, and 12 and varied randomly. An independent administrative employee was responsible for the assignment of participants to their groups. The investigators were blind for block lengths and for the number of participants in each stratification group. After pre-intervention assessments the investigator e-mailed the administrative employee to apply randomization. The same day, the participant (and if applicable, his parents) was notified whether he would receive neurofeedback intervention or not. Participants, parents, neurofeedback trainers and clinical professionals were aware of the allocated arm randomization. The outcome assessor and neurofeedback trainer were not the same person. All data entry was performed blind to the allocated arm and was checked twice by different research interns or assistants.

Previous estimated effect sizes for decreased ADHD symptoms by neurofeedback range from medium to large. Sample size estimation was done by G*power version 3.1.5.1 [34]. For an ANOVA repeated measures, within-between interaction a total sample size of 46 (or 23 per intervention arm) was calculated to be sufficient to detect a medium effect size ($f = 0.25$) with an alpha 0.05 and a power of 90 %.

This trial is registered in the Dutch trial register (Ref. no: 1759) and is funded by: The Netherlands Organization for Health Research and Development (ZonMw): 157 002 004. In this article, the CONSORT 2010 guidelines for reporting parallel-group randomized trials were followed [35].

Interventions

Treatment as usual (TAU)

In the TAU group, the participants received treatment as prescribed by the main therapist of the participating center for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group). TAU was monitored through an intervention questionnaire based on the 'Dutch national basic program ADHD for children and adolescents' [36]. Behavioral interventions included cognitive behavioral therapy, systemic therapy, and/or supportive counseling, either directed at the adolescent and/or at the parent(s). Stimulant medication use included immediate release methylphenidate [11], sustained release methylphenidate [22] and dexamphetamine [1]. Atomoxetine was used by two participants at study entry. Because of the suggested similar clinical effects of stimulant medication and atomoxetine, in the analyses these two participants were categorized within the group of stimulant-medicated adolescents. Adherence to prescribed medication was verified by questioning the participants whether they took the prescribed medication. Stimulant medication use and received behavioral therapy did not differ between the group receiving TAU-only and the group who received neurofeedback in addition to TAU (see Table 1).

Table 1 Group characteristics

	Total	NFB + TAU	TAU	Group	
	$n = 71$	$n = 45$	$n = 26$	F	p
Age in years	16.14 (3.32)	16.09 (3.33)	16.2 (3.37)	0.03	0.86
Primary DSM diagnoses					
ADHD	47 (66 %)	29 (64 %)	18 (69 %)		0.79
ASD + ADHD	24 (34 %)	16 (36 %)	8 (31 %)		0.79
GAF-scores	54.66 (6.74)	53.80 (7.07)	56.15 (5.95)	2.04	0.16
Stimulant medication t1	36 (51 %)	20 (44 %)	16 (62 %)		0.22
Months of intake before t1				3.74	0.46
Up to 3 months	6 (8 %)	4 (9 %)	2 (8 %)		
3–6 months	3 (4 %)	2 (4 %)	1 (4 %)		
6–12 months	4 (6 %)	3 (7 %)	1 (4 %)		
12 months or more	23 (32 %)	11 (24 %)	12 (46 %)		
Stimulant-free	35 (49 %)	25 (56 %)	10 (39 %)		
Started after t1	6 (8 %)	3 (7 %)	3 (12 %)		0.66
Stopped after t1	9 (13 %)	5 (11 %)	4 (15 %)		0.72
Behavioral interventions[a]					
Adolescent	26 (37 %)	14 (31 %)	12 (46 %)		0.32
Parent	20 (28 %)	12 (27 %)	8 (30 %)		0.79
MINI ADHD inattention	5.63 (2.61)	5.38 (2.56)	6.08 (2.68)	1.18	0.28
MINI ADHD H/I	4.00 (2.46)	4.16 (2.58)	3.73 (2.29)	0.49	0.49
ADHD-rating childhood Inattention[b]	6.07 (2.66)	5.67 (2.92)	6.77 (2.01)	2.90	0.09
ADHD-rating childhood H/I[b]	4.94 (2.87)	4.58 (2.99)	5.58 (2.60)	2.02	0.16
IQ discrepancy profile[c]	24 (34 %)	14 (31 %)	10 (38 %)		0.61
Total IQ	100.66 (11.30)	98.62 (10.38)	104.19 (12.15)	4.18	0.05
VIQ	102.37 (12.89)	100.16 (11.43)	106.19 (14.54)	3.76	0.06
PIQ	99.51 (11.93)	98.44 (11.20)	101.35 (13.12)	0.97	0.33

t1 is pre-intervention; data are mean (SD) or numbers (%)

[a] Behavioural interventions followed between pre-and post-intervention (t1–t2)

[b] ADHD-rating scale retrospective self-reported childhood symptoms for Inattention and Hyperactivity/Impulsivity (HI). Group characteristics did not differ between groups

[c] Intelligence quotient (IQ) discrepancy profile is considered as a profile with a difference score between verbal IQ (VIQ) and performance IQ (PIQ) of 15 points or more. Because of the discrepancy profiles VIQ and PIQ are noted separately

Neurofeedback in addition to TAU

Neurofeedback training was carried out over a period of around 5 months (25 weeks), with two to three training sessions every week. Each participant was offered 40 training sessions of 30 min in total. The mean number who followed the training sessions was 37 (36.98 ± 4.94) with a minimum of 19 sessions. A neuropsychologist, EEG Biofeedback EEG Spectrum International Inc. certified, accredited by the Biofeedback Certification International Alliance (BCIA) (MB), trained the psychologists who gave the neurofeedback training. The treatment protocol was based on rationales of Lubar [37], Lubar and Lubar [38], and Fuchs et al. [39].The aim of the treatment was to increase SMR-activity, while simultaneously decreasing theta, alpha and electromyographic (EMG) activity due to muscle tension to ensure an attentive and relaxed state of engagement with an altered EEG state for longer periods of time [37]. The treatment protocol therefore consisted of decreasing low frequency bands (4–11 Hz), increasing SMR-activity (12–15 Hz) and decreasing high beta/gamma (22–36 Hz) at Cz. Inhibition of higher beta/gamma frequency band was conducted in this study to minimize the increase of SMR-activity by increased muscle tension, and to decrease potential high beta that seems to occur in an estimated 10–20 % of children with ADHD [17].

