Attention for Inhibition

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CHAPTER 5

An RCT into the behavioural effects of neurofeedback compared to methylphenidate and physical activity in children with ADHD

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ABSTRACT

Objective: The efficacy of neurofeedback (NF) as treatment for ADHD, and whether NF is a viable alternative for stimulant medication, is still an intensively debated subject. The current randomized controlled trial (RCT) compared NF to (1) optimally titrated methylphenidate (MPH) and (2) a semi-active control intervention, physical activity (PA), to account for non-specific effects. **Methods:** A multicentre three-way parallel group study with balanced randomisation was conducted. Children with a DSM-IV-TR diagnosis of ADHD, aged 7-13, were randomly allocated to receive NF (*n*=39), MPH (*n*=36), or PA (*n*=37) over a period of 10-12 weeks. NF comprised theta/beta training on the vertex (Cz). PA consisted of moderate to vigorous intensity exercises. NF and PA were balanced in terms of number (~30) and duration of sessions. A double-blind pseudo randomized placebo-controlled crossover titration procedure was used to determine an optimal dose in the MPH intervention. Parent and teacher ratings on Strength and Difficulty Questionnaire (SDQ) and Strengths and Weaknesses of ADHD symptoms and Normal behaviour scale (SWAN) were used to assess treatment outcomes. Data collection took place between September 2010 and March 2014. **Results:** Intention-to-treat analyses revealed an improvement on parents reported behavior on the SDQ and SWAN hyperactivity/impulsivity scale, irrespective of received intervention [η_p^2=0.21-0.22, $p \leq .001$], whereas the SWAN inattention scale revealed more improvement in children who received MPH than NF and PA [η_p^2=0.13, $p \leq .001$]. Teachers reported a decrease of ADHD symptoms on all measures for MPH, but not for NF or PA [range of η_p^2=0.14-0.29, $p \leq .001$]. **Conclusion:** The current study showed that optimally titrated MPH is superior to NF and PA in decreasing ADHD symptoms in children with ADHD.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD)(American Psychiatric Association, 2013) is one of the most common childhood neurodevelopmental disorders (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Stimulant medication is a widely used and effective treatment for ADHD (Faraone & Buitelaar, 2010). However, several limitations have been reported, including a substantial group that fails to show improvement and adverse side effects such as sleeping problems, decreased appetite, and headaches (Graham & Coghill, 2008). Furthermore, there is limited evidence for long-term effects of stimulant treatment (van de Loo-Neus, Rommelse, & Buitelaar, 2011). As a result, there is demand for alternative treatments for ADHD.

Neurofeedback has been proposed as a promising nonpharmacological treatment for ADHD (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012). The aim of neurofeedback is to alter brain activity patterns by providing the patient with visual or auditory feedback on electroencephalogram (EEG) activity. Alterations in brain activity patterns have been associated with behavioural problems as seen in ADHD (Banaschewski & Brandeis, 2007; Snyder & Hall, 2006). Compared to typically developing children, children with ADHD show increased theta (4-8 Hz) and decreased beta activity (13-21 Hz) (Snyder & Hall, 2006). Greater theta activity is related to poor vigilance, whereas greater beta activity is related to enhanced attention (Banaschewski & Brandeis, 2007). Accordingly, the most widely studied neurofeedback treatment protocol for ADHD aims at decreasing theta and increasing beta activity at the vertex (Cz) (Lofthouse et al., 2012). However, more recent studies question the association between increased theta/beta ratio and ADHD (Loo et al., 2012). Comorbid disorders might have a mediating effect on the theta/beta ratio (Loo et al., 2012; Snyder, Rugino, Hornig, & Stein, 2015). Meta-analyses evaluating the effects of neurofeedback in children with ADHD are inconclusive, with conclusions ranging from neurofeedback being a non-effective treatment as assessed with blinded assessments (Sonuga-Barke et al., 2013), to neurofeedback being more efficacious than active control conditions (Micoulaud-Franchi et al., 2014), to neurofeedback being a 'efficacious and specific' treatment (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). Inconsistent results might be due to differences between studies in terms of (1) random allocation of participants, (2) controlling for concomitant treatments and/or non-specific treatment effects, and (3) the use of blinded assessment of treatment effects (Gevensleben et al., 2012).

