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Janssen, T.W.P.

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# CHAPTER 6

An RCT into the effects of neurofeedback, methylphenidate and physical activity on EEG power spectra in children with ADHD

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## ABSTRACT

**Objective:** The clinical and neurophysiological effects of neurofeedback as treatment for children with ADHD are still unclear. This randomized controlled trial (RCT) examined EEG power spectra before and after neurofeedback (NF) compared to methylphenidate (MPH) treatment and physical activity (PA) – as semi-active control group – during resting and active (effortful) task conditions, to determine whether neurofeedback can induce sustained alterations in brain function. **Methods:** Using a multicenter three-way parallel group RCT design, 112 children with a DSM-IV diagnosis of ADHD, aged between 7-13 years, were initially included. NF training consisted of 30 sessions of theta/beta training at Cz over a 10-week period. PA training was a semi-active control group, matched in frequency and duration. Methylphenidate was titrated using a double-blind placebo controlled procedure in 6 weeks, followed by a stable dose for 4 weeks. EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 81 children at pre- and post-intervention ( $n=29$  NF,  $n=25$  MPH,  $n=27$  PA). **Results:** Both NF and MPH resulted in comparable reductions in theta power from pre- to post-intervention during the EO condition compared to PA ( $\eta_p^2=.08$  and  $.12$ ). For NF greater reductions in theta were related to greater reductions in ADHD symptoms. During the task condition, only MPH showed reductions in theta and alpha power compared to PA ( $\eta_p^2=.10$  and  $.12$ ). **Conclusions:** This study provides evidence for specific neurophysiological effects after theta/beta NF and MPH treatment in children with ADHD. However, for NF these effects did not generalize to an active task condition, potentially explaining reduced behavioral effects of NF in the classroom.

## INTRODUCTION

ADHD is a common neuropsychiatric disorder in children, affecting 6-7% of the population (Willcutt, 2012), which broadly impacts academic and social functioning (Biederman, 2005; Coghill et al., 2008). Although stimulant medication is effective in short-term symptom reduction (Faraone & Buitelaar, 2010), approximately 30% do not respond favourably (Spencer et al., 1996), or experience adverse effects (Graham & Coghill, 2008). These disadvantages have spurred the development of non-pharmacological treatments for ADHD such as neurofeedback. Despite that neurofeedback aims to target brain function directly, electroencephalographic (EEG) treatment effects have received little consideration.

Neurofeedback is a behavioural therapy that is based on operant conditioning of specific brain states by providing real-time feedback of EEG signals. The feedback signal of interest in ADHD has been derived (Lubar, 1991) from studies that show increased slow wave activity (theta: 4-8Hz) and decreased fast wave activity (beta: 13-21Hz) in the spontaneous EEG of children with ADHD (Snyder & Hall, 2006). Originally, these findings have been interpreted as indices of hypo-arousal that may play a causative role in ADHD symptomology, in line with the cognitive-energetic model of ADHD (Sergeant, 2000; Zentall & Zentall, 1983). Accordingly, decreasing the ratio of theta/beta and/or increasing sensorimotor rhythm (SMR) with neurofeedback was hypothesized to ameliorate symptoms of ADHD. More recent studies, however, question the validity of theta/beta ratio as clinical biomarker of ADHD (Arns, Conners, & Kraemer, 2013; Loo et al., 2013; Snyder, Rugino, Hornig, & Stein, 2015), and several research groups increasingly embrace the possibility that neurofeedback does not address a neural dysfunction, but rather learns compensatory mechanisms (Arns, Heinrich, & Strehl, 2014; Gevensleben, Rothenberger, Moll, & Heinrich, 2012).

The efficacy of neurofeedback as treatment for ADHD is still debated. Although most researchers agree that treatment studies should be randomized and controlled, most of the discussion revolves around which kind of control group is appropriate to control for non-specific treatment effects (Loo & Makeig, 2012). Not surprisingly, systematic reviews differ in conclusions from 'no evidence for effectiveness using blinded assessments' (Sonuga-Barke et al., 2013) to 'neurofeedback is efficacious and specific' (Arns, Ridder, & Strehl, 2009).

Neural mechanisms that could underlie behavioural effects of theta/beta neurofeedback are yet unknown. However, pre- and post-treatment measurements of the spectral content of EEG can indicate if neurofeedback induces sustained alterations in brain function. Few randomized controlled trial (RCT) studies have actually examined EEG changes (Gevensleben

et al., 2009; Ogrim & Hestad, 2013). The study by Gevensleben et al. (2009) is the only RCT that found a reduction in theta activity at midline scalp sites for the neurofeedback group compared to the control group. No changes were demonstrated for beta activity or theta/beta ratio. Furthermore, the theta reduction was only found for the theta/beta and SCP training blocks combined, but not separately, indicating that this effect was not protocol-specific. Clinically, a more relevant finding was that higher theta at baseline was predictive of a greater decrease in ADHD symptoms in the theta/beta neurofeedback group. Another, uncontrolled study, found comparable results of reductions in theta from pre- to post-treatment (Monastra, Monastra, & George, 2002). Two other studies failed to show any changes in power spectra (Kropotov et al., 2007; Ogrim & Hestad, 2013). Overall, preliminary evidence suggests that neurofeedback may induce chronic alterations in brain function; however, the specificity of these treatment effects remains unclear.

