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ORIGINAL CONTRIBUTION

A 6-month follow-up of an RCT on behavioral and neurocognitive effects of neurofeedback in children with ADHD

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Abstract To assess the long-term effects of neurofeedback (NFB) in children with attention deficit hyperactivity disorder (ADHD), we compared behavioral and neurocognitive outcomes at a 6-month naturalistic follow-up of a randomized controlled trial on NFB, methylphenidate (MPH), and physical activity (PA). Ninety-two children with a DSM-IV-TR ADHD diagnosis, aged 7–13, receiving NFB ($n = 33$), MPH ($n = 28$), or PA ($n = 31$), were re-assessed 6-months after the interventions. NFB comprised theta/beta training on the vertex (cortical zero). PA comprised moderate to vigorous intensity exercises. Outcome measures included parent and teacher behavioral reports, and neurocognitive measures (auditory oddball, stop-signal, and visual spatial working memory tasks). At follow-up, longitudinal hierarchical multilevel model analyses revealed no significant group differences for parent reports and neurocognitive measures ($p = .058$–$.997$), except for improved inhibition in MPH compared to NFB ($p = .040$) and faster response speed in NFB compared to PA ($p = .012$) during the stop-signal task. These effects, however, disappeared after controlling for medication use at follow-up. Interestingly, teacher reports showed less inattention and hyperactivity/impulsivity at follow-up for NFB than PA ($p = .004$–$.010$), even after controlling for medication use ($p = .013$–$.036$). Our findings indicate that the superior results previously found for parent reports and neurocognitive outcome measures obtained with MPH compared to NFB and PA post intervention became smaller or non-significant at follow-up. Teacher reports suggested superior effects of NFB over PA; however, some children had different teachers at follow-up. Therefore, this finding should be interpreted with caution.

Clinical trial registration Train your brain and exercise your heart? Advancing the treatment for Attention Deficit Hyperactivity Disorder (ADHD), Ref. no. NCT01363544, https://clinicaltrials.gov/show/NCT01363544.

Keywords Neurofeedback · ADHD · Behavior · Cognition · Naturalistic follow-up

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention, as well as hyperactivity and impulsivity [1], and is often accompanied by impairments in neurocognitive functioning, such as deficits in attention, inhibition, and working memory [2–5]. Stimulant medication is effective and frequently used as a treatment for behavioral [6] and neurocognitive [7] impairments found in ADHD. Despite the benefits, adverse side effects [8] and limited evidence for the long-term effects of stimulant medications [9] have led to the search for alternative treatments for ADHD.

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Neurofeedback has been used as a potentially successful non-pharmacological treatment for ADHD [10, 11]. This alternative treatment intends to alter brain activity by providing feedback of electroencephalogram (EEG) activity. The majority of studies on neurofeedback have made use of EEG training of theta/beta and/or sensorimotor rhythm (SMR) activity [12]. In this study, we focus on EEG training of theta/beta activity. The rationale for this neurofeedback protocol stems from findings of increased theta (4–7 Hz) and decreased beta activity (13–20 Hz) in children with ADHD compared to typically developing (TD) children [13]. Increased theta activity is related to lower vigilance and decreased beta activity is associated with reduced attention [14].

The results of randomized controlled trials on the effects of neurofeedback in children with ADHD are mixed [15, 16]. In a previous study, we reported on the direct post-intervention effects of neurofeedback compared to stimulant medication and physical activity (semi-active control condition), showing superior effects of stimulant medication compared to neurofeedback and the semi-active control condition in decreasing behavioral symptoms [17] and improving neurocognitive functioning [18] in ADHD. An important remaining issue, however, is whether treatment effects persist [19, 20] and/or whether possible delayed effects occur. Findings concerning the long-term effects of neurofeedback, comparing treatment as usual combined with neurofeedback to treatment as usual, are mixed [21, 22]. Bink et al. [21] found no additional effect at 1-year follow-up of theta/SMR neurofeedback training on either behavioral or neurocognitive outcome measures. Steiner et al. [22] found sustained improvement in children in the theta/beta neurofeedback training group on behavioral outcome measures and executive functioning compared to the treatment as usual group at 6-month follow-up. Similar to the findings of Steiner et al. [22], Gevensleben et al. [23] also found positive effects of theta/beta neurofeedback training on behavioral measures compared to computerized attention skills training at 6-month follow-up. There are two RCT studies that compared the long-term effects of neurofeedback to stimulant medication. The study of Meisel et al. [42] found similar behavioral improvement for theta/beta neurofeedback training and stimulant medication both post intervention and at 6-month follow up. In contrast, the study of Moreno-García et al. [24] found better post-intervention attentional functioning assessed by a neurocognitive task in those treated with stimulant medication compared to those treated with theta/beta neurofeedback, but group differences disappeared at 2-month follow-up.

In sum, neurofeedback is a potentially effective treatment for behavioral and neurocognitive symptoms in ADHD. However, the results for both short-term and long-term effects of neurofeedback are mixed. Furthermore, studies on long-term effects are limited in number and vary in terms of control conditions. Therefore, in this RCT, we compared the behavioral and neurocognitive effects of neurofeedback to stimulant medication, and to a semi-active control condition consisting of a physical activity intervention to control for non-specific treatment effects at 6-month naturalistic follow-up. Behavioral effects were evaluated by both parents and teachers. Neurocognitive functioning was assessed using measures of attention, inhibition, and visual spatial working memory. In addition, secondary measures evaluated possible side effects using quality of sleep.

