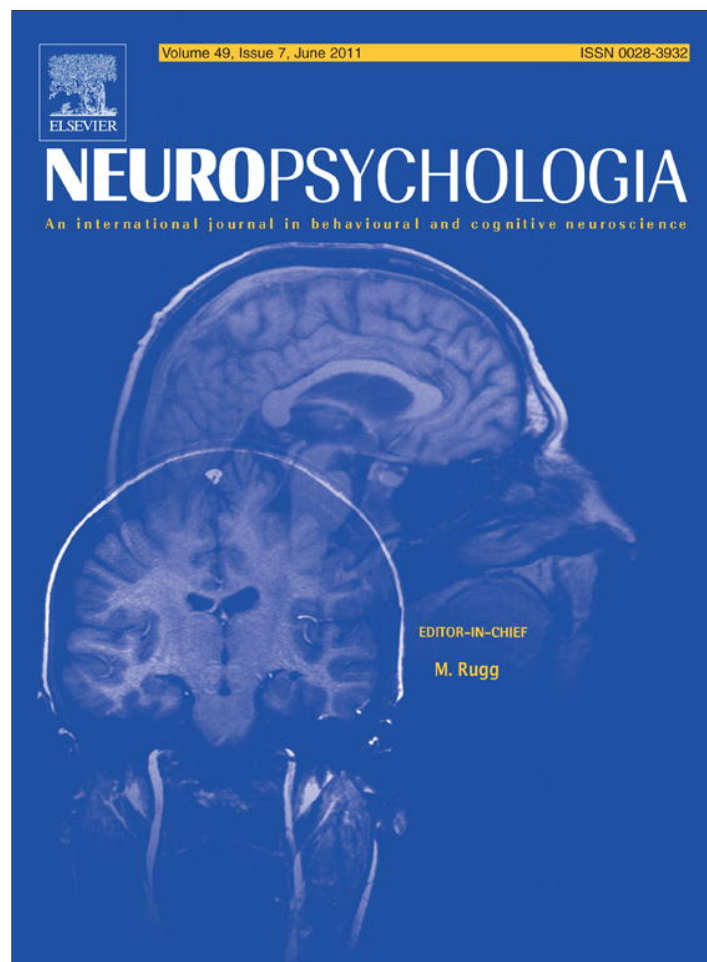


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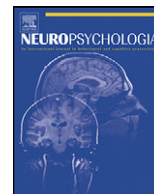
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Impaired engagement of the ventral attentional pathway in ADHD

Päivi Helenius^{a,b,*}, Marja Laasonen^{b,c}, Laura Hokkanen^c, Ritva Paetau^d, Markku Niemivirta^{c,e}^a Brain Research Unit, MEG Core, Low Temperature Laboratory, Aalto University, Espoo, Finland^b Department of Phoniatrics, Helsinki University Central Hospital, Helsinki, Finland^c Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland^d Department of Pediatric Neurology, Helsinki University Central Hospital, Helsinki, Finland^e Helsinki Collegium for Advanced Studies, University of Helsinki, Helsinki, Finland

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ABSTRACT

In the cognitive theories of Attention Deficit Hyperactivity Disorder (ADHD) impaired behavioral adjustment has been linked to a deficit in learning to detect regularities or irregularities in the environment. In the neural level, the P3 component of event-related potential (ERP) is modulated by stimulus probability and has been suggested to index activation of the ventral attention network, which constitutes the reorienting system of the human brain. To explore the cortical basis of late positive ERP components and the engagement of the ventral attentional pathway in ADHD, we used ERP recordings complemented by spatiotemporally sensitive magnetoencephalography (MEG) measurements. We followed the activation evoked by frequent Go and infrequent NoGo stimuli in 10 ADHD adults and 13 control subjects. In the ERP recordings, a prominent positive deflection was detected after the infrequent visual stimuli (late positive component, LPC) in both subject groups. In ADHD adults the difference between the responses evoked by infrequent NoGo and frequent Go stimuli was markedly reduced compared to the control group during the LPC. The MEG recordings revealed that the activation detected during the LPC was localized bilaterally in the posterior temporal cortex. Activation of the left and right temporal regions was enhanced after infrequent NoGo stimuli in both subject groups. In ADHD adults, however, the effect of stimulus frequency was less pronounced. We suggest that the activation in the superior temporal cortices during the LPC reflects the action of ventral attention network. The engagement of this stimulus-driven reorienting system is defective in ADHD.

