Attention for Inhibition

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CHAPTER 7

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

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ABSTRACT

Objective: EEG neurofeedback is considered a non-pharmacological alternative for medication in attention-deficit/hyperactivity disorder (ADHD). Comparisons of the behavioral efficacy of neurofeedback and medication have produced inconsistent results. EEG measures can provide insight into treatment mechanisms, but have received little consideration. In this randomized controlled trial (RCT), effects of neurofeedback (NF) were compared with methylphenidate (MPH), and physical activity (PA) in children with ADHD on event-related potential (ERP) indices of response inhibition, which are involved in ADHD psychopathology. **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 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. ERP measures of response inhibition, N2 and P3, were available for 81 children at pre- and post-intervention (*n*=32 NF, *n*=25 MPH, *n*=24 PA). **Results:** Only the medication group showed a specific increase in P3 amplitude compared to neurofeedback (η_p^2=.121) and physical activity (η_p^2=.283), which was related to improved response inhibition. Source localization of medication effects on P3 amplitude indicated increased activation primarily in thalamic and striatal nuclei. **Conclusions:** This is the first study that simultaneously compared neurofeedback with stimulant treatment and a semi-active control group. Only stimulant treatment demonstrated specific improvements in brain function related to response inhibition. These results are in line with recent doubts on the efficacy and specificity of neurofeedback as treatment for ADHD.

INTRODUCTION

ADHD is the most common neuropsychiatric disorder in children affecting 6-7% of the population (Willcutt, 2012) and is associated with increased risk for a wide range of adverse life events (Biederman, 2005; Coghill et al., 2008). Stimulant medication is the first-choice treatment for ADHD and is effective in short-term symptom reduction (Faraone & Buitelaar, 2010). However, stimulant medication use has several limitations, including a considerable group of non-responders and adverse effects (Graham & Coghill, 2008). These disadvantages have spurred the development of non-pharmacological treatments for ADHD, such as neurofeedback. Although neurofeedback aims to target brain function directly, electroencephalographic (EEG) treatment effects have received little consideration.

Neurofeedback aims to reduce abnormal brain activity by operant conditioning of desired brain states. Although several protocols exist, EEG training of theta/beta and/or sensorimotor rhythm (SMR) activity is used in the majority of studies (Loo & Makeig, 2012). This protocol is based on the observation of 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). The efficacy of neurofeedback in ADHD is still debated, with conclusions of systematic reviews ranging from neurofeedback having non-significant effects as measured by probably blinded assessment (Sonuga-Barke et al., 2013) to neurofeedback being effective and specific (Arns, Ridder, & Strehl, 2009).

Event related potential (ERP) measurements provide a means to study the effects of neurofeedback on brain functioning. Dysfunctional response inhibition is seen as one of the core neurocognitive problems in ADHD (Barkley, 1997), and is therefore an important treatment outcome. Since neurofeedback targets brain activity directly, changes in neurocognitive functioning may accompany treatment-related changes in brain activity. The N2 and P3 components in ERP studies have been associated with the inhibition process (Ramautar, Kok, & Ridderinkhof, 2004; van Boxtel, van der Molen, Jennings, & Brunia, 2001), and have consistently be found to be reduced in amplitude in children with ADHD (Johnstone, Barry, & Clarke, 2013). Effects of neurofeedback on ERPs obtained in inhibition tasks are mixed, with evidence for increased P3 for children that were able to increase relative beta activity (Kropotov et al., 2007) or no P3 increase (Ogrim & Hestad, 2013). Although ERP studies are scarce and inconsistent, some evidence indicates that neurofeedback may exert effects on a key-deficit of response inhibition in children with ADHD.

Methylphenidate (MPH) is the most widely prescribed medication for ADHD and has been

shown not only to ameliorate ADHD symptomology, but also neurocognitive deficits (Coghill et al., 2013), including deficits in inhibitory control. ERP studies found evidence for acute enhancing effects of MPH on N2 and/or P3 amplitudes during inhibition tasks (Groom et al., 2010; Paul-Jordanov, Bechtold, & Gawrilow, 2010; Pliszka et al., 2007; Seifert, Scheuerpflug, Zillessen, Fallgatter, & Warnke, 2003). Possibly, MPH acts on dopamine transmission in striatal nuclei and associated cortical structures (Rosa-Neto et al., 2005), which are involved in response inhibition deficits in ADHD (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013), resulting in enhanced N2/P3 signals. Direct comparisons of neurofeedback and stimulant medication in children with ADHD have produced inconsistent clinical results, with studies showing comparable efficacy (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 ERPs, and found increased P3 amplitudes in eight medication responders as opposed to four medication non-responders and eleven children receiving neurofeedback

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, evidence for beneficial effects of chronic exercise in children with ADHD is scarce and has 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 control group to control for non-specific treatment effects such as parental engagement and personal attention. Therefore, neurofeedback and physical activity training were matched in frequency and duration.