Methods

Participants

Eligible participants were Dutch-speaking children, aged 7–13 years old, with a primary clinical diagnosis of ADHD established using DSM-IV-TR criteria [1]. Children with ADHD were recruited from 15 child mental health outpatient care facilities in the west of the Netherlands. Before entering the study, parent and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS) [25] confirmed the children's diagnosis; at least one of the scores on the Inattention or Hyperactivity/Impulsivity Scales had to be above the 90th percentile for one of the informants, and above the 70th percentile for the other informant (signifying pervasiveness of symptoms). At study entry, all children had been free of stimulant use for at least 1 month. Exclusion criteria were neurological disorders and IQ below 80 as measured by a four subtest version of the Wechsler Intelligence Scale of Children-III (WISC-III), including the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement [26]. No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the clinical records. Comorbid disorders included learning disorders (NFB $n = 5$, MPH $n = 2$, PA $n = 1$), autism spectrum disorders (NFB $n = 3$, MPH $n = 2$, PA $n = 3$), anxiety disorders (NFB $n = 2$, MPH $n = 0$, PA $n = 2$), and mood disorder (NFB $n = 1$, MPH $n = 0$, PA $n = 0$). Chi square testing revealed no significant differences in the distribution of comorbid disorders over groups [χ^2 (8, $n = 112$) = 12.88, $p = .12$].

Initially, 112 children with ADHD were randomized to one of the three intervention groups: NFB ($n = 39$), MPH ($n = 36$), or PA ($n = 37$). At 6-month follow-up, a total of 20 children had dropped out of the study. The numbers of children who dropped out were similarly distributed across the three intervention groups [NFB $n = 6$ (15.4%), MPH $n = 8$ (22.2%), PA $n = 6$ (16.2%), $p = .705$, two-tailed Fisher's exact test). In total, 92 children participated in the 6-month follow-up measurement, NFB ($n = 33$), MPH

($n = 28$), and PA ($n = 31$). Figure 1 presents a flow diagram of participants.

Trial design

A multicenter three-way parallel group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator [27]. Stocks of nine unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing the intervention allocation. Subsequently, children, parents, and teachers were aware of the allocated group. The trial was registered on clinicaltrials.gov (Ref. no. NCT01363544).

Interventions

The NFB and PA treatments consisted of 30 individual training sessions that were offered three times a week over a period of 10–12 weeks. Each session lasted 45 min, including 20 min of effective training. All interventions, as described below, took place after the pre-intervention assessment. A full description of the interventions can be found in previous reports [17, 18].

Neurofeedback (NFB)

Theta/beta training was applied with the aim of inhibiting theta activity (4–8 Hz) and reinforcing beta activity (13–20 Hz) at the vertex [cortical zero (Cz)]. The theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over one trial relative to the session baseline was rewarded with the appearance of a sun and granted credits. To promote generalization of the strategies learned to daily life, transfer trials were used. The mean number of training sessions for participants ($n = 38$) who completed the assessments post intervention was 29 ($M = 28.53$, SD = 2.63, range 19–30). The mean number of training sessions for participants ($n = 33$) who completed the assessments at follow-up was 29 ($M = 28.94$, SD = 1.75, range 22–30).

Methylphenidate (MPH)

After the pre-intervention assessment, a 4-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate (MPH) [28]. In total, 31 children completed the titration procedure. Children were classified by a standardized procedure [29] as responders when their ADHD symptoms decreased significantly compared to placebo ($n = 29$). The two non-responders were treated with 5 mg MPH twice daily. The child's psychiatrist prescribed the optimal dose for the remaining intervention period (5 mg for 10 children, including 8 responders and 2 non-responders; 10 mg for 14 children; 15 mg for 2 children; 20 mg for 5 children). At follow-up, 21 children were using medication, while 6 children discontinued medication usage.

Physical activity (PA) as a semi-active control condition

Each training session started with 5 min of warm up, followed by five 2-min moderate intensity exercises at a level of 70–80% of maximum heart rate (HR_{max}). After a 5-min break, five 2-min vigorous intensity exercises at 80–100% of HR_{max} were performed. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland). The mean number of sessions for participants who completed the assessments post intervention ($n = 34$) was 28 ($M = 27.74$, SD = 3.56, range 12–30). The mean number of training sessions for participants who completed the assessments at follow-up ($n = 31$) was 28 ($M = 28.29$, SD = 2.30, range 19–30).

Outcome measures

A full description of the outcome measures can be found in previous papers [17, 18]. The following behavioral and neurocognitive measures were used to assess long-term outcomes.

Behavioral outcome measures

Scores on the parent- and teacher-reported Strength and Difficulty Questionnaire (SDQ) [30, 31] and Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale (SWAN) [32] were used as primary outcome measures. The Total Scale of the SDQ (assessing behavioral problems) and the SWAN Inattention and Hyperactivity/Impulsivity Scales served as dependent measures.

Neurocognitive outcome measures

The auditory oddball task was used to measure attention [33]. Outcome measures were response speed (mean reaction time; MRT), assessing attention, and the coefficient of variation (CV) (CV = MRT SD/MRT), a measure of attentional lapses. Omission and commission errors were uncommon, and therefore excluded from analyses. The stop-signal task (SST) was primarily used to measure inhibition [34]. Variables of interest were: (1) stop-signal reaction time (SSRT), a measure of the speed of the inhibitory process, calculated by subtracting the mean stop-signal delay (SSD) from MRT; (2) number of commission errors in stop trials, measuring impulsivity; (3) number of omission errors in go trials, assessing attention; (4) response speed (MRT), and