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1. Introduction

Attention Deficit Hyperactivity Disorder, ADHD, is a common neurobehavioral disorder with a worldwide prevalence estimate around 7% (Faraone, Sergeant, Gillberg, & Biederman, 2003; Nigg, 2006). Diagnosis is not based on a single neurobiological or neuropsychological test but, instead, the behavioral history and checklist of current symptoms are used as a guide to diagnosis. ADHD children can be excessively hyperactive and impulsive or inattentive. These symptoms in many cases persist into adulthood. The neuropsychological tests that seem to posit greatest difficulty to most individuals with ADHD are working memory tests (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), interference tasks such as Stroop (Lansbergen, Kenemans, & van Engeland, 2007) and tasks of divided attention (Savage, Cornish, Manly, &

Hollis, 2006) (for reviews, see Frazier, Demaree, & Youngstrom, 2004; Hervey, Epstein, & Curry, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A widespread dysfunction in neural systems involving prefrontal, striatal (Vaidya, Austin, Kirkorian, Ridlehuber, Desmond, & Glover, 1998; Zametkin, Nordahl, Gross, King, Semple, & Rumsey, 1990) and parietal brain regions (Smith, Taylor, Brammer, Toone, & Rubia, 2006; Tamm, Menon, & Reiss, 2006) in ADHD has been suggested (for reviews, see Bush, 2010; Casey & Durston, 2006; Dickstein, Bannon, Xavier Castellanos, & Milham, 2006). These areas regulate attentional and executive processes. The neurocognitive mechanism that dominantly contributes to the disorder may vary between the affected individuals (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Willcutt et al., 2005).

Self-regulation and behavioral adjustment are supported by the ability to detect and predict what and when important events in the environment occur (Nigg & Casey, 2005). In a cognitive control model of ADHD proposed by Nigg and Casey, learning to detect regularities or irregularities in the environment is seen critical for the appropriate functioning of the control systems (Casey & Durston, 2006; Nigg & Casey, 2005). The neural structures implicated to underlie this prediction ability are the prefrontal–striatal

* Corresponding author at: Brain Research Unit, Low Temperature Laboratory, Aalto University, PO Box 15100, 00076 Aalto, Finland. Tel.: +358 50 3442475; fax: +358 9 47022969.

E-mail address: paivi@neuro.hut.fi (P. Helenius).

loop and the prefrontal–cerebellar loop. In the neuroanatomical model of attention by Corbetta and Shulman (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002), prefrontal areas are only one part of the system where components dynamically interact during perception and determine the focus of attention. Within this framework expectations and internal goals are postulated to preactivate and maintain activation in the dorsal frontoparietal attention system. During such goal-directed behavior top-down suppressing signals are sent to the second part of the system, the ventral attention network. However, if something important happens during focused goal-directed task elsewhere in the environment, or an unexpected stimulus is presented, it is essential to quickly change the focus. In these situations, activation of the ventral stimulus-driven attention system is used to redirect attention. Balance between these two anatomically and functionally segregated systems allows an individual to concentrate on something but remain sensitive to forthcoming important events. Anatomically the dorsal attention system is suggested to comprise as core regions the bilateral frontal eye fields and intraparietal sulci. The ventral attention network centers around the right hemisphere middle frontal gyrus and temporoparietal junction (TPJ) (Corbetta et al., 2008).

Only a few functional imaging studies have investigated the engagement of the attention networks in ADHD. In a functional MRI (fMRI) study by Tamm et al. (2006), ADHD adolescents responded with separate button presses to frequent visual standard stimuli and infrequent oddball stimuli. Unlike the control group, ADHD adolescents did not display increased signals to the oddball events in the bilateral parietal areas surrounding intraparietal sulcus. The observed pattern of results for the ADHD group was suggested to derive from impaired engagement of the dorsal parietal network during goal-directed attention. With regards to the integrity of the ventral attention system in ADHD, the results were less conclusive; the posterior part of the ventral stream did not respond to stimulus frequency in this fMRI study although clearest differences between standard stimuli and oddballs should arise from ventral regions (Corbetta et al., 2008).