In the current randomized controlled trial (RCT) we compared the effects of neurofeedback, stimulant medication with methylphenidate (MPH) and physical activity on ERP indices of response inhibition in children with ADHD, to further elucidate possible treatment mechanisms of neurofeedback and methylphenidate. Our aims were threefold: (1) to compare neurofeedback with optimally titrated MPH, (3) to compare neurofeedback with physical activity as semi-active control group, and (3) to anatomically localize treatment effects to gain insights into the involved neural networks.

METHODS

Participants

Eligible participants were Dutch-speaking children, between 7-13 years old, with a primary clinical DSM-IV-TR diagnosis of ADHD. Parent- and teacher ratings on the Disruptive Behavior

Disorders Rating Scale (DBDRS) (Pelham, Gnagy, Greensalade, & 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, MPH group only). 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.

Trial design

A multicenter 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, Erdefelder, 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 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 0.05 and a power of 95%. This trial is registered in the US trial register (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

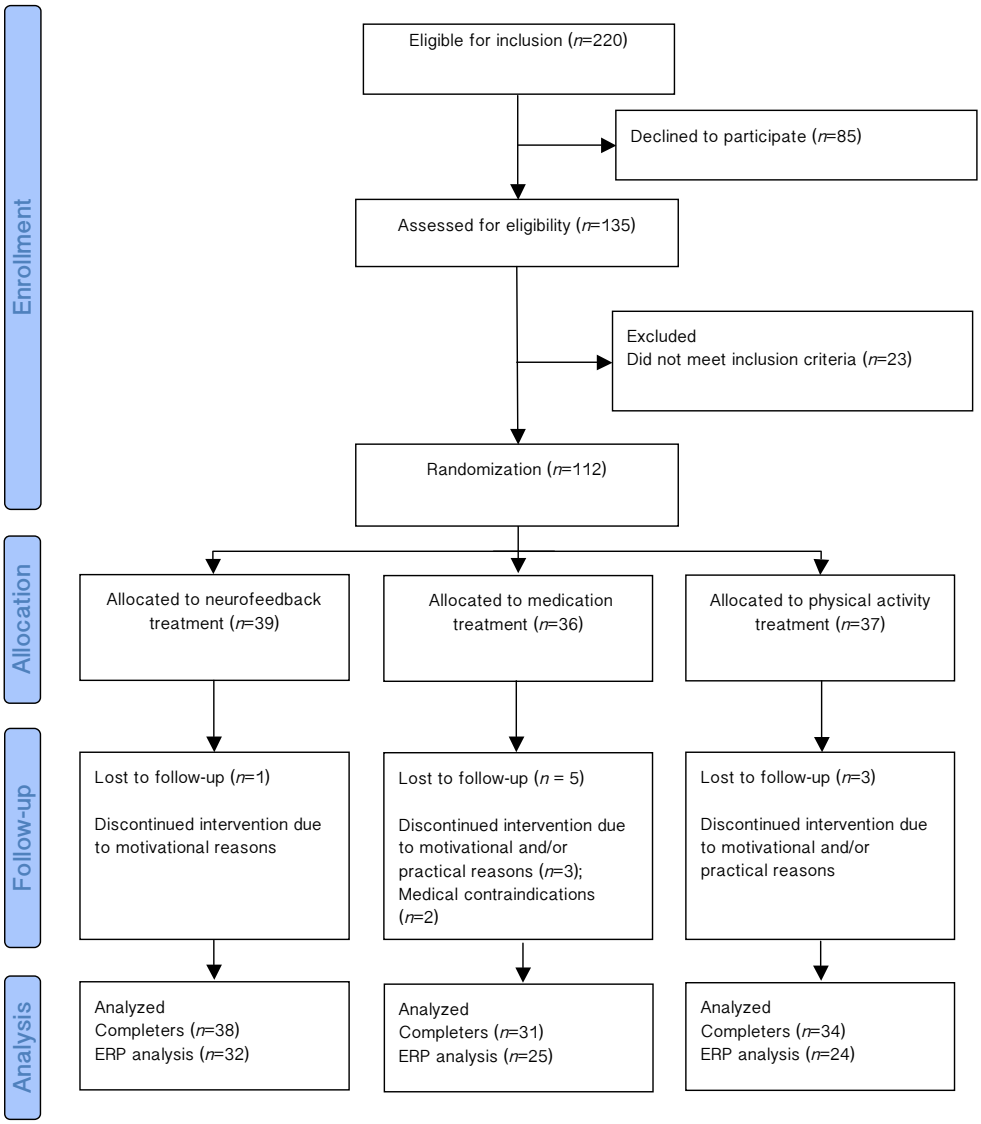

Figure 1. CONSORT flow diagram randomized controlled trial

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. 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).

Stimuli and Task

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. 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. The delay between the go and stop signal (SSD) varied trial-by-trial using a tracking algorithm which increased or decreased the delay with 50ms, depending on whether or not the previous stop trial resulted in successful inhibition. This procedure yielded approximately 50% successful inhibitions (SI) and 50% failed inhibitions (FI). The SST has been more extensively described in Janssen et al. (2015).

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 labeling system, referenced to the active common mode and grounded to the passive driven 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). A band-pass filter of 0.1-30Hz at 24 dB/oct and a 50-Hz notch filter were applied, and scalp electrodes were re-referenced to the average of the mastoids. Ocular