Methylphenidate (MPH) is the most widely prescribed psychostimulant for ADHD, and presumably acts by increasing activation in dopamine and norepinephrine fronto-striatal circuitry (Arnsten, 2006). Surprisingly, most studies on the effects of MPH on EEG power spectra are uncontrolled, with EEG recorded off and on medication. These studies mostly show decreases in theta activity (Clarke et al., 2003; Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Song, Shin, Jon, & Ha, 2005; Swartwood et al., 1998), and/or increases in beta activity with MPH (Clarke et al., 2003; Clarke, Barry, Bond, et al., 2002; Song et al., 2005). Furthermore, clinical responders seem to be characterized by increased theta activity at baseline compared to non-responders (Clarke, Barry, McCarthy, & Selikowitz, 2002; Ogrim et al., 2014). One double-blind placebo-controlled study demonstrated that MPH administration increased parietal alpha activity during a rest condition, and increased beta during a CPT, but had no effects on theta (Loo, Hopfer, Teale, & Reite, 2004). Overall, the literature indicates that MPH may reduce slow wave activity and increase fast wave activity; however, there is considerable variability in study design and outcomes, and lack of controlled studies.

Direct comparisons of neurofeedback and stimulant medication have produced inconsistent results, with studies showing comparable clinical effects (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013) or superior effects for medication (Ogrim & Hestad, 2013). Only the study of Ogrim et al. (2013) examined EEG power spectra as well, and found no changes in both the neurofeedback and medication groups.

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, physical activity was applied as a semi-active treatment condition to control for non-specific treatment effects such as parental engagement and personal attention. Therefore, neurofeedback and physical activity training were matched on duration and intensity.

Few studies into EEG effects of theta/beta neurofeedback and methylphenidate have been randomized and controlled, precluding more definitive evidence for treatment-related changes in power spectra. Furthermore, previous studies have assessed EEG effects with varying study designs, mostly using only an eyes open resting, eyes closed resting or task condition, while differential effects for treatments across these conditions may be more informative. Therefore, the aims of the current RCT were threefold: (1) to explore EEG effects in eyes closed, eyes open and active task conditions, (2) to compare neurofeedback with optimally titrated MPH, and (3) to compare neurofeedback with physical activity as semi-active control group. For the active task condition, we explored effects on the stop-signal task (SST) (Logan & Cowan, 1984), which is a widely used task to measure response inhibition deficits in ADHD (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005) that are considered as one of the core problems in ADHD (Barkley, 1997; Sonuga-Barke, Bitsakou, & Thompson, 2010).

## METHODS

### Participants

Eligible participants were Dutch-speaking children, aged 7-13 years, with a primary clinical DSM-IV-TR diagnosis of ADHD. Parent- and teacher ratings on the Disruptive Behaviour Disorders Rating Scale (DBDRS) (Pelham, Gnagy, Greenslade, & Milich, 1992) required at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales to be above the 90th percentile for one of the informants, and one above the 70th percentile for the other informant. At study entry, all children were stimulant-free for at least one month. Exclusion criteria were neurological disorders and an estimated IQ below 80 on the abbreviated version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), using subtests Vocabulary, Arithmetic, Block Design and Picture Arrangement.

Initially, 112 children with ADHD were randomized over the three interventions: neurofeedback (NF;  $n=39$ ), methylphenidate (MPH;  $n=36$ ) and physical activity (PA;  $n=37$ ).

Hundred-three children completed the study. Nine children dropped out due to motivational ( $n=1$ ) or practical reasons ( $n=6$ ) or medical contraindications ( $n=2$ ). The dropout rate did not differ for NF ( $n=1$ [2.6%]), MPH ( $n=5$ [13.9%]) and PA ( $n=3$ [8.1%]),  $p=.164$ . The consort flow diagram is presented in Figure 1.

EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 81 children at pre- and post-intervention ( $n=29$  NF,  $n=25$  MPH,  $n=27$  PA). Missing data were due to technical reasons ( $n=5$ ), data quality at T0/T1 ( $n=10$ ), extremely poor task performance on more than 4 out of 6 runs of the stop-signal task (SST) at T0/T1 ( $n=6$ ), or motivational problems ( $n=1$ ).

### **Trial design**

A multicentre three-way parallel group study with balanced randomization was conducted. Randomization was established using a computerized random number generator (Dallal, 2007). Stocks of nine unmarked sealed envelopes were presented to parents at intake by the lead investigators. Parents randomly picked an envelope revealing treatment allocation.

For three groups, a total sample size of 66 (i.e. 22 per group) was calculated (by G\*power version 3.1.5 (Faul, Erdfelder, Lang, & Bunchner, 2007) to be sufficient to detect a medium effect size ( $f=0.25$ ) in a repeated measures (RM) analysis of variance (ANOVA) with an alpha of 0.05 and a power of 95%. In case of two groups, 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 of 0.05 and a power of 95%. A medium effect size difference between treatments was considered clinically relevant to detect. This trial is registered in the US trial register (Ref. No. NCT01363544) and the current analyses were planned as secondary outcome measures.