Training was conducted on Cz, referred to linked mastoids. The EEG-signal was transmitted to the computer by the Brainquiry PET EEG 2 channel bipolar system [40]: a DC amplifier with active electrodes, a low-pass anti-aliasing filter of 40 Hz, a sample rate of 200 Hz and a 29 bit AD resolution. Neurofeedback training was conducted with 'EEGer' neurofeedback software version 4.2.1 [41]. The EEG-signal was accordingly band pass-filtered in the different frequency bands with an exponentially weighted moving average filter over 0.5 s to produce a short-term average. Each frequency band involved a 0.25 Hz increment step size reward filter. Each training session was divided into ten 3-min epochs. Artifact rejection thresholds for the raw EEG-signal were set to 60 μV, to prevent the effect of gross movements from the participants. Relative thresholds for each frequency band were set to accept the signal 80 % and to reject the signal 20 % of the time. Thresholds were calculated to correspond to the mean

amplitude in μV of each frequency band over the last 30 s of input and were calculated after 30 s from the beginning of each 3-min session. For the first 30 s, thresholds of former 3-min session were preserved.

The signal was visually presented to the participant on a screen by simple graphics, which represented the different frequency bands by three colored boxes. The colors of the boxes were moving: sometimes a color did not totally fill the box and sometimes the color exceeded the borders of the box. The participant was instructed that the left, purple-colored box represented slow-wave activity (4–11 Hz) and the right, yellow-colored box represented fast-wave activity and muscle tension (22–36 Hz). For both these boxes the colors were to be kept in the drawn box (inhibit). The middle, blue-colored box represented the 'good'waves (SMR 12–15 Hz) and the participant was instructed that this color should exceed the borders of the box and get as wide as possible (reward). At the moment the signal for all frequency bands fulfilled all threshold criteria, audible feedback was given by a short 0.25 s beep. Subsequently, the participants obtained a point that increased the score on the bottom of the screen.

During the neurofeedback training, at each 30 s interval the trainer noted the mean value in μV per frequency band (theta, alpha, SMR and beta). Mean values in μV over all received sessions were calculated. Missing values were replaced based on last observation carried forward (LOCF). To check for within training effects, mean differences were calculated between the mean value in μV over the last 15 min minus the mean value in μV over the first 15 min of each session per frequency band. Difference scores of every session were checked for outliers (>3 box-lengths) and outliers were replaced with the difference score of the previous session (LOCF; in case there was an outlier for the first session, the value was replaced with the value of the second session). To check for learning effects, the mean difference of the first five sessions was compared to the mean difference of session 31–35.

Outcome measures

Primary outcome measures included three behavioral questionnaires. Secondary outcome measures consisted of non-standardized behavioral measures, side effects on reported sleeping problems and headaches, and autism symptoms. Neuropsychological and electro-physiological outcome measures assessed during the study will be reported elsewhere.

Primary behavioral outcome measures

The ADHD-rating scale is a DSM-IV-based self-report for adults [42, 43]. This is an adapted form of DuPaul et al. [44] which contains 23 items rated on a 4-point scale ranging from 'rarely or never' to 'very often'. Items were filled out for occurrence of current symptoms (in the past 6 months) at pre- and post-intervention. Two nine-item subscales were used: inattention and hyperactivity/impulsivity [42, 43].

The Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) [45] are questionnaires that cover, respectively parent-reported and self-reported behavioral and emotional problems for children and adolescents up to 18 years old. In this study, the subscale attention problems, the broadband scale externalizing problems and the global scale total problems were used. For participants over 18 years also the CBCL and YSR were used, since most of them were still attending school and living with their parents.

Secondary outcome measures

Behavioral changes on non-standardized measures, autism symptoms and side effects were included as secondary outcome measures. Experienced behavioral changes on non-standardized measures at post-intervention ['Did you notice any behavioral changes during the last period (6-months)?'] were scored as no improvement (0) or improvement (1) for overall behavior, attention, and hyperactivity/impulsivity.

Autism symptoms were screened with the Autism-Spectrum Quotient (AQ)-adolescent version for individuals with normal intelligence [46]. Parents or other relevant adults filled out the AQ-adolescent. AQ-questionnaires were excluded from analyses when three or more answers were missing.

Headache frequency ['Did you experience headaches during the last 6-months and what was the frequency of the headaches?'] were scored as never (0), sometimes (1), 1–2/month (2), 3–8/month (3) and >3/week (4). Sleep pattern ('Do you have difficulties with: (I) falling asleep/(II) sleeping through/(III) getting up in the morning? and (IV) are you feeling sleepy during the day?'), was scored dichotomously per question (I–IV) as not problematic (0) and problematic (1) and summarized.

Procedure

Prior to the start of the study, approval was obtained from the medical ethics committee for mental health institutions in the Netherlands (Ref.no: NL 24776.097.08 CCMO). The study took place in three centers for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the South of the Netherlands. After the study was explained (verbally and in writing), written informed consent was obtained from each participant. For those younger than 18, parents also provided written informed consent.

At pre-intervention, participants were seen on three occasions for the administration of behavioral questionnaires, neuropsychological tests, an assessment of intellectual functioning using the WAIS- or WISC-intelligence test and EEG measurements. In cases where participants were on medication, medication intake was also continued on the day of assessment.

Interventions took place between December 2009 and July 2012. The duration of the intervention period was approximately 5 months (25 weeks).

At post-intervention assessment, behavioral questionnaires and neuropsychological tests were assessed for all 71 participants. One participant refused to complete the YSR. For two participants, reported headache frequency was missing.

Parents or relevant adults received the parent-report questionnaires (CBCL and AQ-adolescent) by mail, requesting their return pre- and post-intervention. CBCL-data were incomplete or missing for 13 participants. The AQ-questionnaire was missing or incomplete for 19 participants.

Statistical analysis

All analyses were performed using SPSS version 19.0. Effects were considered significant if $p < 0.05$. Differences on group characteristics were analyzed with a one-way ANOVA or a Chi square test (χ^2) with Fisher exact correction. Training effects were investigated using a Generalized Linear Model (GLM) with time as within-subjects factor. Effects were evaluated using multivariate test criteria. Post hoc analyses were performed with the addition of stimulant medication use at pre-intervention and diagnostic group (ADHD or ASD with comorbid ADHD) as between-subject factor to the GLM. Attrition analyses, for behavioral data with smaller sample size than the total sample size due to missing or incomplete data, were performed by comparing the analyzed subsample for a particular measure to the total sample on group characteristics and other pre-intervention primary behavioral outcome measures with a one-way ANOVA.

