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ORIGINAL ARTICLE

Methylphenidate and if-then plans are comparable in modulating the P300 and increasing response inhibition in children with ADHD

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Abstract A disturbed functioning of the prefrontal cortex, the anterior cingulate cortex, and an accordingly reduced P300 presumably underlies executive function deficits of children with attention deficit hyperactivity disorder (ADHD). Using a combined classification and Go/NoGo task paradigm, the present study investigated whether medication with methylphenidate (MPH) modulates the P300 as measured by a high-density electroencephalogram (EEG) and facilitates response inhibition in children with ADHD. Further, effects of MPH were compared with effects of self-regulation by if-then plans (Gollwitzer in Am Psychol 54: 493–503, 1999). MPH as well as if-then plans modulated the P300 and improved inhibition of an unwanted response on a Go/NoGo task to the same level observed in children without ADHD. Importantly, self-regulation strategies might be a valuable alternative to medication with MPH in children with ADHD.

Keywords ADHD · EEG · P300 · Methylphenidate · Implementation intentions

Introduction

Attention deficit hyperactivity disorder (ADHD) affects 3–18% of children (Scahill and Schwab-Stone 2000), estimations varying greatly with the diagnostic tool used and the rater. Various neurocognitive models try to explain executive function deficits in children suffering from ADHD. The most prominent model assumes that deficits in inhibition are the core deficits of executive functioning in individuals with ADHD (Barkley 1997). Inhibition involves the ability to deliberately inhibit dominant, automatic, or pre-potent responses whenever deemed necessary. Children with ADHD perform consistently worse and show a prolonged reaction time when compared to children without ADHD and without any psychiatric diagnosis on inhibition tasks (meta-analysis by Lijffijt et al. 2005).

The majority of children with ADHD are treated with psychotropic medication. Among these, the dopamine (DA) reuptake blocker and psychostimulant methylphenidate (MPH) have been the most widely used. It has been shown to reduce symptom severity, the risk for substance abuse, and to improve performance and conduct in school (Jensen et al. 2001). Despite these desirable effects, the categorical necessity of MPH prescriptions following an ADHD diagnosis might be questioned for at least three reasons:

(1) MPH seems to not always be prescribed as recommended. Based on a large sample of 1,422 adolescents in the United States, it was determined that about half of those who were prescribed with stimulants did not meet diagnostic criteria for ADHD, while about one quarter of those with a full ADHD diagnosis did not receive treatment (Angold et al. 2000).
(2) Disturbed functioning of prefrontal cortex (PFC), anterior cingulate cortex (ACC), and striatum is thought to underlie executive function deficits in ADHD (Bush et al. 2005). Additionally, nucleus accumbens (NAc) and amygdala are thought to be

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involved in dysfunctional reward signalling in ADHD (Tripp and Wickens 2008). Dopaminergic innervations of PFC, NAc, and amygdala mature relatively late and change considerably during adolescence (Grund et al. 2006). Gray and colleagues (Gray et al. 2007) reported that prolonged developmental exposure to MPH increases catecholamine levels in medial prefrontal cortex (mPFC) accompanied by lasting morphological changes in fibre structure. The authors claim that MPH might even delay developmental processes in mPFC and disturb the normal development of mPFC circuitry. It thus appears that brain structures, which are involved in cognitive and motivational deficits in ADHD, might be influenced by early, ongoing administration of MPH.

(3) There are several studies investigating the effect of psychotherapy on behavioural parameters and ADHD symptoms (Van der Oord et al. 2008). Although behavioural psychotherapy alone is associated with smaller effect sizes reducing ADHD symptoms compared to MPH treatment, effect sizes are still moderate to large. One reason for the inferiority of behavioural therapy might be a great variability in and combination of techniques used.

Given the unclear adverse long-term effects of MPH in humans and the alarming long-term effects found in many animal studies, the present study aims to compare the effect of MPH with the effect of the self-regulation strategy of forming *if-then plans* (Gawrilow and Gollwitzer 2008; Gollwitzer 1999) on behavioural performance and corresponding brain activity as measured by electroencephalography (EEG) during a response inhibition task in children with ADHD.

Forming if-then plans is a particularly effective self-regulation strategy. If-then plans (Gollwitzer 1993, 1999) take the format of "If situation X is encountered, then I will perform Y!" and therefore associate a critical situation (if-part) with a goal-directed response (then-part). It is important to recognise that implementation intentions differ from goal intentions: Goal intentions merely specify a desired outcome and have the format of "I intend to achieve Z!" While goal intentions specify preferred finite states (i.e. the performance of a desired behaviour or the attainment of a desired outcome) that an individual feels committed to attain, implementation intentions predetermine how a specified critical situation will be responded to when it is encountered. Accordingly, if-then plans are subordinate to goal intentions and they serve the purpose of enhancing effective goal striving. Implementation intentions offer benefits over and above goal intentions: A meta-analysis by Gollwitzer and Sheeran (2006) involving more than 8,000 participants in 94 independent studies reported an effect size of $d = .65$. This medium-to-large effect size (Cohen 1992) represents the additional facilitation of goal achievement through if-then plans compared to mere goal intentions. As goal intentions by themselves already have a supporting effect on behaviour enactment (Webb and Sheeran 2006), the size of this effect is remarkable.

Even though children with ADHD suffer from deficits concerning executive functions and from deficits concerning their response inhibition in particular (Barkley 1997; Nigg 2001), they should benefit from forming implementation intentions. Indeed, if-then plans supported children with ADHD when solving a Go/NoGo task requiring them to both classify randomised stimuli that were presented on a computer screen by pressing a particular computer key, as well as inhibit classification in response to a NoGo signal. Thus, the task at hand is a classification task combined with a Go/NoGo task and was modelled after both the Continuous Performance Task, CPT (Rosvold et al. 1956), and the Stop Signal Task, SST (Logan and Cowan 1984). The rationale was that in past research, those two tasks have been consistently used to assess the inhibitory ability of children with ADHD. The difference between a NoGo condition in this task and a NoGo condition in a classical Go/NoGo task is that in the newly developed task not different stimuli per se but simply a different preceding stimulus indicated the NoGo condition. The advantage of this paradigm is that both discrimination responses (i.e. errors and response times in Go trials) as well as inhibition responses (in NoGo trials) can be measured.