An event-related potential (ERP) component that is particularly sensitive to stimulus probability is the P3 response; the less probable the stimulus category the larger the P3 (Duncan-Johnson & Donchin, 1977). Numerous ERP studies have investigated the P3 responses during visual task performance in children and adults with ADHD with variable results (Barry, Johnstone, & Clarke, 2003). Majority of studies have found a reduced amplitude of the P3 response in ADHD (Brandeis, Vanleeuwen, Rubia, Vitacco, Steger, & Pascual-Marqui, 1998; Holcomb, Ackerman, & Dykman, 1985; Jonkman, Kemner, Verbaten, Koelega, Camfferman, & van der Gaag, 1997; Klorman, 1991) but abnormalities in P3 latency have also been reported (Strandburg, Marsh, Brown, Asarnow, Higa, & Harper, 1996; Sunohara, Voros, Malone, & Taylor, 1997; Taylor, Voros, Logan, & Malone, 1993). The exact functional role of the P3 component has remained unsettled despite more than 40 years of extensive study (Sutton, Braren, Zubin, & John, 1965). Within the ERP framework, it has been suggested that P3 is related to updating or revision of mental representation in working memory induced by incoming stimulus (Donchin, 1981; Donchin & Coles, 1988; Polich, 2007) or the decision about how to respond (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Verleger, Jaśkowski, & Wascher, 2005) or classify the stimulus (Nieuwenhuis et al., 2005). P3 response has also been suggested to index the activation of the ventral attention network (Corbetta et al., 2008; Nieuwenhuis et al., 2005). Evidence is mostly based on patient studies that have convincingly shown that lesions of the TPJ lead to reduced auditory and visual P3 component (Knight, Scabini, Woods, & Clayworth, 1989; Verleger, Heide, Butt, & Kömpf, 1994). More direct evidence of the involvement of posterior temporal cortex in P3 generation was also recently

acquired in a combined ERP and magnetoencephalography (MEG) study (Helenius, Laasonen, Hokkanen, Paetau, & Niemivirta, 2010).

In the current experiment, we explored the cortical basis of late positive ERP components (P3) and engagement of the posterior part of the ventral attentional pathway in ADHD using combined MEG and ERP measurements. MEG detects weak magnetic fields associated with local neural activation and can readily follow both the spatial and the temporal patterns of cortical activation (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Salmelin & Baillet, 2009). Thus, using MEG it is possible to detect differences between impaired and non-impaired subject groups in the strength of activation within certain time windows and cortical areas. In this experiment, the participants were required to respond to frequent visual stimuli (Go) and to withhold a response to infrequent visual stimuli (NoGo). In ERPs, differences between the trials are detected during two distinct deflections: The N2 deflection peaking around 300 ms is more negative to NoGo than to Go stimuli, and P3, a broad positive component with a typical peak latency between 300 and 400 ms, is enhanced in amplitude for NoGo stimuli (Amodio, Master, Yee, & Taylor, 2008; Kok, 1986; Nieuwenhuis, Yeung, & Cohen, 2004; Pfefferbaum, Ford, Weller, & Kopell, 1985). In our recently published study (Helenius et al., 2010), the P3 (or as called in the study, the late positive component, LPC) was coupled with functionally and temporally equivalent MEG signals arising from the bilateral posterior temporal cortex. During the N2 deflection, NoGo trials were associated with an increased signal in the right posterior occipito-temporal area. In the present study, these signals, i.e., LPC associated activation in bilateral superior temporal areas putatively linked to ventral attentional pathway and N2 activation associated with visual processing (perceptual identification) along the ventral visual stream (Goodale & Milner, 1992), were investigated in adults with a prior diagnosis of ADHD. We hypothesized that, compared to healthy adults, participants with ADHD would show reduced LPC in the ERP recordings and concurrent defective functioning of the ventral attentional pathway in the MEG recordings.

