Neurocognitive Effects of Neurofeedback in Adolescents With ADHD: A Randomized Controlled Trial

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ABSTRACT

Objective: Neurofeedback aims to reduce symptoms of attention-deficit/hyperactivity disorder (ADHD), mainly attention problems. However, the additional influence of neurofeedback over treatment as usual (TAU) on neurocognitive functioning for adolescents with ADHD remains unclear.

Method: By using a multicenter parallel randomized controlled trial (RCT) design, male adolescents with a *DSM-IV-TR* diagnosis of ADHD (mean age = 16.1 years; range, 12–24) were randomized to receive either a combination of TAU and neurofeedback (n = 45) or TAU (n = 26). Randomization was computer generated and stratified by age group (ages 12 through 15, 16 through 20, and 21 through 24 years). The neurofeedback intervention consisted of approximately 37 sessions over a period of 25 weeks of theta/sensorimotor rhythm training on the vertex (Cz). Primary neurocognitive outcomes included performance parameters derived from the D2 Test of Attention, the Digit Span backward, the Stroop Color-Word Test and the Tower of London, all assessed preintervention and postintervention. Data were collected between December 2009 and July 2012.

Results: At postintervention, outcomes of attention and/or motor speed were improved, with faster processing times for both intervention conditions and with medium to large effect sizes (range, $\eta_p^2 = .08–.54$; *P* values < .023). In both groups, no improvements for higher executive functions were observed. Results might partly resemble practice effects.

Conclusions: Although neurocognitive outcomes improved in all adolescents receiving treatment for ADHD, no additional value for neurofeedback over TAU was observed. Hence, this study does not provide evidence for using theta/sensorimotor rhythm neurofeedback to enhance neurocognitive performance as additional intervention to TAU for adolescents with ADHD symptoms.

Trial Registration: Trialregister.nl identifier: 1759

J Clin Psychiatry 2014;75(5):535–542

Submitted: *May 17, 2013; accepted December 20, 2013 (doi:10.4088/JCP.13m08590).*
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Attention deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, with a worldwide prevalence of around 5%.[1,2] In addition, estimations of ADHD comorbidity in autism spectrum disorders range between 30% and 78%.[3–6] Best practice for reducing ADHD symptoms consists of stimulant medication, behavioral therapy, or both. Stimulant medication is effective in reducing ADHD symptoms in children with ADHD,[7,8] and it is effective, although possibly to a lesser extent, for treatment of ADHD in children with combined autism spectrum disorders and ADHD.[9,10] Similarly, neurocognitive dysfunction as associated in ADHD, generally seems to improve with the use of stimulant medication.[11] A recent review indicates that, generally, remittance of ADHD symptoms is not associated with improved neurocognitive functions: adolescents with remitted ADHD still experience decreased neurocognitive performance.[12] This indicates that ADHD symptomatology and neurocognitive functioning should be considered as separate treatment outcome measures.[11] Moreover, although stimulant medication seems effective in reducing ADHD symptoms[7–10] and improving neurocognitive functioning,[11] the majority of adolescents above the age of 15 years discontinue stimulant medication use despite the persistent course of the disorder.[13] Therefore, additional interventions to the current treatment as usual (TAU) to further reduce ADHD symptoms enduringly and simultaneously improve neurocognitive functioning are warranted. In this respect, neurofeedback, which is seen as a potentially effective intervention for reducing ADHD symptoms in ADHD[14,15] and autism spectrum disorders,[16] might as well be able to improve neurocognitive functioning.

Neurofeedback is based on the principle of operant conditioning and aims to alter brain functioning by giving real-time feedback of electroencephalogram (EEG) activity to the patient. Children with ADHD show an increased theta activity and decreased beta activity compared with typically developing children.[17] Accordingly, the most frequently used neurofeedback protocol is the theta/beta training, which aims to decrease theta (4–7 Hz) and increase sensorimotor rhythm (12–15 Hz) or beta (12–20 Hz).[14,15,18] Following theta/beta training, 1 study found changes in brain functioning as reflected in a decrease of posterior-midline theta activity.[19] In addition, the decrease in theta activity was related to the decrease in ADHD symptoms as reported by parents.[19] Two other studies showed similar improvement in attention on behavioral questionnaires over time for children with ADHD who were treated with neurofeedback, stimulant medication, or both.[20,21] Thus, some randomized controlled trials (RCTs)[19–21] have shown improvements in ADHD symptomatology, as reported by parents. However, these studies[19–21] did not report on intervention effects in relation to neurocognitive functioning.

To date, the findings of 4 blinded RCT studies[22–25] on neurofeedback for ADHD in which neurocognitive measures were reported are inconsistent. In 1 single-blinded study, children with ADHD who received neurofeedback improved more in reaction time and accuracy than those

receiving electromyography biofeedback.[22] In contrast, 3 double-blind studies failed to find additional improvement on neurocognitive measures for neurofeedback over sham neurofeedback in children with ADHD[23,25] and healthy students with ADHD features.[24] These neurocognitive outcomes[23–25] are in line with the behavioral outcomes of blinded studies that fail to find additional value of neurofeedback over sham neurofeedback.[23,24,26,27]

To summarize, although neurofeedback is seen as a potentially effective intervention for reduction of ADHD symptoms in children,[14,15] knowledge about the neurocognitive effects of neurofeedback is limited. Therefore, the aim of this study was to investigate the additional effect of neurofeedback to TAU on neurocognitive functioning in adolescents with ADHD, within a multicenter parallel RCT design.

