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CHAPTER 4

An ERP source imaging study of the oddball task in children with attention-deficit/hyperactivity disorder

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ABSTRACT

Objective: Children with ADHD have difficulties attending to task-relevant events, which has been consistently associated with reductions in amplitude of the P3b event-related potential (ERP) component. However, the underlying neural networks involved in this P3b reduction remain elusive. Therefore, this study explored source localization of P3b alterations in children with ADHD, aiming at a more detailed account of attentional difficulties. **Methods:** Dense array ERPs were obtained for 36 children with ADHD and 49 typically developing children (TD) using an auditory oddball task. The P3b component (310-410ms) was individually localized with the LAURA distributed linear inverse solution method and compared between groups. **Results:** The ADHD group showed reduced P3b amplitudes in response to targets compared to the TD group. Differences were located primarily in frontopolar (cinguloopercular network, BA10) and temporoparietal regions (ventral attention network, BA39 and 19) in the left hemisphere. Reductions in P3b amplitudes were related to more inattention and hyperactivity/impulsivity problems in the ADHD group. **Conclusion:** Alterations were found in both top-down and bottom-up attention-related brain areas, which may underlie P3b amplitude reductions in children with ADHD. This study provides novel data on both temporal and spatial aspects of dysfunctional attention processes in ADHD.

INTRODUCTION

Early theoretical models of Attention-Deficit/Hyperactivity Disorder (ADHD) (Barkley, 1997) have emphasized deficiencies in executive processes, closely related to prefrontal-striatal circuits (Castellanos, 1997), to be pivotal in explaining ADHD. More recently, however, it has become evident that multiple large-scale brain systems are affected in ADHD (Castellanos & Proal, 2012). An fMRI meta-analysis on a wide range of cognitive tasks showed a surprisingly large contribution of the ventral attention network in the psychopathology of ADHD (Cortese et al., 2012). The ventral attention network includes the temporoparietal junction (TPJ), the supramarginal gyrus, frontal operculum and anterior insula, and is important in detecting salient stimuli that are behaviourally relevant (Corbetta, Patel, & Shulman, 2008).

Attentional demanding tasks typically require the detection of infrequent, salient target stimuli or 'oddballs'. The oddball task is frequently used to measure the electrical brain response to target stimuli with event-related potentials (ERP), providing excellent temporal resolution to pinpoint when these attentional processes occur. Around 300ms post-stimulus, a posterior distributed positive wave, the P3b, occurs that has been associated with contextual-updating of working memory according to an influential theory by Donchin (1981). This theory states that when a new stimulus is detected, attentional processes update the stimulus representation (Polich, 2007). One of the most consistent findings in children with ADHD is a reduction in P3b amplitude in response to targets (Johnstone, Barry, & Clarke, 2013).

Although reduced P3b amplitude during attention tasks has been frequently replicated in ADHD, the underlying neural networks that are involved are not easily studied with ERPs due to the low spatial resolution of electroencephalography (EEG), as opposed to fMRI. A recent fMRI meta-analysis of attention tasks showed reduced activation in ADHD in the right dorsolateral prefrontal cortex (DLPFC), left putamen, globus pallidus, right pulvinar and caudate tail, right inferior parietal lobule, precuneus and superior temporal lobe, and increased activation in the right cerebellum and left cuneus (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Although several of these areas overlap with the ventral attention network, other networks such as the frontoparietal and dorsal attention system (Cortese et al., 2012) seem to be affected as well. These results emphasize the complex combination of network alterations in ADHD.