2. Methods and materials

2.1. Participants

We recorded data from 13 adults 19–48 years of age (mean 29 years, 7 females) with no history of developmental disorders. The 10 ADHD participants (26–49 years of age, mean 35 years, 4 females) were volunteers from the project Adult Dyslexia and Attention Deficit Disorder in Finland (Laasonen, Leppämäki, Tani, & Hokkanen, 2009). As an inclusion criterion to the project, all participants with ADHD were required to have a prior diagnosis using Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein, Johnson, & Conners, 2001) by a medical doctor specialized in neuropsychiatry. Confounding psychiatric disorders were excluded. In this project, hyperactivity is not a required characteristic and thus also those with only attention deficit were included. ADHD participants used no pharmacological treatment (possible drugs were discontinued at least one week before the study appointments). All participants were right-handed according to their own report. Informed consent was obtained from all subjects, in agreement with the prior approval of the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

2.2. Behavioral testing

All subjects were investigated using a concise neuropsychological test battery tapping vocabulary and non-linguistic reasoning (WAIS-III; Wechsler, 2005), auditory short-term memory (WMS-III; Wechsler, 2008) and reading related skills (naming and reading speed and phonological processing). A measure of oral reading speed was obtained from reading aloud word and pseudoword lists containing 30 items each (Nevala, Kairaluoma, Ahonen, Aro, & Holopainen, 2006). Naming speed was estimated as a time to name color squares, letters and digits in a 5 × 10 matrix (RAS; Wolf, 1986). Phonological processing was tested using the Pig Latin test (Nevala et al., 2006). Executive functioning was screened using the Stroop test (Jensen & Rohwer, 1966).

Table 1 summarizes the behavioral profiles of the two subject groups. The adults participating in this study diagnosed with ADHD did not as a group exhibit psychometrically marked impairments in executive functioning (only suggestive increase of errors in Stroop), general achievement or reading related skills (thus exclud-

Table 1
Cognitive profile of the control and ADHD participants.

	Control Ss	ADHD Ss	
N	13	10	
Mean age (SD)	29.6 (7.8)	35.3 (9.4)	<i>n.s.</i>
Age range	19–48	26–49	
Percent male	46	60	
Behavioral testing			<i>p</i> -Value
Vocabulary (a)	11.7 (1.3)	11.5 (1.7)	<i>n.s.</i>
Matrix reasoning (a)	12.6 (2.8)	11.1 (2.4)	<i>n.s.</i>
Digit span (b)	11.3 (2.5)	10.4 (2.1)	<i>n.s.</i>
Pig Latin (correct items)	14.3 (0.7)	13.0 (4.6)	<i>n.s.</i>
Reading words (ms/item)	617 (191)	620 (97)	<i>n.s.</i>
Reading pseudowords (ms/item)	1190 (255)	1447 (341)	<i>n.s.</i>
Naming speed (ms/item)	432 (83)	476 (79)	<i>n.s.</i>
Stroop color-word (s)	97.7 (14.9)	97.1 (15.5)	<i>n.s.</i>
Stroop color-word (errors)	0.3 (0.4)	1.4 (1.8)	<i>n.s.</i>

(a) Standard scores in WAIS-III and (b) standard scores in WMS-III. Standard deviations in parentheses; *n.s.*, non-significant difference between the subject groups.

ing concurrent dyslexia). The cognitive profile of the ADHD group also corresponds a more representative sample (Laasonen, Lehtinen, Leppämäki, Tani, & Hokkanen, 2010; Laasonen et al., 2009).

2.3. Stimuli and experimental procedures

Our stimuli were arrays composed of 5 visual items (apples and animals) (Fig. 1). The relative position of items varied between successive stimuli presented once every 2.2 s. Display duration of each array was 150 ms. The stimuli were presented on a rear projection screen placed in front of the subject sitting in the magnetically shielded room (Imedco AG, Hägendorf, Switzerland). All images were presented at the same central viewing position occupying a visual angle of about 6 degrees \times 1 degree on a light grey background. The screen background color remained the same between the stimuli. The participants were instructed to make a rapid manual response to a target stimulus (wolf is facing a pig; probability 83%) and avoid responding to a non-target stimulus (wolf is not facing a pig; probability 17%). The response button was in the subject's right hand.

