Behavioral Effects of Neurofeedback Compared to Stimulants and Physical Activity in Attention-Deficit/Hyperactivity Disorder: A Randomized Controlled Trial

Katleen Geladé, MSc[a,b,*]; Tieme W. P. Janssen, PhD[b]; Marleen Bink, PhD[b]; Rosa van Mourik, PhD[c]; Athanasios Maras, MD, PhD[a]; and Jaap Oosterlaan, PhD[b]

ABSTRACT

Objective: The efficacy of neurofeedback as a treatment for attention-deficit/hyperactivity disorder (ADHD), and whether neurofeedback is a viable alternative for stimulant medication, is still an intensely debated subject. The current randomized controlled trial compared neurofeedback to (1) optimally titrated methylphenidate and (2) a semi-active control intervention, physical activity, to account for nonspecific effects.

Methods: A multicenter 3-way parallel-group study with balanced randomization was conducted. Children with a *DSM-IV-TR* diagnosis of ADHD, aged 7–13 years, were randomly allocated to receive neurofeedback (n = 39), methylphenidate (n = 36), or physical activity (n = 37) over a period of 10–12 weeks. Neurofeedback comprised theta/beta training on the vertex (Cz). Physical activity consisted of moderate to vigorous intensity exercises. Neurofeedback and physical activity were balanced in terms of number (~30) and duration of sessions. A double-blind pseudorandomized placebo-controlled crossover titration procedure was used to determine an optimal dose in the methylphenidate intervention. Parent and teacher ratings on the Strengths and Difficulties Questionnaire (SDQ) and Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) were used to assess intervention outcomes. Data collection took place between September 2010 and March 2014.

Results: Intention-to-treat analyses revealed an improvement in parent-reported behavior on the SDQ and the SWAN Hyperactivity/Impulsivity scale, irrespective of received intervention ($\eta_p^2 = 0.21–0.22$, $P \leq .001$), whereas the SWAN Inattention scale revealed more improvement in children who received methylphenidate than neurofeedback and physical activity ($\eta_p^2 = 0.13$, $P \leq .001$). Teachers reported a decrease of ADHD symptoms on all measures for methylphenidate, but not for neurofeedback or physical activity (range of $\eta_p^2 = 0.14–0.29$, $P < .001$).

Conclusions: The current study found that optimally titrated methylphenidate is superior to neurofeedback and physical activity in decreasing ADHD symptoms in children with ADHD.

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[a]Yulius Academy, Yulius Mental Health Organization, Barendrecht, the Netherlands
[b]Department of Clinical Neuropsychology, VU University Amsterdam, Amsterdam, the Netherlands
[c]Royal Dutch Kentalis, Utrecht, the Netherlands
**Corresponding author:* Katleen Geladé, MSc, Dennenhout 1, 2994 GC Barendrecht, the Netherlands (k.gelade@yulius.nl).

Attention-deficit/hyperactivity disorder (ADHD)[1] is one of the most common childhood neurodevelopmental disorders.[2] Stimulant medication is a widely used and effective intervention for ADHD.[3] However, several limitations have been reported, including lack of improvement in a substantial group of patients and adverse side effects such as sleeping problems, decreased appetite, and headaches.[4] Furthermore, there is limited evidence for long-term effects of stimulant treatment.[5] As a result, alternative interventions for ADHD are in demand.

Neurofeedback has been proposed as a promising nonpharmacologic intervention for ADHD.[6,7] 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 behavioral problems as seen in ADHD.[8,9] Compared to typically developing children, children with ADHD show increased theta (4–7 Hz) and decreased beta activity (13–20 Hz).[8] Greater theta activity is related to poor vigilance, whereas greater beta activity is related to enhanced attention.[9] Accordingly, the most widely studied neurofeedback treatment protocol for ADHD aims at decreasing theta and increasing beta activity at the vertex (Cz).[7] However, more recent studies question the association between increased theta/beta ratio and ADHD.[10] Comorbid disorders might have a mediating effect on the theta/beta ratio.[10,11] Meta-analyses evaluating the effects of neurofeedback in children with ADHD are inconclusive, with conclusions ranging from neurofeedback being a noneffective treatment as assessed with blinded assessments,[12] to neurofeedback being more efficacious than active control conditions,[13] to neurofeedback being an "efficacious and specific" treatment.[14] Inconsistent results might be due to differences between studies in terms of (1) random allocation of participants, (2) controlling for concomitant treatments and/or nonspecific treatment effects, and (3) the use of blinded assessment of treatment effects.[6]