In two experiments (Gawrilow and Gollwitzer 2008), the authors randomly assigned children with ADHD to one of two groups: Children in the goal intention group formed a goal to inhibit a classification response for marked stimuli ("I will not press a key for pictures that have a sound!"), while children in the implementation intention group, in addition to forming a goal intention, formed an if-then plan ("And if I hear a sound, then I will not press any key!") In the first study, it was observed that children with ADHD who furnished a suppression goal with implementation intentions improved inhibition of an unwanted response on a Go/NoGo task to the same level observed in children without ADHD. The second study compared the performances of children with ADHD with and without MPH and showed that a combination of if-then plans and MPH resulted in the highest level of suppression performance in children with ADHD (Gawrilow and Gollwitzer 2008).

Using the same task paradigm, Paul et al. (2007) measured EEG data of un-medicated children with and without ADHD in a baseline condition without a self-regulation strategy and a condition that involved the making of if-then plans: The if-then plans did not only improve response inhibition behaviourally, but they also increased

the NoGo-P300 in children with ADHD compared with the baseline condition in this study. As the NoGo-P300 represents response control and conflict monitoring (Picton 1992; Fallgatter et al. 2002, 2004), which are both reduced in untreated children with ADHD, apparently, the self-regulation strategy of forming if-then plans alters both behavioural and EEG indices of performance in a Go/NoGo task among children with ADHD. Without this self-regulation strategy, children with ADHD made more inhibition errors following NoGo trials and had a significantly smaller *NoGominusGo* amplitude difference than control children during the first half of the P300 component. No difference was observed between the control and ADHD groups when the children were given the self-regulation strategy.

As we were able to demonstrate the potential of *if-then plans* in a controlled EEG experiment (Paul et al. 2007), the present study aims at comparing the effect of self-regulation with the effect of methylphenidate using the same paradigm.

Methods

Participants

Medication experiment

Eleven (all boys) children diagnosed with ADHD and sixteen (three girls) age-matched control children (12.4 ± 0.4 years and 12.5 ± 0.3 years, respectively) participated after giving written informed consent. All of the children with ADHD were prescribed medication but only took it during school term. This enabled us to test them during holidays without medication and during school term with medication. None of the control children had any clinically relevant diagnoses or took any medication as reported by the parents.

Instruction experiment

Thirteen (one girl) children diagnosed with ADHD and sixteen (one girl) age-matched control children (12.4 ± 0.4 years and 12.9 ± 0.3 years, respectively) participated after giving informed consent. None of the children with ADHD had been prescribed medication with MPH or other drugs within the previous 12 months and did not received cognitive behaviour therapy as ADHD treatment. Again, none of the control children had any clinically relevant diagnoses or took any medication as reported by the parents.

The study was approved by the research ethics committee of the University of Konstanz and is compliant with the world medical association declaration of Helsinki (http://www.wma.net/e/policy/b3.htm). Children with ADHD were recruited through a collaborating child psychiatric outpatient centre in Konstanz (Germany). The children were selected by the head child psychiatrist to be diagnosed with ADHD combined type (APA 1994) only as their primary disorder (i.e. further or comorbid disorders were secondary). Control children were contacted through the participant record system of the University of Konstanz. The parents of all participating children were asked to fill out the Child Behaviour Check List (CBCL, Arbeitsgruppe Deutsche Child Behavior Checklist 1998) to measure different aspects concerning the children's behaviour (e.g. social withdrawal, somatic disturbances, and anxiety/depression in the internalising scale; antisocial and aggressive behaviour in the externalising scale; social problems, schizoid/obsessive compulsive behaviour and attention problems plus the aforementioned internalising and externalising scales in the total CBCL) as well as the Conners Rating Scale (Steinhausen 1993). CBCL results confirmed the diagnosis and suggested the presence of comorbid disorders in the ADHD groups as values of the total, internalised, and externalised scale were higher than the norm (all Ts > 63). Hence, the ADHD groups were in clinically significant ranges on the reported three scales of the CBCL, whereas the control groups were in a normative range (all Ts < 56.91). Moreover, children with ADHD did not differ as regards the total CBCL means in the *Medication* ($M = 68.62$, SD $= 13.3$) and *Instruction Experiment* ($M = 69.42$, SD $= 14.1$). In the same vein, differences in the hyperactivity/attention deficit scale of the Conners Rating Scale (Steinhausen 1993) occurred between children with ADHD ($M = 1.56$, SD $= .5$) and without ADHD ($M = .76$, SD $= .8$) in both the medication and instruction experiments. Furthermore, participating children were matched concerning a socioeconomic status index obtained from parents' education (i.e. less than 10 years of education, more than 10 years of education) and job status (i.e. unemployed, part-time, full-time).

Each child underwent two EEG measurements on separate days, 4–6 weeks apart (*Medication Experiment*: Controls 34.6 ± 5.7 days ± SE, ADHD 42.5 ± 6.9 days; *Instruction Experiment*: Controls 44.2 ± 5.7 days, ADHD 41.9 ± 6.3 days), and was rewarded with 20 Euro after finishing the second session.