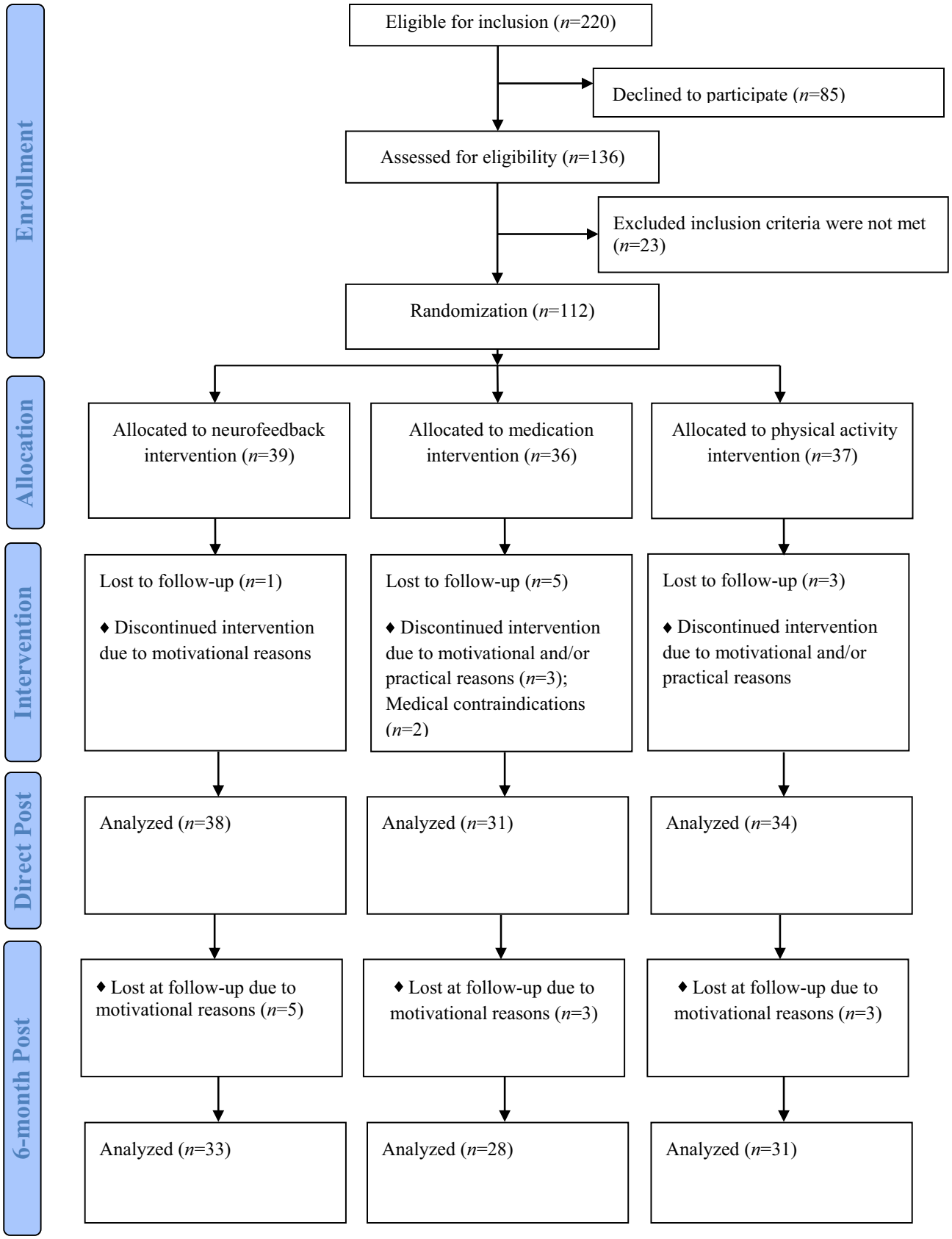

Fig. 1 Flow diagram of study (n = 112)

(5) variability of response speed calculated by the coefficient of variation (CV), measuring lapses of attention. The visual spatial working memory task (VSWM) [35, 36] was used to assess short-term storage or maintenance of visuospatial information (forward condition) and visuospatial working memory (backward condition). Variables of interest were the number of correct trials taken from the two conditions.

Secondary outcome measures

Secondary measures included the Sleep Disturbance Scale (SDSC), used to assess the quality of sleep as reported by parents [37]. The total score was used as the dependent measure.

Procedure

The study was approved by the national medical ethics committee (NL 31641.029.10 CCMO). Written informed consent was obtained before participation from all parents and children aged 11 years and older.

Pre-intervention assessment took place in the week prior to the start of the intervention. Post-intervention assessment took place 1 week after the last training. At follow-up, 6 months later, the assessment included measurements identical to those used in prior assessments. Post-intervention effects have been reported previously [17, 18, 38–40]. During post-intervention assessment, the MPH group continued use of medication. Interventions took place between September 2010 and March 2014. The 6-month follow-up was naturalistic and children were allowed to start, continue, or stop interventions, including the use of stimulant medication.

Statistical methods

Statistical analyses were performed in IBM SPSS Statistics, version 20.0 [41]. Differences between intervention groups in terms of background characteristics were analyzed using a Chi square (χ^2) test or one-way analysis of variance (ANOVA) with Tukey post hoc analyses for group comparison. Attrition analyses were performed with ANOVAs on sample characteristics and pre-intervention outcome measures comparing the initially randomized sample to the sample that completed the assessment at follow-up. At post-intervention assessment, teacher reports on the SDQ and the SWAN were missing for 2 participants, and the SDSC was missing for 10 participants. At follow-up, parent reports on the SDQ and the SWAN were missing for 2 participants, and teacher reports on the SDQ and the SWAN were missing for 3 participants. SDSC data were missing for 6 participants. At post-intervention assessment, data for 23 participants on the oddball task and 10 participants on the stop-signal task were not available for analysis due to technical problems or misinterpretation of the task, respectively. At follow-up, data for 19 participants on the oddball task and 4 participants on the stop-signal task were not available for analysis.