Results of randomized controlled trial (RCT) studies comparing the effects of neurofeedback and stimulant medication in children with ADHD are mixed. Two of 3 RCTs showed that neurofeedback is as effective as stimulant medication,[15,16] with the third study[17] showing superior effects for medication compared to neurofeedback on ADHD symptoms. 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 intervention.

Clinical Points

- Results of randomized controlled trials on the efficacy of neurofeedback compared to stimulant medication in children with attention-deficit/hyperactivity disorder (ADHD) are mixed.
- Optimally titrated methylphenidate was superior to neurofeedback in decreasing ADHD symptoms in children with ADHD. Effects of neurofeedback were comparable to the effects of the semi-active control condition.
- Results do not support the use of theta/beta neurofeedback as an alternative treatment for ADHD in clinical practice.

Physical activity could be another treatment approach for ADHD that utilizes protective effects of exercise on brain functioning.[18] However, beneficial effects of chronic exercise in children with ADHD are preliminary and have yet to be established in RCTs.[19] In the current study, physical activity was applied as a semi-active control condition to control for nonspecific 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 with (1) stimulant medication (methylphenidate) and (2) physical activity as a semi-active control condition in children with ADHD.

METHODS

Participants

Eligible participants were Dutch speaking children, 7–13 years of age, with a primary clinical *DSM-IV-TR* diagnosis of ADHD.[1] Children with ADHD were recruited from 15 child mental health outpatient care facilities in the west of the Netherlands. Before children entered the study, parent and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[20] 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 1 month. Exclusion criteria were neurologic disorders and intelligence quotient (IQ) below 80 as measured by a 4-subtest version of the Wechsler Intelligence Scale of Children-III (WISC-III) that included the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement.[21] 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 learning disorders (neurofeedback, n = 5; methylphenidate, n = 2; and physical activity, n = 1), autism spectrum disorders (neurofeedback, n = 3; methylphenidate, n = 2; and physical activity, n = 3), anxiety disorders (neurofeedback, n = 2; methylphenidate, n = 0; and physical activity, n = 2), and mood disorder (neurofeedback, n = 1; methylphenidate, n = 0; and physical activity, n = 0). χ^2 test revealed no significant difference in the distribution of comorbid disorders over groups (N = 112, $\chi^2_8 = 12.88$, $P = .12$).

Initially, 112 children with ADHD were randomized over the 3 interventions, with 103 children completing their intervention. Figure 1 presents a flow diagram of participants.

Trial Design

A multicenter 3-way parallel-group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator.[22] Stocks of 9 unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing intervention allocation. Subsequently, children, parents, and teachers were aware of the allocated group. Data collection took place between September 2010 and March 2014.