2.4. Data acquisition

During two 12-min sessions, 3 ERP channels and a whole-head MEG system were used to record stimulus-locked signals. The stimulus-locked signals were averaged for target stimuli (Go correct trials) and for those non-target stimuli that were correctly not responded to (NoGo correct trials). In Go correct trials, only responses following the stimuli within 700 ms were included. The response-locked and error-related ERP/MEG data (Helenius et al., 2010), containing relatively small number of averages, are not presented here (see Section 3).

ERP signals were measured from Fz, Cz and Pz according to the International 10–20 system (reference electrode AFz, ground neck). Neuromagnetic brain responses were recorded using a 306-channel Elekta Neuromag™ neuromagnetometer (Elekta Oy, Helsinki, Finland) that measures magnetic field strength in 102 locations over the scalp (two planar gradiometers and one magnetometer at each location). Prior to measurements, four head-position indicator coils were attached to the subject's scalp, and the locations of these coils were determined in relation to three anatomical landmarks (preauricular points and nasion) with a 3-D digitizer. At the beginning of the experimental session, an electric current was fed to the coils and their locations with respect to the MEG helmet were measured.

The MEG and EEG signals were band-pass filtered at 0.1–200 Hz and sampled at 600 Hz. Stimulus-locked responses were averaged across trials from 200 ms before

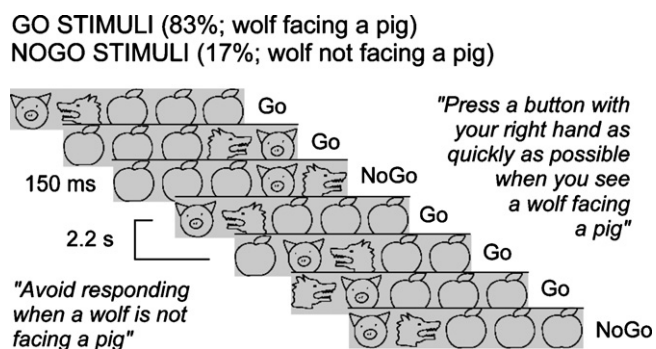


Fig. 1. The visual stimuli used in the study.

Table 2
Task performance during the MEG/EEG recordings.

	Control Ss Mean (SD)	ADHD Ss Mean (SD)	<i>p</i> -Value
Reaction times (ms)			
Go correct responses	419 (37)	451 (63)	<i>n.s.</i>
NoGo error responses	361 (29)	398 (84)	<i>n.s.</i>
Amount of NoGo errors			
% of all non-targets	29 (18)	19 (14)	<i>n.s.</i>

SD, standard deviation; *n.s.*, non-significant.

to 800 ms after the stimulus onset (Go correct trials, NoGo correct trials). Vertical and horizontal eye movements were continuously recorded and epochs contaminated by ocular signals were rejected. The number of artifact-free trials was on average 472 for Go correct trials in control subjects and 430 in ADHD subjects, and 68 for NoGo correct trials in control subjects and 77 in ADHD subjects (non-significant differences between subject groups in both trial types).

2.5. MEG data analysis

We localized the active source areas using Minimum Current Estimates (MCE; Uutela, Hämäläinen, & Somersalo, 1999) and Equivalent Current Dipole analysis (ECD analysis; Hämäläinen et al., 1993). MCE accounts for the measured signals by a distribution of electric current that has the minimum total amplitude. MCEs were first calculated from the data of each individual participant and, thereafter, averaged across participants. ECD analysis reduces the signals detected by the MEG sensors into the time behavior of distinct cortical areas. Each ECD represents the centre of an active cortical patch and the strength and direction of electric current in that area. Individually in each subject, for each distinct dipolar field pattern, a subset of planar gradiometer sensors was selected that optimally covered the pattern, and the location of the neural population generating that response was determined. Thereafter, the locations and orientations of the ECDs were fixed while their amplitudes were allowed to vary to achieve maximal explanation of the recorded whole-head data (for an example of MEG data recorded from one subject and an associated multipole model, see Helenius et al., 2010). Structural MR images were not available for most of the participants. Therefore, a default model of the brain was used in the MCE analysis and the ECD sources of each individual are displayed on an average brain.