Task

The classification task combined with a Go/NoGo task consisted of 360 stimuli (50% coloured drawings of transportation vehicles, 50% coloured drawings of animals) that were presented on a computer screen (SAMSUNG Samtron 96 BDF 19″) ~60 cm away from the children's eyes using E-Prime® (http://www.pstnet.com/products/e-prime/). Stimuli lasted 1000 ms and were presented with an ISI of 1,500 ms. About 500 ms before each

stimulus, a fixation cross was shown for 500 ms in the middle of the screen. Children were asked to respond to animals and vehicles by pressing one of two coloured buttons, respectively. The correspondence of stimulus type and response button was reversed after the first half of the experiment in order to prevent the task of becoming too easy. Thirty training trials, which were excluded from further analysis, introduced each half of the experiment to ensure that children understood the task. In one-third of the trials, a NoGo sign was presented for 150 ms following/after the fixation cross. The NoGo sign was a white sprawled out hand on a circular purple background indicating that no response was to be given on the following trial. The trials following NoGo signs were treated as NoGo trials; all other trials were Go trials. The instruction for performing the task was standardised and did not differ between children (see below).

Procedure and EEG recordings

Medication experiment

All children with ADHD had been un-medicated for 48 h before the first session and had taken their usual dose of medication ca. 2 h before the second testing.

Instruction experiment

At the first session, children received a regular instruction of how to perform the task (neutral instruction condition). The neutral instruction contained information concerning the task (e.g. pressing one button for animals and the other for vehicles and not pressing a button at times the hand was shown). At the second session, they additionally received an instruction involving an if-then plan (planning instruction condition). The if-then plan was formulated as follows: *If* I see a hand, *then* I will not press any button. The planning instruction condition did not involve *more* instructions than the neutral instruction condition; the conditions only differed in the nature of the phrasing. Instructions in both conditions were standardised and did not differ between children.

The order of testing without/with medication and with a neutral/planning instruction was not counterbalanced for reasons of comparability between all participant groups in the larger experimental context. This was necessary to make sure that children in the instruction manipulation group would not utilise the self-regulation strategy in both sessions. In principal, this design does not allow the interpretation of main effects of factor SESSION, since the medication effect or the instruction effect cannot be told apart from a repetition effect. However, since control children were tested in two identical sessions, as well, GROUP*SESSION interactions are still meaningful, since both groups were subject to the same repetition effect.

While the children performed the Go/NoGo task, their EEG was recorded using a high-density 257-channel cap (Geodesic Sensor Net 200) chosen to optimally fit each child's head. Data were recorded continuously with a sampling rate of 250 Hz and an online band-pass filter of 0.1–100 Hz after making sure that impedance values did not exceed 30 kΩ.

EEG data analysis

All EEG data analysis was performed using BESA®. EEG data epochs (−100 to 800 ms in relation to stimulus onset) for Go trials (i.e. trials that were followed by a button press) and correct NoGo trials (i.e. trials that were followed by no response) were averaged per participant and session (first/un-medicated, second/medicated) after baseline correction (baseline −100 to 0 ms) and correction of eye-blinks (BESA®), excluding epochs containing artefacts (signal amplitudes >250 μV). *NoGominusGo* difference waveforms were created by subtracting Go trials from NoGo trials. Data were band-pass filtered between 0.01 and 30 Hz. Grand average waveforms were computed by averaging Go, NoGo, and *NoGominusGo* epochs across subjects within group and condition. A prominent P300 in NoGo trials and *NoGominusGo* difference waves were found at fronto-central channels.

Channel groups and time windows of interest for statistical analysis differed between the *medication experiment* and the *instruction experiment*, since the GROUP*SESSION interaction had a different scalp distribution and time course in the two experiments. While the GROUP*SESSION interaction was observable in a right lateralised fronto-central channel group in the *medication experiment*, it occurred in a more central channel group in the *instruction experiment*. Further, while in the *medication experiment*, the P300 effect was characterised by larger amplitudes in the control group compared to the ADHD group throughout the whole P300 time range and in both sessions, a single time window was chosen (see below). In contrast, in the instruction experiment, the ADHD group had higher amplitudes than the control group in the later P300 time range in the second session, while the early P300 time range was again characterised by larger amplitudes for the control group. Therefore, two time windows were chosen in order to accommodate for this effect.

Medication experiment

For statistical analysis, mean amplitudes were computed for the *NoGominusGo* difference wave per participant and session between 260 and 328 ms after averaging the

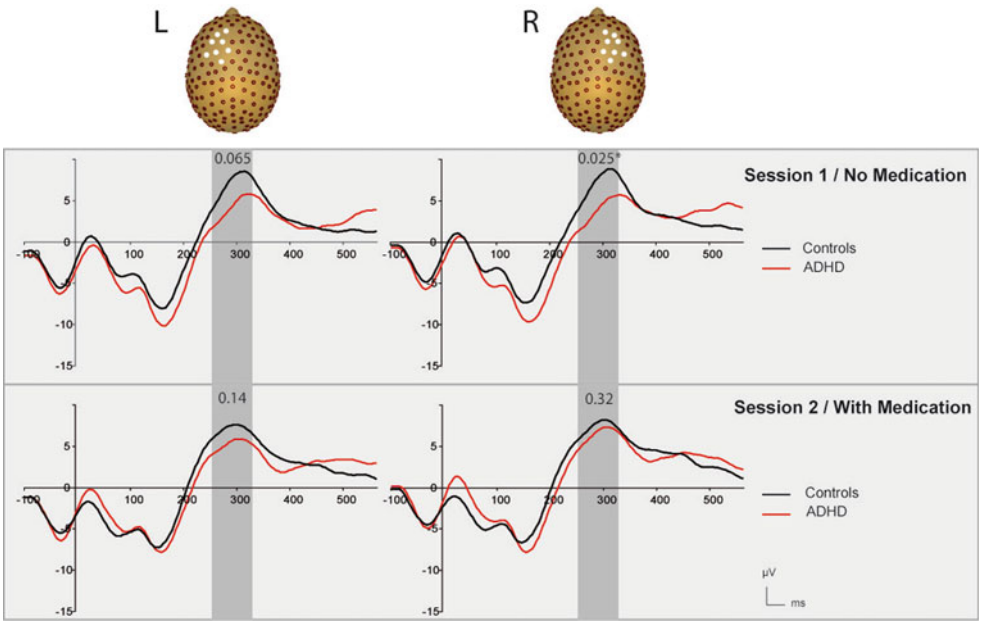

Fig. 1 Grand average display of MPH effect on the *NoGominusGo* P300

waveforms of a left and right fronto-central channel group (each containing 8 electrodes, see Fig. 1).