### **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 unidirectionally, 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

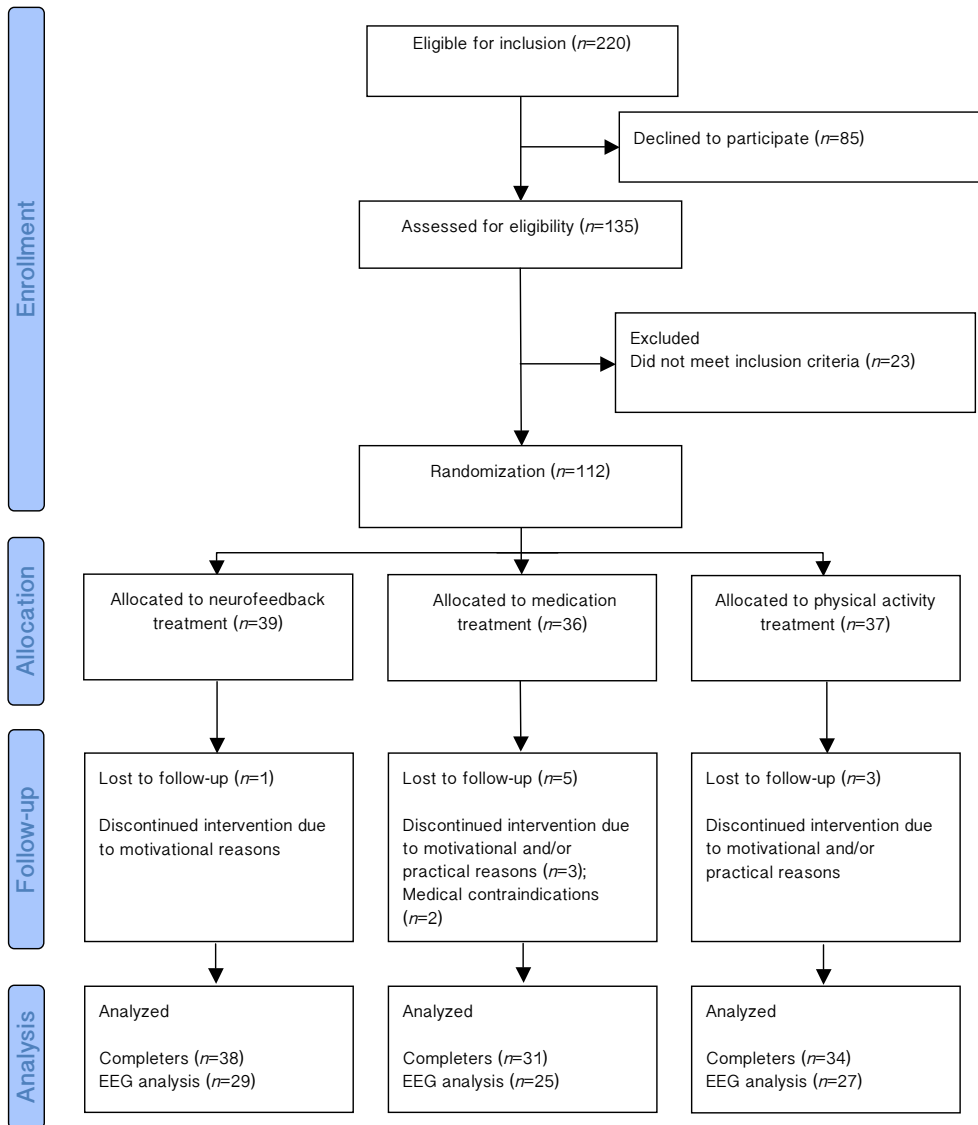


Figure 1. CONSORT flow diagram randomized controlled trial



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 [ $\frac{\text{theta}(\mu\text{V}/\text{Hz}) - \text{beta}(\mu\text{V}/\text{Hz})}{\text{theta}(\mu\text{V}/\text{Hz}) + \text{beta}(\mu\text{V}/\text{Hz})}$ ] 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. During transfer trials, patients received feedback on their performance after the trial was completed and did not receive feedback during the trial. 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 during the intervention period. 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. The mean number of completed training sessions was 27 (27.74±3.56) with a minimum of 12 sessions. Each training session started with 5-minutes of warming up followed by five 2-minute exercises at a level of 70-80% of HRmax. After a 5-minute break, five 2-minute exercises of 80-100% of HRmax were performed. The training finished with a 5 minute cool down. Time and heart rate were monitored and registered using POLAR (model FTM4).

### **Behavioural assessment**

Behavioural outcome measures included parent and teacher reports on the Strengths and Weaknesses of ADHD symptoms and Normal behaviour scale (SWAN; Swanson, Schuck, Mann, & Carlson, 2006).

### **Physiological measures**

EEG recording started with 3 minutes eyes open (EO) and 3 minutes eyes closed (EC) resting conditions, followed by a task condition. The stop-signal task (SST) involved two types of stimuli: go stimuli and stop stimuli. Go stimuli were left or right pointing airplanes requiring either a left or right button response. Each trial started with a black fixation cross, centred on a white background for 500ms, followed by a go stimulus for 1250ms and a blank screen for 650ms. In a randomly selected 25% of the trials, go stimuli were followed by a visual stop signal (traffic stop sign) superimposed on the go stimulus, requiring the participants to withhold their response. Participants were instructed to respond both quickly and accurately to the go stimuli and withhold their response when a stop signal was presented. They were told that they would be unable to withhold their responses on all stop trials, and that they should not wait for the stop sign. To ensure that basic requirements of the task were met, only runs were analysed that contained at least 70% correct go trials.