Results of randomized controlled trial (RCT) studies comparing the effects of neurofeedback and stimulant medication in children with ADHD are mixed. Two out of three

RCTs showed that neurofeedback is as effective as stimulant medication (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013), with the third study (Ogrim & Hestad, 2013) showing superior effects for medication compared to neurofeedback. Mixed findings across studies may be the result of varying protocols for both neurofeedback and medication interventions.

In the current study, we compared neurofeedback to both stimulant medication and a physical activity (PA) intervention. Physical activity could be another treatment approach for ADHD that utilizes protective effects of exercise on brain functioning (Rommel, Halperin, Mill, Asherson, & Kuntsi, 2013). However, beneficial effects of chronic exercise in children with ADHD are preliminary and have yet to be established in randomized controlled trials (Halperin, Berwid, & O'Neill, 2014). In the current study, PA was applied as a semi-active control condition to control for non-specific effects, such as parental engagement and personal attention. Therefore, neurofeedback and physical activity training were matched on duration and intensity. The aim of the present RCT study was to compare the effects of neurofeedback (NF) with (1) stimulant medication (MPH) and (2) physical activity (PA) as semi-active control condition in children with ADHD.

METHODS

Participants

Eligible participants were Dutch speaking children, 7-13 years, with a primary clinical DSM-IV-TR diagnosis of ADHD (American Psychiatric Association, 2013). Children with ADHD were recruited from fifteen 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) (Pelham, Gnagy, Greensalade, & Milich, 1992) confirmed their 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. At study entry, all children were free of stimulant use for at least one 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 (Kaufman, Kaufman, Balgopal, & Mclean, 1996). No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the medical records. Comorbid disorders included