artifacts were estimated and corrected with a semi-automatic independent component analysis (ICA) using a restricted infomax algorithm (Jung et al., 2000), and automatic artifact rejection was applied to segments based on the following criteria: maximum allowed voltage step of 50μV/ms, maximal peak-to-peak amplitude difference of ±100μV, and minimal low activity of 0.50μV for 100ms intervals. Broken electrodes were interpolated with the spherical splines method (Perrin, Pernier, Bertrand, & Echallier, 1989).

Correct go trials were segmented from 700ms pre-stimulus to 1700ms post-stimulus and baseline-corrected for the interval -700 to -500ms; this interval precedes the fixation cross during the presentation of a blank screen between trials. Both SI and FI trials were first segmented at the preceding go stimulus using an equal interval and baseline correction as previously described. Due to the adjacency between go and stop stimuli, go and stop responses in the EEG overlap. We corrected for this with ADJAR (Woldorff, 1993), which filters out overlap of previous go responses, using the correct go ERP. After this correction, trials were segmented from -100ms to 800ms relative to the stop stimulus. Subsequently, a 100ms pre-stimulus baseline was applied and averages were obtained for SI and FI. Grand average ERPs, scalp topographies and difference waves for SI and FI were inspected to define analysis windows for N2 (215-265ms) and P3 (300-400ms). Mean voltage amplitudes of midline electrodes, Fz, Cz and Pz, were used for statistical analyses.

LAURA source estimation

Sources underlying specific treatment effects were estimated for each time-window using the LAURA distributed linear inverse solution method (Grave de Peralta Menendez, Gonzalez Andino, Lantz, Michel, & Landis, 2001; Grave de Peralta Menendez, Murray, Michel, Martuzzi, & Gonzalez Andino, 2004; Michel et al., 2004). The analysis was performed using the Cartool software by Denis Brunet (brainmapping.unige.ch/cartool). Only within-treatment group effects were explored. LAURA incorporates biophysical constraints by selecting a source configuration that better mimics biophysical principles of electric vector fields. Inverse solutions were calculated for each participant separately on a realistic head model that included 5004 equally distributed nodes within the gray matter of the Montreal Neurological Institute (MNI) transformed NIHPD pediatric brain atlas based on 7.5-13.5 years old children (Vladimir Fonov et al., 2011; VS Fonov, Evans, McKinstry, Almli, & Collins, 2009).

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 behavioral 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.