A completion analysis was applied involving the participants who finished all assessments up to post-intervention (including neurofeedback training, if applicable), to determine whether neurofeedback had additional value after completion of the training. The effect of neurofeedback training on behavior was investigated using a Generalized Linear Model (GLM) with between- and within-subjects factors. The analysis was applied for all the primary behavioral outcome measures separately with intervention group as between-subject factors and time [e.g. between pre-intervention (t1) and post-intervention (t2)] as within-subjects factor. The full factorial models were tested. All behavioral effects were evaluated using multivariate test criteria. Effect sizes are expressed in percentage of explained variance in partial η^2 (η_p^2). In addition, the adjusted difference at post-intervention (AD_{t2-t1}) and 95 % confidence interval [95 % CI] were noted. Post hoc analyses were performed with the addition of stimulant medication use at pre-intervention and diagnostic group (ADHD or ASD with comorbid ADHD) as between-subject factor to the GLM. To control for potential outcome bias of the drop-outs ($n = 16$) after randomization post hoc analyses were performed based on imputation with Last Observation Carried Forward (LOCF) for the total group as randomized with the exception of the three excluded participants.

Non-standardized secondary behavioral measures were examined by calculation of the relative risk (RR). Change is considered significant when the RR and 95 % CI do not include [1.0]. Frequency of headaches, total sleeping problems and autism symptoms were analyzed using a GLM with between- and within-subjects factors as described in the primary outcome measures.

Results

Group characteristics

There were no baseline differences for group characteristics between the NFB + TAU group and the TAU group (Table 1). In both groups, most participants who used stimulant medication started taking stimulant medication more than 6 months before pre-intervention. The mean (standard deviation) doses of stimulant medication in mg was 36.48 (15.69), 95 % CI = [30.92, 42.05], range [10, 72] and did not differ between the groups, F (1.32) = 0.57, $p = 0.46$, $\eta_p^2 = 0.02$. The dose Atomoxetine was 60 mg for both participants. One participant used dexamphetamine with a dose of 15 mg. The kind of prescribed medication (immediate release methylphenidate, sustained release methylphenidate, dexamphetamine oratomoxetine) did not differ between the groups, $\chi^2 = 2.48$, $p = 0.63$. The TAU group seemed to have a somewhat higher total intelligence quotient (TIQ) than the NFB + TAU group. Performance intelligence quotient (PIQ) was similar for both groups. There were no group differences at pre-intervention assessment for behavioral primary outcome measures.

There were no pre-intervention differences between stimulant-medicated ($n = 36$) and stimulant-free adolescents ($n = 35$) with regard to diagnoses, Global Assessment of Functioning (GAF) scores or behavioral measures. The only exception was TIQ: Stimulant-medicated adolescents had a somewhat higher TIQ, $M = 103.28$, SD = 11.41, than stimulant-free adolescents, $M = 103.28$, SD = 11.41.

Table 2 Training effects between the first 5 sessions and session 31–35

	Between training effects				Within training effects									
	Mean in μV total sessions 1–5 (30 min)	Mean in μV total sessions 31–35 (30 min)	ANOVA time (t1–t2)		Mean within session difference 1–5 in μV (t1)		Mean within session difference 31–35 in μV (t2)	Adjusted difference [95 % CI] at session 31–35 (t2–t1)	ANOVA time (t1–t2)[a]		Post hoc med. Use over time[b]		Post hoc ASD+ and ADHD over time[c]	
	Mean (SD)	Mean (SD)	*F*	η_p^2	Mean (SD)		Mean (SD)		*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
Theta (4–7 Hz)	12.62 (3.08)	12.65 (3.29)	0.03	0.00	0.04 (0.32)		−0.14 (0.38)	−0.18 [−31, −0.05]	7.31**	0.14	0.27	0.01	0.02	0.00
Alpha (8–11 Hz)	8.89 (2.02)	9.11 (2.28)	3.41	0.07	−0.03 (0.31)		−11 (0.36)	−0.08 [−0.20, 0.03]	2.100.05		0.32	0.01	0.03	0.00
SMR (12–15 Hz)	6.18 (1.24)	6.24 (1.27)	0.44	0.01	0.03 (0.18)		−0.02 (0.19)	−0.05 [−0.13, 0.02]	1.91	0.04	0.83	0.02	3.08	0.07
High beta (22–36 Hz)	6.74 (1.56)	6.50 (1.22)	2.29	0.05	−0.05 (0.35)		−0.02 (0.53)	0.02 [−0.16, 0.21]	0.06	0.00	0.01	0.00	2.41	0.05

Total sessions mean in μV of session 1–5 and session 31–35; Mean within session difference is the difference in μV between the last 15 min and the first 15 min. [a] GLM ANOVA with time (t1–t2) as within factor *df* (1.44) post hoc analysis for [b] stimulant medication use *df* (1.43) or [c] diagnostic group (ADHD versus ASD + ADHD) *df* (1.43) did not reveal significant interactions with between trainings or within training learning effects over time

** $p < 0.01$

Note that both mean scores lie within the average range [95–105].

Training effects

Mean power in μV over the first five sessions and over the sessions 31–35, for each frequency band are presented in Table 2. None of the frequency bands showed an effect over time for mean power between the first five sessions and session 31–35. However, the mean difference in theta between the last 15 min and the first 15 min during session 31–35 was larger than the mean difference in session 1–5, F (1.44) = 7.31, $p = 0.010$, $\eta_p^2 = 0.14$. This indicates that during the latter sessions, adolescents were better able to suppress theta than in the first five sessions. For the other frequency bands no learning effects were observed. Stimulant medication use and diagnostic group did not interact with training difference scores.

Attrition analysis

Attrition analysis showed that the drop-out group ($N = 16$) did not differ from the completers ($N = 71$) on group characteristics or primary behavioral outcome measures. Attrition analyses for the subsamples with respect to the YSR ($N = 70$), CBCL ($N = 58$), reported headaches frequency ($N = 69$) or AQ-adolescent ($N = 52$) showed no difference from the completers ($N = 71$) on group characteristics or primary behavioral outcome measures at pre-intervention.