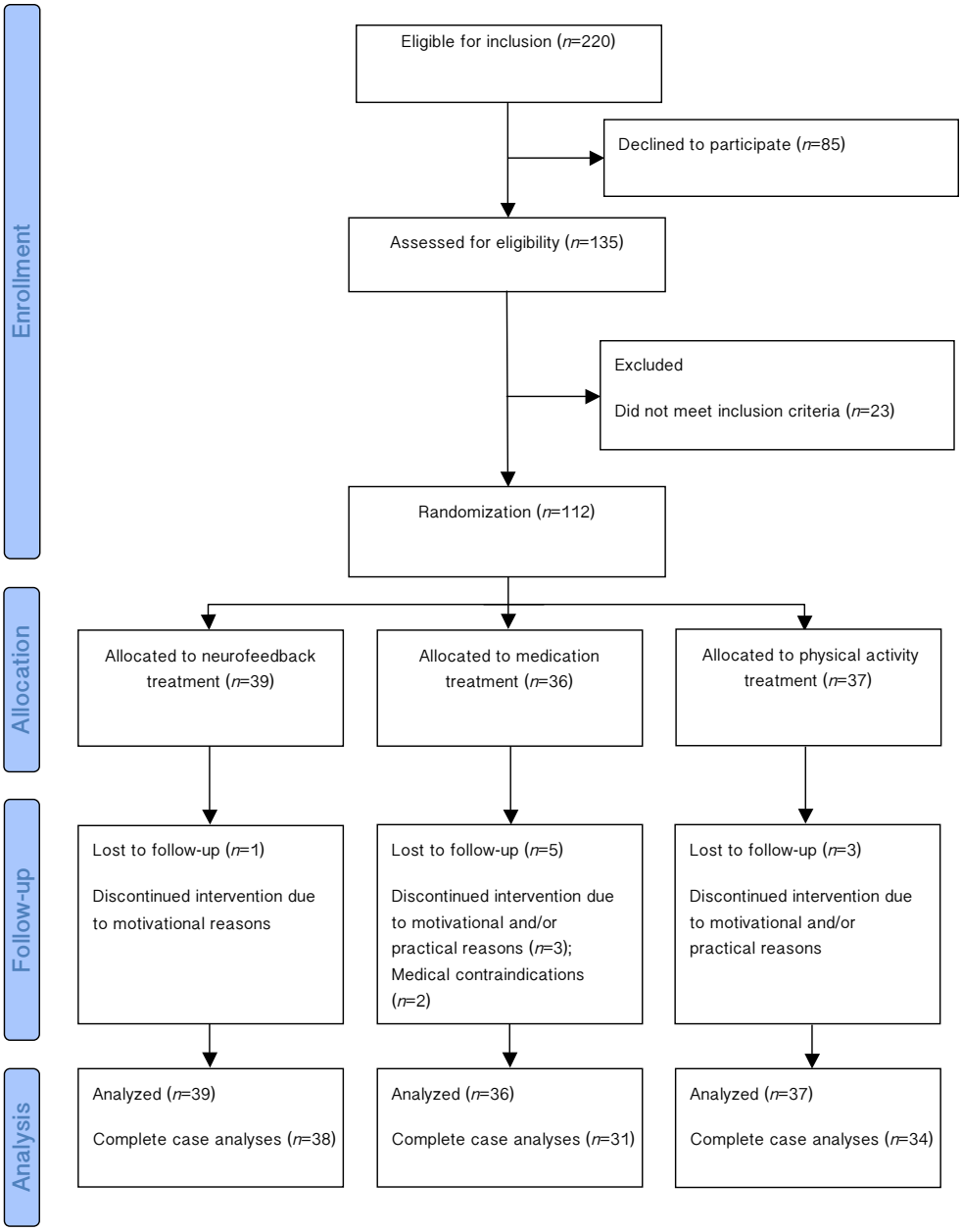

Figure 1. CONSORT flow diagram randomized controlled trial

learning disorders (NF; *n*=5, MPH; *n*=2, PA; *n*=1), autism spectrum disorders, (NF; *n*=3, MPH; *n*=2, PA; *n*=3), anxiety disorders (NF; *n*=2, MPH; *n*=0, PA; *n*=2), and mood disorder (NF; *n*=1, MPH; *n*=0, PA; *n*=0). Chi-square test revealed no significant difference in the distribution of comorbid disorders over groups (χ^2 (8, N=112)=12.88, *p*=.12).

Initially, 112 children with ADHD were randomized over the three interventions, with 103 children completing their intervention. Figure 1 presents a flow diagram of participants.

Trial design

A multicentre three-way parallel group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator (Dallal, 2007). Stocks of nine unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing treatment allocation. Subsequently, children, parents, and teachers were aware of the allocated group. Data collection took place between September 2010 and March 2014.

To detect a medium effect size (f=0.25) for three groups to be sufficient in a repeated measures (RM) analysis of variance (ANOVA) with an alpha 0.05 and a power of 95%, using G*power version 3.1.5 (Faul, Erdefelder, Lang, & Bunchner, 2007), a total sample size of 66 (i.e. 22 per group) was calculated. In case of two groups, to perform relevant post-hoc analysis, a total sample size of 54 (i.e. 27 per group) was calculated to detect a medium effect size (f=0.25) in a RM ANOVA with an alpha 0.05 and a power of 95%. In the current study, the smallest group size was 29. Consequently, all groups had enough participants to the detect a medium effect size. This report complies with the CONSORT 2010 guidelines for reporting parallel group randomized trials (Schulz, Altman, & Moher, 2010). The trial was registered on clinicaltiral.gov (Ref. No. NCT01363544).

Interventions

Neurofeedback and physical activity treatment comprised three individual training sessions a week, over a period of around 10 weeks. One training session lasted 45 minutes, with 20 minutes of effective training.

Neurofeedback. Theta/beta training was applied with the aim to inhibit theta (4-8Hz) and reinforce beta (13-20Hz) activity at Cz. The THERAPRAX® EEG Biofeedback system (Neuroconn GmbH, Germany) with a DC-amplifier and a sampling rate of 128 Hz was used to transmit and analyse the EEG signal. Reference and ground electrodes were attached to right

and lefty mastoids respectively. Electro-oculogram (EOG) was obtained with two electrodes at external canthi, and two electrodes at infra- and supra-orbital sides. Ocular correction was applied as described in Schlegelmilch et al. (2004). Subsequently, theta/beta index [theta(μV/Hz)-beta(μV/Hz)/theta(μV/Hz)+beta(μV/Hz)] was computed with a short-time-fourier transformed moving average for direct feedback.

The mean number of training sessions of participants who completed the assessments at post intervention (*n*=38) was 29 (*M* = 28.53, *SD* = 2.63, range between 19-30). Each training session started with a 1-minute baseline theta/beta index measurement, followed by 10 runs of neurofeedback. Each run comprised four 30-second epochs. 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 epoch relative to the baseline, was rewarded with the appearance of a sun and granted with credits. The first run of the first training started on a training level with the aim to reduce the theta/beta index with 3%. The training level increased or decreased based on performance of former runs and could range between 3-52%, relative to training session baseline, over the total treatment period of 10 weeks. Higher training levels were rewarded with more credits.