Nine children were dropouts due to motivational/practical reasons (NF=1, PA=3, MPH=5 [2 medical contra-indications]), see Figure 1. The remaining missing data (n=22) was mostly due to technical reasons at baseline (n=14) or post-intervention (n=8). At baseline (T0), 12 measurements were excluded due to technical problems (e.g. missing markers, disconnected reference [n=8] or insufficient data quality [n=4]), and 2 measurements due to extremely poor task performance (adopting an incorrect strategy of always responding to stop signals or excessively waiting for the stop signal on all trials). At post-intervention (T1), 5 measurements were excluded due to technical problems (e.g. missing markers, disconnected reference [n=2] or insufficient data quality [n=3]), and 3 measurements due to extremely poor task performance.

Statistics

Statistical analyses were performed with SPSS 20 (Corp IBM, 2011). Significance was assumed if p<0.05. Demographic and performance data were compared between groups with one-way ANOVA or a χ^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 randomized sample with the ERP subsample (available ERP data at T0 and T1) on group characteristics, and by exploring possible interactions with treatment group.

General Linear Model (GLM) MANOVAs were used for the primary ERP measures with time (pre-intervention [T0], and post-intervention [T1]), condition (successful inhibition [SI], and failed inhibition [FI]) and location (Fz,Cz,Pz) as within-subject factors and treatment group as between-subject factor. Significant interactions involving group were further explored with separate post-hoc GLM MANOVAs for each pair of treatments. ERP effects were evaluated

using multivariate test criteria, because it is more robust in case of violations of sphericity (Vasey & Thayer, 1987). Only time effects and interactions with group are reported. For the main outcomes, mean difference and 95% confidence interval [95% CI] are reported. Effect sizes are reported as partial eta-squared (η_p^2), with effects interpreted as small (.01), medium (.06) or large (.14).

Pearson correlations were computed between ERP component amplitudes at baseline and SSRT and between treatment accompanied amplitude changes (T1-T0) and SSRT changes. To reduce the number of correlations, and to avoid potential effects of manual responses (button press) during FI, only ERPs at Cz during SI were considered. If time and treatment group interacted in the main analyses, correlations with SSRT were calculated for treatment groups separately. To test if correlation coefficients were different between groups, Fisher's r-to-z transformation was used, and z-scores were compared as described in Cohen et al. (2013).
For the LAURA estimations, treatment effects were tested with paired t-tests for each node. Significance was assumed if $p<0.01$. Coordinates were converted from MNI to Talairach space with the icbm2tal algorithm (Lancaster et al., 2007) using GingerALE software (Laird et al., 2005).

RESULTS

Group characteristics

At T0 there were no differences between the treatment groups in age, IQ, gender, symptom severity or task performance (see Table I). Furthermore, treatment groups did not differ in ERP measures at T0 (all $p>.05$).

Number of artefact-free segments at T0 did not differ between groups for SI trials (mean=65), $F(2,78)=1.53$, $p=.223$, and FI trials (mean=51), $F(2,78)=0.52$, $p=.598$. At T1, groups did not differ on number of segments for FI (mean=52), $F(2,78)=0.62$, $p=.540$; however, for SI, the medication group had more segments than the physical activity group (NF=67, PA=62, MPH=72), $F(1,47)=7.84$, $p=.007$.

Attrition analysis

There were no differences in group characteristics between children contributing data to the current study and the total randomized group, nor were there any interactions with treatment group.

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

	NF (*n*=32)		MPH (*n*=25)		PA (*n*=24)		Group	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*(2,78)	*p*
Demographic data								
Age (years)	9.89	1.78	9.24	1.25	9.82	1.97	1.17	ns
IQ	99.06	12.34	100.76	14.29	98.25	13.76	0.23	ns
Gender (M/F)	23/9	N/A	19/6	N/A	19/5	N/A	0.40a	ns
DBDRS parents								
Inattention	16.34	4.76	16.28	6.03	16.50	4.86	0.01	ns
Hyperactivity /Impulsivity	14.28	5.97	12.48	6.00	13.46	6.06	0.63	ns
DBDRS teacher								
Inattention	15.06	5.58	16.32	6.63	15.46	5.00	0.34	ns
Hyperactivity/ Impulsivity	13.97	7.05	11.12	9.74	12.29	6.62	0.95	ns
Stop-Signal Task								
SSRT (ms)	269.09	75.57	276.19	87.62	244.09	77.10	1.10	ns
MRT (ms)	643.64	125.40	681.14	119.26	616.53	112.76	1.80	ns
CV	.28	.04	.27	.03	.28	.03	0.56	ns
Omissions	15.35	13.93	13.12	9.85	12.21	8.85	0.57	ns

Note. DBDRS = Disruptive Behaviour Disorder rating scale; *M* = Mean; *SD* = Standard Deviation; MRT=mean reaction time on correct Go trials; CV=coefficient of variation; SSRT=stop-signal reaction time; [a]$\chi^2(2)$

ERP results

Mean amplitudes of the ERP components for each location, condition and treatment group for T0 and T1, and MANOVA results are shown in Table 2. Waveforms are shown in Figure 2.