ERP and fMRI studies of attention tasks in ADHD complement each other, however due to the poor temporal resolution of fMRI, neural network alterations that are specifically related to the P3b remain elusive. Although agreement on the neural generator of the P3b in healthy populations still lacks, there appears consensus that multiple brain regions are involved

(Nieuwenhuis, Aston-Jones, & Cohen, 2005). Lesion and intracranial studies point to two main contributors to the signal, the TPJ and the lateral prefrontal cortex (Baudena, Halgren, Heit, & Clarke, 1995; Verleger, Heide, Butt, & Kompf, 1994). A combined ERP and fMRI study by Bledowski et al. (2004) using a visual oddball task, localized the P3 in the inferior parietal lobule (IPL), near the TPJ, the posterior parietal cortex and inferior temporal cortex. Furthermore, a study employing LORETA distributed source localization found P3b generators in a more extended network of bilateral frontal, parietal, limbic, cingulate and temporo-occipital areas (Volpe et al., 2007). The regions in these studies partly correspond to brain areas implicated in fMRI findings of reduced activation in the ventral attention network in ADHD (Hart et al., 2013).

ERP source localization has become more feasible lately due to affordable computational power and data-driven distributed models, which are less prone to operator-bias and capable of localizing multiple spatially extended sources. These models may aid to further understanding of the attentional processes in ADHD and complement insights provided by ERP and fMRI studies. The current study therefore aimed to localize P3b abnormalities in children with ADHD by applying the LAURA distributed linear inverse solution method to electrophysiological data gathered during the oddball task. We hypothesized reduced P3b amplitudes in children with ADHD compared to typically developing (TD) children and disruptions primarily in the ventral attention network (temporoparietal areas) and lateral prefrontal cortex.

METHODS

Participants

Complete data were available for 85 children aged between 7 and 14 years, with 36 children in the ADHD group (26 males, 10 females) and 49 children in the TD group (30 males, 19 females), see Table 1. Inclusion required an estimated full scale IQ > 80, measured with a short version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), using subtests Vocabulary, Arithmetic, Block Design and Picture Arrangement. Children were excluded if there was a known history of neurological conditions.

The ADHD group was recruited through mental health outpatient facilities in the West of the Netherlands. All children obtained a clinical diagnosis of ADHD (28 combined type and 8 inattentive type) according to the DSM-IV (American Psychiatric Association 1994) as established by a child psychiatrist. ADHD diagnosis was confirmed with the parent version of the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, &

Schwab-Stone, 2000), and by parent and teacher ratings on the Disruptive Behaviour Disorders Rating Scale (DBDRS; Pelham, Gnagy, Greenslade, & Milich, 1992), which required at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales to be in the clinical (>90th percentile) range for both informants. Seventy-five per cent of children were naïve for stimulant medication and the remaining children discontinued use of stimulants at least four weeks before testing. Children with a clinical DSM-IV diagnosis of autism spectrum disorder were excluded.

The TD group was recruited through three primary schools and a sports club in the same recruitment area as the ADHD group. Control children were required to obtain normal scores on the DBDRS (<90th percentile) for both informants and to be free of any psychiatric disorder.

Procedure

The study was conducted according to the Declaration of Helsinki, and approved by the local ethics committee. Parents and children aged 12 years or older signed informed-consent. The current study sample partly overlaps with a sample participating in a randomized controlled trial on the effects of neurofeedback, methylphenidate and physical activity as treatments for ADHD (trial number: NCT01363544).

Behavioural assessment

Symptom scales of Inattention and Hyperactivity/Impulsivity from parent and teacher reports on the Strengths and Weaknesses of ADHD symptoms and Normal behaviour scale (SWAN; Swanson, Schuck, Mann, & Carlson, 2006) were used for correlational analyses with the primary outcome measures.

Stimuli and Task

The auditory oddball task consisted of 255 standards (523Hz, 85%) and 45 targets (1046Hz, 15%), presented pseudo-randomly for 100ms, with 10ms rise/fall times at 60dB through two speakers 50cm in front of the participant. The interstimulus interval varied randomly between 950-1450ms. Participants were instructed to attend to the stimuli and to press a button on a response box with the right index finger when they heard a target. After a practice run of 10 trials, the experimental run took approximately 6 minutes to complete.