Clinical Points

- Neurofeedback was proposed as a potentially effective treatment for symptoms of attention-deficit/hyperactivity disorder (ADHD).
- No additional value of neurofeedback to supplement treatment as usual was found in the current study, which is in line with previous double-blind studies that did not show effectiveness of neurofeedback over sham neurofeedback.
- Current evidence does not support the use of neurofeedback to enhance neurocognitive functioning in ADHD in clinical practice for adolescents and young adults with ADHD.

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)[28] or the Wechsler Adult Intelligence Scale (WAIS-III).[29] Adolescents diagnosed with autism spectrum disorders (including autism, Asperger's syndrome, and pervasive developmental disorder) with confirmed symptoms of clinical ADHD—equal to a full ADHD diagnosis—were also included. Diagnosed ADHD symptoms were verified by a *DSM-IV*–based Dutch semistructured ADHD interview for adults[30] and the Mini-International Neuropsychiatric Interview (MINI).[31,32] Trained psychologists administered the semistructured interviews. Exclusion criteria were neurologic disorders, schizophrenia, and other psychotic disorders.

Initially, a total of 90 adolescents were randomized over the interventions: combined neurofeedback and TAU (n = 59) or TAU (n = 31). The dropout rate did not differ for the neurofeedback plus TAU group (n = 14 [23.7%]) and the TAU group (n = 5 [16.1%]), $P = .778$, 2-tailed Fisher exact test. At direct analysis after intervention, neurofeedback plus TAU and TAU groups comprised 45 and 26 adolescents, respectively. The participant flow diagram is presented in Figure 1.

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

Trial Design

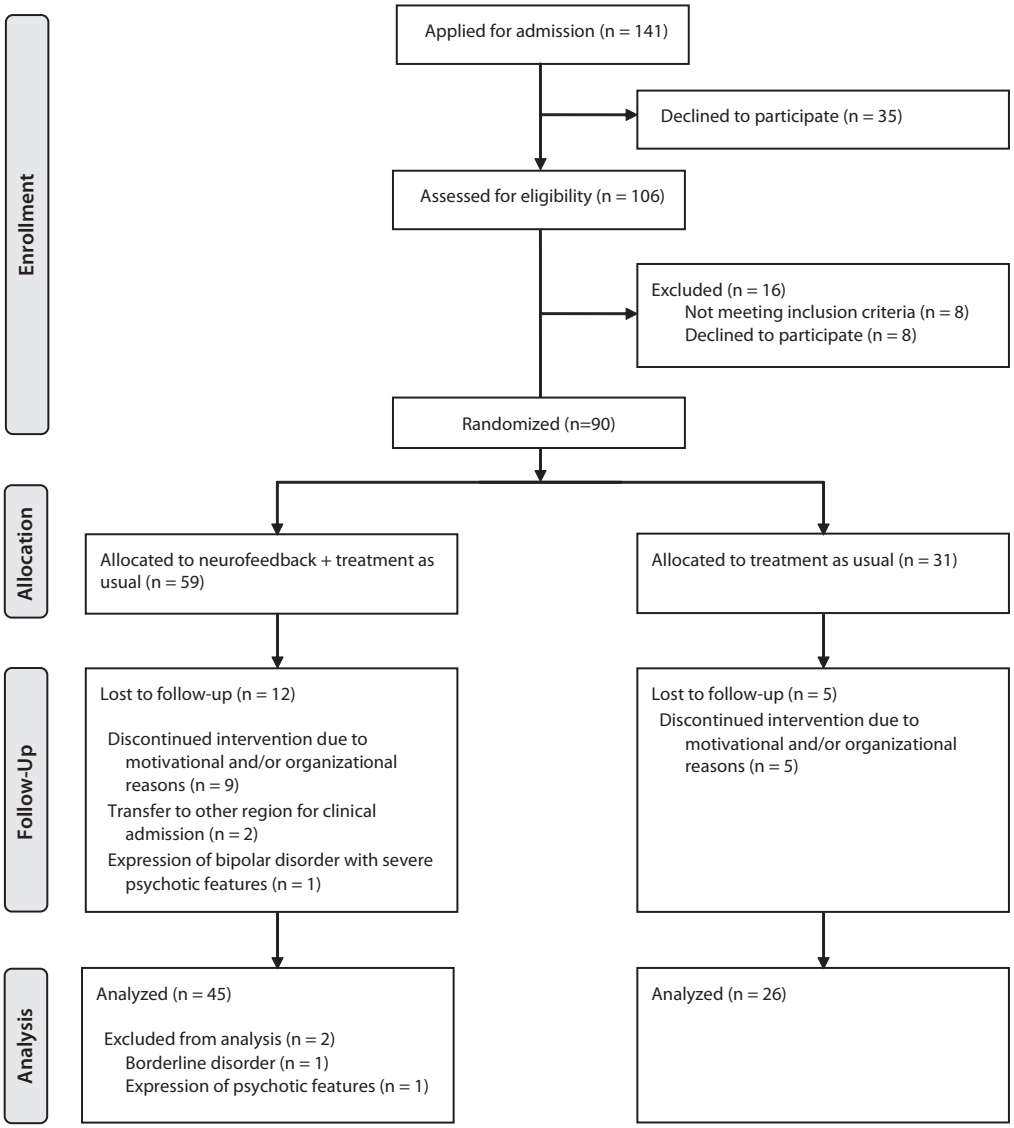
A multicenter parallel-group study was conducted, with stratification for age group (ages 12 through 15, 16 through 20, and 21 through 24 years) and imbalanced randomization (2:1) for neurofeedback plus TAU versus TAU. Randomization was computer generated,[33] with block lengths of 3, 6, 9, and 12 that varied randomly. An independent administrative employee was responsible for the assignment of participants to their groups immediately after preintervention assessment. The participant (and, if applicable, his parents) was notified the same day as to whether he would receive neurofeedback intervention or not. Participants, parents, neurofeedback trainers, outcome assessor, and clinical professionals were aware of the allocated group. The outcome assessor and neurofeedback trainer were not the same person. All data entry was performed blind to allocated intervention (neurofeedback plus TAU or TAU) and was checked twice by different research assistants.