Post-intervention effects have been reported previously [17, 18]. This study evaluated long-term effects, analyzed with linear mixed models. Mixed models were used because the outcomes post intervention and at follow-up were clustered within subjects. The between-subject factor "group", the within-subject factor "time" (post intervention and follow-up), and the interaction "group × time" were added in the model while adjusting for possible pre-intervention group differences on the dependent measures. NFB was used as a reference group to compare intervention effects with those obtained using stimulant medication (MPH versus NFB) and physical activity (PA versus NFB). For all group comparisons, we report the difference scores, beta scores, and the 95% confidence interval (95% CI). Results were regarded significant at $p \leq .05$.

Because children were allowed to start, continue, or stop stimulant medication use during the follow-up interval (post intervention to follow-up), we also performed sensitivity analyses. These sensitivity analyses included only those children in the NFB and PA intervention groups who were not using medication at follow-up, and children in the MPH intervention who continued the use of stimulant medication at follow-up.

Results

Group characteristics

Group characteristics are displayed in Table 1. Group characteristics did not differ between treatment groups for the participants who completed the study at 6-month follow-up, except for medication use at follow-up ($p < .05$). Post-hoc tests showed less stimulant medication use at follow-up in the NFB and PA groups compared to the MPH group. Medication use at follow-up did not differ between the NFB and PA group. In addition, behavioral and neurocognitive outcome measures did not differ between treatment groups for participants who completed the study at 6-month follow-up.

Attrition analysis

There were no differences in sample characteristics and pre-treatment behavioral and neurocognitive outcome measures between the initially randomized sample and the sample that completed follow-up assessment.

Table 1 Group characteristics assessed pre-intervention

	Total	NFB	MPH	PA	Group	
n	92	33	28	31		
Age, (M and SD), y	9.46 (1.67)	9.81 (1.86)	8.97 (1.22)	9.55 (1.76)	1.98	0.15
Gender (M/F)	70/22	24/9	22/6	24/7	0.33[a]	0.85
Stimulant medication at T2 (on/off)	47/44	12/20	21/7	14/17	8.70	0.01
IQ, M (SD)	100.61 (13.78)	100.88 (13.84)	102.14 (14.90)	98.94 (12.91)	0.40	0.67
DBDRS parent						
Inattention (SD)	16.21 (5.24)	16.58 (5.12)	16.00 (5.71)	16.00 (5.00)	0.13	0.88
H/I (SD)	13.10 (5.91)	13.73 (5.84)	12.50 (5.75)	12.97 (6.24)	0.33	0.72
DBDRS teacher						
Inattention (SD)	16.00 (5.76)	15.76 (5.27)	17.00 (6.44)	15.26 (5.68)	0.70	0.50
H/I (SD)	12.82 (8.00)	13.90 (7.00)	12.11 (9.64)	12.32 (7.42)	0.46	0.64

DBDRS Disruptive Behavior Disorder Rating Scale, *H/I* Hyperactivity/Impulsivity Scale, *M* mean, *SD* standard deviation, *y* years

[a] χ^2

Behavioral outcome measures

Behavioral results are presented in Table 2. Sensitivity analyses, considering medication use at follow-up, are presented in Supplement 1.

Parent reports

For the parent-reported SDQ Total Scale score, no significant group × time effects were found and no significant group differences were found at follow-up. On the SWAN Inattention Scale, parent-reported inattention showed a significant group × time interaction for the MPH and NFB group contrast ($p = .002$). Post intervention, children in the MPH group showed fewer inattention symptoms compared to the NFB group ($p < .001$). However, this difference disappeared at follow-up. For the PA versus NFB group contrast, we found no significant group × time effect, nor did the two groups differ at follow-up. For parent-reported values on the SWAN Hyperactivity/Impulsivity Scale, the group × time interaction was significant for the MPH and NFB group contrast ($p = .002$). Post intervention, children in the MPH group showed fewer symptoms of hyperactivity/impulsivity than those who had received NFB ($p = .014$). However, this difference disappeared at follow-up. For the PA and NFB group contrast, the group × time interaction was not significant and groups did not differ at follow-up.

When the analyses were rerun comparing only those children in the NFB and PA groups who were not using medication at follow-up, and children in the MPH group who continued stimulant medication use at follow-up, the results remained unchanged.

In sum, the results of parent reports showed that from post intervention to follow-up, children initially randomized to NFB caught up with children who participated in the MPH group. There were no differences over time between children who received NFB and PA.

Teacher reports

Teacher reports on the SDQ Total Scale score showed a significant group × time interaction for the MPH and NFB group contrast ($p = .038$). Post intervention, children in the MPH group showed fewer behavioral problems compared to the NFB group ($p < .001$). This difference disappeared at follow-up. For the PA versus NFB group contrast, a significant group × time interaction was also found ($p = .033$). Post intervention, the two groups did not differ; however, at follow-up, children in the NFB group showed fewer behavioral problems compared to children in the PA group ($p = .010$).

On the SWAN Inattention Scale, teacher-reported inattention showed a significant group × time interaction for the MPH versus NFB group contrast ($p = .010$). Post intervention, children in the MPH group showed fewer inattention symptoms compared to the NFB group ($p < .001$); however, this difference disappeared at follow-up. For the PA and NFB group contrast, a significant interaction was also found ($p = .024$). Post intervention, the PA and NFB groups did not differ; however, at follow-up, children in the NFB group showed fewer inattention symptoms than the PA group ($p = .006$).