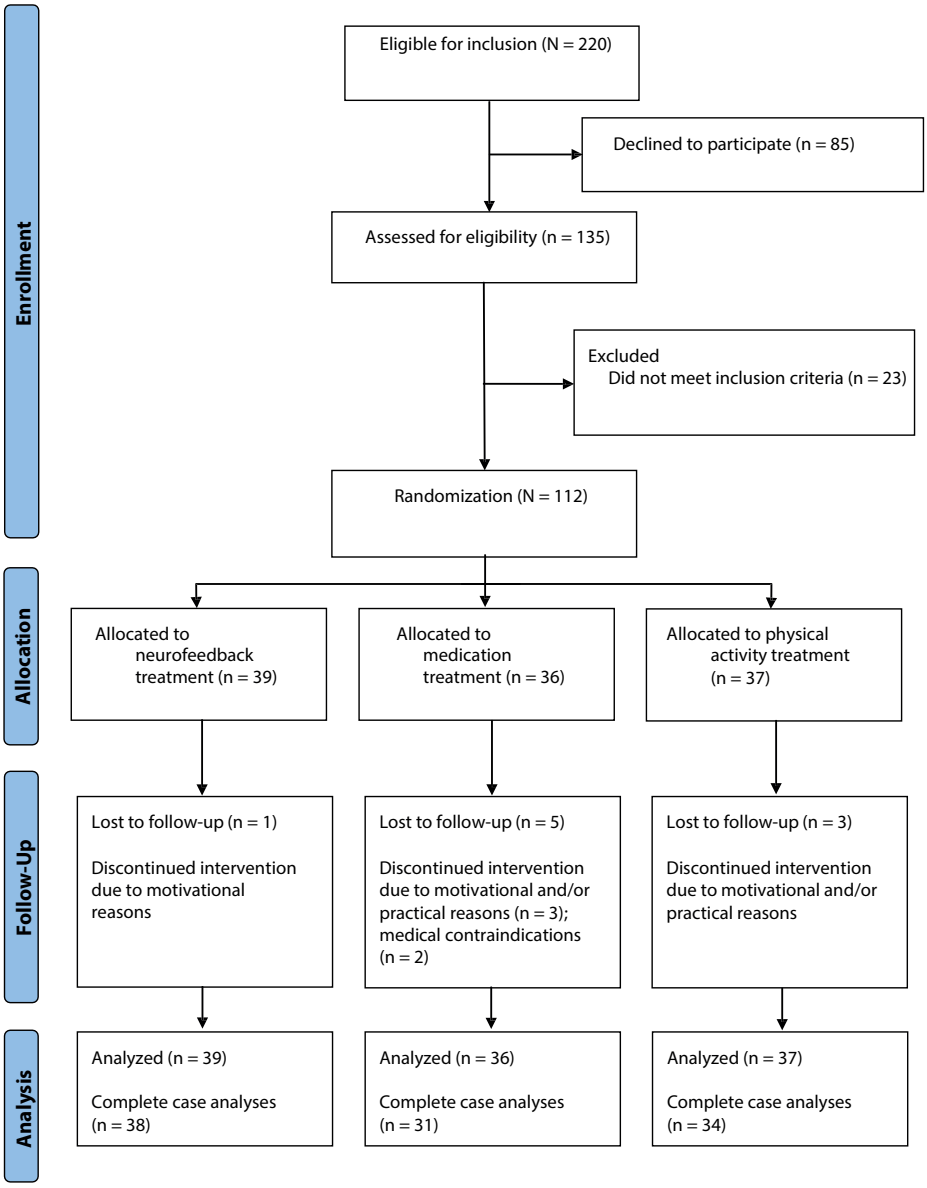
To detect a medium effect size ($f = 0.25$) for 3 groups to be sufficient in a repeated-measures analysis of variance (ANOVA) with an α of .05 and a power of 95%, using G*Power version 3.1.5,[23] a total sample size of 66 (ie, 22 per group) was calculated. In case of 2 groups, to perform relevant post hoc analysis, a total sample size of 54 (ie, 27 per group) was calculated to detect a medium effect size ($f = 0.25$) in a repeated-measures ANOVA with an α of .05 and a power of 95%. In the current study, the smallest group size was 29 participants. Consequently, all groups had enough participants to detect a medium effect size. This report complies with the CONSORT 2010 guidelines (eAppendix 1) for reporting parallel-group randomized trials.[24] The trial was registered on ClinicalTrials.gov (NCT01363544).

Interventions

Neurofeedback and physical activity interventions consisted of 3 individual training sessions a week, with each session lasting 45 minutes including 20 minutes of effective training, over a period of 10–12 weeks.

Neurofeedback. Theta/beta training was applied with the aim to inhibit theta (4–8 Hz) and reinforce beta (13–20 Hz) activity at Cz. The mean number of training sessions of participants who completed the assessments at postintervention (n = 38) was 29 (mean = 28.53; SD = 2.63; range, 19–30 sessions). Theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over 1 trial relative to session baseline was rewarded with the appearance of a sun and yielded credits. To promote generalization of the learned strategies into daily life, transfer trials were used. Transfer trials were presented without immediate visual feedback and were included from session 11 (25%) and session 21 (50%) onward. To further transfer learned behaviors, 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 as to whether they used the transfer cards over the intervention period. Transfer cards were used by 84% of the participants. See eAppendix 2 for more detailed information about the neurofeedback intervention.