Behavioral measures

Behavioral primary outcome measures are summarized in Table 3. The ADHD-rating scale showed that both inattention and hyperactivity/impulsivity (HI) decreased over time, for the NFB + TAU group and TAU group alike. The YSR and the CBCL revealed the same pattern for attention, externalizing and total problems, again, irrespective of the groups.

Stimulant medication use and diagnostic group

Post hoc analysis for stimulant medication use or diagnostic group showed no difference between stimulant-medicated and stimulant-free adolescents or diagnosis on the behavioral primary outcome measures.

LOCF

Post hoc analysis, to control for potential outcome bias due to drop-out, showed similar outcomes on all measures with a decrease of behavioral problems over time for all adolescents ($N = 87$), irrespective of treatment group (NFB + TAU or TAU).

Table 3 Behavioral primary outcome measures

	Pre-intervention		Post-intervention		Adjusted difference [95 % CI] at post-intervention (t2–t1)	Time (t1–t2)[c]		NFB + TAU and TAU over time		Post hoc med. Use over time[d]		Post hoc ASD + and ADHD over time[e]		Post hoc time based on LOCF[f]	
	NFB + TAU	TAU	NFB + TAU	TAU											
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
ADHD-rating[a]	$n = 45$	$n = 26$	$n = 45$	$n = 26$											
Inattention	4.40 (2.49)	5.27 (2.16)	2.84 (2.59)	3.62 (2.45)	−1.61 [−2.17, −1.04]	31.57***	0.31	0.03	0.00	1.13	0.02	0.91	0.01	30.08***	0.26
H/I	3.44 (2.12)	3.27 (2.01)	2.36 (2.16)	2.38 (2.14)	−0.99 [−1.53, −0.44]	13.01***	0.16	0.14	0.00	1.20	0.02	1.10	0.02	12.52***	0.13
YSR[b]	$n = 44$	$n = 26$	$n = 44$	$n = 26$											
Attention	9.45 (3.29)	9.92 (3.24)	7.45 (3.45)	9.27 (3.55)	−1.33 [−2.13, −0.53]	11.00**	0.14	2.83	0.04	0.01	0.00	0.34	0.01	10.14**	0.11
Extern.	15.95 (10.02)	14.92 (7.38)	13.77 (7.42)	12.73 (7.60)	−2.19 [−3.69, −0.68]	8.42**	0.11	0.00	0.00	0.48	0.01	0.79	0.01	8.26**	0.09
Total	48.50 (22.01)	52.58 (18.89)	40.43 (18.24)	46.12 (20.17)	−7.27 [−11.39, −3.14]	12.35***	0.15	0.15	0.00	0.07	0.00	3.15†	0.05	11.85***	0.12
CBCL[b]	$n = 37$	$n = 21$	$n = 37$	$n = 21$											
Attention	11.16 (3.64)	12.33 (2.67)	9.67 (3.24)	10.48 (3.53)	−1.63 [−2.41, −0.85]	17.46***	0.24	0.34	0.00	0.05	0.00	0.47	0.01	16.18***	0.18
Extern.	18.05 (11.46)	18.95 (12.35)	16.41 (12.75)	15.95 (13.72)	−2.32 [−4.50, −0.15]	4.59*	0.08	0.39	0.01	0.03	0.00	1.25	0.02	4.48*	0.06
Total	60.81 (28.57)	63.77 (27.00)	53.35 (27.55)	52.81 (30.28)	−9.16 [−14.44, −3.88]	12.08***	0.18	0.42	0.01	0.30	0.01	1.44	0.03	11.45**	0.13

[a] ADHD-rating scale self-reported current symptoms for Inattention and Hyperactive/Impulsive (H/I)

[b] YSR and CBCL scales: attention problems, externalizing (Extern.) problems and total problems

[c] GLM ANOVA with time (t1–t2) as within factor and NFB + TAU and TAU as between factor ADHD-rating scale *df* (1.69); YSR *df* (1.68); CBCL *df* (1.56)

[d] Post hoc analysis for stimulant medication use; ADHD-rating scale *df* (1.67); YSR *df* (1.66); CBCL *df* (1.54)

[e] Post hoc analysis for diagnostic group ADHD versus ASD with comorbid ADHD; ADHD-rating scale *df* (1.67); YSR *df* (1.66); CBCL *df* (1.54). There were no interactions between time, intervention group and stimulant medication use or time, intervention group and diagnostic group (ADHD or ASD + ADHD)

[f] Post hoc analysis as randomized based on LOCF, ADHD-rating scale *df* (1.85); YSR *df* (1.85); CBCL *df* (1.76). There were no interactions between time and intervention group

† $p < 0.10$,* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Secondary outcome measures

A larger percentage of NFB + TAU participants reported improvement in attention, compared to TAU on the non-standardized behavioral question. Overall improvement was reported by 29 of the 45 (64 %) in the NFB + TAU group and by 10 of the 26 (38 %) in the TAU group, RR = 1.68, 95 % CI = [0.98, 2.85]. More specifically, improvement in attention was reported by 17 (38 %) of the NFB + TAU group and in 3 (12 %) of the TAU group. Participants in the NFB + TAU group were 3.27 times more likely to report attention improvement than the TAU group, RR = 3.27, 95 % CI = [1.06, 10.12]. Improvement in hyperactivity/impulsivity did not differ between the groups and was reported in the NFB + TAU group by 16 (36 %) participants and by 6 (23 %) in the TAU group, RR = 0.84; 95 % CI = [0.62, 1.13].

Parent-reported autism symptoms showed no decline over time (Table 4). No differences in autism symptoms between the NFB + TAU group and TAU group were found or interactions for time and group.

There were no changes over time or interactions between time and group for headache frequency and sleeping problems. The frequency of headaches and amount of reported sleeping problems stayed the same over time for both groups (Table 4).

Stimulant medication use and diagnostic group

There was an interaction for stimulant medication use over time with post hoc analyses showing that stimulant-free adolescents report fewer headaches over time [$n = 33$, pre-intervention (t1) $M = 1.67$, SD = 1.05, post-intervention (t2) $M = 1.06$, SD = 1.27, $AD_{t2-t1} = -0.61$, 95 % CI = (−0.99, −0.22), $\eta_p^2 = 0.24$, whereas for stimulant-medicated adolescents the amount of headaches stayed the same over time ($n = 36$, pre-intervention (t1) $M = 1.58$ SD = 0.97, post-intervention (t2) $M = 1.83$, SD = 1.28, $AD_{t2-t1} = 0.25$, 95 % CI = (−0.17, 0.67)], $F(1.65) = 5.45$, $p = 0.023$, $\eta_p^2 = 0.08$. The AQ-adolescent version and sleep problems revealed no interactions with stimulant medication use. Post hoc analysis for diagnostic group showed no differences between adolescents with ADHD or combined ASD + ADHD on the AQ-adolescent version, sleeping problems or headache frequency.