Transfer trials without immediate visual feedback were included from session 11 (25%) and session 21 (50%) onwards. To further transfer learned behaviours, participants were instructed to retrieve their neurofeedback experiences by watching printed graphics of the training during school and homework. Compliance was verified by questioning the participants whether they used the transfer cards over the intervention period. Transfer cards were used by 84% of the participants.

Medication. A four-week double-blind randomized placebo-controlled titration was used to determine the optimal individual dose of short-acting methylphenidate (MPH). The titration was preceded by a baseline week to determine ADHD symptoms without MPH, followed by a lead-in week in which on three consecutive days, twice-daily (at breakfast and lunch time) doses of 5mg, 10mg, and 15mg (<25kg body weight) or 20mg (>25kg body weight) MPH were used to assess adverse effects. During the titration phase, children received in a pseudo-random order each of the three doses of MPH or placebo for one week, twice daily. At the end of each week, parents and teacher were asked to evaluate inattention and hyperactivity/impulsivity symptoms on the DBDRS, and adverse effects on the MTA Side Effect Rating Scale (Greenhill et al., 1996). A standardized procedure (Greenhill, Halperin, & Abikoff, 1999) was used to classify children as responder (*n*=29), or non-responder (*n*=2). Both non-responders were treated with 5mg MPH

twice daily. The child's psychiatrist prescribed the twice-daily optimal dose for the remaining intervention period for responders (5mg to 10 (8 responders and 2 non-responders), 10mg to 14, 15mg to 2, and 20mg to 5 children).

Physical activity. Maximum heart rate (HRmax) was determined before the start of the first training session using a standard maximum heart rate test. Each training session started with 5 minutes of warming up, followed by five 2-minute moderate intensity exercises at a level of 70-80% of HRmax. After a 5-minute break, five 2-minute vigorous intensity exercises of 80-100% of HRmax were performed. Each training finished with a 5-minute cool down. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland). The mean number of sessions of participants who completed the assessments at post intervention (n=34) was 28 (M=27.74, SD=3.56, range 12-30).

Outcome Measures

Primary outcome measures included parent and teacher reports on the Strength and Difficulty Questionnaire (SDQ) (Goodman, Meltzer, & Bailey, 1998; Goodman, 1997) and the Strengths and Weaknesses of ADHD symptoms and Normal behaviour scale (SWAN) (Swanson, Schuck, et al., 2001). The Total scale of the SDQ and the SWAN scales Inattention and Hyperactivity/Impulsivity were used to assess treatment effects.

Secondary outcome measures included a custom-made expectancy scale filled out pre-intervention by parents and teachers. Quality of sleep was assessed using the total scale of the Sleep Disturbance Scale (SDSC) (Bruni et al., 1996) as evaluated by parents.

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 one week after the last training. In addition to the data presented here, neuropsychological and electroencephalogram data were collected. During post-intervention assessment, the MPH-group continued use of medication at the optimal titrated dose. Interventions took place between September 2010 and March 2014.

Statistics

Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM Corp, 2011). Differences between intervention groups in terms of background characteristics were analyzed with a chi-square test (χ^2) or a one-way ANOVA with Tukey post-hoc analyses to compare intervention groups. Attrition analyses were performed with ANOVAs comparing the initially randomized sample to the sample that completed the interventions on group characteristics and outcome measures. At pre-intervention, teacher ratings were incomplete for 5 participants on the SDQ and SWAN. The SDSC was not available for 4 participants.

Intention-to-treat analyses were performed using imputation with Last Observation Carried Forward (LOCF). To compare intervention effects, Generalized Linear Model (GLM) repeated measures (RM) ANOVAs, with time (between pre-intervention (T0) and post-intervention(T1)) as within-subject factor and group (NF, MPH and PA) as between-subject factor were applied. For these analyses, the adjusted difference at post-intervention (ADt1-t0) and accompanying 95% confidence interval [95%CI] are reported. Effect size are expressed in percentage of explained variance in partial eta squared (η_p^2; small, medium, and large effects correspond to η_p^2=.01, η_p^2=.06, and η_p^2=.14 respectively) (Cohen, 1977). In case of significant time by group interactions two-way between-groups interactions post-hoc analyses were performed separately for the between-subject factors (1) NF and MPH, (2) MPH and PA and (3) NF and PA with time (T0, T1) as within-subject factor. Differences on expectancies were analyzed with one-way ANOVAs. To explore the relation between expectancy and difference scores (T1-T0) of primary behavioral outcome measures, Pearson correlations were computed within groups. Only significant correlations of $p \leq .05$ were reported. Complete case analyses were performed for participants who completed pre- and post-intervention assessments. For participants who completed the intervention, all parent reported primary outcome measures were complete, however, at post-intervention teacher rating on the SDQ and the SWAN were missing for two participants and SDSC data was missing for 10 participants.