Figure 1. Flow Diagram of Randomized Controlled Trial



Medication. A 4-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate.[25] The titration phase was preceded by a baseline week to determine ADHD symptoms without methylphenidate and was followed by a lead-in week in which on 3 consecutive days, twice-daily (at breakfast and lunchtime), doses of (1) 5 mg, (2) 10 mg, and (3) 15 mg (≤ 25 kg body weight) or 20 mg of methylphenidate (> 25 kg body weight) were used to assess possible adverse effects. During the 4-week titration phase, children received in pseudorandom order (1) 5 mg, (2) 10 mg, or (3) 15 mg or 20 mg of methylphenidate or (4) placebo for 1 week, twice daily. During the titration phase, children, parents, and teachers as well as the researchers were blinded with regard to the prescribed dose (placebo and 5, 10, or 15/20 mg of methylphenidate). At the end of each week, parents and teachers were asked to evaluate inattention and hyperactivity/impulsivity symptoms on the DBDRS and adverse effects on the Side Effect Rating Scale of the National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA) study.[26] Children were classified by a standardized procedure[27] as responders when their ADHD symptoms significantly decreased compared to placebo (n = 29). The standardized procedure[27] classified children as nonresponders when they did not show any decrease in inattention and hyperactivity/impulsivity symptoms across methylphenidate doses and placebo (n = 2). When children were found to respond equally well across different methylphenidate doses, the

lowest methylphenidate dose was prescribed. The 2 nonresponders were treated with 5 mg of methylphenidate twice daily. The child's psychiatrist prescribed the optimal dose of methylphenidate for the remaining intervention period (5 mg to 10 children including 8 responders and 2 nonresponders, 10 mg to 14 children, 15 mg to 2 children, and 20 mg to 5 children).

Physical activity. Maximum heart rate (HRmax) was determined before the start of the first training session using a standard HRmax 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 session 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 postintervention (n = 34) was 28 (mean = 27.74; SD = 3.56; range, 12–30).

Outcome Measures

Primary outcome measures included parent and teacher reports on the Strengths and Difficulties Questionnaire (SDQ)[28,29] and the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale.[30] The total scale of the SDQ and the SWAN scales of Inattention and Hyperactivity/Impulsivity were used to assess intervention effects.

Secondary outcome measures included a custom-made expectancy scale filled out preintervention by parents and teachers. Quality of sleep was assessed using the total scale of the Sleep Disturbance Scale for Children (SDSC)[31] 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.

Preintervention assessment took place in the week prior to the start of the intervention. Postintervention assessment took place 1 week after the last training. In addition to the data presented here, neuropsychological and electroencephalogram data were collected. During postintervention assessment, the methylphenidate group continued use of medication at the optimal titrated dose. Interventions took place between September 2010 and March 2014.

Statistical Methods

Statistical analyses were performed with IBM SPSS Statistics, version 20.0.[32] Differences between intervention groups in terms of background characteristics were analyzed with a χ^2 test or a 1-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 preintervention, teacher ratings on the SDQ and SWAN were incomplete for 5 participants. 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 ANOVAs, with time (between preintervention [t0] and postintervention [t1]) as within-subject factor and group (neurofeedback, methylphenidate, and physical activity) as between-subject factor, were applied. For these analyses, the adjusted difference at postintervention (t1 – t0) and accompanying 95% confidence interval (95% CI) are reported. Effect sizes are expressed in percentage of explained variance in partial eta squared (η_p^2; small, medium, and large effects correspond to $\eta_p^2 = 0.01$, $\eta_p^2 = 0.06$, and $\eta_p^2 = 0.14$, respectively).[33] In case of significant time by group interactions, post hoc analyses of 2-way between-groups interactions were performed separately for the between-subject factors: (1) neurofeedback and methylphenidate, (2) methylphenidate and physical activity, and (3) neurofeedback and physical activity with time (t0, t1) as within-subject factor. Differences on expectancies were analyzed with 1-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 postintervention assessments. All parent-reported primary outcome measures were complete for participants who completed the intervention; however, at postintervention, teacher ratings on the SDQ and the SWAN were missing for 2 participants and SDSC data were missing for 10 participants.