Electrophysiological recordings

Continuous electroencephalogram (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 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 0.1-40Hz 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 artefacts were estimated and corrected with a semi-automatic independent component analysis (ICA) using a restricted infomax algorithm (Jung et al., 2000), and automatic artefact rejection was applied to segments based on the following criteria: maximum allowed voltage step of 50 μ V/ms, maximal peak-to-peak amplitude difference of \pm 100 μ V, and minimal low activity of 0.50 μ V for 100ms intervals. Broken electrodes were interpolated with the spherical splines method (Perrin, Pernier, Bertrand, & Echallier, 1989).

Target trials were segmented at 200ms pre-stimulus and 800ms post-stimulus and baseline corrected for the interval -100 to 0ms. Grand average ERPs, scalp topographies and difference waves were inspected to define the analysis window for P3b (310-410 ms). Mean amplitude of this analysis window was extracted for each participant and used as dependent variable in all further analyses.

LAURA source estimation

Sources underlying the P3b component were estimated for each participant for the 310-410ms time-window using the LAURA (Local Auto-Regressive Averages) 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 Cartool software by Denis Brunet (brainmapping.unige.ch/cartool).

LAURA is a regularization method that incorporates biophysical laws to obtain the optimal solution that fulfills both the observed data and bio-electromagnetic constraints. In this approach, the relationship between brain activity at one point and its neighbors is expressed

in terms of local autoregressive estimator with coefficients depending upon a power of the distance from the point (Grave de Peralta Menendez et al., 2004). Cartool software uses the L-curve method to find the optimal regularization parameter for a given data file (Hansen, 1992). We used the Locally Spherical Model with Anatomical Constraints (LSMAC) as lead field model, which has been shown to perform as well as more computationally intensive models like the Boundary Element Model (BEM) (Birot et al., 2014). 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 (Fonov et al., 2011). The dependent variable that was used for statistical evaluation was the norm of the vector (intensity) of each node, which is the positive length or size of each vector.

The stability and reliability of LAURA and other distributed inverse solution methods have been validated by direct comparisons with intracranial recordings, lesion studies and other imaging methods (Pascual-Marqui, Sekihara, Brandeis, & Michel, 2009). Furthermore, we have conducted an fMRI and LAURA source imaging study of a response inhibition task in two separate ADHD populations, showing similar results for the two approaches (Janssen, Heslenfeld, van Mourik, Logan, & Oosterlaan, 2015; Janssen, Heslenfeld, van Mourik, Gelade, et al., 2015).

Statistics

Demographic, performance and ERP data were compared between groups using General Linear Model (GLM) ANOVA or chi square test in SPSS 20 (Corp IBM, 2011). For all analyses, alpha was set at 0.05, two-tailed. Pearson correlations were computed between P3 amplitudes, mean reaction time (MRT) on target trials and and SWAN Inattention and Hyperactivity/Impulsivity scales. Only significant correlations are reported.

For the P3 analysis, multivariate test statistics are reported, a method known to be robust against violations of sphericity (Vasey & Thayer, 1987). GLM MANOVA was performed with Group as between-subject factor (TD, ADHD) and two within-subject factors: Lateral (left, midline, right) and Sagittal (frontal, central, posterior). For these analyses 9 electrodes were used in a 3x3 grid (D4, D19, A7, C21, A1, A19, C4, B22 and B4). Only findings involving group were further explored with post-hoc tests. When appropriate, electrode locations were averaged for further post-hoc analysis. IQ was not entered as covariate in any of the analyses, as lower IQs are associated with ADHD (Frazier, Demaree, & Youngstrom, 2004), which violates

Table I. Group characteristics and task performance

	ADHD (<i>n</i> =36)		TD (<i>n</i> =49)		Between-group difference	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i> (1,83)	<i>p</i>
Demographics						
Age (years)	10.03	1.77	10.04	1.33	0.00	ns
IQ	95.97	12.05	108.96	14.05	19.96	<.001
Gender (M/F)	26/10		30/19		1.12 ^a	ns
DBDRS parents						
Inattention	17.69	4.91	3.50	3.38	251.98	<.001
Hyperactivity/ Impulsivity	15.47	5.59	3.10	2.78	180.12	<.001
DBDRS teacher						
Inattention	16.22	5.36	1.76	3.18	242.07	<.001
Hyperactivity/ Impulsivity	13.67	7.99	1.37	2.60	101.89	<.001
Oddball Task						
MRT (ms)	435.58	76.47	403.57	67.09	4.20	<.05
Omissions	1.22	1.61	0.69	1.56	2.33	ns

Note. DBDRS=Disruptive Behavior Disorders Rating Scale; M = male, F = female; MRT = mean reaction time on target trials; omissions = no response to target; ^a $\chi^2(1)$

assumptions of ANCOVA (Dennis et al., 2009).