### **Electrophysiological recordings**

Continuous EEG was recorded at 512Hz using the ActiveTwo Biosemi system and ActiView software (Biosemi, Amsterdam, The Netherlands) from 128 scalp electrodes according to the ABC labelling system, referenced to the active common mode and grounded to the passive

right leg, which functions as a feedback loop to drive average potentials across electrodes to the amplifier zero. The electro-oculogram (EOG) was obtained using two electrodes at the external canthi, and two electrodes at infra- and supra-orbital sides. Reference electrodes were placed at both mastoids.

Off-line analysis was performed with Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). The sampling rate was down-sampled to 256Hz and scalp electrodes were re-referenced to the average of the mastoids. Data were band-pass filtered at 0.1-30Hz at 24 dB/oct and a 50-Hz notch filter was applied. Ocular artefacts were corrected with the method of Gratton & Coles (Gratton, Coles, & Donchin, 1983). The continuous EEG was segmented in 2-second intervals and automatic artefact rejection was applied to segments with amplitudes exceeding  $\pm 100\mu\text{V}$ . At least 30 artefact-free segments were required for EC, EO and task conditions for further analysis. The remaining segments were Fast Fourier-transformed and averaged. Mean power was calculated for theta (4-8Hz), alpha (8-12Hz) and beta (13-20Hz) frequency bands at midline electrodes (Fz, Cz, Pz).

### **Procedure**

The study was approved by the national medical ethics committee, the central committee on research involving human subjects (NL 31641.029.10 CCMO). Written informed consent was obtained before participation from parents and children aged 11 years or older. Children were recruited through mental health outpatient facilities in the West of the Netherlands.

Pre- and post-intervention measures included behavioural questionnaires, neuropsychological tasks, and electroencephalogram. Pre-intervention assessment took place in the week prior to the start of the intervention. Post-intervention assessment took place approximately one week after the last training. The MPH group continued use of medication up to post-intervention. Interventions took place between September 2010 and March 2014.

### **Statistics**

Statistical analyses were performed with SPSS 20 (Corp IBM, 2011). Significance was assumed if  $p < 0.05$  (two-tailed). Demographic data were compared between groups with one-way ANOVA or  $\chi^2$  test with Fisher exact correction. Significant group effects were further explored with pairwise group comparisons to locate group differences. Attrition analysis was performed with ANOVA by comparing the total sample with the EEG subsample on group characteristics, and by exploring possible interactions with treatment group.

Power spectra measures were log<sub>10</sub>-transformed to obtain normally distributed data. Separate General Linear Model (GLM) ANCOVAs were used for each condition (EC, EO, task) and frequency band (theta, alpha, beta) with time (pre-intervention [T0], and post-intervention [T1]), and location (Fz,Cz,Pz) as within-subject factors and treatment group as between-subject factor. Since it is known that EEG power spectra change during maturation (Clarke, Barry, McCarthy, & Selikowitz, 2001), age was inserted as covariate in all analyses. Significant interactions involving group were further explored with separate post-hoc GLM ANCOVAs for each pair of treatments. EEG effects were evaluated using multivariate test criteria, because multivariate results are more robust in case of violations of sphericity (Vasey & Thayer, 1987). Only time effects, group main effects, and interactions with group are reported (see Supplementary Material for Location effects). For the main outcomes, mean difference and 95% confidence interval [95% CI] are reported. Effect sizes are reported as partial eta-squared ( $\eta_p^2$ ), with effects interpreted as small (.01), medium (.06) or large (.14).

Pearson correlations were calculated in the total sample between baseline EEG power measures and both SWAN scales and performance measures on the SST, covarying for age, in order to obtain functional correlates of the frequency bands of interest. The predictive power of baseline power spectra and power spectra changes from pre- to post-intervention in relation to changes in ADHD symptoms, were explored with multiple linear regression. Only frequency bands and conditions that were significantly different between treatment groups from pre- to post-intervention were considered. Separate backward regressions were performed for the neurofeedback and methylphenidate groups. Dependent variables were teacher and parent rated SWAN Inattention and Hyperactivity/Impulsivity scores, and predictors were age, baseline power and change in power, with  $p > .10$  as removal criterion. Additionally, the same analyses were performed exploratory with the dependent variables stop-signal reaction time (SSRT) as measure of response inhibition speed, mean reaction time (MRT) on go trials as measure of processing speed, and commission and omission errors during go trials on the SST as measures of accuracy.

## RESULTS

### Group characteristics

At T0 there were no differences between the treatment groups in age, IQ, gender, and symptom severity (see Table I). Furthermore, groups did not differ in baseline measures of theta power

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

	NF		MPH		PA		Group	
	(n=29)		(n=25)		(n=27)			
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i> (2,78)	<i>p</i>
Demographic data								
Age (years)	10.02	1.77	9.09	1.10	9.79	1.92	2.29	ns
IQ	99.28	12.58	100.28	14.69	98.00	12.47	0.20	ns
Gender (M/F)	21/8		19/6		21/6		0.28 <sup>a</sup>	ns
DBDRS parents								
Inattention	15.79	4.81	16.40	5.91	16.30	5.10	0.11	ns
Hyperactivity	13.93	5.66	12.76	5.80	13.07	6.17	0.29	ns
/Impulsivity								
DBDRS teacher								
Inattention	15.17	5.46	16.72	6.54	16.00	4.91	0.51	
Hyperactivity/	14.10	7.26	11.72	9.61	13.19	7.36	0.59	ns
Impulsivity								

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

(all  $p > .10$ ). However, there were some baseline differences between groups in beta and alpha power during the EO and task conditions at Cz and Pz electrodes ( $p < .05$ ). Post-hoc tests showed less beta power in the physical activity group than the neurofeedback and methylphenidate groups. During the task condition, the physical activity group demonstrated less alpha power at Fz than the methylphenidate group ( $p = .010$ ).