Beforehand, a total sample size of 46 was calculated with G*power version 3.1.5.1[34] to be sufficient to detect a medium effect size ($f = 0.25$) in a repeated-measures analysis of variance (ANOVA), with an α of .05 and a power of 90%. In this article, the CONSORT 2010 guidelines for reporting parallel-group randomized trials were followed (eAppendix 1).[35] This trial was registered on trialregister.nl (identifier: 1759).

Interventions

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). Treatment as usual 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 on a regular basis at least once every 2 weeks and a general session duration of 45 minutes. The interventions were directed at the adolescent (n = 26 [36.6%]) or the parent(s) (n = 20 [28.2%]) (see Table 1). Stimulant medication use (n = 36 [50.7%]) included immediate-release methylphenidate, sustained-release methylphenidate, or dexamphetamine. Atomoxetine was used by 2 participants at study entry. Because of the suggested similar clinical effects of stimulant medication and atomoxetine, in the analyses, these 2 participants were categorized within the group of stimulant-medicated adolescents. Adherence to prescribed medication was verified by questioning the participants

Figure 1. Flow Diagram Neurofeedback in Attention-Deficit/Hyperactivity Disorder



as to 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).

Neurofeedback in addition to TAU. Neurofeedback training was carried out over a period of around 25 weeks, with 2 to 3 training sessions every week. Each participant was offered 40 training sessions of 30 minutes in total. The number of training sessions was approximately 37 (mean ± SD = 36.98 ± 4.94), with a minimum of 19 sessions. A neuropsychologist (M.B.) certified in EEG by Biofeedback EEG Spectrum International Inc and accredited by the Biofeedback Certification International Alliance (M.B.) trained the psychologists who gave the neurofeedback training.

Theta/sensorimotor rhythm training[37,38]—a form of theta/beta training—was applied, with thresholds to inhibit theta/alpha frequency bands (4–7 Hz and 8–11 Hz), to reward sensorimotor rhythm activity (13–15 Hz) and inhibit beta/gamma (22–36 Hz). Inhibition of the higher beta/gamma frequency band was conducted in this study to minimize the increase in sensorimotor rhythm activity by increased muscle tension and to decrease potentially 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[39]: 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.[40] The EEG signal was accordingly bandpass filtered in the different frequency bands with an exponentially weighted moving average filter over 0.5 seconds 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-minute epochs. Artifact rejection thresholds for the raw EEG signal were set to 60 μV. Relative thresholds for each frequency band were set to accept the signal 80% of the time and to reject the signal 20% of the time. Thresholds were calculated to correspond to the mean amplitude in microvolts of each frequency band over the last 30 seconds of input and were calculated after 30 seconds from the beginning of each 3-minute part session. For the first 30 seconds, thresholds of former 3-minute session were preserved.

The trained frequency bands were represented in visual information to the participant on a screen by simple graphics. At the moment the signal for all frequency bands fulfilled all threshold criteria, auditory feedback was given by a short 0.25-second beep, and the participants obtained a credit that increased the total session score.