For the LAURA estimations, group differences were tested with unpaired t-tests for each node. P-values were Bonferroni-corrected based on the number of independent measures (128 electrodes) with $p=.05/128=.0004$ (Grave de Peralta Menendez et al., 2004).

RESULTS

Group characteristics and behavioural data

Table I summarizes the group characteristics and task performance data. Groups did not differ on age and gender. As expected, IQ was lower in the ADHD group. The ADHD group showed slower MRTs on target trials compared to the TD group. Number of accepted target segments

after artifact rejection did not differ between groups (mean=33), $F(1,83)=0.23$, $p=.635$.

ERP results

Mean amplitudes of the ERP components for each location and group, and MANOVA results are shown in Table II. Waveforms and topographic maps are shown in Figure 1 and Figure 2, respectively.

The P3 component showed maximum amplitude at posterior midline locations, see Figure 1 and Figure 2. Group interacted with Lateral. Post-hoc tests revealed that the ADHD group had reduced P3 amplitudes at the right hemispheric region (average amplitude of C4, B22 and B4 electrodes) compared to the TD group, $F(1,83)=4.33$, $p=.041$, in line with the right-lateralized topographic difference between groups that is apparent in Figure 2.

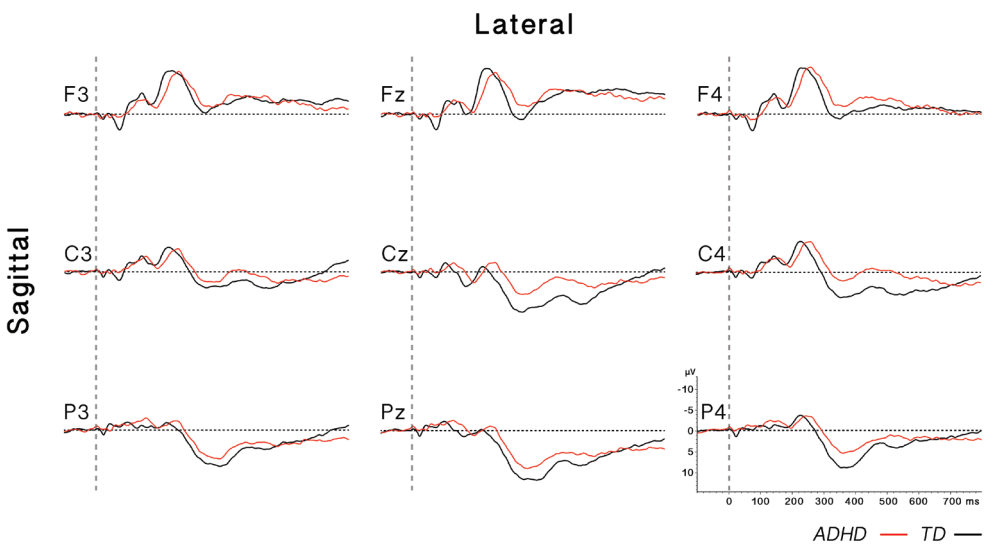


Figure 1. Grand average target ERPs for the ADHD and TD groups

Note. Grand average ERPs for the ADHD and TD groups, for the target stimulus at nine representative electrode locations of the 10/20 system (Jasper, 1958). F3, F4, P3 and P4 are approximations of D4, C4, A7 and B4 of the ABC 128 electrode system; μV = microvolt, ms = millisecond.