RESULTS

Group Characteristics

At preintervention, group characteristics and behavioral measures did not differ between the 3 intervention groups (Table 1).

Attrition Analysis

No differences were found in group characteristics and preintervention 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 the 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 methylphenidate showed greater improvement over

Table 1. Group Characteristics

	Total	Neurofeedback	Methylphenidate	Physical Activity	Group *F*	Group *P*
N (%)	112 (100)	39 (34.8)	36 (32.1)	37 (33.0)		
Age, mean (SD), y	9.63 (1.76)	9.96 (1.88)	9.11 (1.26)	9.80 (1.96)	2.48	.09
Gender (male/female)	85/27	30/9	27/9	28/9	0.04[a]	.98
IQ, mean (SD)	99.75 (13.36)	100.56 (13.18)	101.11 (14.24)	97.57 (12.74)	0.75	.48
DBDRS Parent, mean (SD)						
Inattention	16.24 (5.30)	16.56 (5.10)	16.33 (5.65)	15.81 (5.26)	0.20	.82
Hyperactivity/Impulsivity	13.73 (6.12)	14.31 (6.03)	13.42 (6.40)	13.43 (6.03)	0.26	.77
DBDRS Teacher, mean (SD)						
Inattention	16.25 (5.78)	15.56 (5.36)	17.61 (6.30)	15.65 (5.63)	1.48	.23
Hyperactivity/Impulsivity	13.33 (8.07)	14.13 (7.12)	12.75 (9.70)	13.05 (7.44)	0.30	.74

[a] χ^2.
Abbreviations: DBDRS = Disruptive Behavior Disorders Rating Scale, SD = standard deviation.

Table 2. Intention-to-Treat Analyses of Outcome Measures and Side Effects

Questionnaire	N	Preintervention Mean (SD)	Postintervention Mean (SD)	Adjusted Difference (95% CI) at Postintervention (t1 – t0)	Time (t0 to t1) *df*	*F*	η_p^2	*P*	Neurofeedback, Physical Activity, and Methylphenidate Over Time *df*	*F*	η_p^2	*P*
Parent ratings												
SDQ					(1,109)	29.22	0.21	<.001	(2,109)	1.07	0.02	.35
Neurofeedback	39	16.90 (4.54)	14.92 (5.98)	−1.97 (−3.32 to −0.63)								
Methylphenidate	36	15.64 (4.23)	12.86 (5.15)	−2.78 (−4.14 to −1.41)								
Physical activity	37	17.22 (3.93)	15.81 (4.62)	−1.41 (−2.69 to −0.12)								
SWAN												
Inattention					(1,109)	45.70	0.30	<.001	(2,109)	8.30	0.13	<.001
Neurofeedback	39	1.42 (0.52)	1.11 (0.67)	−0.32 (−0.53 to −0.10)								
Methylphenidate	36	1.39 (0.70)	0.61 (0.83)	−0.78 (−1.03 to −0.53)								
Physical activity	37	1.28 (0.70)	1.11 (0.72)	−0.17 (−0.37 to 0.02)								
Hyperactivity/ Impulsiveness					(1,109)	30.61	0.22	<.001	(2,109)	2.30	0.04	.11
Neurofeedback	39	1.30 (0.70)	1.02 (0.81)	−0.29 (−0.50 to −0.07)								
Methylphenidate	36	1.14 (0.72)	0.62 (0.90)	−0.52 (−0.74 to −0.30)								
Physical activity	37	1.28 (0.82)	1.07 (0.80)	−0.21 (−0.41 to −0.01)								
Teacher ratings												
SDQ					(1,104)	3.42	0.03	.07	(2,104)	9.10	0.15	<.001
Neurofeedback	39	14.51 (4.71)	15.38 (5.14)	0.87 (−0.46 to 2.21)								
Methylphenidate	33	13.48 (5.43)	10.30 (6.34)	−3.18 (−4.86 to −1.50)								
Physical activity	35	15.91 (5.17)	15.97 (4.90)	0.06 (−1.21 to 1.33)								
SWAN												
Inattention					(1,104)	34.76	0.25	<.001	(2,104)	20.82	0.29	<.001
Neurofeedback	39	1.40 (0.90)	1.30 (0.76)	−0.10 (−0.31 to 0.11)								
Methylphenidate	33	1.52 (0.62)	0.57 (0.79)	−0.95 (−1.23 to −0.68)								
Physical activity	35	1.38 (0.69)	1.33 (0.72)	−0.05 (−0.23 to 0.12)								
Hyperactivity/ Impulsiveness					(1,104)	10.64	0.09	.001	(2,104)	8.37	0.14	<.001
Neurofeedback	39	1.18 (0.92)	1.16 (1.11)	−0.03 (−0.28 to 0.23)								
Methylphenidate	33	0.93 (1.25)	0.23 (0.90)	−0.70 (−1.05 to −0.34)								
Physical activity	35	1.12 (0.92)	1.10 (0.94)	−0.02 (−0.18 to 0.13)								
Side effects												
SDSC					(1,105)	3.51	0.03	.06	(2,105)	0.53	0.01	.60
Neurofeedback	38	45.32 (10.55)	43.16 (9.45)	−2.16 (−4.82 to 0.51)								
Methylphenidate	35	45.09 (9.11)	44.54 (9.42)	−0.54 (−2.90 to 1.81)								
Physical activity	35	44.97 (12.70)	44.94 (10.98)	−1.03 (−2.86 to 0.80)								