LOCF

Post hoc analysis, to control for potential outcome bias due to drop-out, showed similar outcomes for the parent-reported autism symptoms, sleeping problems and headache frequency for all adolescents ($N = 87$), irrespective of treatment group (NFB + TAU or TAU).

Table 4 Secondary outcome measures: autism symptoms and side effects

	Pre-intervention		Post-intervention		Adjusted difference [95 % CI] at post-intervention (t2–t1)	ANOVA time (t1–t2)[a]		ANOVA NFB + TAU and TAU over time[a]		Post hoc med. Use over time[b]		Post hoc ASD+ and ADHD over time[c]		Post hoc time based on LOCF[d]	
	NFB + TAU	TAU	NFB + TAU	TAU											
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
AQ-adolescent version	$n = 32$	$n = 20$	$n = 32$	$n = 20$											
Parent report	26.27 (8.09)	23.40 (5.24)	25.19 (8.16)	22.90 (6.78)	−0.79 [−2.30, 0.72] 1.10	0.02	0.15	0.00	0.02	0.00	0.81	0.02	1.07	0.01	
Headaches	$n = 45$	$n = 24$	$n = 45$	$n = 24$											
Scale 0–4	1.56 (0.97)	1.75 (1.07)	1.33 (1.37)	1.71 (1.23)	−0.13 [−0.44, 0.18] 0.71	0.01	0.33	0.00	5.45*	0.08	1.22	0.02	0.72	0.01	
Sleep problems	$n = 45$	$n = 26$	$n = 45$	$n = 26$											
Scale 0–4	1.44 (1.03)	1.73 (1.04)	1.62 (1.05)	1.46 (0.99)	−0.05 [−0.33, 0.24] 0.10	0.00	2.43	0.03	0.45	0.01	0.00	0.00	0.12	0.03	

[a] GLM ANOVA with time (t1–t2) as within factor and NFB + TAU and TAU as between factor; AQ-adolescent *df* (1.50); headaches *df* (1.67); sleep problems *df* (1.69)

[b] Post hoc analysis for stimulant medication use; AQ-adolescent *df* (1.48); headaches *df* (1.65); sleep problems *df* (1.67)

[c] Post hoc analysis for diagnostic group ADHD versus ASD with comorbid ADHD; AQ-Adolescent *df* (1.48); headaches *df* (1.65); sleep problems *df* (1.67). There were no interactions between time, intervention group and stimulant medication use or time, intervention group and diagnostic group (ADHD or ASD + ADHD)

[d] Post hoc analyses as randomized based on LOCF, AQ-adolescent *df* (1.73); headaches *df* (1.80); sleep problems *df* (1). There were no interactions between time and intervention group

* $p < 0.05$

Discussion

The present study examined the additional value of neurofeedback on behavior over TAU with a multicenter parallel-randomized controlled trial design. A decline in behavioral problems of ADHD in adolescents in both treatment groups was found. Hence, an additional effect of neurofeedback over TAU on the primary behavioral outcome measures was not observed. However, when asked for changes, adolescents who received neurofeedback in addition to TAU more often reported improvement in attention than adolescents who received only TAU.

As for the large decrease in behavioral problems of ADHD between pre- and post-intervention assessment on behavioral outcome measures, a recently published randomized controlled trial showed similar behavioral improvements in children with ADHD receiving neurofeedback alone, stimulant medication, or combined stimulant medication and neurofeedback [47]. In line with the present results, improvement was observed regardless of type of treatment. In addition, double-blinded RCT's also were not able to show superiority for neurofeedback over sham-neurofeedback to improve behavior [48–51] or neurocognitive functioning [51] in children with ADHD. The results of the current RCT are in line with the neurocognitive outcomes [32]. In contrast, a previous large non-randomized study found additional effects on behavior with more improvement in attention for children who received neurofeedback in addition to a combined intervention of medication and behavioral therapy than children who received only medication and behavioral therapy 1 year post-intervention [52]. Possibly, the non-randomized nature of this study may have caused selection biases such as differences between parents with a preference for neurofeedback and parents who choose conventional treatment that may account for this discrepancy. Parents with a preference for neurofeedback might be more inclined to motivate their child to change and thereby make an environment that enables the child to improve more on behavioral attention measures.

In this study, improvement in attention was reported more often by adolescents who received neurofeedback in addition to TAU than adolescents who received TAU-only. This is remarkable when compared to the outcome on the other standardized self- and parent-reported questionnaires, which show similar behavioral improvements over time for both groups. It might be that either the standardized questionnaires were not sensitive enough to measure the difference or that the adolescents in the NFB + TAUgroup were more aware of the improvement, or more prone to point out the improvement, because of the investment they put into the neurofeedback intervention.

Stimulant medication did not influence the results: stimulant-medicated adolescents improved as much as stimulant-free adolescents, nor were there interactions between stimulant medication and treatment condition (NFB + TAU or TAU). Furthermore, with the exception of TIQ, there were no differences in reported behavioral problems at pre-intervention between adolescents who used stimulant medication and those who did not use stimulant medication. The absence of differences between the stimulant-medicated adolescents and stimulant-free adolescents might be explained by the fact that all adolescents participated voluntarily in the present study and were seeking additional treatment for their perceived problems. Note also that the majority of the adolescents who used stimulant medication did so for 6 months or longer. Irrespective of received treatment (NFB + TAU or TAU-only) or stimulant medication use, both groups showed large improvements on behavioral measures, indicating that there was room for improvement. If these improvements were the result of TAU or pediatric development, additional value of NFB would be harder to find. It could be argued that neurofeedback might be more effective in adolescents who do not want to use stimulant medication or for those adolescents for who stimulant medication is not effective enough. However, the absence of an interaction between stimulant medication use and treatment condition in the current study does not support this hypothesis. Nevertheless, it might be that neurofeedback could be used as a substitute for stimulant medication. There are two studies that directly compared stimulant medication with neurofeedback and showed comparable improvements for both conditions [47, 53]. Both studies applied medication titration with the daily dosage depending on weight, with 1 mg per kg [47, 53]. In contrast, there is another study that found stimulant medication to be superior to neurofeedback [54]. This latter study applied individualized medication by incorporating a double-blind placebo controlled medication trial [54]. Titrating stimulant medication based on body weight is applied often in research. However, several studies criticize this way of stimulant titration in ADHD [55, 56]. Accordingly, it might be that stimulant medication did not reach an optimal effect in the first two studies. Further research, comparing neurofeedback with stimulant medication, titrated with a stepwise double-blind placebo controlled protocol is essential to see if neurofeedback is able to serve as an alternative for stimulant medication.