Instruction experiment

Mean amplitudes were computed for the *NoGominusGo* difference wave per participant and condition in two consecutive time windows (160–312 ms and 312–452 ms) after averaging the waveforms of Cz and the nine surrounding electrodes (see Fig. 2).

Within the time windows, mean amplitudes were compared between groups (ADHD, control) using repeated measures ANOVAs with within-subject factor SESSION (first/un-medicated, second/medicated or neutral instruction, planning instruction). In the *medication experiment*, HEMISPHERE (left, right) was used as an additional factor. Planned comparisons were computed in case of statistically significant interactions.

Dipole analysis

In a first step, a regional dipole (source with three single dipoles at the same location but with orthogonal orientations) was fitted per group and condition (time range 260–328 ms medication experiment, 160–452 ms instruction experiment) for the grand average NoGo waveforms. The first component of a principal component analysis (PCA) of the grand average signal explained >97% of the variance of the signal, suggesting that a single source would be an adequate characterisation of the underlying activity. As a second step, a distributed source model (minimum L2 norm) was computed per group and condition, regarding the more complicated underlying source structure of the difference *NoGominusGo*, as a single source cannot account for brain activation *differences* (NoGo and Go P300 most likely have different underlying generators (Fallgatter and Strik 1999; Tekok-Kilic et al. 2001). The minimum norm approach (the minimum L2 norm) is a common method to estimate brain activation using current dipoles (Hamalainen and Ilmoniemi 1994) that are evenly distributed at 1,426 standard locations 10 and 30% below the smoothed standard brain surface as implemented in BESA.

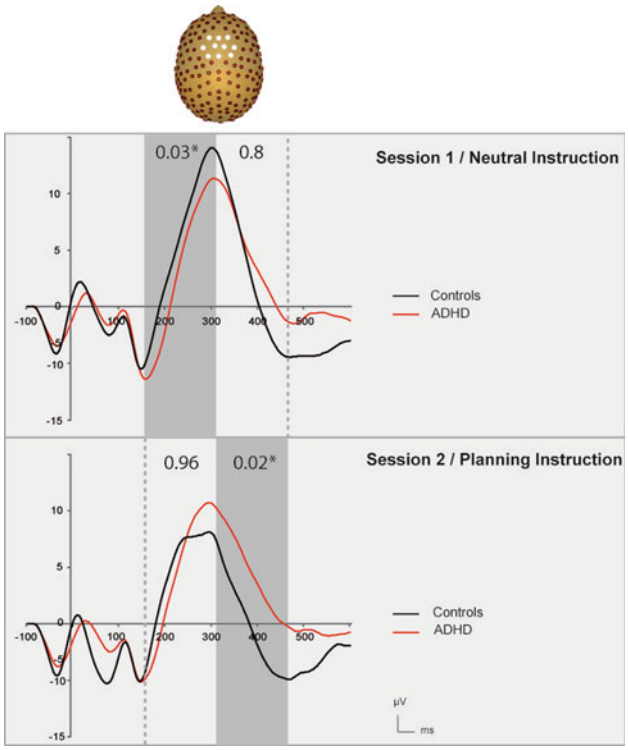

Fig. 2 Grand average display of instruction effect on the *NoGominusGo* P300

Behavioural data analysis

Behaviourally, the number of correct responses following Go trials, the number of correctly inhibited responses following NoGo trials, as well as reaction times in correct Go trials, was analysed. Response data were not normally distributed; therefore, Wilcoxon tests for paired samples were computed for within-group differences between conditions. For between-group comparisons, Mann–Whitney *U*-tests were used. Reaction time was normally distributed, therefore a repeated measures ANOVA was computed with SESSION (first/un-medicated, second/medicated or neutral instruction, planning instruction) as within-group factors and GROUP (ADHD, control) as between-group factor.

Non-parametric Spearman correlations were calculated between *NoGominusGo* mean amplitudes and behavioural NoGo performance in the individual groups and conditions. The significance level of all statistical analyses was 5%.

Results

Medication experiment behavioural results

Children with ADHD made more errors than control children on both, Go trials and NoGo trials, during the first (un-medicated) session ($Z = -2.94$, $P = .002$ and $Z = -2.13$, $P = .03$, respectively, see Table 1). During the second (medicated) session, ADHD and control children only differed on Go trials ($Z = -2.1$, $P = .03$), they did not differ on NoGo trials ($Z = -0.7$, $P = .5$). No within-group differences between the first and the second session were revealed for either group (ADHD: $Z = 0.3$, $P = .76$ and $Z = 1.2$, $P = .23$ for Go and NoGo trials, respectively; control: $Z = 0.9$, $P = .36$ and $Z = 0.1$, $P = .91$ for Go and NoGo trials, respectively).

Table 1 Behavioural results (% correct Go responses; % correct inhibitions after NoGo sign) for the *medication* experiment

Group	Trial	Session	Median % correct	Minimum % correct	Maximum % correct
ADHD	Go	Un-medicated/1	77.1*	55.8	86.3
		Medicated/2	80.4*	53.3	87.1
	NoGo	Un-medicated/1	88.3*	45.8	99.2
		Medicated/2	91.7 n.s.	42.5	99.2
Control	Go	1	85.4	74.2	90.8
		2	84.2	74.2	90.8
	NoGo	1	95.4	80.8	99.2
		2	96.3	87.5	98.3

* Significant differences between children with ADHD and control children in corresponding conditions

Within the ADHD group, significant correlations were found between task performance and *NoGominusGo* amplitudes. The higher the left- and right-hemispheric *NoGominusGo* amplitude was in the *un-medicated* session, the better the children inhibited their response on NoGo trials ($r = .66$ and $r = .67$, respectively). During the *medicated* session, correlations between the left- and right-hemispheric *NoGominusGo* amplitude and inhibition performance were similar to the *un-medicated* session but more pronounced ($r = .83$ and $r = .81$, respectively). Again, the higher the P300 amplitude was, the better the children were able to inhibit their response. No significant correlations between the EEG signal and task performance were found within the control group in either session.