Outcome Measures

Primary outcome measures consisted of behavioral, neurocognitive, and electrophysiological measures. Behavioral measures included the *DSM-IV*–based ADHD Rating Scale,[41] the Child Behavior Checklist,[42] and the Youth Self-Report.[42]

Neurocognitive measures of sustained and selective attention, interference, concentration, working memory, and executive planning were applied. The D2 Test of Attention[43] was administered, and the raw scores of the total number of processed items and total number of correctly processed items were analyzed. Three Digit Span backward[29,44] versions were constructed for the current study (eAppendix 2) and applied alternately across the participants and the preintervention and postintervention assessments. Raw scores were computed for the total score—the amount of correctly recalled rows—and the amount of numbers of the longest recalled row. The Stroop Color-Word Test[45,46] was applied; for analysis, raw scores of total execution time for the color-word card and the interference time—the difference in time between the color-word card and color card—were used. The Tower of London[47] was applied according to the age of the participant: either the 7–15 years form or the 16+ years form. Raw scores used were the total correct score (tasks performed in the fewest number of moves possible), the total move score (number of moves, above the minimally required steps per task), initiation time (time before the first move), executive time (time from the first move to task completion), and total time (initiation time plus executive time). Tower of London scores were summed scores over all 10 tasks.

Procedure

Prior to the start of the study, approval was obtained from the medical ethics committee for mental health institutions in the Netherlands (reference number: NL 24776.097.08 CCMO). The study took place in 3 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 years, parents also provided written informed consent.

At preintervention, participants were seen on 3 occasions for the administration of behavioral questionnaires, neurocognitive tests, the WAIS-III or WISC-III 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. Duration of the intervention period was approximately 25 weeks.

Postintervention assessment included behavioral questionnaires and neurocognitive tests for all 71 participants.

Because of test administration problems, 5 participants were excluded for analysis of the D2 Test of Attention, Stroop Color-Word Test, or Tower of London. One participant was excluded from analysis for the D2 Test of Attention because of misinterpretation of the instructions at the second measurement. Two participants were excluded from analysis for the Stroop Color-Word Test: one because he refused to cooperate with the test and the other because of a broken timer. For 1 participant, a version of the Tower of London that was not age appropriate was mistakenly administered, and he was therefore excluded from further analysis.

Statistical Analysis

All analyses were performed using SPSS version 21.[48] Effects were considered significant if $P < .05$. Differences on group characteristics were analyzed with a 1-way ANOVA or a χ^2 test with Fisher exact correction. Attrition analyses compared the analyzed subsample to the total sample on group characteristics, behavioral and neurocognitive measures with a 1-way ANOVA.

A generalized linear model ANOVA was applied for all the primary neurocognitive outcome measures, with intervention group as between-subjects factor and time (eg, between preintervention [t1] and postintervention [t2]) as within-subjects factor. The full factorial models were tested. All neurocognitive effects were evaluated using multivariate test criteria. Effect sizes are expressed in percentage of explained variance in partial $\eta 2(\eta_p^2)$. In addition, the adjusted difference at postintervention (AD_{t2-t1}) and 95% confidence interval (CI) were reported. Post hoc analyses were performed, with separate addition of stimulant medication use at preintervention and diagnostic group (ADHD or autism spectrum disorders with comorbid ADHD) as between factor to the generalized linear model.

RESULTS

Group Characteristics

At preintervention, there were no differences in group characteristics and behavioral and neurocognitive primary outcome measures between the neurofeedback plus TAU group and the TAU group (Table 1). The only exception was the result for TIQ: although TIQ for both groups was within the average range (95–105), TIQ was higher for the TAU group than for the neurofeedback plus TAU group.