RESULTS

Group Characteristics

At pre-intervention, group characteristics and behavioral measures did not differ between the three intervention groups (Table 1).

Table I. Group characteristics at pre-intervention (T0)

	NF (*n*=38)		MPH (*n*=31)		PA (*n*=34)		Group	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*(2,100)	*p*
Demographic data								
Age (years)	9.87	1.81	9.04	1.24	9.60	1.87	2.13	ns
IQ	100.45	13.34	101.61	14.71	98.00	12.80	0.61	ns
Gender (M/F)	29/9		24/7		25/9		0.15[a]	ns
DBDRS parents								
Inattention	16.63	5.15	16.52	5.69	16.24	4.92	0.05	ns
Hyperactivity /Impulsivity	14.50	5.99	13.16	6.00	13.09	6.05	0.63	ns
DBDRS teacher								
Inattention	15.37	5.29	17.48	6.55	15.79	5.71	1.22	ns
Hyperactivity/ Impulsivity	13.79	6.90	12.65	10.02	12.41	7.42	0.30	ns

Note. DBDRS = Disruptive Behaviour Disorder rating scale; *M* = Mean; *SD* = Standard Deviation; [a]$\chi^2(2)$

Attrition Analysis

No differences were found in group characteristics and pre-intervention measures between the participants as randomized and the participants who completed the intervention.

Intention-to-treat Analyses

Primary Outcome measures. See Table 2 for the main results. Parents reported improvements on the SDQ and SWAN Hyperactivity/Impulsivity scale regardless of intervention group. For the SWAN Inattention scale there was a group by time interaction. Post-hoc analyses revealed that (1) MHP showed greater improvement over time than NF, $F(1,73)=8.24$, $p=.005$, $\eta_p^2=0.10$, and (2) PA, $F(1,71)=15.05$, $p<.001$, $\eta_p^2=0.18$. No difference was found between (3) NF and PA, $F(1,74)=0.99$, $p=.323$, $\eta_p^2=0.01$.

Teacher reports on the SDQ and the SWAN showed differential intervention effects in the three groups as evidenced by significant group by time interactions. On the SDQ, (1) MPH showed greater improvement than NF, $F(1,70)=15.13$, $p<.001$, $\eta_p^2=0.18$, and (2) PA, $F(1,66)=9.94$, $p=.002$, $\eta_p^2=0.13$, (3) NF and PA did not differ, $F(1,72)=0.80$, $p=.375$, $\eta_p^2=0.01$. Similarly, on

the SWAN-Inattention scale, post-hoc analyses showed that (1) MPH displayed greater improvement over time than NF, $F(1,70)=25.98$, $p<.001$, $\eta_p^2=0.27$, and (2) PA, $F(1,66)=32.40$, $p<.001$, $\eta_p^2=0.33$. No difference was found between (3) NF and PA, $F(1,72)=0.13$, $p=.721$, $\eta_p^2=0.002$. Likewise, for the SWAN Hyperactivity/Impulsivity scale, post-hoc analyses indicated that (1) MPH showed greater improvement over time than NF, $F(1,70)=9.87$, $p=.002$, $\eta_p^2=0.12$ and (2) PA, $F(1,66)=12.80$, $p=.001$, $\eta_p^2=0.16$. Again, no difference was found between (3) NF and PA, $F(1,72)=<0.01$, $p=.98$, $\eta_p^2<0.01$.

Secondary Outcome measures. At pre-intervention, no differences between groups in expectancy of both parents and teachers were found. Only NF showed a negative correlation between parent rated expectancy and change in inattentiveness as measured by the SWAN, $r(39)=-0.36$, $p=0.02$. This result reveals that parents with higher treatment expectations of neurofeedback also rated their child as more improved in terms of inattentive symptoms. Quality of sleep (SDSC) did not change over time for any of the intervention groups.

Complete Case Analyses

All analyses were rerun using complete case analysis, and revealed results comparable to the intention-to-treat analysis. See also the Supplementary eTable 1: Complete case analyses of outcome measures and side effects.