N2 (215-265ms). A medium to large sized main effect for time was found, indicating larger N2 amplitudes at post-intervention than pre-intervention.

P3 (300-400ms). Time and group interacted. Post-hoc analysis showed a larger P3 amplitude increase from pre- to post-intervention for methylphenidate than for neurofeedback, $F(1,55)=7.58$, $p=.008$, $\eta_p^2=.121$, mean difference$_{(MPH-NF)}=5.29$, 95%CI=[1.44,9.15], or physical activity, $F(1,47)=18.56$, $p=<.0001$, $\eta_p^2=.283$, mean difference$_{(MPH-PA)}=7.38$, 95%CI=[3.93,10.82].

Neurofeedback and physical activity did not differ from each other between pre- and post-intervention, $F(1,54)=1.24$, $p=.271$, $\eta_p^2=.022$, mean difference$_{(NF-PA)}=2.08$, 95%CI=[-1.67,5,83].

LAURA source estimation results

The medication effects on P3 amplitude were further explored with LAURA source estimation. Figure 3 shows the statistical parametric maps of the within-group comparison of pre- and post-intervention.

During SI, increased activation at post-intervention was found in bilateral thalamus and caudate nuclei. During FI, a more extended increase in activation at post-intervention was found in bilateral thalamus, caudate and lentiform nuclei, parahippocampal and medial frontal gyri.

Correlations

Pre-intervention. N2 amplitude was not related to SSRT, $r(79)=-.086$, $p=.446$. P3 amplitude and SSRT showed a strong negative correlation, $r(79)=-.566$, $p<.001$, signifying larger P3 amplitudes in children with fast SSRTs, indicating better inhibition.

Intervention effects. For the total group, change in N2 amplitude (T1-T0) was weakly related to change in SSRT (T1-T0), $r(79)=-.284$, $p=.010$, with larger increases in N2 amplitudes associated with larger SSRT increases (worse inhibition). For the medication group, change in P3 amplitude and change in SSRT were strongly correlated, $r(23)=-.625$, $p<.001$, indicating that children with greater P3 amplitude increases also had greater SSRT decreases (better inhibition). This relation was not found in the neurofeedback and physical activity groups, $r(30)=-.214$, $p=.240$ and $r(22)=-.171$, $p=.425$, respectively. Furthermore, the correlation for the medication group was significantly stronger than the neurofeedback, $z=1.82$, $p=.034$ (1-sided), and physical activity groups, $z=1.84$, $p=.033$ (1-sided).