For the Hyperactivity/Impulsivity Scale, teacher-reported hyperactivity/impulsivity showed a significant group × time interaction for the MPH versus NFB group contrast ($p = .005$). Post intervention, children in the MPH group showed fewer hyperactivity/impulsivity symptoms compared to the NFB group ($p < .001$). This difference disappeared at follow-up. For the PA and NFB group contrast,

Table 2 Results of mixed models analyses evaluating long-term effects of neurofeedback

	Pre-intervention		Post-intervention		Follow-up		Comparison groups	Difference score post-intervention			Difference score follow-up			Group × time
	n	M (SD)	*n*	M (SD)	*n*	M (SD)		*β*	95% confidence interval	*p*	*β*	95% confidence interval	*p*	*p*
Behavioral outcome measures														
Parent reports														
SDQ														
NFB	39	16.90 (4.54)	38	14.74 (5.95)	32	13.34 (5.87)	MPH vs NFB	− 1.40	(− 3.43, 0.64)	.177	0.03	(− 2.14, 2.20)	.977	.279
MPH	36	15.64 (4.23)	31	12.81 (5.33)	28	12.50 (4.41)	PA vs NFB	0.70	(− 1.29, 2.68)	.490	1.55	(− 0.58, 3.68)	.152	.507
PA	37	17.22 (3.93)	34	15.97 (4.55)	30	15.30 (4.46)								
SWAN														
Inattention														
NFB	39	1.42 (0.52)	38	1.12 (0.67)	32	0.81 (0.72)	MPH vs NFB	− 0.60	(− 0.90, − 0.29)	< .001	− 0.06	(− 0.38, 0.26)	.720	.002
MPH	36	1.39 (0.70)	31	0.49 (0.82)	28	0.60 (0.62)	PA vs NFB	0.09	(− 0.21, 0.39)	.561	0.29	(− 0.02, 0.61)	.068	.211
PA	37	1.28 (0.70)	34	1.14 (0.71)	31	1.02 (0.82)								
H/I														
NFB	39	1.30 (0.70)	38	1.01 (0.82)	32	0.60 (0.71)	MPH vs NFB	− 0.38	(− 0.68, − 0.08)	.014	0.09	(− 0.22, 0.41)	.551	.002
MPH	36	1.14 (0.72)	31	0.49 (0.82)	28	0.55 (0.71)	PA vs NFB	0.03	(− 0.26, 0.32)	.823	0.22	(− 0.09, 0.52)	.162	.198
PA	37	1.28 (0.82)	34	0.98 (0.77)	31	0.83 (0.92)								
Teacher reports														
SDQ														
NFB	39	14.51 (4.71)	37	15.14 (5.15)	33	11.24 (5.15)	MPH vs NFB	− 4.64	(− 7.10, − 2.19)	< .001	− 1.21	(− 3.80, 1.40)	.355	.038
MPH	33	13.48 (5.43)	30	10.23 (6.35)	27	9.52 (6.10)	PA vs NFB	− 0.11	(− 2.60, 2.37)	.929	3.41	(0.84, 6.00)	.010	.033
PA	35	15.91 (5.17)	29	15.93 (5.12)	29	15.83 (6.63)								
SWAN														
Inattention														
NFB	39	1.40 (0.90)	37	1.26 (0.76)	33	0.59 (1.00)	MPH vs NFB	− 0.86	(− 1.22, − 0.51)	< .001	− 0.28	(− 0.65, 0.10)	.148	.010
MPH	33	1.52 (0.62)	30	0.49 (0.75)	27	0.39 (0.97)	PA vs NFB	0.01	(− 0.35, 0.37)	.956	0.52	(0.15, 0.90)	.006	.024
PA	35	1.38 (0.69)	29	1.25 (0.72)	29	1.08 (0.74)								
H/I														
NFB	39	1.18 (0.92)	37	1.12 (1.13)	33	0.40 (0.96)	MPH vs NFB	− 0.83	(− 1.21, − 0.45)	< .001	− 0.18	(− 0.60, 0.21)	.366	.005
MPH	33	0.93 (1.25)	30	0.18 (0.92)	27	0.04 (0.80)	PA vs NFB	0.01	(− 0.40, 0.40)	.961	0.60	(0.20, 0.98)	.004	.013
PA	35	1.12 (0.92)	29	1.14 (0.91)	29	0.98 (0.89)								
Neurocognitive outcome measures														
Oddball task														
MRT														
NFB	32	442.88 (97.05)	31	438.27 (93.60)	25	420.51 (88.18)	MPH vs NFB	− 56.44	(− 85.00, − 28.00)	< .001	− 29.00	(− 61.15, 3.17)	.077	.081
MPH	30	464.31 (69.12)	28	398.19 (60.46)	21	417.40 (79.38)	PA vs NFB	13.63	(− 13.90, 41.12)	.328	17.30	(− 11.67, 46.25)	.240	.793

Table 2 (continued)