Number of artefact-free segments at T0 did not differ between groups for EC (mean=79), EO (mean=84), and task condition (mean=580) (all  $p > .10$ ). At T1, groups did not differ on number of segments for EO (mean=86); however, the medication group had more segments than the physical activity group for the EC (NF=79, MPH=85, PA=74),  $F(1,50)=7.66$ ,  $p=.008$ , and task condition (NF=620, MPH=665, PA=526),  $F(1,50)=7.77$ ,  $p=.008$ .

### Attrition analysis

There were no differences in group characteristics between the EEG subgroup and the total randomized group, nor were there any interactions with treatment group.

## EEG results

ANCOVA results for each condition and frequency band are shown in Table II. Log transformed EEG power spectra of theta, alpha and beta frequency bands at pre- (T0) and post- (T1) intervention are shown in Figure 2. Figure 3 shows the 95% confidence intervals of treatment-related changes for the significant Time x Group interactions.

Main findings were Time x Group interactions for the theta band during EO and task conditions, and for the alpha band during the task condition. Post-hoc tests for the EO condition revealed that both neurofeedback and methylphenidate showed greater reductions in theta power than physical activity from pre- to post-measurement,  $F(1,53)=4.48$ ,  $p=.039$ ,  $\eta_p^2=.08$ , mean difference<sub>(NF-PA)</sub>=-0.073, 95%CI=[-0.142,-0.004], and  $F(1,49)=6.96$ ,  $p=.011$ ,  $\eta_p^2=.12$ , mean difference<sub>(MPH-PA)</sub>=-0.092, 95%CI=[-0.162,-0.022] respectively, with medium/large effect sizes. Neurofeedback and methylphenidate showed comparable decreases in theta,  $F(1,51)=0.16$ ,  $p=.691$ ,  $\eta_p^2=.00$ , mean difference<sub>(NF-MPH)</sub>=-0.012, 95%CI=[-0.074,0.050].

Post-hoc tests for the task condition showed a larger decrease in theta power for methylphenidate compared to physical activity,  $F(1,49)=5.35$ ,  $p=.025$ , mean difference<sub>(MPH-PA)</sub>=-0.092, 95%CI=[-0.173,-0.012], with a medium/large effect size,  $\eta_p^2=.10$ . No effects were found for neurofeedback compared to physical activity,  $F(1,53)=2.52$ ,  $p=.120$ ,  $\eta_p^2=.05$ , mean difference<sub>(NF-PA)</sub>=-0.053, 95%CI=[-0.120,0.014] or neurofeedback compared to methylphenidate,  $F(1,51)=1.00$ ,  $p=.322$ ,  $\eta_p^2=.02$ , mean difference<sub>(NF-MPH)</sub>=0.027, 95%CI=[-0.027,-0.080]. For the alpha band, the methylphenidate group showed a greater reduction in power compared to the physical activity group,  $F(1,49)=6.68$ ,  $p=.013$ ,  $\eta_p^2=.12$ , mean difference<sub>(MPH-PA)</sub>=-0.104, 95%CI=[-0.184,-0.023]. Again, no effects were found for neurofeedback compared to physical activity,  $F(1,53)=2.17$ ,  $p=.147$ ,  $\eta_p^2=.04$ , mean difference<sub>(NF-PA)</sub>=-0.053, 95%CI=[-0.125,0.019], or neurofeedback compared to methylphenidate,  $F(1,51)=1.79$ ,  $p=.187$ ,  $\eta_p^2=.03$ , mean difference<sub>(NF-MPH)</sub>=0.041, 95%CI=[-0.020,0.102].

Table II. GLM MANCOVA analyses of pre- and post-intervention power spectra

	T			T x G			T x L			T x G x L		
	$F(1,78)$	$\eta^2$		$F(2,78)$	$\eta^2$		$F(2,76)$	$\eta^2$		$F(4,154)$	$\eta^2$	
EC	Theta	0.09	.00	2.14	.05		0.34	.01		1.27	.03	
	Alpha	0.02	.00	0.96	.03		0.26	.01		0.41	.01	
	Beta	1.73	.02	0.63	.02		0.90	.02		0.33	.00	
EO	Theta	0.00	.00	3.71*	.09		0.11	.00		1.34	.03	(NF=MPH)>PA
	Alpha	1.17	.02	2.87	.07		0.11	.00		1.20	.03	
Task	Beta	0.63	.01	1.77	.04		0.45	.01		0.74	.02	
	Theta	0.02	.00	3.62*	.09		0.48	.01		0.89	.02	MPH>PA, NF=PA, NF=MPH
	Alpha	0.03	.00	4.01*	.09		0.24	.01		0.82	.02	MPH>PA, NF=PA, NF=MPH
	Beta	1.72	.02	1.80	.05		0.47	.01		0.49	.01	