A significant interaction was revealed for reaction time on correct Go trials ($F(1,24) = 7.24$, $P = .013$, see Table 2). While children with ADHD had significantly slower reaction times than control children in the first, un-medicated session ($P = .004$), the groups did not differ for the second, medicated session ($P = .13$). This was due to the children with ADHD having significantly quicker reaction times in the medicated session compared to the un-medicated session ($P = .001$). No differences between the sessions were found for control children ($P = .80$).

Medication experiment P300

In the time window between 260 and 328 ms, the significant interaction SESSION*HEMISPHERE*GROUP was revealed ($F(1,25) = 5.09$, $P = .03$, see Figs. 1, 3). During the first (un-medicated session), children with ADHD had lower amplitudes in right fronto-central channels compared to children without ADHD ($P = .025$). The same was true on

Table 2 Reaction time results (Go trials) for the *medication* experiment

Group	Session	Mean reaction time (ms)	95% confidence interval Lower boundary	95% confidence interval Upper boundary
ADHD	Un-medicated/1	656.26*	598.68	713.84
	Medicated/2	584.96 n.s.	537.35	632.56
Control	1	542.96	497.43	588.48
	2	538.93	501.30	576.57

* Significant differences between children with ADHD and control children in corresponding conditions

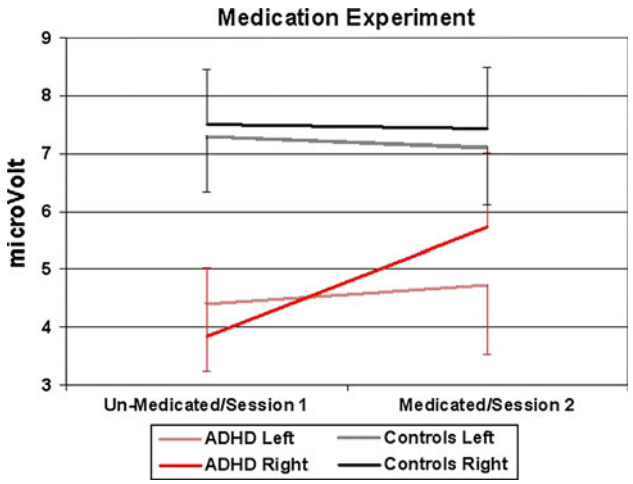

Fig. 3 Line-graph of interaction effect Medication Experiment

a trend level for left fronto-central channels ($P = .065$). No group differences were found during the second (medicated) session for either hemisphere (left: $P = .14$ and right: $P = .32$). Children with ADHD had higher right-hemispheric amplitudes in the second (medicated) session than in the first (un-medicated) session ($P = .05$). No differences between conditions were revealed for the left hemisphere ($P = .74$). Control children did not differ between sessions for either hemisphere ($P = .81$ and $P = .94$ for left- and right-hemispheric channels, respectively).

Medication Experiment Source Localisation

A regional source was fitted for the grand average NoGo waveforms per group and session. Localisation was performed in the time window between 260 and 328 ms component. Estimated Talairach coordinates of the sources corresponded to the vicinity of the cingulate cortex in all cases (Talairach coordinates in mm: controls first session 1.3, −9, 19.6; controls second session 4.9, −13.4, 17.9; ADHD un-medicated session −3.5, −23.1, 31.1; ADHD medicated session 9.9, −28.9, 22.7). A distributed source solution (minimum L2 norm) was computed at the global field power peak latency (308 ms) of the grand average *NoGominusGo* difference waves for children with and without ADHD for each session, respectively. Control children were characterised by a temporo-parietal activation focus and a more central focus in both sessions (Fig. 4, upper panels). Children with ADHD on the other hand only showed a central focus and lacked the temporo-parietal focus for the un-medicated session (Fig. 4, bottom left panel). During the medicated session, source activation was markedly decreased (Fig. 4, bottom right panel, please note the scaling difference), while the source activation distribution remained very similar to the un-medicated session.

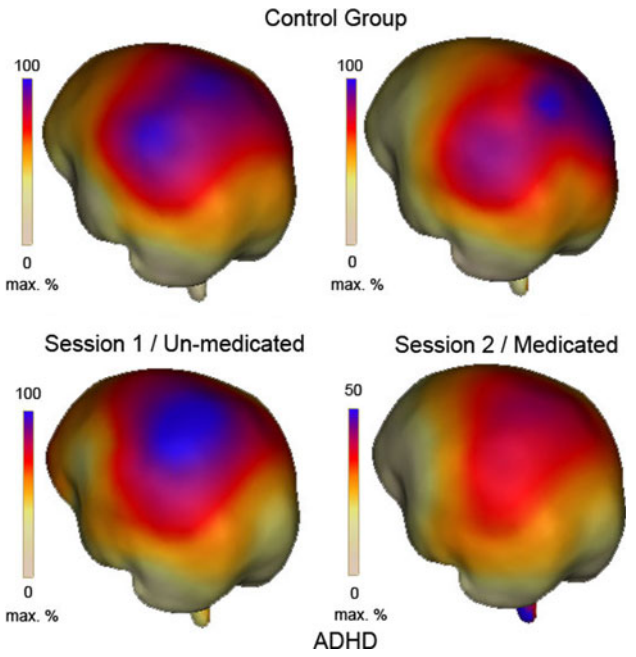

Fig. 4 Grand average minimum norm results for the MPH effect in control children (*upper panel*) and children with ADHD (*lower panel*). Please note the scaling difference for the medicated session in children with ADHD