Table 2. Intention-to-treat analyses of primary outcome measures and side effects

Questionnaire			Pre-Intervention	Post-Intervention	Adjusted difference	Time			Group x Time		
		n	*M(SD)*	*M(SD)*	*M*[95%CI]	*F*	η_p^2	*p*	*F*	η_p^2	*p*
Parent ratings											
SDQ	NF	39	16.90(4.54)	14.92(5.98)	-1.97[-3.32, -0.63]	29.22	0.21	<.001	1.07	0.02	.35
	MPH	36	15.64(4.23)	12.86(5.15)	-2.78[-4.14, -1.41]						
	PA	37	17.22(3.93)	15.81(4.62)	-1.41[-2.69, -0.12]						
SWAN-IN	NF	39	1.42(0.52)	1.11(0.67)	-0.32[-0.53, -0.10]	45.70	0.30	<.001	8.30	0.13	<.001
	MPH	36	1.39(0.70)	0.61(0.83)	-0.78[-1.03, -0.53]						
	PA	37	1.28(0.70)	1.11(0.72)	-0.17[-0.37, 0.02]						
SWAN-H/I	NF	39	1.30(0.70)	1.02(0.81)	-0.29[-0.50, -0.07]	30.61	0.22	<.001	2.30	0.04	.11
	MPH	36	1.14(0.72)	0.62(0.90)	-0.52[-0.74, -0.30]						
	PA	37	1.28(0.82)	1.07(0.80)	-0.21[-0.41, -0.01]						
Teacher ratings											
SDQ	NF	39	14.51(4.71)	15.38(5.14)	0.87[-0.46, 2.21]	3.42	0.03	.07	9.10	0.15	<.001
	MPH	33	13.48(5.43)	10.30(6.34)	-3.18[-4.86, -1.50]						
	PA	35	15.91(5.17)	15.97(4.90)	0.06[-1.21, 1.33]						
SWAN-IN	NF	39	1.40(0.90)	1.30(0.76)	-0.10[-0.31, 0.11]	34.76	0.25	<.001	20.82	0.29	<.001
	MPH	33	1.52(0.62)	0.57(0.79)	-0.95[-1.23, -0.68]						
	PA	35	1.38(0.69)	1.33(0.72)	-0.05[-0.23, 0.12]						
SWAN-H/I	NF	39	1.18(0.92)	1.16(1.11)	-0.03[-0.28, 0.23]	10.64	0.09	.001	8.37	0.14	<.001
	MPH	33	0.93(1.25)	0.23(0.90)	-0.70[-1.05, -0.34]						
	PA	35	1.12(0.92)	1.10(0.94)	-0.02[-0.18, 0.13]						
Side effects											
SDSC	NF	38	45.32(10.55)	43.16(9.45)	-2.16[-4.82, 0.51]	3.51	0.03	.06	0.53	0.01	.60
	MPH	35	45.09(9.11)	44.54(9.42)	-0.54[-2.90, 1.81]						
	PA	35	44.97(12.70)	44.94(10.98)	-1.03[-2.86, 0.80]						

Note. H/I=Hyperactivity/Impulsivity scale, IN=Inattention scale; *M*=Mean, *SD*=Standard Deviation, SDSC=Sleep Disturbance Scale for Children, SDQ=Strength and Difficulty Questionnaire, SWAN=Strengths and Weaknesses of ADHD and Normal Behaviours; *df* Time: *df*(1,109) Parent Ratings, *df*(1,104) Teacher Ratings, *df*(1,105) Side Effects; *df* Group x Time: *df*(2,109) Parent Ratings, *df*(2,104) Teacher Ratings, *df*(2,105) Side Effects

Supplementary eTable 1. Complete case analyses of outcome measures and side effects