Table 1. Group Characteristics and Treatment as Usual

Characteristic	Total (N = 71)	Neurofeedback + TAU (n = 45)	TAU (n = 26)	F^a	*P*
Age, mean (SD), y	16.1 (3.3)	16.1 (3.3)	16.2 (3.4)	0.0	.864
DSM-IV-TR diagnosis, n (%)					
ADHD	47 (66.2)	29 (64.4)	18 (69.2)		.797
ASD + ADHD	24 (33.8)	16 (35.6)	8 (30.7)		.797
GAF score, mean (SD)	54.7 (6.7)	53.8 (7.1)	56.2 (5.95)	2.0	.157
Treatment as usual					
Stimulant medication preintervention, n (%)	36 (50.7)	20 (44.4)	16 (61.5)		.220
Dose, mean (SD), mg[b]	37.2 (16.4)	36.1 (17.1)	38.6 (15.9)	0.2	.647
Months of intake before preintervention, n (%)				3.7	.457
Up to 3	6 (8.5)	4 (8.9)	2 (7.7)		
3 to 6	3 (4.2)	2 (4.4)	1 (3.8)		
6 to 12	4 (5.6)	3 (6.7)	1 (3.8)		
12 or longer	23 (32.4)	11 (24.4)	12 (46.2)		
Stimulant free, n (%)	35 (49.3)	25 (55.6)	10 (38.5)		
Stimulant medication started after preintervention, n (%)	6 (8.5)	3 (6.7)	3 (11.5)		.662
Stimulant medication stopped after preintervention, n (%)	9 (12.7)	5 (11.1)	4 (15.4)		.716
Behavioral interventions adolescent,[c] n (%)	26 (36.6)	14 (31.1)	12 (46.2)		.318
Behavioral interventions parent,[c] n (%)	20 (28.2)	12 (26.6)	8 (30.7)		.787
Behavioral measure, mean (SD)					
MINI ADHD inattention	5.6 (2.6)	5.4 (2.6)	6.1 (2.7)	1.2	.280
MINI ADHD hyperactivity/impulsivity	4.0 (2.5)	4.2 (2.6)	3.7 (2.3)	0.5	.489
ADHD Rating Scale					
Inattention childhood symptoms[d]	6.1 (2.7)	5.7 (2.9)	6.8 (2.0)	2.9	.093
Hyperactivity/impulsivity childhood symptoms[d]	4.9 (2.9)	4.6 (3.0)	5.6 (2.6)	2.0	.160
Inattention current symptoms	4.7 (2.4)	4.4 (2.5)	5.3 (2.2)	2.2	.142
Hyperactivity/impulsivity current symptoms	3.4 (2.1)	3.4 (2.1)	3.3 (2.5)	0.1	.734
YSR total problem score	49.7 (20.9)	48.0 (22.0)	52.6 (18.9)	0.8	.382
YSR attention problems	9.6 (3.3)	9.4 (3.32)	9.9 (3.2)	0.5	.487
CBCL total problem score[e]	62.3 (27.6)	61.1 (28.0)	64.1 (27.3)	0.2	.662
CBCL attention problems[e]	11.5 (3.4)	11.2 (3.7)	12.0 (3.1)	0.9	.359
Intelligence					
IQ discrepancy profile,[f] n (%)	24 (33.8)	14 (31.1)	10 (38.5)		.606
Total IQ, mean (SD)	100.7 (11.3)	98.6 (10.4)	104.2 (12.2)	4.2	.045
Verbal IQ, mean (SD)	102.4 (12.9)	100.2 (11.4)	106.2 (14.5)	3.8	.057
Performance IQ, mean (SD)	99.5 (11.9)	98.4 (11.2)	101.3 (13.1)	1.0	.327

[a] *df* = 1,69.
[b] Doses for the adolescents on stimulant medication (n = 35).
[c] Behavioral interventions followed between preintervention and postintervention as followed by the adolescents or 1 of the parents, respectively.
[d] Retrospective self-reported childhood symptoms (primary school period) and current symptoms (in the past 6 months).
[e] CBCL data; N = 66 participants: neurofeedback (n = 40), TAU (n = 26); *df* = 1,64.
[f] IQ discrepancy profile is considered as a profile with a difference score between verbal IQ and performance IQ of 15 points or more. Because of the discrepancy profiles, verbal IQ and performance IQ are noted separately.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, CBCL = Child Behavior Checklist, GAF = Global Assessment of Functioning, IQ = intelligence quotient, MINI = Mini-International Neuropsychiatric Interview, TAU = treatment as usual, YSR = Youth Self-Report.

Attrition Analysis

Attrition analysis showed that the dropout group (n = 16), due to transfer, motivational, and/or organizational reasons, did not differ from the total analyzed group (N = 71) on group characteristics and behavioral and neurocognitive measures at preintervention. In addition, the subsamples of the D2 Test of Attention (n = 70), Stroop Color-Word Test (n = 69), and Tower of London (n = 70) did not differ from the total analyzed sample (N = 71) on group characteristics and behavioral and neurocognitive measures at preintervention.

Neurocognitive Measures

Neurocognitive outcome measures are summarized in Table 2. On the D2 Test of Attention, there was a large improvement over time for the adolescents on attention and motor speed, with more processed items and more correctly processed items over the whole test. The Digit Span backward showed a medium improvement in attention for the adolescents, with an increased total score over time. On the other hand, working memory, as estimated with the longest recalled row, did not change over time. Medium improvements were found on the Stroop Color-Word Test, with shorter execution times for the color-word and shorter interference times at postintervention. Similarly, the Tower of London revealed a medium improvement, with shorter executive and total times. However, planning as estimated with the total move score, total correct score, and initiation time revealed no improvement over time. Neurocognitive measures were similar for the neurofeedback plus TAU and the TAU group and did not differ between the groups over time.

Post hoc analyses for stimulant medication use and autism spectrum disorders. Stimulant-medicated adolescents did not differ over time from stimulant-free adolescents

Table 2. Raw Scores Preintervention and Postintervention on the D2 Test of Attention, Digit Span Backward, Stroop Color-Word Test, and Tower of London