Results show that autism symptoms were not influenced by treatment (NFB + TAU or TAU). Parents did not report significant changes in autism symptoms over time. This is in line with a recent review, which concluded that neurofeedback treatment does not seem to improve core autistic symptoms [16]. On the other behavioral measures used in the current study, it seems that behavioral problems diminished over time for the adolescents with ADHD as well as for the adolescents with ASD and comorbid ADHD.

Side effects as a result of neurofeedback were not found: no differences in negative adverse effects with respect to sleep pattern or headaches were found between the intervention groups. This is in accordance with two double-blinded studies that showed no adverse effects for neurofeedback or placebo-neurofeedback training [49, 50]. The other randomized trials did not address adverse effects. Positive effects of SMR neurofeedback in relation to quality of sleep, have been hypothesized [57]. Sleep spindle activity is in the SMR frequency band (12–15 Hz). Neurofeedback aimed at increasing SMR-activity has been positively related to an increase of sleep spindle density during sleep and thereby the quality of sleep [57]. However, the present study did not find improvements in sleep patterns. There was a decrease in the frequency of headaches over time for stimulant-free adolescents. Headache is a common adverse effect of stimulant medication use [12], as a result, this might be the reason that stimulant-medicated adolescents did not experience a reduction in headache frequency over time.

Within training effects showed that over time adolescents were better at decreasing theta activity during a training session. For the other power spectra no such effects were found. Stimulant medication use and diagnostic group did not influence these results. Further research into EEG power spectra in comparison to a control group is warranted to determine whether the ability to decrease theta during neurofeedback sessions also results in adaptation of theta outside training sessions. This is especially important, since the mean activity over the entire treatment did not change over time.

Aside from the discussion whether patients are able to self-regulate EEG activity, the kind of training protocol that should be used in ADHD is actively debated (see also Holtmann et al. [58]) and this should also be taken into account in this study. Theta/beta and theta/SMR neurofeedback protocols are based on the assumption that ADHD is associated with increased theta activity. Although several studies showed increased theta activity in children with ADHD compared to TD children [17], other studies failed to find increased theta activity in ADHD during rest conditions [59, 60]. Besides theta/beta another kind of neurofeedback protocol is the training of slow cortical potentials (SCP < 0.1 Hz). Negative and positive very slow brain waves are related to increased and decreased cortical activation, respectively [61]. Accordingly, neurofeedback training of SCP is based on the idea that patients learns to increase and decrease the activation level of the brain. A study that followed 11 children with ADHD and 10 TD children into young adulthood, indicated that diminished contingent negative variation (CNV) was related to ADHD and that this was a stable trait into young adulthood [62]. If CNV is a more stable trait of ADHD than theta activity, training of SCP may lead to better results.

The present study is the first to investigate effects of neurofeedback as an additional treatment to TAU in a naturalistic multimodal treatment setting applying a randomized controlled trial design. The implementation of neurofeedback in addition to TAU increases the ecological validity of the study. Although there was no selective drop-out, this design also includes several limitations. For example, the target population consists of a heterogeneous group of male adolescents with complex problems. It might be that neurofeedback is only effective for a specific part of the population with ADHD symptoms. Furthermore, the applied theta/SMR-training is potentially not the most optimal neurofeedback protocol for ADHD in adolescents. Loo and Makeig [22] stated that, based on the current literature, theta/beta training results do not support applying this training as an additional treatment to standard practice. Other neurofeedback protocols, like the training of other frequency bands or training of slow cortical potentials (SCP < 0.1 Hz) [63, 64], might lead to better results. Further controlled research, preferable with double-blinded RCT designs and reported following the CONSORT guidelines [35], is warranted to investigate the effects of other neurofeedback protocols. Another limitation is the intensity of the training: adolescents who received neurofeedback were trained approximately twice a week over a total period of 5 months. Perhaps a shorter and more intensive training period, with three or more training sessions a week, is needed for inducing clinical relevant behavioral changes. Another limitation is the use of self- and parent-reported behavioral measures in combination with the non-blinded nature of the study. Because of the investment of parents and participants in the neurofeedback intervention, this might have increased the risk of a bias. It could be expected that the outcomes for the NFB + TAU condition were positively biased compared to TAU. A recent meta-analysis [24] pointed out that the neurofeedback treatment showed significant effects when non-blinded assessments were considered, but not when only probably blinded assessments were considered. In the current study, however, results showed no additional effects of neurofeedback on behavioral measures and as a consequence the effects were not likely influenced by such a positive bias. Nonetheless, teacher report forms would have added more objective measures of the effects of the treatment conditions in school settings. Another limitation is that ceiling effects in improvement on the behavioral measures by the TAU or as a result of developmental related improvement and multiple testing could be the cause for not finding additional effects for neurofeedback. Given the sample size of the study, effects of neurofeedback should be medium to large to be reliably detected; as a result small effects might be missed. Nevertheless, neurofeedback is a costly intervention in time investment for patients, parents, therapists, and

health care resources. The important question therefore is what effect size would make neurofeedback cost-effective and clinically relevant.