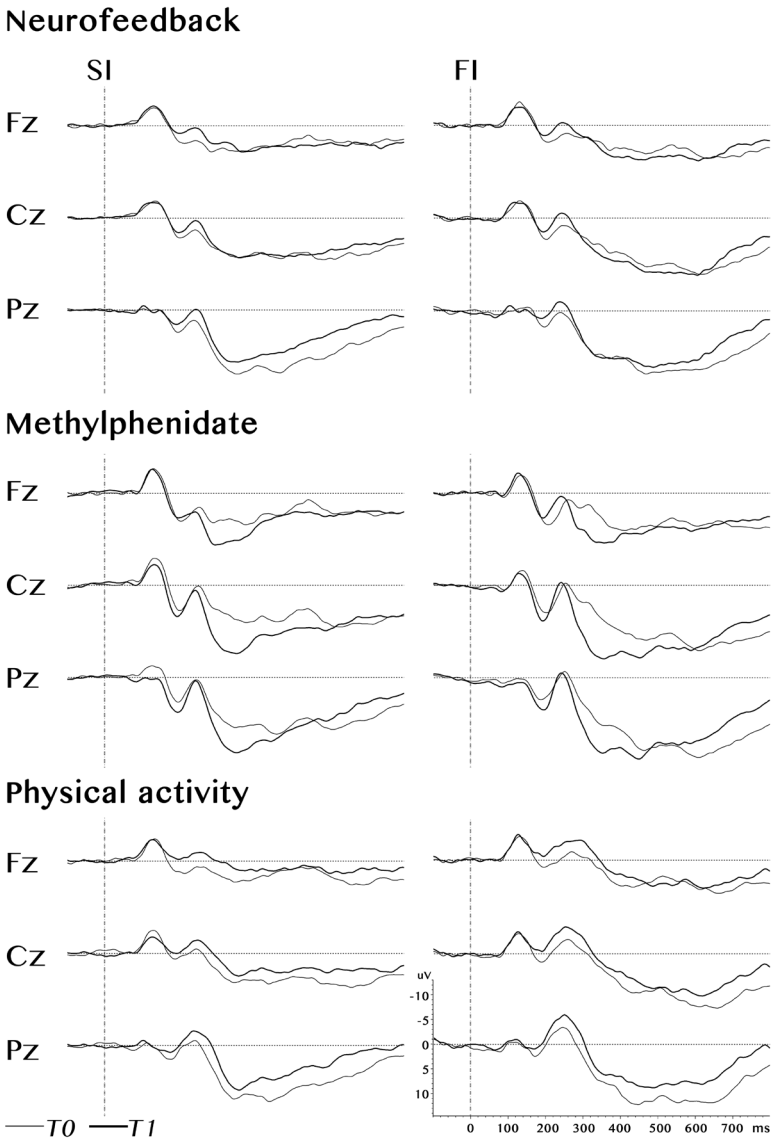

Figure 2. Grand average ERPs at pre (T0) and post (T1) intervention at midline electrodes

Note. Grand average ERPs at T0 and T1 for the neurofeedback, methylphenidate and physical activity groups, for successful inhibition (SI) and failed inhibition (FI) at midline electrodes (Fz, Cz, Pz); μV = microvolt, ms = millisecond

Table II. GLM MANOVAs of pre- and post-intervention mean ERP amplitudes for the stop-signal task

			T0		T1		T		T x G		T x G x C		T x G x L	
			SI	FI	SI	FI	$F(1,78)$	η_p^2	$F(2,78)$	η_p^2	$F(2,78)$	η_p^2	$F(4,156)$	η_p^2
N2	MPH	Fz	3.68(7.82)	3.54(6.07)	4.39(9.15)	1.50(7.94)	7.13**	.08	1.87	.05	0.64	.02	0.18	.01
		Cz	1.40(7.38)	1.61(6.03)	2.41(9.14)	1.04(7.01)								
		Pz	1.41(5.81)	0.18(5.26)	2.24(8.70)	0.59(6.47)								
	NF	Fz	3.30(7.01)	2.26(7.62)	0.79(5.71)	0.02(6.36)								
		Cz	2.95(7.16)	2.09(7.21)	1.19(7.30)	-0.28(6.79)								
		Pz	2.82(6.79)	0.89(6.67)	0.62(7.10)	-1.17(7.04)								
	PA	Fz	-1.59(6.95)	-0.19(7.27)	-1.43(6.93)	-3.12(6.83)								
		Cz	-0.37(5.40)	-1.88(6.62)	-2.19(6.51)	-4.55(6.13)								
		Pz	-0.36(5.32)	-2.88(5.75)	-2.45(5.12)	-5.17(5.15)								
P3	MPH	Fz	5.67(7.54)	4.90(7.17)	9.30(8.52)	9.38(8.64)	2.01	.03	7.87***	.17	0.44	.01	1.64	.04
		Cz	6.60(7.08)	6.39(6.89)	12.95(8.08)	13.74(10.43)								
		Pz	9.48(7.78)	8.71(6.07)	14.24(7.17)	13.92(8.58)								
	NF	Fz	4.90(7.82)	3.70(8.75)	4.36(6.57)	4.64(7.55)								
		Cz	7.41(8.89)	5.75(9.68)	7.43(8.45)	7.25(9.00)								
		Pz	12.08(10.53)	8.71(10.11)	10.00(10.60)	8.89(9.31)								
	PA	Fz	3.71(7.85)	2.19(8.36)	1.19(9.36)	0.18(6.91)								
		Cz	5.21(8.11)	2.81(8.49)	3.40(9.81)	1.26(8.29)								
		Pz	9.69(7.63)	6.91(7.73)	7.34(8.58)	4.68(8.11)								