Measure	Preintervention (t1)		Postintervention (t2)		Adjusted Difference (95% CI) at Postintervention (t2 – t1)	ANOVA Time (t1 to t2)[a]			ANOVA Neurofeedback + TAU and TAU Over Time[a]			Post Hoc Medication Use Over Time[b]			Post Hoc ASD + ADHD and ADHD Over Time[b]		
	Neurofeedback + TAU, Mean (SD)	TAU, Mean (SD)	Neurofeedback + TAU, Mean (SD)	TAU, Mean (SD)		*F*	η_p^2	*P*	*F*	η_p^2	*P*	*F*	η_p^2	*P*	*F*	η_p^2	*P*
D2 Test of Attention	n = 44	n = 26	n = 44	n = 26													
Total no. of processed items	400.1 (64.5)	421.3 (68.9)	452.8 (77.2)	457.6 (73.9)	44.5 (32.3 to 56.6)	53.1	.44	.000	1.8	.03	.184	2.2	.03	.139	0.2	.00	.632
Total no. of correctly processed items	158.6 (25.8)	161.8 (25.9)	179.5 (32.3)	182.2 (29.0)	21.6 (16.8 to 26.4)	80.7	.54	.000	0.3	.00	.605	0.6	.01	.456	0.3	.00	.614
Digit Span backward	n = 45	n = 26	n = 45	n = 26													
Total score	6.5 (1.6)	6.7 (2.0)	6.7 (1.6)	7.6 (2.3)	0.6 (0.1 to 1.0)	6.9	.09	.010	2.2	.03	.140	0.2	.00	.642	0.2	.00	.627
Longest row	4.7 (.9)	5.0 (1.0)	4.8 (.9)	5.2 (1.3)	0.2 (–0.1 to 0.4)	1.3	.02	.250	0.3	.00	.608	0.2	.00	.675	0.0	.00	.906
Stroop Color-Word Test[c]	n = 43	n = 26	n = 43	n = 26													
Color/word card	99.8 (22.6)	99.4 (25.7)	91.9 (20.4)	95.9 (32.4)	–6.1 (–10.7 to –1.5)	7.0	.09	.010	0.6	.01	.454	3.0	.04	.087	1.7	.03	.201
Interference	34.7 (14.4)	35.2 (18.1)	30.2 (12.9)	30.5 (19.9)	–4.5 (–8.5 to –0.7)	5.4	.08	.023	0.0	.00	.979	3.0	.04	.086	2.3	.03	.137
Tower of London	n = 45	n = 25	n = 45	n = 25													
Correct score	3.5 (1.8)	3.6 (1.6)	3.2 (1.9)	4.3 (2.1)	0.2 (–0.3 to 0.7)	0.7	.01	.401	3.2	.05	.077	2.4	.03	.129	0.0	.00	.983
Move score	31.5 (16.0)	32.9 (13.6)	31.4 (16.3)	28.5 (15.3)	–2.3 (–6.4 to 1.9)	1.2	.02	.277	1.1	.02	.297	0.1	.00	.710	0.0	.00	.729
Initiation time	23.3 (16.6)	20.1 (10.2)	22.6 (21.5)	22.7 (12.2)	–0.9 (–2.3 to 4.2)	0.3	.00	.574	1.0	.01	.322	0.5	.01	.485	2.5	.04	.117
Execution time	174.7 (71.0)	173.5 (50.3)	144.8 (40.2)	151.4 (51.8)	–26.0 (–41.6 to –10.4)	11.1	.14	.001	0.2	.00	.624	0.1	.00	.713	0.1	.00	.816
Total time	198.0 (77.1)	193.6 (52.4)	167.4 (45.7)	174.0 (52.6)	–25.1 (–41.5 to –8.7)	9.3	.12	.003	0.4	.00	.507	0.0	.00	.832	0.3	.00	.592

[a]Time from preintervention to postintervention; D2 Test of Attention, $df = 1,68$; Digit Span backward, $df = 1,69$; Stroop Color-Word Test, $df = 1,67$; Tower of London, $df = 1,68$. [b]Post hoc addition for medication use and ASD separately; D2 Test of Attention, $df = 1,66$; Digit Span backward, $df = 1,67$; Stroop Color-Word Test, $df = 1,65$; Tower Of London, $df = 1,66$. No interaction effects were found for time, intervention group, and stimulant medication use. [c]Time in seconds.

$^*P < .05$. $^{**}P < .005$. $^{***}P < .001$.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ANOVA = analysis of variance, ASD = autism spectrum disorder, TAU = treatment as usual.

on the neurocognitive measures. Likewise, there were no differences over time on neurocognitive measures between adolescents with ADHD or combined autism spectrum disorders with ADHD.

DISCUSSION

The present study examined the additional value of neurofeedback to TAU on neurocognitive functioning in adolescents with ADHD, using a multicenter parallel RCT design. Results showed an improvement in neurocognitive measures of attention and/or motor skills at postintervention for all adolescents with ADHD. Adolescents needed less time to process information and performed tasks with the same level of accuracy. Working memory and planning estimations remained stable over time.

Neurocognitive functioning improved as much for the adolescents who received neurofeedback in addition to the TAU as for the adolescents who received only TAU. The neurocognitive outcomes are in agreement with the behavioral outcomes of the current study that showed large improvements on parent as well as on self-reported behavior irrespective of treatment allocation. This is in line with results from 2 double-blind studies with children with ADHD that also failed to find more improvement on behavioral questionnaires[23,26] and neurocognitive measures[23,25] for neurofeedback over sham neurofeedback. Furthermore, a study in healthy students who scored relatively high on ADHD symptoms found similar results for neurofeedback and sham neurofeedback on self-reported attention problems as well as reaction time and accuracy.[24] In contrast, positive results were shown in a study[22] with better performance for neurofeedback compared to electromyography biofeedback on reaction time and accuracy in children with ADHD.