	Pre-intervention		Post-intervention		Follow-up		Comparison groups	Difference score post-intervention			Difference score follow-up			Group × time
	n	M (SD)	*n*	M (SD)	*n*	M (SD)		*β*	95% confidence interval	*p*	*β*	95% confidence interval	*p*	*p*
PA	33	441.08 (89.34)	28	440.85 (90.12)	27	424.13 (88.40)								
CV														
NFB	32	0.30 (0.08)	31	0.28 (0.07)	25	0.28 (0.08)	MPH vs NFB	− 0.02	(− 0.05, 0.01)	.139	− 0.04	(− 0.07, < 0.01)	.058	.573
MPH	30	0.28 (0.04)	28	0.28 (0.12)	21	0.24 (0.04)	PA vs NFB	< − 0.01	(− 0.03, 0.03)	.866	< − 0.01	(− 0.04, 0.03)	.851	.979
PA	33	0.29 (0.06)	28	0.28 (0.07)	27	0.27 (0.05)								
Stop-signal task														
SSRT														
NFB	37	270.61 (75.06)	35	254.36 (84.34)	30	216.05 (69.17)	MPH vs NFB	− 74.73	(− 106.56, − 42.91)	< .001	− 35.28	(− 68.88, − 1.68)	.040	.018
MPH	33	278.08 (91.36)	28	182.32 (75.41)	24	188.04 (87.66)	PA vs NFB	− 2.52	(− 33.64, 28.60)	.873	− 0.11	(− 31.80, 31.59)	.995	.878
PA	37	257.61 (89.40)	30	237.81 (87.39)	31	214.07 (83.58)								
Commission														
NFB	37	20.08 (13.83)	35	18.51 (15.11)	30	15.53 (11.37)	MPH vs NFB	− 6.58	(− 11.81, − 1.34)	.014	− 4.20	(− 9.78, 1.38)	.139	.433
MPH	33	19.67 (11.35)	28	11.93 (9.43)	24	12.46 (15.50)	PA vs NFB	2.68	(− 2.45, 7.80)	.304	3.60	(− 1.64, 8.84)	.176	.749
PA	37	18.43 (10.26)	30	19.47 (12.40)	31	19.00 (15.38)								
Omission														
NFB	37	15.57 (13.74)	35	13.97 (14.28)	30	10.17 (10.22)	MPH vs NFB	− 7.21	(− 12.37, − 2.05)	.006	− 2.86	(− 8.42, 2.69)	.311	.223
MPH	33	14.18 (11.05)	28	5.43 (7.34)	24	6.67 (9.90)	PA vs NFB	4.36	(− 0.72, 9,45)	.092	3.81	(− 1.39, 9.01)	.150	.872
PA	37	14.95 (11.74)	30	16.03 (15.16)	31	13.20 (13.75)								
MRT														
NFB	37	635.11 (130.39)	35	613.91 (122.00)	30	550.36 (113.91)	MPH vs NFB	− 15.20	(− 61.28, 30.88)	.515	27.37	(− 21.54, 76.30)	.271	.104
MPH	33	679.78 (122.31)	28	625.26 (132.21)	24	598.82 (125.40)	PA vs NFB	13.56	(− 31.10, 58.23)	.549	58.94	(13.26, 104.61)	.012	.071
PA	37	636.85 (109.25)	30	610.16 (122.10)	31	605.32 (115.74)								
CV														
NFB	37	0.28 (0.04)	35	0.27 (0.05)	30	0.27 (0.05)	MPH vs NFB	− 0.01	(− 0.03, 0.01)	.348	− 0.01	(− 0.03, 0.01)	.374	.998
MPH	33	0.27 (0.03)	28	0.25 (0.05)	24	0.26 (0.05)	PA vs NFB	0.01	(− 0.01, 0.03)	.464	< 0.01	(− 0.01, 0.03)	.437	.952
PA	37	0.28 (0.4)	30	0.27 (0.03)	31	0.28 (0.04)								
VSWM														
Forward														
NFB	39	12.26 (2.92)	38	12.74 (3.58)	33	13.70 (2.94)	MPH vs NFB	0.63	(− 0.53,1.78)	.284	0.78	(− 0.42, 2.00)	.201	.797
MPH	36	10.97 (2.58)	31	12.39 (2.75)	28	13.71 (3.07)	PA vs NFB	− 0.21	(− 1.34, 0.92)	.716	− 0.50	(− 1.67, 0.68)	.404	.621
PA	37	11.16 (2.73)	34	11.53 (3.61)	31	12.55 (2.64)								
Backward														
NFB	39	10.90 (3.08)	38	11.68 (3.44)	33	11.42 (3.62)	MPH vs NFB	1.06	(− 0.18, 2,30)	.093	0.93	(− 0.36, 2.22)	.158	.843
MPH	36	9.58 (2.45)	31	11.71 (3.66)	28	11.82 (3.53)	PA vs NFB	0.17	(− 1.04, 1.38)	.784	0.43	(− 0.83, 1.70)	.497	.687

Table 2 (continued)

	Pre-intervention		Post-intervention		Follow-up		Comparison groups	Difference score post-intervention			Difference score follow-up			Group × time
	n	M (SD)	*n*	M (SD)	*n*	M (SD)		*β*	95% confidence interval	*p*	*β*	95% confidence interval	*p*	*p*
PA	37	9.95 (2.95)	34	10.76 (3.32)	31	11.26 (3.56)								
Side effects														
SDSC														
NFB	38	45.32 (10.55)	39	42.82 (9.56)	32	42.81 (8.64)	MPH vs NFB	1.41	(− 1.84, 4.65)	.393	− 0.70	(− 4.15, 2.74)	.687	.247
MPH	35	45.09 (9.11)	30	43.93 (10.47)	26	42.00 (7.83)	PA vs NFB	1.51	(− 1.65, 4.70)	.348	1.34	(− 2.10, 4.77)	.442	.926
PA	35	45.97 (12.70)	33	45.85 (11.14)	28	45.96 (11.50)								

Neurofeedback was used as a reference group to compare intervention effects with stimulant medication (MPH versus NFB) and physical activity (PA versus NFB)

M Mean, *SD* standard deviation, *SDQ* Strength and Difficulty Questionnaire, *SWAN* Strengths and Weaknesses in ADHD and Normal Behaviors, *H/I* Hyperactivity/Impulsivity Scale, *MRT* mean reaction time, *CV* coefficient of variation, *SSRT* stop-signal reaction time, *VSWM* visual spatial working memory, *SDSC* Sleep Disturbance Scale for Children

the group × time interaction was also significant ($p = .013$). At post-intervention assessment, no difference was found between NFB and PA; however, at follow-up, children in the NFB group showed fewer hyperactivity/impulsivity symptoms compared to the PA group ($p = .004$).