Note. EC = eyes closed, EO = eyes open; NF = neurofeedback, MPH = methylphenidate, PA = physical activity; T = time,

G = group, C = condition, L = location

\* $p < .05$

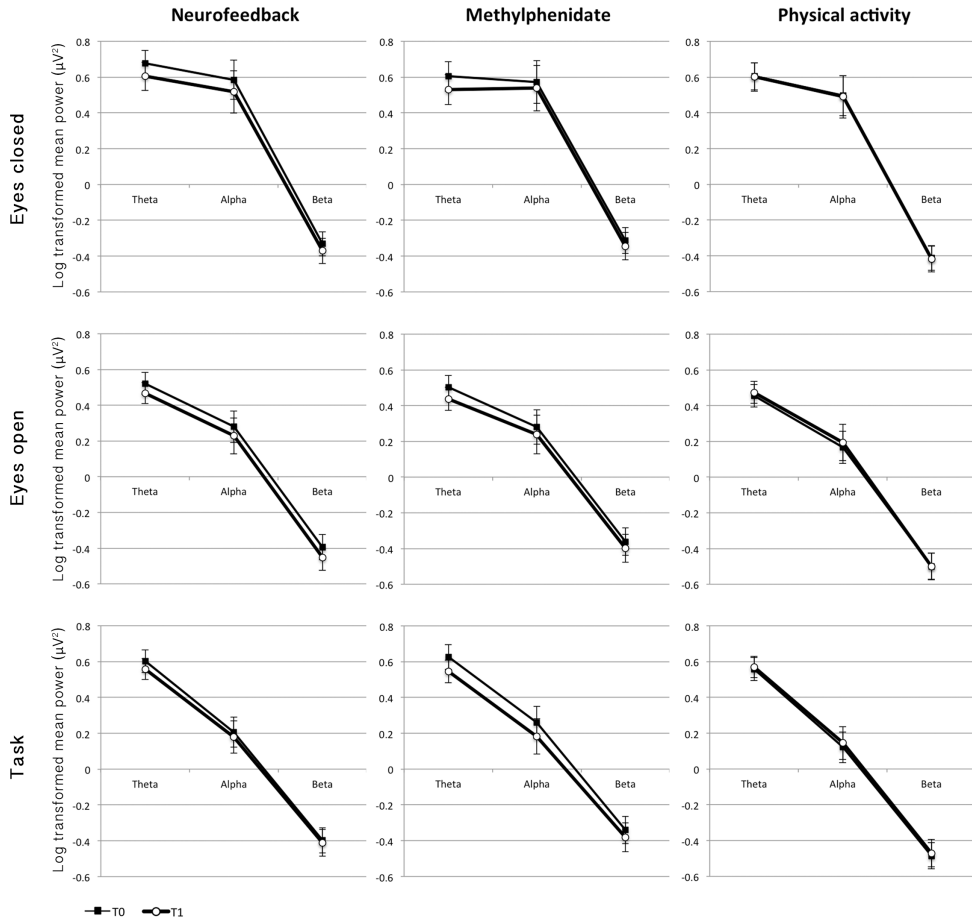
### Relations between EEG, behaviour and cognition

Since electrode location proved to be irrelevant for the results of this study, correlational and regression analyses were only performed for the Cz electrode to limit the number of tests.

*Pre-intervention.* Moderate sized correlations were found between theta power at T0 and teacher rated inattention and hyperactivity/impulsivity, for EO, EC and task conditions (correlations between  $r(80)=.33$ ,  $p<.01$  and  $r(80)=.39$ ,  $p<.001$ ), indicating that children with greater theta power display greater ADHD symptom severity. No other significant correlations were found, except a weak correlation between alpha power during the EO condition and the parent reported inattention,  $r(80)=-.22$ ,  $p=.048$ . Furthermore, alpha power at T0 correlated weakly with number of commission errors,  $r(77)=.274$ ,  $p=.015$ , and a trend was found with SSRT,  $r(77)=.219$ ,  $p=.052$ , on the task condition (SST).

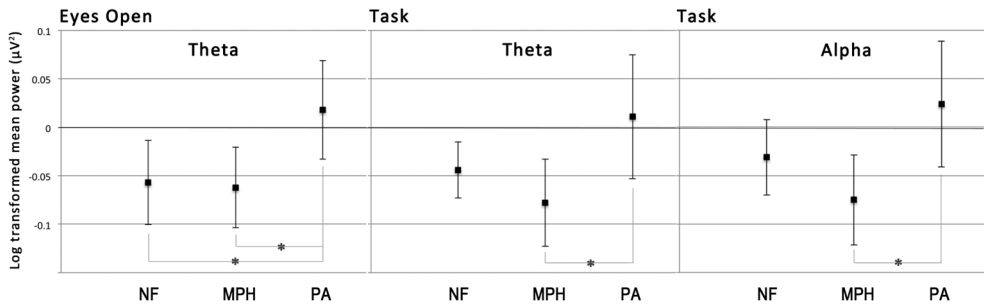
*Intervention effects.* For the EO condition, reductions in theta power from pre- to post-intervention were predictive of reductions in parent rated inattention symptoms, only for the neurofeedback group,  $R^2=.24$ ,  $F(1,27)=8.60$ ,  $p=.007$ . Furthermore, baseline theta power and reductions in theta power over time were predictive of parent rated reductions in hyperactivity/impulsivity symptoms in the neurofeedback group,  $\beta=.60$ ,  $t(26)=2.51$ ,  $p=.019$ , and  $\beta=.81$ ,  $t(26)=3.37$ ,  $p=.002$ , respectively. The overall model fit was  $R^2=.30$ ,  $F(2,26)=5.68$ ,  $p=.009$ . During the task condition, lower alpha power at baseline was predictive for greater reductions in teacher rated hyperactivity/impulsivity in the medication group,  $R^2=.20$ ,  $F(1,23)=5.67$ ,  $p=.026$ . No effects were found for the cognitive measures.