Questionnaire			Pre-Intervention	Post-Intervention	Adjusted difference	Time			Group x Time		
		n	*M(SD)*	*M(SD)*	*M*[95%CI]	*F*	η_p^2	*p*	*F*	η_p^2	*p*
Parent ratings											
SDQ	NF	39	16.76(4.52)	14.74(5.95)	-2.03[-3.40, -0.65]	30.70	0.24	.001	1.44	0.03	.24
	MPH	36	16.03(4.15)	12.81(5.33)	-3.23[-4.76, -1.69]						
	PA	37	17.50(3.69)	15.97(4.55)	-1.53[-2.93, -0.13]						
SWAN-IN	NF	39	1.44(0.51)	1.12(0.67)	-0.33[-0.54, -0.11]	51.93	0.34	<.001	10.54	0.17	<.001
	MPH	36	1.40(0.73)	0.50(0.82)	-0.90[-1.17, -0.64]						
	PA	37	1.33(0.68)	1.14(0.71)	-0.19[-0.40, 0.23]						
SWAN-H/I	NF	39	1.30(0.71)	1.01(0.82)	-0.29[-0.52, -0.07]	32.84	0.25	<.001	3.00	0.06	.06
	MPH	36	1.10(0.67)	0.49(0.82)	-0.61[-0.85, -0.36]						
	PA	37	1.21(0.82)	0.98(0.77)	-0.23[-0.45, -0.01]						
Teacher ratings											
SDQ	NF	39	14.22(4.65)	15.14(5.15)	0.92[-0.49, 2.33]	3.46	0.04	.066	8.03	0.16	.001
	MPH	33	13.73(5.28)	10.23(6.35)	-3.50[-5.31, -1.70]						
	PA	35	15.86(5.46)	15.93(5.12)	0.07[-1.48, 1.62]						
SWAN-IN	NF	39	1.37(0.91)	1.26(0.76)	-0.11[-0.33, 0.11]	36.09	0.28	<.001	21.79	0.32	<.001
	MPH	33	1.53(0.60)	0.49(0.75)	-1.05[-1.33, -0.77]						
	PA	35	1.31(0.70)	1.25(0.72)	-0.07[-0.28, 0.15]						
SWAN-H/I	NF	39	1.15(0.92)	1.12(1.13)	-0.03[-0.30, 0.25]	10.56	0.10	.002	8.38	0.15	<.001
	MPH	33	0.94(1.30)	0.18(0.92)	-0.76[-1.15, -0.38]						
	PA	35	1.16(0.88)	1.14(0.91)	-0.03[-0.22, 0.16]						
Side effects											
SDSC	NF	38	45.32(10.55)	43.16(9.45)	-2.16[-4.82, 0.51]	3.24	0.03	.075	0.39	0.01	.68
	MPH	35	45.41(9.22)	44.76(9.61)	-0.66[-3.52, 2.21]						
	PA	35	46.72(13.00)	45.59(11.22)	-1.13[-3.14, 0.89]						

Note. H/I=Hyperactivity/Impulsivity scale, IN=Inattention scale; *M*=Mean, *SD*=Standard Deviation, SDSC=Sleep Disturbance Scale for Children, SDQ=Strength and Difficulty Questionnaire, SWAN=Strengths and Weaknesses of ADHD and Normal Behaviours; *df* Time: *df*(1,100) Parent Ratings, *df*(1,93) Teacher Ratings, *df*(1,96) Side Effects; *df* Group x Time: *df*(2,100) Parent Ratings, *df*(2,93) Teacher Ratings, *df*(2,93) Side Effects

DISCUSSION

The present study used a three-way parallel-randomized controlled trial design and is the first to compare behavioral effects of neurofeedback, optimally titrated stimulant medication and a semi-active control condition, physical activity, in children diagnosed with ADHD. Main results revealed that neurofeedback applied as a stand-alone intervention was less effective than stimulant medication. The behavioral effects of neurofeedback were similar to the semi-active control condition.

Parent reports revealed a superior effect of medication over neurofeedback to decrease inattention problems. Our findings are in line with the results of the RCT by Ogrim and Hestad (2013) who compared the effects of neurofeedback and medication. This RCT (Ogrim & Hestad, 2013) study applied a double blind titration procedure to determine an optimal dose of medication similar to the current study. However, they used two different types of stimulant medication whereas our study applied one type of stimulant medication. In contrast, two other RCTs comparing the effects of neurofeedback and stimulant medication, using weight-adjusted dosing, found similar reductions in ADHD behaviors for the two treatment approaches (Duric et al., 2012; Meisel et al., 2013). The use of disparate medication protocols might explain these discrepant findings. The superiority of the titration protocol has been supported by findings of the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/ Hyperactivity Disorder (MTA). The MTA study revealed that a titration procedure, comparable to the procedure used in the current study, established higher success rates compared to standard community care (Swanson, Kraemer, et al., 2001).