The differences in outcomes of the studies might be a result of the applied training protocol. The RCT studies that failed to find significant effects for neurofeedback in the treatment of ADHD,[23,24,26] like the current study, combined inhibition of theta with reward of sensorimotor rhythm (12–15 Hz) activity in the majority of the applied (sometimes individualized) training protocols. In contrast, the neurofeedback versus electromyography biofeedback study by Bakhshayesh et al[22] applied a somewhat different protocol with also inhibition of theta, but reward of beta (16–20 Hz) instead of sensorimotor rhythm activity. Similarly, reward of the higher beta range (16–20 Hz) in the training protocol was also applied in the study by Gevensleben et al,[49] which showed neurofeedback to be more effective in reducing ADHD symptoms than computerized attention training, and in the studies that compared neurofeedback to stimulant medication.[20,21] It might be that training protocols aimed at (also) rewarding beta (16–20 Hz) are more favorable in the training of attention. However, at this moment, training protocols are used alternately in

clinical practice as well as in research. There is no consensus on the exact kind of protocol to apply for the treatment of ADHD. Therefore, additional knowledge about specific working mechanisms of neurofeedback on the brain is necessary before neurofeedback protocols can be adapted appropriately for the treatment of psychiatric disorders.

Stimulant medication use by the participants was allowed in the current study as a part of TAU. Therefore, it could be hypothesized that medication could have mediated the effect of neurofeedback. Overall, stimulant medication improves neurocognitive functioning.[11] It could be that the magnitude of the improvement depends on the cognitive domain. Task improvements by stimulant medication were seen, especially in reaction time variability as measured during less cognitively demanding repetitive tasks that need sustained attention and less in more complex cognitive tasks.[50] Comparably, the current study shows improvement over time in measures of attention and processing speed but not in more complex cognitive tasks. However, we did not find the expected better performance in stimulant-medicated adolescents compared to stimulant-free adolescents. The long-term effects of stimulant treatment on neurocognitive functioning are less well known.[50] Three-fourths of the adolescents who used stimulant medication started intake 6 months or longer before study entrance. Consequently, this long-term intake of stimulant medication might contribute to the absence of differentiation by stimulant medication use.

Although neurofeedback does not seem effective for autism symptoms, a review[16] indicated it could be effective for comorbid ADHD symptoms in autism spectrum disorders. Therefore, adolescents with clinical ADHD symptoms and autism spectrum disorders were also included in the current study. None of the outcomes differentiated between adolescents with ADHD versus combined autism spectrum disorders and ADHD; both diagnostic groups showed similar improvements over time. This suggests that the co-occurrence of autism spectrum disorders did not influence the outcomes.

The present study contributes to the literature by applying an RCT design in a naturalistic multimodal treatment setting, thereby increasing the ecological validity of the study. However, as a consequence, the target population consisted of a heterogeneous group of male adolescents with complex problems. Previous research[49] that showed positive results on measures of attention was based on more homogeneous populations with ADHD. Another point of consideration is that the current study included adolescents who were older than the children in previous research. Studies that revealed positive results all aimed at children with a mean age of around 10 years, whereas the mean age of the participants was 16 years in the current study. Developmentally related large increases in attention and/or (motor) speed during adolescence[51] might have induced ceiling effects on the neurocognitive tests. Furthermore, practice effects by multiple testing are known to have a considerable impact on test outcomes.[52] Consequently, outcomes might reflect practice effects rather than improved neurocognitive functioning. In addition, TIQ was somewhat higher for the TAU group than the neurofeedback plus TAU group. As a result, it could be assumed that with a higher TIQ, practice effects could be larger[52] and could conceal potential treatment effects in the neurofeedback plus TAU group. Diminished and improved learning curves have indeed been found in low and high average TIQ, respectively.[53,54] Note that both intervention groups had a mean TIQ within the average range (95–105) and did not differ significantly on any of the other measures, including performance IQ. Therefore, we consider the impact of the difference is likely to be minimal. Overall, the large improvement over time might reflect practice effects, developmental changes, learning effects, as well as effects of TAU.

In conclusion, adolescents both in the neurofeedback plus TAU and in the TAU groups showed significantly improved neurocognitive outcomes—mainly processing speed—at postintervention. No additional value of neurofeedback over TAU was found. Hence, this study does not provide evidence for using theta/sensorimotor rhythm neurofeedback to enhance neurocognitive performance as additional intervention to TAU for adolescents with ADHD and comorbid disorders in clinical practice.

Drug names: atomoxetine (Strattera), methylphenidate (Concerta, Ritalin, and others).

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Potential conflicts of interest: The authors declare no potential conflicts of interest.

Funding/support: This trial is funded by The Netherlands Organization for Health Research and Development (ZonMw): 157 002 004.

Role of the sponsor: ZonMw had no role in the data analysis, manuscript preparation, or decision to publish this article.

Previous presentation: Bink M, Bongers IL, Popma A, et al. Effectiveness of neurofeedback in adolescents with ADHD-features and comorbid disorders: a randomized controlled trial. Presented at the symposium "The Future of Neurofeedback: insights from theory and practice"; November 28, 2012; Nijmegen, the Netherlands.