**Figure 2.** EEG power spectra at pre (T0) and post (T1) intervention for the average of midline electrodes Fz, Cz, and Pz

*Note.* Estimated marginal means are log-transformed absolute power ( $\mu V^2$ ) with 95% confidence intervals, adjusted for covariate age at 9.66 years. During the eyes open condition both the neurofeedback and methylphenidate groups showed greater reductions in theta power than the physical activity group. During the task condition, only the methylphenidate group showed greater reductions in theta and alpha power than the physical activity group.



**Figure 3.** EEG power changes between pre- and post-intervention (T1-T0)

*Note.* Estimated marginal means are log-transformed absolute power ( $\mu\text{V}^2$ ) differences from pre (T0) to post (T1) intervention, with 95% confidence intervals. During the eyes open condition both the neurofeedback (NF) and methylphenidate (MPH) groups showed greater reductions in theta power than the physical activity (PA) group. During the task condition, only the methylphenidate group showed greater reductions in theta and alpha power than the physical activity group.

## DISCUSSION

The efficacy of neurofeedback as treatment for children with ADHD is still debated and direct comparisons between neurofeedback and stimulant medication have produced inconsistent results. An important part of this debate revolves around whether neurofeedback induces specific treatment effects that are related to alterations in brain function. This randomized controlled trial examined EEG power spectra before and after neurofeedback, stimulant medication and physical activity - as semi-active treatment group - to determine whether neurofeedback can induce sustained alterations in brain function, and how results compare to effects of stimulant medication. Both neurofeedback and medication treatment resulted in reductions in theta power from pre- to post-intervention during the eyes open resting condition, compared to the physical activity group. During the effortful (task) condition, only the medication group showed reductions in theta and alpha power compared to the physical activity group.

Our results are similar to Gevensleben et al. (2009) in respect to three main findings: (1) neurofeedback induced a reduction in theta power during an eyes open resting condition compared to an active control group, (2) higher baseline theta power at pre-intervention was predictive of greater ADHD symptom reduction from pre- to post-intervention, and (3) greater changes in theta power from pre- to post-intervention were predictive of greater ADHD symptom reductions. However, the study of Gevensleben et al. (2009) found this theta reduction only

for the combined effects of theta/beta (18 sessions) and SCP training (18 sessions) blocks, but not for any of the training blocks separately. Although this could mean that changes in theta power are not protocol-specific, another explanation, as suggested by the authors, is the relatively small number of sessions per training block, which might not be enough to reveal protocol specific effects. Protocol specific decreases in theta were found by the study of Bink et al. (2015), who showed that over the course of theta/SMR neurofeedback training, youngster became better able in suppressing theta activity within training sessions. In contrast to the findings of the current study, Gevensleben et al. (2009) and Bink et al. (2015), the study by Ogrim et al. (2013) did not find evidence for changes in theta power in eyes open resting and task conditions. This may be attributable to the individualized neurofeedback protocols - only half of the children received theta/beta training ( $n=7$ ) - that could have produced more heterogeneous EEG responses, or the relatively small sample size.

Although the neurofeedback group showed a specific reduction in theta power during the eyes open resting condition, no such effects were found during eyes closed and task (effortful) conditions. Especially the lack of any effects during the task condition may be surprising, as children had to produce an active attentive state during the neurofeedback sessions, while during the eyes open condition children had to remain relaxed and inactive. Hence, one would expect neurofeedback effects to transfer to the task condition rather than the eyes open resting condition. It may be speculated that theta/beta neurofeedback produces sustained alterations in brain function that are indeed related to an activated attentional state during rest, but still in a 'passive' context as far that there is no goal-directed task to perform during neurofeedback. This could explain why the EEG alterations did not generalize to the goal-directed task condition in our study. Furthermore, this interpretation is in line with the meta-study by Sonuga-Barke et al. (2013) on the effectiveness of neurofeedback, in which no evidence was found for probably blinded informants that were mostly teachers. Teachers observe a child mainly during goal-directed and task-related activities. Behavioural and neurophysiological effects of neurofeedback may not generalize to this particular context. Our finding that changes in theta were specifically predictive of parent-informed ADHD symptom reductions, but not for the teacher reports, further supports our interpretation.