3. Results

The ADHD and control participants did not differ in task performance during the MEG/EEG recording (Table 2). All participants responded significantly slower to target stimuli (Go correct responses) than to non-target stimuli, i.e., when they made a NoGo error response ($F(1,21) = 58.2, p < .001$). NoGo error response rates were on average 29% in control and 19% in ADHD participants and varied considerably between individuals (from 6 to 70% in control and 4 to 51% in ADHD participants). In 2 out of 13 control subject and in half of the ADHD participants, the NoGo error rates were below 15%.

3.1. Analysis of the stimulus-locked ERP signals

The stimulus-locked ERP waveforms associated with target and non-target stimuli calculated across 13 control subjects and 10 ADHD participants are shown in Fig. 2. In both groups, the NoGo correct trials elicited a more negative going deflection compared to Go correct trials 390 ms after the stimulus presentation in all three channels. In each participant, the N2 was identified as the peak negative deflection occurring 330–430 ms after the onset of the stimuli in NoGo correct trials. As in three subjects none of the three channels showed a distinct peak during the 330–430 ms time window, the time point of the maximal difference between NoGo correct and Go correct trials was used instead. In a 3 (Fz, Cz, Pz) \times 2 (Go, NoGo) \times 2 (controls, ADHD) mixed ANOVA, a significant main effect of channel, stimulus and subject group was detected. During the individually determined N2 peaks, the responses were more negative for NoGo correct trials than for Go correct trials ($F(1,21) = 50.3, p < .001$). The responses were also more negative in the frontal than in the posterior channel ($F(2,20) = 20.1, p < .001$).

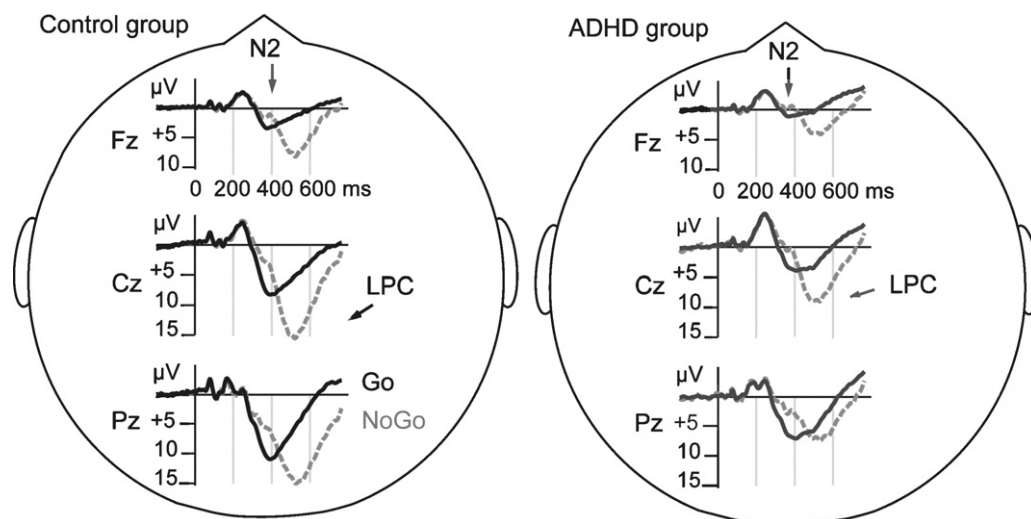


Fig. 2. ERP responses in electrodes Fz, Cz and Pz. The responses were averaged with respect to stimulus presentation across all control (left) and ADHD (right) subjects for correct Go and correct NoGo trials.

and the responses were overall more positive in the control group than in the ADHD group ($F(1,21)=4.9$, $p<.04$). As the late positive component partly overlaps the N2 response, we high-pass filtered the waveforms above 2 Hz (for a similar approach, see Jodo & Kayama, 1992). After the removal of the LPC component by high-pass filtering, the difference between subject groups became non-significant ($F(1,21)=0.1$, *n.s.*). The size of the N2 effect, calculated as the difference between Go correct trials and NoGo correct trials, was also comparable between the two subject groups ($F(1,21)=1.1$, *n.s.*).