Abbreviations: SD = standard deviation, SDSC = Sleep Disturbance Scale for Children, SDQ = Strengths and Difficulties Questionnaire, SWAN = Strengths and Weaknesses of ADHD and Normal Behavior.

time than (1) neurofeedback ($F_{1,73} = 8.24$, $P = .005$, $\eta_p^2 = 0.10$) and (2) physical activity ($F_{1,71} = 15.05$, $P < .001$, $\eta_p^2 = 0.18$). No difference was found between (3) neurofeedback and physical activity ($F_{1,74} = 0.99$, $P = .323$, $\eta_p^2 = 0.01$).

Teacher reports on the SDQ and the SWAN showed differential intervention effects in the 3 groups as evidenced by significant group-by-time interactions. On the SDQ, methylphenidate showed greater improvement than (1) neurofeedback ($F_{1,70} = 15.13$, $P < .001$, $\eta_p^2 = 0.18$) and (2) physical activity ($F_{1,66} = 9.94$, $P = .002$, $\eta_p^2 = 0.13$, and (3) neurofeedback and physical activity 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 methylphenidate displayed greater improvement over time than (1) neurofeedback ($F_{1,70} = 25.98$, $P < .001$, $\eta_p^2 = 0.27$) and (2) physical activity ($F_{1,66} = 32.40$, $P < .001$, $\eta_p^2 = 0.33$).

No difference was found between (3) neurofeedback and physical activity ($F_{1,72} = 0.13$, $P = .721$, $\eta_p^2 = 0.002$). Likewise, for the SWAN Hyperactivity/Impulsivity scale, post hoc analyses indicated that methylphenidate showed greater improvement over time than (1) neurofeedback ($F_{1,70} = 9.87$, $P = .002$, $\eta_p^2 = 0.12$) and (2) physical activity ($F_{1,66} = 12.80$, $P = .001$, $\eta_p^2 = 0.16$). Again, no difference was found between (3) neurofeedback and physical activity ($F_{1,72} < 0.01$, $P = .98$, $\eta_p^2 < 0.01$).

Secondary outcome measures. At preintervention, we found no differences between groups in expectancy of parents. Only neurofeedback showed a negative correlation between parent-rated expectancy and change in inattentiveness as measured by the SWAN ($r_{39} = -0.36$, $P = .02$). This result reveals that parents with higher treatment expectations of neurofeedback also rated their child as more improved in terms of inattentive symptoms. Teachers had higher expectations of medication compared to neurofeedback and physical activity; however this was not associated with reported changes by teachers. 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 Supplementary eTable 1 for the complete case analyses of outcome measures and side effects.