Instruction experiment behavioural results

Children with ADHD made more inhibition errors than control children during the neutral instruction condition ($Z = -2.01$, $P = .04$, see Table 3). This group difference disappeared during the planning instruction condition ($Z = -1.2$, $P = .25$). ADHD and control children did not differ on Go-trials during either instruction condition (neutral: $Z = -0.64$, $P = .53$; planning: $Z = -0.02$, $P = .98$). No within-group differences between the instruction conditions were revealed for either group (ADHD: $Z = 0.55$,

Table 3 Behavioural results (% correct Go responses; % correct inhibitions after NoGo sign) for the *instruction* experiment

Group	Trial	Session	Median % correct	Minimum % correct	Maximum % correct
ADHD	Go	Neutral Instr.	85.0 n.s.	42.5	93.3
		Planning Instr.	87.1 n.s.	46.3	94.6
	NoGo	Neutral Instr.	91.7*	48.3	98.3
		Planning Instr.	93.3 n.s.	50.8	100
Control	Go	Neutral Instr.	87.7	66.7	91.3
		Planning Instr.	86.0	67.5	91.3
	NoGo	Neutral Instr.	96.3	79.2	99.2
		Planning Instr.	96.7	89.2	99.2

* Significant differences between children with ADHD and control children in corresponding conditions

Table 4 Reaction time results (Go trials) for the *instruction* experiment

Group	Session	Mean reaction time	95% confidence interval Lower boundary	95% confidence interval Upper boundary
ADHD	Un-medicated	606.2*	561.4	650.9
	Medicated	624.9*	578.1	671.6
Control	1	509.1	473.7	544.4
	2	490.2	453.2	527.1

* Significant differences between children with ADHD and control children in corresponding conditions

$P = .58$ and $Z = 0.87$, $P = .39$ for Go and NoGo trials, respectively; control: $Z = 0.0$, $P = 1.0$ and $Z = 0.0$, $P = 1.0$ for Go and NoGo trials, respectively).

Within the ADHD group, significant correlations were found between task performance and *NoGominusGo* amplitudes. The higher the *NoGominusGo* amplitude was in the planning instruction condition, the better the children inhibited their response on NoGo trials ($r = .76$). This correlation was non-significant in the neutral instruction condition. No correlations between performance and EEG signal were found for the control group in either condition.

A significant group effect was revealed for reaction time ($F(1,24) = 26.4$, $P < .001$, see Table 2). Children with ADHD had significantly slower reaction times than control children across both instruction conditions (Table 4).

Instruction experiment P300

In the time window between 160 and 312 ms, the significant interaction GROUP*SESSION was revealed ($F(1,27) = 5.22$, $P = .04$, see Figs. 2, 5). Children with ADHD had lower amplitudes at central channels compared to control children in the neutral instruction condition ($F(1,27) = 5.22$, $P = .03$). No group differences were found when children were given the planning instruction ($F(1,27) = 0.07$; $P = .80$). Children with ADHD had higher amplitudes in the planning instruction condition than in the neutral instruction condition ($F(1,27) = 4.33$, $P = .047$). Control children did not differ between sessions ($F(1,27) = 0.93$, $P = .34$).

In the consecutive time window 312–452 ms, the interaction GROUP*SESSION ($F(1,27) = 4.22$, $P = .049$ see Fig. 3) was revealed. In the neutral instruction condition, no difference in P300 amplitude was found between children with and without ADHD ($F(1,27) = 0.003$, $P = .96$). In the planning instruction condition, however, children with ADHD had a significantly larger *NoGominusGo* amplitude difference than control children ($F(1,27) = 6.67$, $P = .02$). The *NoGominusGo* amplitude difference did not differ between conditions in the ADHD group ($F(1,27)$, $P = 0.57$, $P = 0.46$). It was significantly smaller in the planning instruction condition compared to the neutral instruction condition in the control group ($F(1,27) = 4.99$, $P = .03$).

Instruction experiment source localisation

A regional source was fitted for the grand average NoGo waveforms per group and session. Localisation was performed in the time window centred on the P300 component. Estimated Talairach coordinates of the sources corresponded to the vicinity of the cingulate cortex in all cases (Talairach coordinates in mm: controls neutral instruction condition −2, 1, 29; controls planning instruction condition 4, −8, 26; ADHD neutral instruction condition −3, 0, 26; ADHD planning instruction condition −2, −4, 41). A distributed source solution (minimum L2 norm) was computed at the global field power peak latency (308 ms) of the grand average *NoGominusGo* difference waves for children with and without ADHD for each session, respectively. Control children were characterised by a temporo-parietal activation focus in both conditions, activation being weaker in the planning instruction condition (Fig. 6, upper panel right). Children with ADHD on the other hand showed a central focus in the neutral instruction condition (Fig. 6, bottom left panel). During the planning instruction condition, the activation focus was comparable to the control children (Figs. 5, 6).