Another notable observation is that beta power did not change between pre-and post-intervention for the neurofeedback group, as opposed to theta power. Other studies also failed to demonstrate treatment effects in the beta power band (Bink et al., 2015; Gevensleben et al., 2009; Kropotov et al., 2007). This may be explained by several factors. First, increased

theta power seems to be a more robust marker of ADHD than decreased beta power (Loo & Barkley, 2005). This seems to be true for the current study as well, as we found highly significant correlations between teacher reported ADHD symptoms and theta power, but not for beta power. The theta band, therefore, may be more sensitive to change in ADHD symptoms. Second, theta power may be more reliably measured with EEG than beta power. Conventional EEG frequency bands overlap with the frequency spectrum of electromyographic (EMG) activity produced by skeletal muscles (Goncharova, McFarland, Vaughan, & Wolpaw, 2003; McMenamin, Shackman, Greischar, & Davidson, 2011). Although the peak frequency of EMG is at relatively high frequencies, the spectrum of EMG is very broad and may influence adjacent beta frequencies more than lower frequency bands such as theta. Despite specific instructions during neurofeedback training to prevent excessive muscular tension, it cannot be ruled out that some children used more subtle covert muscular tension to influence the theta/beta ratio. Third, in this study we used a theta/beta index as feedback signal that was biased to represent theta more than beta. This bias was implemented by correcting theta and beta bands for their bandwidth. An advantage of this index calculation is that extreme theta/beta values, which may result from muscular artefacts, have less disruptive effects on the training. However, our method of index calculation may have reduced training effects in the beta band

The medication group showed similar reductions in theta power from pre- to post-intervention as obtained in the neurofeedback group, however, for the medication group this effect was also demonstrated for the task condition. Reductions in theta power with methylphenidate have been found in other, but uncontrolled studies, focusing on chronic effects (six months) during an eyes closed resting condition (Clarke, Barry, Bond, et al., 2002; Clarke et al., 2003) or acute effects during task conditions (Song et al., 2005; Swartwood et al., 1998), while a double-blind placebo controlled study did not demonstrate theta reduction (Loo et al., 2004), although the authors speculated that large variability and low statistical power may have resulted in only a statistical trend for theta. In contrast to other studies, we found no effects in the beta frequency band (Clarke, Barry, Bond, et al., 2002; Loo et al., 2004; Song et al., 2005).

An additional finding for children that received medication was a decrease in alpha power during the stop-signal task, which is in line with other studies (Loo, Teale, & Reite, 1999; Swartwood et al., 1998). This finding is in contrast with Loo et al. (2004), who demonstrated increased alpha power during an eyes open resting condition. The alpha increase as found by Loo et al. (2004) is somewhat surprising, considering that alpha seems inversely related to arousal: lower alpha power has been associated with higher cortical function (Gevins et al.,

1979), visual spatial attention (Vázquez Marrufo, Vaquero, Cardoso, & Gómez, 2001), increased BOLD response in fMRI (Herrmann & Debener, 2008) and increased skin conductance level (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009). The association between alpha and cognition may be positive as well, according to the neural efficiency hypothesis, where alpha amplitude reflects inhibition of non-essential activity, which may in turn facilitate task performance (Bazanov & Vernon, 2013). However, in our study, lower alpha power was related to better task performance at baseline, even though we could not demonstrate a relation between change in alpha power and performance improvement.

Taken together, our RCT results replicate previous uncontrolled methylphenidate studies concerning theta reduction; however, additional RCTs are required to demonstrate the robustness of the findings and to address the contradicting findings in the alpha frequency band.

Theta/beta has originally been interpreted as a marker for central nervous system (CNS) arousal, however this proposition is increasingly challenged. Studies have failed to find a relation between theta/beta and skin conductance level (SCL), which is considered as the gold-standard index of arousal. In contrast, alpha power shows a negative relation with SCL (Barry et al., 2005; Barry, Clarke, Johnstone, Brown, et al., 2009). Barry et al. (2009) suggest that elevated theta/beta in ADHD may not reflect an arousal deficit, but rather an activation or processing deficit, as theta/beta is related to task performance. However, this hypothesis remains to be further explored, as it does not readily explain elevated theta/beta in ADHD during resting conditions. Our findings of a relation between alpha power and task performance at baseline, but no evidence for a relation between theta power and task performance, further contradict this hypothesis. The conceptual shift away from arousal does consequently challenge the interpretation of our treatment findings and studies into the functional significance of theta and alpha power are especially needed to improve our understanding of electrophysiological treatment effects.

Some limitations of this study should be mentioned. Although treatment groups were comparable in age, IQ, gender and ADHD severity, the findings for the alpha band should be interpreted more cautiously because of baseline differences between the medication and physical activity group. Baseline differences were also apparent for the beta band, however, considering the lack of any time or interaction effects with treatment group, or relation with ADHD symptomology, it is unlikely to have confounded the results.

In conclusion, we found evidence for specific neurophysiological effects after theta/beta

neurofeedback and stimulant treatment in children with ADHD. However, for neurofeedback these effects did not generalize to an active task-related and goal-directed condition, potentially explaining reduced behavioural effects of neurofeedback in the classroom as reported by teachers (Sonuga-Barke et al., 2013). These findings are in concordance with the behavioural (Geladé et al., in press) and event-related potential (Janssen et al., in press) results of the current study as well, which showed small behavioural improvements over time as reported by parents (although not more than the semi-active control group), but no changes according to the teacher. Additionally, at post-intervention, ERP effects during the task condition were found only for children that received stimulant medication. Considering the fact that effects of neurofeedback were confined to the theta band during rest, and that children with increased theta showed larger improvements, neurofeedback protocols may benefit from training solely theta activity during both task and non-task conditions in children with elevated theta.

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