In conclusion, the present study showed that on behavioral outcome measures, the combination of neurofeedback and TAU was as effective as TAU-only for adolescents with ADHD symptoms. Neurofeedback in combination with TAU and TAU-only both showed significantly improved behavior, mainly in attention, at post-intervention. Considering the absence of additional behavioral effects in the current study, in combination with the limited knowledge of specific treatment effects of neurofeedback, it is questionable whether theta/SMR neurofeedback for adolescents with ADHD and comorbid disorders should be used in clinical practice. Further research is warranted to investigate possible working mechanisms and (long-term) specific treatment effects of neurofeedback.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders. Fourth edition, text revision edn. American Psychiatric Association, Washington, DC
2. Willcutt EG (2012) The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 9(3):490–499. doi:10.1007/s13311-012-0135-8
3. Barkley RA (2006) Comorbid disorders, social and family adjustment, and subtyping. In: Barkley RA (ed) Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. The Guilford Press, New York, pp 184–218
4. Larson K, Russ SA, Kahn RS, Halfon N (2011) Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. Pediatrics 127(3):462–470. doi:10.1542/peds.2010-0165
5. Lee DO, Ousley OY (2006) Attention-deficit hyperactivity disorder symptoms in a clinic sample of children and adolescents with pervasive developmental disorders. J Child Adolesc Psychopharmacol 16(6):737–746. doi:10.1089/cap.2006.16.737
6. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G (2008) Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 47(8):921–929. doi:10.1097/CHI.0b013e318179964f
7. Gjevik E, Eldevik S, Fjaeran-Granum T, Sponheim E (2011) Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders. J Autism Dev Disord 41(6):761–769. doi:10.1007/s10803-010-1095-7
8. Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S (2011) ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 128(5):1007–1022. doi:10.1542/peds.2011-2654
9. Faraone SV, Buitelaar J (2010) Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 19(4):353–364. doi:10.1007/s00787-009-0054-3
10. Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, Arnold LE, Abikoff HB, Bukstein OG, Conners CK, Elliott GR, Hechtman L, Hinshaw SP, Hoza B, Jensen PS, Kraemer HC, March JS, Newcorn JH, Severe JB, Wells K, Wigal T (2001) Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. J Am Acad Child Adolesc Psychiatry 40(2):180–187. doi:10.1097/00004583-200102000-00012
11. Research Units on Pediatric Psychopharmacology Autism Network (2005) Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 62(11):1266–1274. doi:10.1001/archpsyc.62.11.1266
12. Graham J, Coghill D (2008) Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs 22(3):213–237
13. Lofthouse N, Arnold LE, Hersch S, Hurt E, DeBeus R (2012) A review of neurofeedback treatment for pediatric ADHD. J Atten Disord 16(5):351–372. doi:10.1177/1087054711427530
14. Gevensleben H, Rothenberger A, Moll GH, Heinrich H (2012) Neurofeedback in children with ADHD: validation and challenges. Expert Rev Neurother 12(4):447–460. doi:10.1586/ern.12.22
15. Moriyama TS, Polanczyk G, Caye A, Banaschewski T, Brandeis D, Rohde LA (2012) Evidence-based information on the clinical use of neurofeedback for ADHD. Neurotherapeutics 9(3):588–598. doi:10.1007/s13311-012-0136-7
16. Holtmann M, Steiner S, Hohmann S, Poustka L, Banaschewski T, Bolte S (2011) Neurofeedback in autism spectrum disorders. Dev Med Child Neurol 53(11):986–993. doi:10.1111/j.1469-8749.2011.04043.x
17. Snyder SM, Hall JR (2006) A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. J Clin Neurophysiol 23(5):440–455. doi:10.1097/01.wnp.0000221363.12503.78
18. Banaschewski T, Brandeis D (2007) Annotation: what electrical brain activity tells us about brain function that other techniques cannot tell us—a child psychiatric perspective. J Child Psychol Psychiatry 48(5):415–435
19. Sterman MB, Wyrwicka W (1967) EEG correlates of sleep: evidence for seperate forbrain substrates. Brain Res 6:143–163
20. Sterman MB, Wyrwicka W, Roth S (1969) Electrophysiological correlates and neural substrates of alimentary behavior in the cat. Ann N Y Acad Sci 157:723–739
21. Lubar JF, Shouse MN (1976) EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report. Biofeedback Self-Regul 1(3):293–306
22. Loo SK, Makeig S (2012) Clinical utility of EEG in attention-deficit/hyperactivity disorder: a research update. Neurotherapeutics 9(3):569–587. doi:10.1007/s13311-012-0131-z
23. Arns M, de Ridder S, Strehl U, Breteler M, Coenen A (2009) Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. Clin EEG Neurosci 40(3):180–189

24. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, van der Oord S, Dopfner M, Dittmann RW, Simonoff E, Zuddas A, Banaschewski T, Buitelaar J, Coghill D, Hollis C, Konofal E, Lecendreux M, Wong IC, Sergeant J (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. doi:10.1176/appi.ajp.2012.12070991
25. Wechsler D (1991) Wechsler intelligence scale for children, 3rd edn. TX: The Psychological Corporation, San Antonio
26. Wechsler D (1997) Wechsler adult intelligence scale, 3rd edn. The Psychological Corporation, San Antonio
27. Kooij JJS (2002) ADHD bij volwassenen. Inleiding bij diagnostiek en behandeling [ADHD in adults. Introduction to diagnosis and treatment (in Dutch, 1st. ed.)]. 1st edn. Swets & Zeitlinger, Lisse
28. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC (1997) The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 12(5):232–241
29. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The mini-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(20):22–33; quiz 34–57
30. Hermens DF, Kohn MR, Clarke SD, Gordon E, Williams LM (2005) Sex differences in adolescent ADHD: findings from concurrent EEG and EDA. Clin Neurophysiol 116(6):1455–1463. doi:10.1016/j.clinph.2005.02.012
31. Hermens DF, Williams LM, Lazzaro I, Whitmont S, Melkonian D, Gordon E (2004) Sex differences in adult ADHD: a double dissociation in brain activity and autonomic arousal. Biol Psychol 66(3):221–233. doi:10.1016/j.biopsycho.2003.10.006
32. Bink M, van Nieuwenhuizen C, Popma A, Bongers IL, van Boxtel GJM (2014) Neurocognitive effects of neurofeedback in adolescents with ADHD: an RCT. J Clin Psychiatry 75(5):535–542. doi:10.4088/JCP.13m08590
33. Dallal GE (2007) Randomization plan generator; first generator. http://www.randomization.com
34. Faul F, Erdefelder E, Lang AG, Buchner A (2007) G*power 3: a flexible statistical power analysis program for the social, behavioral and biomedical sciences. Behav Res Methods 39(2):175–191
35. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8:18. doi:10.1186/1741-7015-8-18
36. Vink M, Van Wamel A (2007) Landelijk basisprogramma ADHD bij kinderen en jeugdigen [Dutch basic ADHD program for children and adolescents (in Dutch)]. Trimbos-instituut, Netherlands Institute of Mental Health and Addiction, Utrecht
37. Lubar JF (2003) Neurofeedback for the management of attention deficit disorders. In: Schwartz MS, Andrasik F (eds) Biofeedback a practitioner's guide, 3rd edn. The Guilford Press, New York, pp 409–437
38. Lubar JO, Lubar JF (1984) Electroencephalographic biofeedback of SMR and beta for treatment of attention deficit disorders in a clinical setting. Biofeedback Self-Regul 9(1):1–23
39. Fuchs T, Birbaumer N, Lutzenberger W, Gruzelier JH, Kaiser J (2003) Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl Psychophysiol Biofeedback 28(1):1–12
40. Braininquiry PET EEG 2.0 duo channel bipolar system
41. EEGer Spectrum Systems EEGer neurofeedback software. 4.2.1.S edn
42. Kooij JJS, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, Hodiamont PP (2005) Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med 35(6):817–827
43. Kooij JJS, Boonstra AM, Swinkels SHN, Bekker EM, Noord Id, Buitelaar JK (2008) Reliability, validity, and utility of instruments for self-report and informant report concerning symptoms of ADHD in adult patients. J Atten Disord 11(4):445–458. doi:10.1177/1087054707299367
44. DuPaul GJ, Anastopoulos AD, Power TJ, Reid R, Ikeda MJ, McGoey KE (1998) Parent ratings of attention-deficit/hyperactivity disorder symptoms: factor structure and normative data. J Psychopathol Behav Assess 20(1):83–102
45. Achenbach TM (1991) Integrative guide for the 1991 CBCL/4-18, YSR and TRF profiles. University of Vermont Department of Psychiatry, Burlington
46. Baron-Cohen S, Hoekstra RA, Knickmeyer R, Wheelwright S (2006) The autism-spectrum quotient (AQ)—adolescent version. J Autism Dev Disord 36(3):343–350. doi:10.1007/s10803-006-0073-6
47. Duric NS, Assmus J, Gundersen D, Elgen IB (2012) Neurofeedback for the treatment of children and adolescents with ADHD: a randomized and controlled clinical trial using parental reports. BMC Psychiatry 12:107. doi:10.1186/1471-244X-12-107
48. van Dongen-Boomsma M, Vollebregt MA, Slaats-Willemse D, Buitelaar JK (2013) A randomized placebo-controlled trial of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry 74(8):821–827. doi:10.4088/JCP.12m08321
49. Arnold LE, Lofthouse N, Hersch S, Pan X, Hurt E, Bates B, Kassouf K, Moone S, Grantier C (2013) EEG neurofeedback for ADHD: double-blind sham-controlled randomized pilot feasibility trial. J Atten Disord 17(5):410–419. doi:10.1177/1087054712446173
50. Perreau-Linck E, Lessard N, Levesque J, Beauregard M (2010) Effects of neurofeedback training on inhibitory capacities in ADHD children: a single-blind, randomized, placebo-controlled study. J Neurother 14:229–242. doi:10.1080/10874208.2010.501514
51. Vollebregt MA, van Dongen-Boomsma M, Buitelaar JK, Slaats-Willemse D (2013) Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study. J Child Psychol Psychiatry. doi:10.1111/jcpp.12143
52. Monastra VJ, Monastra DM, George S (2002) The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. Appl Psychophysiol Biofeedback 27(4):231–249
53. Meisel V, Servera M, Garcia-Banda G, Cardo E, Moreno I (2013) Neurofeedback and standard pharmacological intervention in ADHD: a randomized controlled trial with six-month follow-up. Biol Psychol 94(1):12–21. doi:10.1016/j.biopsycho.2013.04.015
54. Ogrim G, Hestad KA (2013) Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: a randomized pilot study. J Child Adolesc Psychopharmacol 23(7):448–457. doi:10.1089/cap.2012.0090
55. Greenhill LL, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J, Benson RS, Bukstein O, Bukstein O, Kinlan J, McClellan J, Rue D, Shaw JA, Stock S, American Academy of C, Adolescent P (2002) Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 41(2 Suppl):26S–49S
56. Rapport MD, Denney C (1997) Titrating methylphenidate in children with attention-deficit/hyperactivity disorder: is body mass predictive of clinical response? J Am Acad Child Adolesc Psychiatry 36(4):523–530. doi:10.1097/00004583-199704000-00015
57. Arns M, Kenemans JL (2012) Neurofeedback in ADHD and insomnia: vigilance stabilization through sleep spindles and circadian networks. Neurosci Biobehav Rev. doi:10.1016/j.neubiorev.2012.10.006

58. Holtmann M, Sonuga-Barke E, Cortese S, Brandeis D (2014) Neurofeedback for ADHD: a review of current evidence. Child Adolesc Psychiatr Clin N Am 23(4):789–806. doi:10.1016/j.chc.2014.05.006
59. Liechti MD, Valko L, Muller UC, Dohnert M, Drechsler R, Steinhausen HC, Brandeis D (2013) Diagnostic value of resting electroencephalogram in attention-deficit/hyperactivity disorder across the lifespan. Brain Topogr 26(1):135–151. doi:10.1007/s10548-012-0258-6
60. Poil SS, Bollmann S, Ghisleni C, O'Gorman RL, Klaver P, Ball J, Eich-Hochli D, Brandeis D, Michels L (2014) Age dependent electroencephalographic changes in attention-deficit/hyperactivity disorder (ADHD). Clin Neurophysiol. doi:10.1016/j.clinph.2013.12.118
61. Birbaumer N, Elbert T, Canavan AG, Rockstroh B (1990) Slow potentials of the cerebral cortex and behavior. Physiol Rev 70(1):1–41
62. Doehnert M, Brandeis D, Schneider G, Drechsler R, Steinhausen HC (2013) A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry 54(3):260–270. doi:10.1111/j.1469-7610.2012.02572.x
63. Drechsler R, Straub M, Doehnert M, Heinrich H, Steinhausen HC, Brandeis D (2007) 1Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). Behav Brain Funct: BBF 3:35. doi:10.1186/1744-9081-3-35
64. Strehl U, Leins U, Goth G, Klinger C, Hinterberger T, Birbaumer N (2006) Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. Pediatrics 118(5):e1530–e1540. doi:10.1542/peds.2005-2478