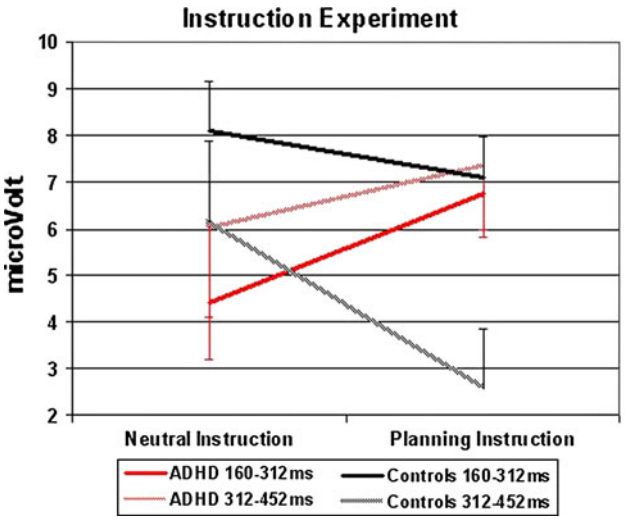

Fig. 5 Line-graph of interaction effect Instruction Experiment

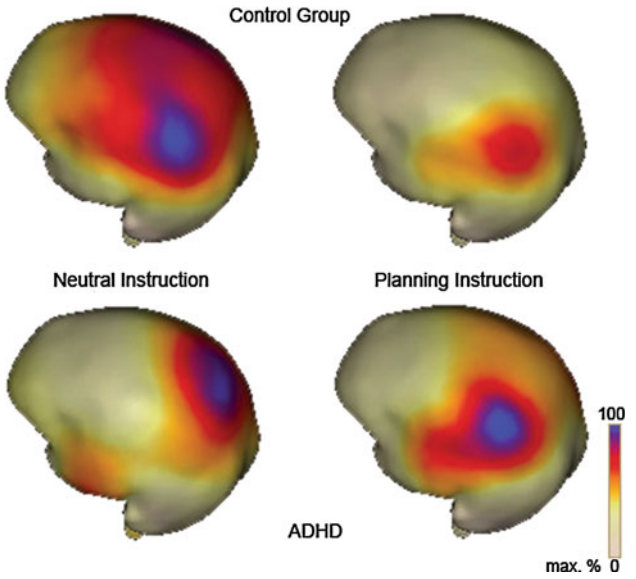

Fig. 6 Grand average minimum norm results for the instruction effect in control children (*upper panel*) and children with ADHD (*lower panel*)

Discussion

Children with ADHD versus children without ADHD

In both experiments, un-medicated children with ADHD who had been given a neutral instruction made more inhibition errors and had reduced P300 amplitudes compared to control children. Inhibition errors in a Go/NoGo design likely reflect impulsivity, one of the core symptoms of ADHD. The P300 component in the EEG occurs, when participants need to pay attention to the stimuli within the experimental design and are faced with response decision. Generally, NoGo stimuli evoke a higher-amplitude P300 than Go stimuli, which suggests that the P300 might reflect conflict monitoring and/or endogenous response evaluation (Picton 1992). Since in the current experiment, NoGo trials signalled no response, while Go trials signalled a button press, it seems plausible that the NoGo P300 and accordingly the *NoGominusGo* (NoGo *minus* Go) P300 might also reflect response inhibition mechanisms. A reduced *NoGominusGo* amplitude in children with ADHD thus might be interpreted as inefficient conflict monitoring, response evaluation, and inhibition. Replicating other findings (Fallgatter et al. 2002, 2004), we localised the NoGo P300 to the ACC. It is influenced by the mesencephalic DA system and is often co-activated with the dorsolateral PFC (Holroyd and Coles 2002), making the ACC an important part in the route for the regulation of motor behaviour. The reduced *NoGominusGo* amplitude in children with ADHD might reflect deficient functioning of the ACC and its circuits. In line with this notion, the dopaminergic input to the ACC by mesencephalic structures is known to be altered in ADHD (Krause et al. 2003).

Deficient or altered functioning of circuits underlying response control and evaluation are also suggested by the minimum norm results localising the *NoGominusGo* difference. Unlike control children, who were characterised by a temporo-parietal and a more central source, children with ADHD only showed more central activation. While no firm conclusions can be drawn where the sources producing the result patterns are truly located (minimum norm solutions are projected onto the cortical surface of an average brain but stem from deeper areas), un-medicated children with ADHD in neutral instruction conditions seem to have a different underlying source structure for response inhibition than children without ADHD.

Children with ADHD had slower reaction times on Go trials than control children. This contradicts the idea of impulsivity. It is more likely that slow reaction time on Go trials reflect inattention or less efficient conflict monitoring (children had to decide, which button to press). Un-medicated children with ADHD in the *medication experiment* also made significantly more commission errors than control children. This supports the interpretation of inattention and/or deficient conflict monitoring. However, un-medicated children with ADHD in the *instruction experiment* did not make more commission errors than control children (despite slower reaction times). One possible explanation might be that the children with ADHD in the *medication experiment* had more severe symptoms in general—hence, they were prescribed with medication during school term. Children with ADHD who took part in the *instruction experiment* did not usually take medication or had stopped taking medication for at least 12 months. It seems possible that their overall symptoms were relatively less severe compared to the medicated children with ADHD. However, as indicated in parents' ratings in the CBCL, both ADHD groups are similar affected as regards internalised and externalised disturbances. Therefore, commission errors seem to be a rather unspecific than valid indicator of ADHD status (Epstein et al. 2003).

Slower reaction times have been reported repeatedly for children with ADHD compared to children without ADHD (Lijffijt et al. 2005; Oosterlaan and Sergeant 1996; Smith and Taylor 2006). However, faster reaction times have also been reported whereby these results are possibly related to greater reaction time variability in ADHD (Oosterlaan and Sergeant 1996).

Increase of *NoGominusGo* amplitude

ADHD children in both experiments were characterised by an increase in *NoGominusGo* amplitudes. This can be the result of changes of both Go and NoGo activation. Further

inspection of this effect revealed that in both experiments, the NoGo P300 (including the rising and falling slope) occurred earlier in the respective second session (*Medication Experiment*: Latency at the beginning of the rising slope without medication: 156.36 ± 5.81 ms vs. with medication 132.00 ± 5.81 ms, $F(1,20) = 8.87$, $P = .008$); *Instruction Experiment*: Latency at the beginning of the rising slope with neutral instruction: 155.38 ± 4.13 ms vs. with planning instruction 125.84 ± 4.13 ms, $F(1,24) = 25.5$, $P = .00004$, data not shown), while Go activation was not subject to a latency change in the second session (*Medication Experiment*: Latency at the beginning of the rising slope without medication: 166.90 ± 9.90 ms vs. with medication 165.45 ± 9.90 ms, $F(1,20) = 0.01$, $P = .92$); *Instruction Experiment*: Latency at the beginning of the rising slope with neutral instruction: 176.62 ± 8.16 ms vs. with planning instruction 164.61 ± 8.16 ms, $F(1,24) = 1.08$, $P = .31$, data not shown). The NoGo latency shift led to larger *NoGominusGo* mean amplitudes without inhibition activation changing its strength. It thus appears that both medication and the planning instruction facilitated inhibition in the ADHD groups by making it faster and—as suggested by behavioural data—more efficient.