LAURA source estimation results

Figure 3 and Figure 4 show the statistical parametric maps of the group comparisons on LAURA source estimations for the P3 (310-410ms). Two main clusters were found in the left hemisphere. Frontally, the ADHD group showed reduced activation in the middle frontal and superior frontal gyri (Brodmann Area [BA] 10), and bilaterally – though more dominantly in the left hemisphere – reduced activation in adjacent, and more ventral BA11. The second cluster showed reduced activation for the ADHD group at the junction of temporal, parietal and occipital cortices, in angular, middle temporal and superior temporal gyri (BA 39 and 19). At last, reduced activation for the ADHD group was found in a relatively small area in the right posterior insula.

Correlations

To reduce the number of correlations, only the average amplitude of the right-sided electrodes (C4, B22, B4) was used, which showed a group difference between TD and ADHD in the main analysis. Only for the ADHD group, teacher-reported inattention and hyperactivity/impulsivity scores were negatively related to P3 amplitudes, $r(34)=-.473$, $p=.004$, and $r(34)=-.335$, $p=.046$, respectively, with more ADHD symptoms related to smaller amplitudes. The TD group showed a negative correlation between MRT and P3 amplitude, $r(47)=-.557$, $p<.001$, with faster MRTs related to larger amplitudes.

Table II. GLM MANOVA of mean target P3 amplitudes for the TD and ADHD groups

P3	Electrode	Group		Sagittal (S)	Lateral (L)	Group (G)	G x S		G x L		G x S x L				
		ADHD	TD				$F(2,82)$	η^2	$F(2,82)$	η^2	$F(4,80)$	η^2			
Frontal	F3	-2.5 (6.9)	-1.5 (9.0)	100.58***	.71	24.00***	.37	2.58	.03	0.96	.02	3.66*	.08	0.98	.05
	Fz	-2.7 (6.7)	-0.5 (10.2)												
	F4	-2.7 (5.9)	0.1 (9.4)												
Central	C3	1.8 (8.0)	3.2 (9.1)												
	Cz	4.4 (7.4)	8.4 (9.6)												
Posterior	C4	1.1 (6.7)	5.0 (9.0)												
	P3	5.7 (6.9)	7.5 (8.6)												
	Pz	7.8 (7.2)	10.7 (8.9)												
	P4	4.3 (7.3)	7.7 (8.0)												

Note. Data presented are mean (SD) in μV ; TD = typically developing; * $p < .05$, *** $p < .001$

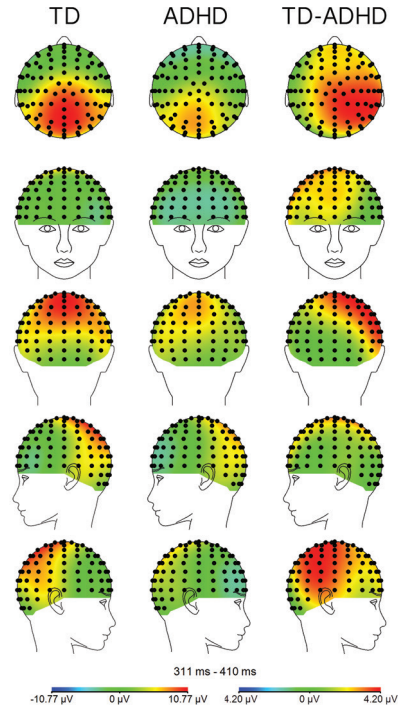


Figure 2. Topographic maps of group average target P3

Note. Target P3 between 310-410ms post-stimulus, for the TD and ADHD groups and differences between groups (TD-ADHD); μV = microvolt, ms = millisecond