Teachers indicated that ADHD symptoms reduced with stimulant medication. In contrast to parents, however, teachers did not report any decrease in ADHD symptoms in children who received neurofeedback or physical activity. The discrepancy between the effectiveness of the three interventions as reported by parents and teachers might be explained in terms of differences between raters in their investment in the intervention (Sonuga-Barke et al., 2013). Neurofeedback and physical activity required direct involvement and devotion of parents, while teachers held more passive roles. Another possibility is that treatment expectancy of parents and teachers confounded our measures. However, treatment expectancy of both parents and teachers did not differ between groups. This indicates that all parents and teachers evaluated the three intervention conditions as potentially equally effective. However, the association between expectancy and behavioral treatment effects were different among groups. Only for the neurofeedback group, higher parent expectations were predictive of greater improvements

on inattention symptoms. This finding suggests that the parent reported decrease of inattention problems in the neurofeedback group may be (partly) explained by parental expectations.

Sleep quality was not affected by any of the received interventions. This is remarkable, since sleep disturbances are one of the most common reported side effects of stimulant medication use (Corkum, Panton, Ironside, MacPherson, & Williams, 2008; Stein, 1999). However, in our study, stimulant medication was titrated up to the most effective dose, while minimizing side effects. Therefore our titration procedure might explain that side effects were less present in our study compared to most other studies. A study by Faraone et al. (2009) used, similar to our study, a titration protocol to determine the optimal dose of long acting methylphenidate. This study also found no effects on sleep quality after a prolonged period of stimulant medication use (Faraone et al., 2009). Whereas stimulant medication is known for a negative impact on sleep quality (Stein, 1999), it has been theorized that neurofeedback would improve sleep quality. The training of sensorimotor-rhythm (SMR) 12-15Hz, as part of theta/beta and theta/SMR training, would enhance sleep spindle density during sleep. Enhanced sleep spindle density has been found to decrease sleep latency and increase total sleep time in a healthy human population (Hoedlmoser et al., 2008). Accordingly, after theta/beta neurofeedback, sleep quality would be expected to improve. However, in line with previous RCTs testing the effects of neurofeedback (Bink, van Nieuwenhuizen, Popma, Bongers, & van Boxtel, 2014; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013), the current study did not show such positive effects.

The present study is a valuable contribution to the current neurofeedback literature in children with ADHD as it compared neurofeedback, as a stand-alone intervention, with an optimal dose of methylphenidate, the most widely used intervention for ADHD. This study successfully randomly allocated participants to intervention groups, did not suffer from selective drop out, and groups did not differ from each other at pre-intervention. During the neurofeedback sessions, active learning strategies were applied. Nevertheless, there are also some limitations that should be addressed. First, the present study used a theta/beta neurofeedback protocol with the aim to decrease symptoms of ADHD. The selection and application of the training protocol for neurofeedback in ADHD is a prominently debated topic. Recent findings on theta/beta training revealed non-significant results as rated by probably blinded assessors (Sonuga-Barke et al., 2013). Up until now, slow cortical potential training, another type of neurofeedback protocol, has not been subjected to intensive research in ADHD and might lead to better results (Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014). Second, in contrast to the effects

of physical activity found in the current study, a recent study of Hoza et al. (2014) revealed that physical activity led to a larger decrease in inattentive behavior in children at risk for developing ADHD and TD children, than a sedentary control condition (Hoza et al., 2014). This difference in findings might be the result of differences in ADHD-symptom severity, with the current study including children with more severe ADHD-symptoms and a DSM-IV-TR diagnosis of ADHD. Furthermore, the study of Hoza et al. (2014) applied a more intensive physical activity protocol than the current study, with three bounds of eight minutes, five times a week for 12 successive weeks. In the current study, the physical activity intervention was implemented as a semi-active control condition, where frequency and intensity were adjusted to be similar to the neurofeedback intervention. Therefore, a less intensive protocol was applied with 10 bounds of two minutes moderate to vigorous physical activity, three times a week for 10 successive weeks. Accordingly, the physical activity protocol of the current study does not correspond with the recommendations on physical activity found in the literature (Halperin et al., 2014). More research on physical activity is necessary to substantiate its possible chronic effects on problem behavior as seen in ADHD. Third, in the current study children in the medication condition were prescribed short-acting MPH. However, for some patients the use of long-acting MPH might be preferable over short-acting MPH, considering the increased compliance and reduced social stigma associated with long-acting MPH (Coghill et al., 2013).

In the present study we found superior behavioral effects of stimulant medication compared to neurofeedback. Furthermore, similar effects were found for neurofeedback and the semi-active control intervention. Neurofeedback is an expensive and time-consuming intervention. Hence, the current study does not support the use of theta/beta neurofeedback training as a stand-alone intervention for children with ADHD.

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