Note. Data presented are mean (SD) in μV; NF = neurofeedback, MPH = methylphenidate, PA = physical activity; SI = successful inhibition, FI = failed inhibition; T = time from pre-intervention (T0) to post-intervention (T1), G = group [NF, MPH and PA], C = condition [SI and FI], L = location [Fz, Cz and Pz]; *p<.05, **p<.01, ***p<.001

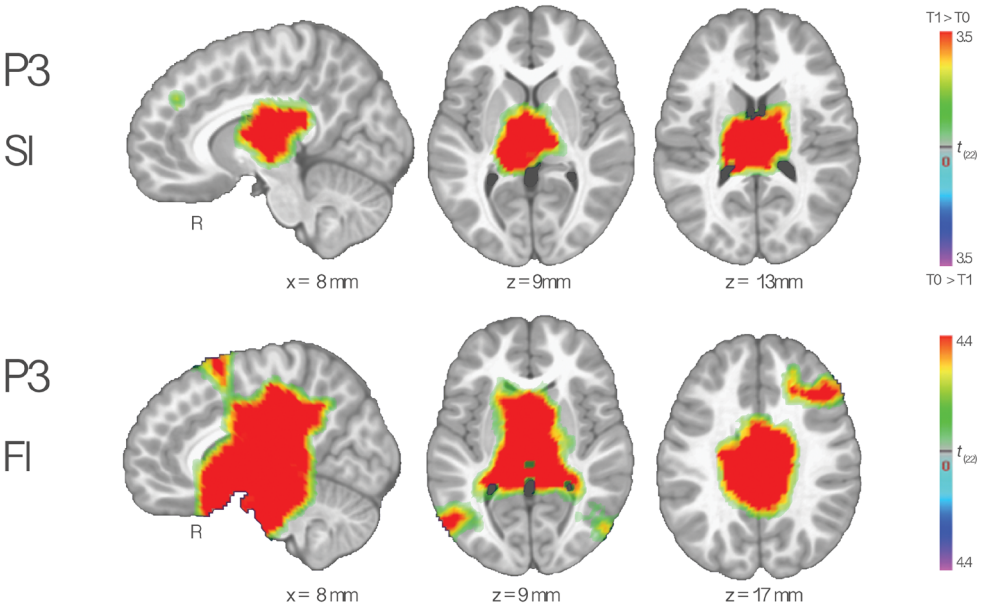

Figure 3. Significant medication effects on LAURA source estimations of P3

Note. Significant medication effects on LAURA source estimations over the analysis window of P3 during successful inhibition (SI) and failed inhibition (FI), shown on a pediatric MNI template brain. Illustrated coordinates were converted from MNI to Talairach space. Color indicates the *t*-values. Lower-bound significance threshold is $p<.01$. For viewing purposes, images were interpolated with the 4-nearest-neighbor (4NN) method.

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 (Duric et al., 2012; Meisel et al., 2013; Ogrim & Hestad, 2013). Furthermore, neural mechanisms underlying the behavioral effects of neurofeedback are yet unknown. EEG measures could provide a means to explore potential mechanisms of action. Therefore, this randomized controlled trial compared the effects of neurofeedback, stimulant medication and physical activity – as semi-active treatment group – on ERP indices of response inhibition. Dysfunctional response inhibition plays a key role in theoretical models of ADHD (Barkley, 1997). The principal finding of this study was a specific increase in P3 amplitude with stimulant treatment that reflected improved response inhibition. However, no specific effects were found

for the neurofeedback intervention.

Although an N2 amplitude increase from pre- to post-intervention was observed across groups, there was no evidence for specific treatment effects for neurofeedback or medication. Therefore, the N2 increase probably reflects practice or developmental effects. The N2 component in inhibition tasks has frequently been associated with the initiation of the inhibitory process (van Boxtel et al., 2001); however, this functional interpretation has received considerable competition from conflict monitoring theories (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010), which state that frequent (go trials) and infrequent (stop trials) responses compete and therefore result in conflict. Our results challenge the inhibition interpretation as well, as there was no relation between N2 and SSRT at baseline, as opposed to P3.