DISCUSSION

The present study used a 3-way parallel RCT 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[17] who compared the effects of neurofeedback and medication. Their RCT study[17] applied a double-blind titration procedure to determine an optimal dose of medication similar to the current study. However, they used 2 different types of stimulant medication, whereas our study applied 1 type of stimulant medication. In contrast, 2 other RCTs[15,16] comparing the effects of neurofeedback and stimulant medication, using weight-adjusted dosing, found similar reductions in ADHD behaviors for the 2 treatment approaches. The use of disparate medication protocols might explain these discrepant findings. The superiority of the titration protocol has been supported by findings of the MTA study. 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.[25]

Teachers indicated that ADHD symptoms were 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 3 interventions as reported by parents and teachers might be explained in terms of differences between raters in their investment in the intervention.[12] 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, 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 commonly reported side effects of stimulant medication use.[34,35] However, in our study, stimulant medication was titrated up to the most effective dose, while minimizing side effects. Therefore our titration procedure might explain why fewer side effects were present in our study compared to most other studies. The study by Faraone et al[36] used, similar to our study, a titration protocol to determine the optimal dose of long acting methylphenidate. Their study[36] also found no effects on sleep quality after a prolonged period of stimulant medication use. Whereas stimulant medication is known for a negative impact on sleep quality,[35] it has been theorized that neurofeedback would improve sleep quality. The training of sensorimotor-rhythm 12–15 Hz, as part of theta/beta and theta/sensorimotor-rhythm 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.[37] Accordingly, after theta/beta neurofeedback, sleep quality would be expected to improve. However, in line with previous RCTs testing the effects of neurofeedback,[38,39] 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 and did not suffer from selective drop out and groups did not differ from each other at preintervention. 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 are prominently debated. Recent findings on theta/beta training revealed nonsignificant results as rated by probably

blinded assessors.[12] 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.[40] Second, in contrast to the effects of physical activity found in the current study, a recent study by Hoza et al[41] revealed that physical activity led to a larger decrease in inattentive behavior in both children at risk for developing ADHD and typically developing children than did a sedentary control condition.[41] 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 by Hoza et al[41] applied a more intensive physical activity protocol than the current study, with 3 sets of 8 minutes, 5 times a week for 12 successive weeks. In the current study, the physical activity intervention was implemented as a semi-active control condition, whereby frequency and intensity were adjusted to be similar to the neurofeedback intervention. Therefore, a less intensive protocol was applied with 10 sets of 2 minutes of moderate to vigorous physical activity, 3 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.[19] 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 methylphenidate. However, for some patients, the use of long-acting methylphenidate might be preferable over short-acting methylphenidate, considering the increased compliance and reduced social stigma associated with long-acting methylphenidate.[42]

CONCLUSION

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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Drug names: methylphenidate (Ritalin and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Behavioral Effects of Neurofeedback Compared to Stimulants and Physical Activity in Attention-Deficit/Hyperactivity Disorder: A Randomized Controlled Trial

Author(s): Katleen Geladé, MSc; Tieme W. P. Janssen, MSc; Marleen Bink, PhD; Rosa van Mourik, PhD; Athanasios Maras, MD, PhD; and Jaap Oosterlaan, PhD

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List of Supplementary Material for the article

1. **eAppendix 1** CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial
2. **eAppendix 2** Supplementary Methods
3. **eTable 1** Complete Case Analyses of Outcome Measures and Side Effects

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.

eAppendix 1: 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)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	n/a
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	n/a

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	2
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3
	13b	For each group, losses and exclusions after randomisation, together with reasons	3
Recruitment	14a	Dates defining the periods of recruitment and follow-up	1 & 2 &4
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	3 & 4-6
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)	5
	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	4-6
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	6-7
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	6-7
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	6-7
Other information			
Registration	23	Registration number and name of trial registry	1 & 2
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

eAppendix 2

Methods

Interventions

Neurofeedback. The THERAPRAX® EEG Biofeedback system (Neuroconn GmbH, Germany) with a DC-amplifier and a sampling rate of 128Hz was used to transmit and analyze the EEG signal. Reference and ground electrodes were attached to right and left mastoids, respectively. Electro-oculogram was obtained with two electrodes at external canthi, and two electrodes at supra- and infraorbital sides. Ocular correction was applied as described in Schlegelmilch et al.(2004). Subsequently, a 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.