Acknowledgments: The authors thank Jeroen Bink (Ir) (Actiflow BV, Breda, the Netherlands) for programming the digit span generator; Ad Denissen (Ir) (Philips Research, Eindhoven, the Netherlands) for technical assistance and advice; Carlijn Berghout (MD) (GGzE, Eindhoven, the Netherlands/Dimence, Almelo, the Netherlands), Marilyn Peeters (MSc) (GGzE, Eindhoven, the Netherlands), and Thomas Widdershoven (MSc) (GGzE, Eindhoven, the Netherlands) for administering the neurofeedback training; and the students and research assistants for their contribution to the test assessments as well as all participating adolescents and families for their contribution and persistence. Ms Peeters was paid for her contribution to the data collection of the study by the ZonMw funding. The authors declare that Ms Berghout and Messrs Bink, Denissen, and Widdershoven have no potential conflicts of interest.

Supplementary material: Available at PSYCHIATRIST.COM.

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THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Neurocognitive Effects of Neurofeedback in Adolescents With ADHD: A Randomized Controlled Trial

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DOI Number: 10.4088/JCP.13m08590

List of Supplementary Material for the article

1. **eAppendix 1** Supplement effects of Neurofeedback in ADHD: CONSORT CHECKLIST

2. **eAppendix 2** Digit Span Backward

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and	2a	Scientific background and explanation of rationale	3-4
objectives	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6-
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	6

	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	6
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	6
concealment		describing any steps taken to conceal the sequence until interventions were assigned	
mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	6
		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6 n/a
		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	5 +Figure 1
diagram is strongly		were analysed for the primary outcome	
recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	5+Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9

	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10+11 Table 1+2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10+11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-14
Other information			
Registration	23	Registration number and name of trial registry	2 abstract
Protocol	24	Where the full trial protocol can be accessed, if available	2 abstract
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1 Title page

eAppendix 2. Digit Span Backward

Three digit span backwards (DSB)[1, 2] versions were constructed for the current study. The constructed DSB is based on the DSB of the WAIS.[2] Digits spans constituted digit rows that are two to eight digits long. The assessor read each row one time to the participant. Participants were asked to repeat the digits in reverse order. The test was terminated when two successive rows of the same length were not recalled correctly. The DSB was assessed pre-intervention, direct post-intervention and at one-year follow-up. For each assessment the participant received another version. Version order (1, 2, 3; 2, 3, 1; or 3, 1, 2) was assigned at pre-intervention measurement and was divided equally over the participants.

The three DSB (see Figure A) were generated by the following rules: each row contains digits ranging from 1 to 9; each digit is represented not more than once in a row; the starting digit of a row is unequal to the last digit of the former row; two successive rows do not end with the same digit; not more than two rows end with the same digit, a digit is never placed at the same place in the row in two successive rows; a digit is never placed more than two times in the total span in the same place in a row; the total span contains the same digit a maximum 8 times (each digit is represented 7 or 8 times in the total span); a pattern of two digits is never repeated (example: if one row contains 2-3 than an other in the total span will not contain 2-3 in another row; 3-2 can be used in another row); a pattern of 3 digits is never repeated, not even in another order (example: if one row contains 3-8-2, another row will not contain 3-8-2 or 2-3-8); a pattern will never contain 3 successive ascending or descending digits (example: 2-3-4 or 4-3-2 are not included in the span).

Figure A: Digit Spans backwards

Digit span A	Digit span B	Digit Span C
6- 3	1- 4	9- 8
2- 1	7- 2	4- 7
5- 8 -7	4- 8- 9	5- 6- 4
2- 4- 6	6- 7- 5	3- 5- 8
9- 7- 1- 3	8- 6- 1- 7	2- 3- 6- 5
8- 5- 3- 6	2- 4- 5- 8	9- 1- 2- 4
7- 2- 6- 1- 5	3- 8- 1- 5- 9	3- 2- 5- 7- 6
9- 4- 1- 7- 8	2- 1- 8- 7- 3	5- 4- 8- 6- 3
1- 9- 2- 8- 4- 5	5- 2- 3- 6- 9- 1	8- 2- 7- 9- 4- 1
3- 7- 9- 6- 5- 2	6- 3- 4- 2- 7- 8	6- 7- 1- 4- 3- 9
7- 3- 2- 5- 4- 9- 8	1- 9- 7- 6- 8- 4- 3	2- 6- 9- 5- 1- 8- 7
5- 1- 4- 2- 3- 8- 9	9- 3- 2- 8- 5- 6- 4	1- 3- 7- 8- 5- 9- 2
3- 9- 5- 7- 6- 4- 8- 1	3- 7- 4- 9- 6- 5- 1- 2	7- 5- 3- 1- 6- 2- 8- 9
8- 2- 7- 4- 3- 1- 6- 9	4- 1- 3- 5- 7- 9- 2- 6	6- 8- 1- 9- 7- 3- 4- 2

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