In a later time window, the NoGo correct trials elicited a broad positive component maximal in the averaged waveforms around 530 ms after the stimulus onset. In each participant this late positive component (LPC) was identified as the peak positive deflection occurring after 510 ms from the onset of the stimuli in the NoGo correct trials. In a 3 (Fz, Cz, Pz) \times 2 (Go, NoGo) \times 2 (controls, ADHD) mixed ANOVA, a significant main effect of channel, stimulus and subject group was detected. During the LPC peaks the responses were more positive for NoGo correct trials than for Go correct trials ($F(1,21)=137.8$, $p<.001$). The responses were also more positive in the posterior than in the frontal channel ($F(2,20)=32.6$, $p<.001$) and the responses were overall more positive in the control group than in the ADHD group ($F(1,21)=6.4$, $p<.02$). Further, the stimulus \times subject group interaction ($F(1,21)=7.6$, $p<.01$, stronger LPC in control group than in ADHD group for NoGo correct trials) and the channel \times stimulus \times subject group interaction ($F(2,20)=5.3$, $p<.02$, stronger LPC in control group than in ADHD group for NoGo correct trials particularly in the posterior channels) were significant. We also calculated the size of the LPC effect as the difference between the NoGo correct trials and Go correct trials. Statistical testing revealed that the size of the LPC effect differed between channels ($F(2,20)=16.7$, $p<.001$, maximal at Cz and Pz) and between the two subject groups ($F(1,21)=7.6$, $p<.01$). Further, the significant channel \times subject group interaction ($F(2,20)=5.3$, $p<.02$) indicated that the effect size difference between groups was particularly evident at Pz.

Fig. 3 depicts the relationship between the strength of the LPC deflection and the size of the LPC effect in each individual at electrode Pz. A statistically significant correlation was observed between these two measures that also fairly effectively separated the majority of the control adults from the ADHD participants ($r=-0.79$, $p\leq.001$ when calculated across all subjects; $r=-0.73$ in control subjects and $r=-0.55$ in ADHD subjects).

3.2. MCE analysis of the stimulus-locked MEG data

We calculated the minimum current estimates around the N2 peak (355–405 ms) for the Go correct and NoGo correct trials across all subjects, and separately for 13 control subjects and 10 ADHD participants (Fig. 4). The activation elicited by NoGo correct and Go correct trials was compared in four left hemisphere, four right hemisphere and midline anterior regions of interest (ROI). Only one ROI, centered in the right occipito-temporal border, displayed stronger activation during the N2 peak to NoGo correct than to Go correct trials (across all subjects 5.8 ± 3.2 nAm vs. 4.3 ± 2.6 nAm, respectively; paired t -test $p<.002$). The difference was statistically significant even when tested separately in the control group ($p<.05$) and in the ADHD group ($p<.005$). The motor responses (right hand button presses) elicited already at this time window stronger activation to Go correct trials than to NoGo correct trials in the left motor (across all 23 participants 5.4 ± 4.8 nAm vs. 4.0 ± 4.0 nAm, respectively; paired t -test $p<.01$) and primary somatosensory cortex (across all 23 participants 5.7 ± 4.0 nAm vs. 4.4 ± 2.9 nAm, respectively; paired t -test $p<.04$). The overall level of activation to Go correct and NoGo correct trials in all the ROIs was comparable between control and ADHD participants.

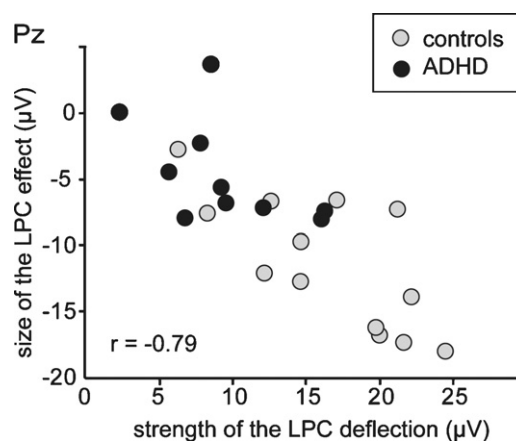


Fig. 3. Strength of the LPC deflection plotted against the size of the LPC effect (the difference between the NoGo correct trials and Go correct trials) in electrode Pz. These two correlating measures differed between control and ADHD adults.