In contrast to the N2 findings, the medication group showed a specific increase in P3 amplitude from pre- to post-intervention compared to the neurofeedback and physical activity groups. This result is in line with Ogrim et al. (2013) who showed superior P3 increases in medication responders compared to non-responders and neurofeedback. It is worth noting that the study of Ogrim and colleagues is the only study that found superior behavioral effects for medication treatment compared to neurofeedback. Possibly, the double-blind medication management procedure that was used in one-third of the participants, similarly to the current study, resulted in more optimal doses and therefore greater clinical and electrophysiological effects. Although neurofeedback could be less effective in ameliorating neurophysiological deficits in ADHD than optimally titrated methylphenidate, smaller-sized specific effects could potentially exist. However, direct comparisons between neurofeedback and physical activity, which was designed to control for non-specific effects, could not establish evidence for this proposition. The absence of specific ERP effects for neurofeedback is in line with recent double-blind placebo-controlled trials (Arnold et al., 2013; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013) that found no specific behavioral effects for neurofeedback compared to sham-neurofeedback.

Correlational analyses and source localization of P3 effects provided further insights into the neuropharmacological mechanisms of methylphenidate in children with ADHD. First, our results suggest that P3 is strongly related to SSRT, and therefore offers a physiological index of response inhibition. Furthermore, the strong relation between larger increases in P3 amplitude and improved response inhibition (shorter SSRT) in the medication group shows that the effect of methylphenidate is closely related to this inhibition mechanism. Source localization of P3 changes from pre- to post-intervention indicated increased activation primarily in thalamic and

striatal (caudate and lentiform) nuclei during successful and failed inhibition. FMRI studies show that these areas are under activated in children with ADHD during inhibition tasks (Hart et al., 2013) and PET studies in adults with ADHD indicate lower D2/D3 dopamine receptor availability in the caudate (Volkow et al., 2009). The therapeutic action of methylphenidate seems to concentrate on the striatum by inhibiting the reuptake of dopamine and thereby increasing extracellular concentrations of dopamine (Rosa-Neto et al., 2005). In line with this putative mechanism, a meta-study by Hart et al. (2013) found that percentages of patients on long-term medication correlated with increased activation in the right caudate.

The absence of specific ERP effects of theta/beta neurofeedback in this study should be considered in the context of possible limitations. First, although the neural mechanisms behind neurofeedback are yet unknown, physiological effects may be observed in other neurocognitive domains than response inhibition. One other study looked at ERP effects on an attention task, and found decreased P3 at post-intervention for the children receiving neurofeedback as well as the control group (Wangler et al., 2011). However, the authors suggested that this effect may indicate task adaptation. Second, the effects of neurofeedback may be of a transitory nature and therefore not observable in a laboratory setting. Third, although the theta/beta ratio is increased in ADHD at the group level (Snyder & Hall, 2006), several studies found considerable heterogeneity in power spectra measures within ADHD (Loo & Makeig, 2012). The effects of neurofeedback may therefore be dependent upon etiological subtypes. Other 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). Fourth, the analyzed sample is considerably smaller than the randomized sample (72%), due to several reasons, such as dropouts (n=9), technical issues/insufficient data quality or incorrect performance strategies at pre- or post-intervention (n=22). This accumulated in different, albeit non-significant, group sizes at follow-up. However, attrition analyses could not demonstrate differences in completers compared to the total randomized sample. Last, visually inspecting the ERP waveforms or mean voltage data may indicate other differences between groups, while non-significant in our analyses. Although groups may be equal, we can not demonstrate this with conventional statistics and current group sizes. Otherwise, groups may differ, but large variation in ERP amplitudes, and small effect sizes, may have diminished statistical power.

Taken together, the medication group showed a specific increase in P3 amplitude that was related to improved response inhibition, however no specific ERP effects were found for theta/

beta neurofeedback training. Our study is the first that simultaneously compared neurofeedback with a consistently employed double-blind medication management protocol – to objectively determine individual doses of methylphenidate – and with a semi-active control group to control for non-specific effects. An important clinical observation is that the type of medication protocol constitutes a major factor in treatment outcome, as has been demonstrated in earlier studies (The MTA Cooperative Group, 1999), and could potentially explain the disparate results of studies that compare neurofeedback with medication. In conclusion, this study showed specific and superior effects for medication treatment with methylphenidate compared to theta/beta neurofeedback training on ERP indices of response inhibition. These findings are in accordance with the behavioral findings of the same RCT and in line with recent doubts on the efficacy and specificity of theta/beta neurofeedback as treatment for ADHD.

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