The results of sensitivity analyses for the SDQ were similar to the main analyses for the MPH versus NFB group contrast. Only for the PA versus NFB group contrast, did the time × group interaction ($p = .033$) turn non-significant ($p = .205$). The results of sensitivity analyses for the SWAN Scales were similar to our main analyses, except for the significant group × time interaction in hyperactivity/impulsivity symptoms for the PA versus NFB group contrast ($p = .013$), which became non-significant when excluding stimulant-using children in the PA and NFB groups, and non-stimulant users in the MPH group ($p = .110$).

In sum, the results of the teacher reports showed that from post intervention to follow-up, children who received NFB caught up with children in the MPH group. Analyses of the teacher reports for children in the NFB group and the PA group showed that at follow-up children in the NFB group had improved to a greater extent compared to those in the PA group. Sensitivity analyses showed similar results at follow-up compared to the main analyses. However, two of the three significant group × time interactions between NFB and PA disappeared.

Neurocognitive outcome measures

The neurocognitive results are presented in Table 2. Sensitivity analyses are presented in Supplement 1.

Oddball task

For both MRT and CV, no significant group × time effects and no significant group differences were found at follow-up, indicating groups did not differ on attentional functioning. Due to technical problems or misinterpretation of the oddball task, the groups became too small to perform sensitivity analyses.

Stop-signal task

For SSRT, the group × time interaction was significant for the MPH versus NFB group contrast ($p = .018$). Post intervention, children in the MPH group showed faster inhibitory control processes compared to children in the NFB group ($p < .001$), and although differences became smaller, differences between the two groups remained significant at follow-up ($p = .040$). For the PA versus NFB group contrast, the group × time interaction was not significant and the two groups did not differ at follow-up.

For commission and omission errors, no significant group × time effects were found and no significant group differences were found at follow-up, indicating groups did not differ on impulsivity and attention, respectively.

In terms of MRT, no significant group × time effects and no significant group differences were found at follow-up for the MPH and NFB group contrast. For the PA versus NFB group contrast, no significant group × time interaction was found. Post intervention the two groups did not differ; however, at follow-up, children in the NFB group showed a faster MRT compared to those in the PA group ($p = .012$). For CV, response speed variability, no significant group × time effects were found and no significant group differences were found at follow-up.

The results of sensitivity analyses for the stop-signal task were similar to those of our main analyses, except for measures of SSRT, omission errors, and MRT. For SSRT, the MPH and NFB group contrast revealed a non-significant group × time interaction ($p = .188$), and group differences at follow-up also disappeared ($p = .098$). For omission errors, the MPH and NFB group contrast became significant for group differences at follow-up, showing fewer omission errors for children in the MPH group compared to the NFB group at follow-up ($p = .046$). The PA and NFB group difference for MRT at follow-up turned non-significant ($p = .221$).

Visual spatial working memory (VSWM) task

The results of the VSWM for the forward and backward condition showed no significant group × time effects and no significant group differences at follow-up, indicating no difference between groups for short-term storage and working memory. The results of the sensitivity analyses for the VSWM task for both conditions were similar to those obtained in the main analyses.

In sum, the neurocognitive measures showed no differences between children in the MPH and NFB groups at follow-up, except for faster inhibitory control processes in the MPH group measured by SSRT in the stop-signal task. However, this effect disappeared in the sensitivity analyses. The PA and NFB group contrasts showed no group differences at follow-up on the neurocognitive measures, except for faster MRTs measured with the stop-signal task in the NFB group. However, this finding was not substantiated in the sensitivity analyses. Taken together, no differences were found at follow-up on any of the neurocognitive measures between the MPH and NFB groups or between the PA and NFB groups.

Secondary outcome measures

On the SDSC Total Scale we found no significant effects for quality of sleep as reported by parents. The results of the sensitivity analyses were similar to those of the main analyses.

Discussion

In this study, we analyzed the long-term behavioral and neurocognitive effects of neurofeedback compared to stimulant medication and physical activity in children diagnosed with ADHD. Physical activity was used as a semi-active control condition to control for non-specific effects. Our findings indicate that the superior results previously found in parent reports and neurocognitive outcome measures obtained with stimulant medication post intervention [17, 18], became smaller or non-significant at follow-up. Interestingly, at follow-up, teacher reports showed larger improvements for neurofeedback than for the semi-active control condition. These results might suggest that neurofeedback can have delayed beneficial effects. To rule out confounding effects of medication use during the 6-month follow-up, sensitivity analyses were performed only including those subjects assigned to the neurofeedback and semi-active control groups who refrained from the use of stimulant medication to follow-up, and those subjects assigned to the methylphenidate group who continued use of stimulant medication to follow-up. These analyses confirmed our findings obtained in the full sample, with teacher reports showing better results at follow-up for neurofeedback than for the semi-active control condition. However, the results of teacher reports should be interpreted with caution as some children had different teachers at follow-up.

Parent reports and neurocognitive measures showed comparable long-term effects for children who received neurofeedback and for those who were receiving stimulant medication at follow-up, except for the measure of inhibitory control. Similar to the results post intervention, children with stimulant medication showed improved inhibitory control compared to the neurofeedback group at follow-up. However, in line with our other outcome measures, the difference between the two treatment groups became smaller at follow-up compared to post intervention. After controlling for medication use, the difference between the two groups disappeared at follow-up.