Medication effect

Medication significantly increased the *NoGominusGo* P300 in a right fronto-central channel cluster, leading to comparable amplitudes in children with and without ADHD. The according effect almost reached significance for the left-hemispheric channel cluster. Other authors have reported MPH effects in right-frontal areas: Pliska and colleagues (Pliszka et al. 2007) linked a higher right-frontal N2 amplitude with better response inhibition. Akay et al. (2006) showed reduced hypoperfusion in right-frontal areas after 2 months of MPH treatment. The question remains why MPH seems to have a more pronounced effect on right-frontal compared to left-frontal areas. Higher right-hemispheric DA levels in frontal and striatal areas have been shown in rats (Thiel and Schwarting 2001). If the same was true for humans, this could lead to a larger right-hemispheric MPH effect, given that MPH blocks DA reuptake. In line with this, it has been shown that left-sided inattention (caused by disturbed right-hemispheric fronto-parietal functioning) is related to ADHD symptoms (Bellgrove et al. 2005). Interestingly, the authors could show that left-sided inattention could be reduced by MPH. The explanation for this effect might lie in the higher DA transporter density in ADHD (Krause et al. 2003), which might be particularly prominent in the right hemisphere, thus leading to an increased DA reuptake and accordingly lower DA levels in the right compared to the left hemisphere when unmedicated and a reversal of this effect when DA transporters are blocked by MPH.

During the un-medicated session, children with ADHD made more inhibition errors and commission errors than control children in the present study. During the medicated session, children with ADHD resembled control children regarding inhibition errors, while they still made more commission errors. This result pattern indicates that MPH has a positive influence on impulsive behaviour and complements the P300 findings. The strong correlation between performance on NoGo trials and right-hemispheric P300 amplitude suggests a direct connection between behaviour and EEG activity.

Reaction times were faster in the medicated session in children with ADHD. On the first glance, this contrasts the finding of reduced inhibition errors. However, faster reaction times might reflect more efficient processing of response conflict leading to improved inhibition performance and facilitated response control. This interpretation is supported by minimum norm results, where children with ADHD showed a prominent decrease in source activation in the medicated session.

If-then plan effect

If-then plans significantly increased the *NoGominusGo* P300 in children with ADHD. Moreover, if-then plans supported children with ADHD to elevate their performance up to the level of children without ADHD, as there was no group difference on inhibition errors during the planning instruction condition. Without the self-regulation strategy of forming if-then plans, children with ADHD made more inhibition errors following NoGo trials and had a significantly smaller *NoGominusGo* amplitude difference than children without ADHD during the first half of the P300 component.

In the instruction experiment, children with ADHD had slower reaction times in the neutral and in the planning instruction condition compared to children without ADHD. However, children with ADHD inhibited their response less efficiently after NoGo trials than control children in the neutral instruction condition but not in the planning instruction condition. Therefore, one might argue that an if-then plan stating the response inhibition following a NoGo signal lead to the utilisation of prolonged reaction times for a more advanced stimulus analysis in children with ADHD in the planning instruction condition.

In the same vein, the significant correlations between task performance and *NoGominusGo* amplitudes in the ADHD planning group suggest that response control becomes more efficient. The minimum norm results complement these results: Children with ADHD in the planning condition looked very similar to children without ADHD

(in all conditions) as both were characterised by additional temporo-parietal activation.

Comparison of medication and if-then plan effects

Comparing the results of the medication and instruction experiment, medication as well as the instruction with if-then plans led to an improvement of efficient inhibition after NoGo trials in children with ADHD. Accompanying the behavioural effect, an increase in the P300 component was demonstrated in both experiments. Despite the P300 effect being right-lateralised in the MPH experiment (potentially due to DA transporter distribution), results were quite similar in both experiments. Concerning the minimum norm results, children with ADHD who were medicated with MPH showed a general decrease in activation of central brain areas but no obvious change in source activation and no similarity with control children who displayed an additional temporo-parietal source. Instruction with an if-then plan did not result in decreased activation in children with ADHD, but an additional temporo-parietal source in the planning condition, thus resembling the source activation distribution of the control children. This might indicate that MPH facilitates response inhibition (less activation is needed for better response control), while if-then plans lead to the recruitment of additional cortical areas.

Limitations

Our research certainly has several limitations at present. First and foremost, mainly boys took part in the study owing to the heightened prevalence of ADHD in boys when compared to girls. A second limitation of the present study is that the participating children's overall intellectual ability was not assessed. In the light of recent discussions (e.g. Frazier et al. 2004) whether the weaker performances on executive functions tasks observed in children with ADHD compared to children without ADHD are the result of either an overall lower intellectual ability level or specific executive dysfunctions, it would have been interesting to know our research participants' general intelligence scores. This would have also allowed us to explore whether if-then plans help performance on the Go/NoGo task for high- versus low-intelligence children alike. A third limitation is that we used a Go/NoGo task that is not classical. Thus, further research might want to investigate the effect of medication and if-then plans on classical inhibition tasks (e.g. Stop Signal task, Antisaccade task). That we observed a lower performance during Go trials compared to NoGo trials in our task might be due to the reason that responding to Go stimuli was more difficult in the long run, as it required sustained attention over approximately 21 min. NoGo trials were more rare and maybe less prone to sustained attention effects. Despite these limitations, we consider the present research as a valid test of the abilities of children with ADHD in Go/NoGo task with differing instructions and medication status.

Conclusion

In sum, medication with MPH and application of self-regulation strategies both lead to similar cortical (increased P300) and behavioural (improved response inhibition) changes. This further suggests that the development of treatments involving self-regulation strategies (e.g. if-then planning) might be beneficial to children with ADHD. Due to the fact that prescription of MPH increased enormously during the past years within the treatment of ADHD, self-regulation strategies might be a valuable alternative without unwanted side effects.

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