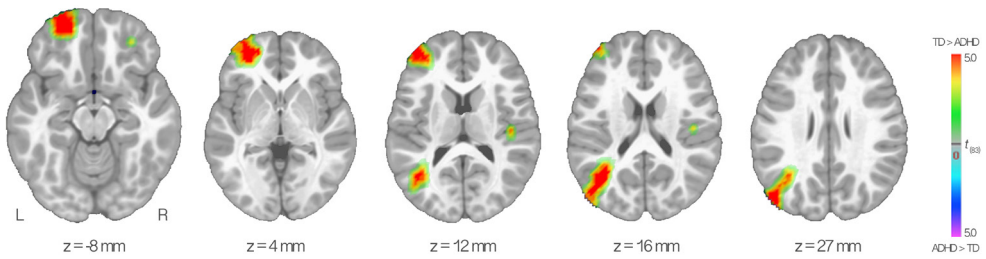


Figure 3. Statistical differences between ADHD and TD groups in source localization of target P3
Note. Significant differences between the ADHD and TD groups in LAURA source estimations for the P3 analysis windows during the target condition, shown on a pediatric MNI template brain. Illustrated coordinates were converted from MNI to Talairach space. Color indicates the t -values. Lower-bound Bonferroni-corrected significance is $p < .0004$. For viewing purposes, images were interpolated with the 4-nearest-neighbor (4NN) method.

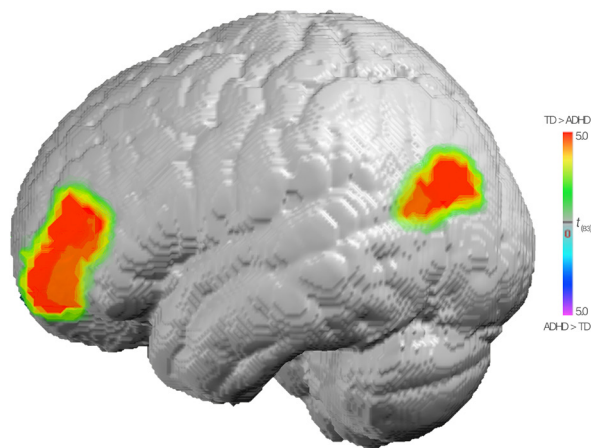


Figure 4. Lateral view of differences between ADHD and TD groups in source localization of target P3
Note. Lateral view of a 3-dimensional rendering of the paediatric MNI template brain with significant differences between the ADHD and TD groups in LAURA source estimations for the P3 analysis window during the target condition. Colour indicates the t -values. Lower-bound Bonferroni-corrected significance is $p < .0004$. For viewing purposes, images were interpolated with the 4-nearest-neighbor (4NN) method.

DISCUSSION

This study aimed to further our understanding of the neural networks involved in attention problems in children with ADHD. More specifically, differences in the neural generators of the P3b component during the oddball task were compared between ADHD and typically developing children to identify brain regions that are associated with well-documented findings of reduced P3b amplitudes in ADHD. As hypothesized, children with ADHD showed reduced P3b amplitudes in response to target stimuli. These differences were located primarily in frontal and temporoparietal regions in the left hemisphere. For the ADHD group, smaller P3b amplitudes were associated with more severe inattention and hyperactivity/impulsivity problems.

In line with other studies, the P3b topography in response to targets had a typical posterior maximum (Johnson, 1993) within both groups, and P3b amplitude was reduced in children with ADHD compared to typically developing children (Brown et al., 2005; Senderecka, Grabowska, Gerc, Szewczyk, & Chmylak, 2012; Tsai, Hung, & Lu, 2012; Yorbik et al., 2008). This reduction was restricted to the right scalp area in accordance with Senderecka et al. (2012), who found larger differences over midline and right hemisphere regions in ADHD. Although the authors suggested that this right hemispheric focus might imply the involvement of an altered right-lateralized attention system in ADHD, this interpretation is difficult due to the ambiguity of EEG signals (Michel et al., 2004). Maximal differences at certain electrodes do not necessarily equate to the cortical generators, as many different source configurations can generate the same distribution of potentials. ERPs generated in one part of the brain can lead to substantial voltages at distant parts of the brain (Luck, 2014). This is exemplified in simulations of cortical EEG sources, which can induce maximum amplitudes in the opposite hemisphere, for an example see Loo et al. (2012). Our source localization findings of left-hemispheric abnormalities, despite a similar right lateralized topographic difference, do indeed underline this conception.