Furthermore, our results are in accordance with some but not all previous studies. The RCT study of Meisel et al. [42] also found neurofeedback to be as effective as stimulant medication at follow-up. However, in that study, post-intervention effects revealed no significant differences between neurofeedback and stimulant medication [42], while our study revealed superior post-intervention effects of medication assessed with parent reports [17] and neurocognitive outcome measures [18]. The results of our study are in line with those of the RCT conducted by Moreno-García et al.

[24], who compared the effects of neurofeedback, standard pharmacological treatment, and behavioral therapy. Their study applied the Integrated Visual and Auditory Continuous Performance Test to determine therapeutic effects on attention and response control variables at pre- and post-testing, and follow-up. Post intervention, treatment with medication showed superior effects compared to treatment with neurofeedback on measures of attention. However, comparable to our findings, their treatment differences were not maintained at follow-up. In this study, we speculate that the effects of stimulant medication remained more or less stable over time, while the neurofeedback and the semi-active control groups revealed similar improvements over time on both parent reports and the neurocognitive outcome measures, except for response speed. However, the superior effect of neurofeedback compared to the semi-active control group on response speed at follow-up disappeared after controlling for medication use. Furthermore, considering that we aimed to control for non-specific effects with the semi-active control group, these improvements over time probably reflect non-specific effects, such as developmental effects and/or regression to the mean, unrelated to specific treatment components.

In contrast to our results for parent reports, Gevensleben et al. [23] found favorable results for neurofeedback at 6-month follow-up compared to computerized attention skill training used as a semi-active control intervention. In their study, however, analyses were limited to children who were not taking medication at follow-up, potentially influenced by selection bias. In this study, to avoid such selection bias, we included all children regardless of medication use at follow-up. Moreover, we performed sensitivity analyses comparing non-users in the neurofeedback and semi-active control groups to children in the medication group who continued the use of medication at follow-up. Overall, comparable results were obtained for this sub-group.

Unlike parent reports, teacher reports provided possible evidence of the specificity of improvements for the neurofeedback group compared to the semi-active control group. Our findings may be interpreted as demonstrating the delayed effects of neurofeedback. Arns and Kenemans [43] presented a model in which neurofeedback altered both sleep and ADHD problems in a sub-group of ADHD. They suggested that neurofeedback affects the sleep spindle circuitry, resulting in increased sleep spindle density and normalization of sleep onset insomnia (SOI), thereby affecting the noradrenergic locus coeruleus (LC). This cascade would result in vigilance stabilization and delayed improvements in ADHD symptoms. However, in this study no evidence was found for this hypothesis as we demonstrated comparable improvements in sleep quality for all interventions. According to other predictions of the model, delayed effects of neurofeedback should also be expressed in reduced frontal theta and alpha power. Further research should focus on verifying these predictions by analyzing EEG power spectra at follow-up.

Previous results of studies using teacher reports to assess long-term effects of neurofeedback showed evidence for the effectiveness of a multimodal, combined medication and neurofeedback intervention in children with ADHD [44, 45]. The study of Duric et al. [44] compared the efficacy of three interventions in children with ADHD: medication only, neurofeedback only, and medication and neurofeedback combined (multimodal). None of the three interventions resulted in changes in hyperactivity reported by teachers throughout the entire study. At follow-up, comparable improvements in symptoms of inattention were found for the multimodal and the medication only interventions. In addition, while Duric et al. [44] found neurofeedback to be as effective as medication post intervention, teacher reports at follow-up seemed to indicate an increase in inattention symptoms for the neurofeedback only intervention. These results are in contrast to our results on teacher ratings, which indicated superior effects of methylphenidate compared to neurofeedback post intervention, while similar effects were found for neurofeedback and methylphenidate at follow-up. However, it should be noted that in our study some children had different teachers at follow-up. For this reason, Gevensleben et al. [23] and Steiner et al. [22] excluded teacher reports at follow-up. We reasoned that due to the randomized nature of the trial, the results were not likely to be confounded. However, this made overall teacher reports less reliable and therefore the results should be interpreted with caution.

Some strengths and limitations of the current study should be mentioned. The strengths of this study were the low attrition rates, no baseline group differences at pre-intervention, and the inclusion of both an active control group to account for non-specific changes and a medication control group to assess whether neurofeedback may be a viable alternative for stimulant treatment.

Inevitably, the study comes with some limitations. First, we performed a naturalistic, not experimentally controlled follow-up. Therefore, it is difficult to determine whether the interventions improved long-term functioning at follow-up or potentially unknown factors may have influenced our results. However, controlling for medication use with sensitivity analyses did not fundamentally alter the results. Second, in this study we enrolled 112 participants of the 186 planned. Although the final sample size was more than sufficient to detect medium effect size differences between groups, larger groups would have allowed more statistical power for exploratory analyses. Third, in recent years, the rationale for the theta/beta ratio as a clinical biomarker of ADHD has been questioned [46–48]. Moreover, several research groups have speculated that neurofeedback does not focus on adjusting the neural dysfunction, but rather on learning compensatory mechanisms [10, 49], which may

also involve central nervous system (CNS)-specific effects. Fourth, the statistical power of sensitivity analyses was reduced because of the smaller sample size.

In conclusion, our naturalistic long-term follow-up shows that previously established superior post-intervention effects on parent reports and neurocognitive outcome measures of stimulant medication compared to neurofeedback [17, 18] become smaller or disappear at follow-up. Only teacher reports show superior effects for the neurofeedback group compared to the semi-active control group at follow-up. However, these results must be interpreted with caution as some children had different teachers at follow-up.

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Compliance with ethical standards

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

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