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. 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. Number of credits per trial depended on the training level, with more credits for higher levels.

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

Questionnaire			Pre-Intervention	Post-Intervention	Adjusted difference [95% *CI*] at post-intervention t1-t0	Time (T0 to T1)				NFB, PA and MPH over time			
		n	*M(SD)*	*M(SD)*		*df*	*F*	η_p^2	*p*	*df*	*F*	η_p^2	*p*
Parent ratings													
SDQ						(1,100)	30.70	0.24	.001	(2,100)	1.44	0.03	.24
	NFB	38	16.76(4.52)	14.74(5.95)	-2.03[-3.40, -0.65]								
	MPH	31	16.03(4.15)	12.81(5.33)	-3.23[-4.76, -1.69]								
	PA	34	17.50(3.69)	15.97(4.55)	-1.53[-2.93, -0.13]								
SWAN Inattention						(1,100)	51.93	0.34	<.001	(2,100)	10.54	0.17	<.001
	NFB	38	1.44(0.51)	1.12(0.67)	-0.33[-0.54, -0.11]								
	MPH	31	1.40(0.73)	0.50(0.82)	-0.90[-1.17, -0.64]								
	PA	34	1.33(0.68)	1.14(0.71)	-0.19[-0.40, 0.23]								
H/I						(1,100)	32.84	0.25	<.001	(2,100)	3.00	0.06	.06
	NFB	38	1.30(0.71)	1.01(0.82)	-0.29[-0.52, -0.07]								
	MPH	31	1.10(0.67)	0.49(0.82)	-0.61[-0.85, -0.36]								
	PA	34	1.21(0.82)	0.98(0.77)	-0.23[-0.45, -0.01]								
Teacher ratings													
SDQ						(1,93)	3.46	0.04	.066	(2,93)	8.03	0.16	.001
	NFB	37	14.22(4.65)	15.14(5.15)	0.92[-0.49, 2.33]								
	MPH	30	13.73(5.28)	10.23(6.35)	-3.50[-5.31, -1.70]								
	PA	29	15.86(5.46)	15.93(5.12)	0.07[-1.48, 1.62]								
SWAN Inattention						(1,93)	36.09	0.28	<.001	(2,93)	21.79	0.32	<.001
	NFB	37	1.37(0.91)	1.26(0.76)	-0.11[-0.33, 0.11]								
	MPH	30	1.53(0.60)	0.49(0.75)	-1.05[-1.33, -0.77]								
	PA	29	1.31(0.70)	1.25(0.72)	-0.07[-0.28, 0.15]								
H/I						(1,93)	10.56	0.10	.002	(2,93)	8.38	0.15	<.001
	NFB	37	1.15(0.92)	1.12(1.13)	-0.03[-0.30, 0.25]								
	MPH	30	0.94(1.30)	0.18(0.92)	-0.76[-1.15, -0.38]								
	PA	29	1.16(0.88)	1.14(0.91)	-0.03[-0.22, 0.16]								
Side effects													
SDSC						(1,96)	3.24	0.03	.075	(2,93)	0.39	0.01	.68
	NFB	38	45.32(10.55)	43.16(9.45)	-2.16[-4.82, 0.51]								
	MPH	29	45.41(9.22)	44.76(9.61)	-0.66[-3.52, 2.21]								
	PA	32	46.72(13.00)	45.59(11.22)	-1.13[-3.14, 0.89]								

Note. H/I=Hyperactivity/Impulsivity scale, M=Mean, SD=Standard Deviation, SDSC=Sleep Disturbance Scale for Children, SDQ=Strength and Difficulty Questionnaire, SWAN=Strengths and Weaknesses in ADHD and Normal Behaviors