Source localization of the P3b demonstrated reduced activation in the ADHD group in a ventral region of the left frontal pole, including middle and superior frontal gyri, mainly located in Brodmann area (BA)10. This region coincides with reduced activation in fMRI studies of the oddball task in children and adolescents with ADHD (Rubia et al., 2009; Stevens, Pearlson, & Kiehl, 2007) and adults with ADHD (Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011), and with localization of the P3b in a healthy population using LORETA (Volpe et al., 2007). The frontopolar cortex has been suggested to be a hub region in a cinguloopercular network that is associated with the ability to maintain the representation of task rules (Dosenbach et al., 2007).

This would be in line with a meta-analysis that showed this area to be activated in working memory and memory retrieval tasks (Gilbert et al., 2006), and studies in patients with lesions in BA10 that demonstrate difficulties in sustained, self-maintained attending behaviour (Burgess, Dumontheil, & Gilbert, 2007). Taken together, our results may suggest that children with ADHD have difficulties with top-down attentional control, which may be related to working memory, consistent with the P3b model by Donchin & Coles (1988).

The second major cluster that showed reduced activation in the ADHD group was localized in the left angular gyrus (AG), at the boundary of superior temporal, inferior parietal and occipital cortices. Although the fMRI meta-analysis by Hart et al. (2013) found reduced activation in the right inferior parietal lobe (IPL) across different attention tasks in ADHD, Cao et al. (2008) located reduced activation in the left IPL during a target condition in children with ADHD. The left hemispheric focus may be surprising, considering that target detection is thought to be lateralized to the right hemisphere of the brain (Corbetta et al., 2008). This view, however, is increasingly challenged. A review of fMRI studies found evidence for a mediating role of the left IPL in bottom-up attentional capture by memory content (Ciaramelli, Grady, & Moscovitch, 2008), and a recent review on the ventral attention system indicated evidence for the involvement of this area in attentional reorienting and processing of rare deviant stimuli (Vossel, Geng, & Fink, 2014). It has been proposed that the AG is an important interface between converging bottom-up inputs and top-down predictions (Seghier, 2013). It could be speculated that children with ADHD have difficulty in maintaining task rule representations (reduced activation in left frontopolar region) and therefore introduce less consistent top-down control (predictions), thereby affecting the AG. Conversely, these systems may influence each other in reversed order, reciprocally, or may be affected independently. This hypothesis remains to be tested experimentally.

Some limitations to this study should be noted. First, source imaging is an estimation of brain activity instead of a measurement like fMRI, with less spatial resolution, and should therefore be interpreted with some caution. Replication of the current study is needed to increase confidence in our findings. Second, distributed source imaging can produce spurious activations, or 'ghost' sources (Fuchs, Wagner, Kohler, & Wischmann, 1999). However, both problems were reduced in the current study by calculating individual source estimations, which make it unlikely that spurious activations will be consistently observed across individuals. Furthermore, instead of only localizing group average ERPs or group differences, we statistically tested for group differences with stringent statistical criteria. Third, motor related activity was not controlled, as

participants were instructed to respond with their right index finger. Future studies could require simultaneous left and right button presses or counterbalance the required response. At last, it should be emphasized that the network alterations found in the current study may not be exhaustive, as the aims of this study were specifically focused on the underlying alterations of the P3b (over a 100ms window) in children with ADHD. Indeed, fMRI studies of attention tasks in ADHD have shown evidence of several disrupted networks besides those implicated in our study (Hart et al., 2013).

In conclusion, this study provides evidence for alterations in both top-down (frontopolar cortex) and bottom-up (inferior parietal/superior temporal cortex) attention-related brain areas, which may underlie P3b amplitude reductions in children with ADHD. These brain areas seem to play central roles in a cinguloopercular and ventral attention network, respectively. Our findings largely converge anatomically and functionally with models of P3b that associate this component with contextual-updating of working memory (Emanuel Donchin & Coles, 1988). Future studies may extend our findings using connectivity measures, to explore how top-down and bottom-up alterations during attentional processing are interrelated in children with ADHD.

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