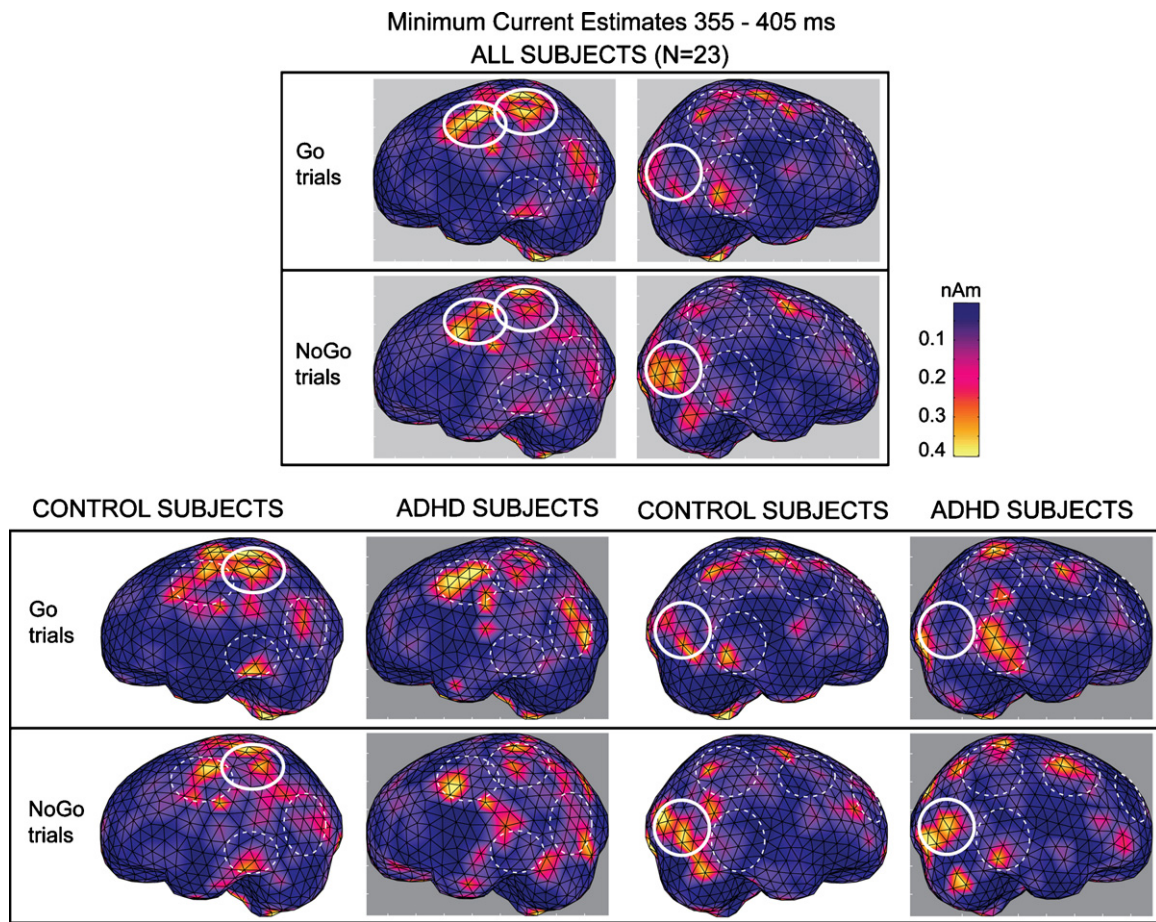


Fig. 4. Minimum current estimates for Go correct and NoGo correct trials during the N2 peak across all subjects ($n = 23$) and separately for control ($n = 13$) and ADHD subjects ($n = 10$). Activation is integrated over 355 and 405 ms. The color display shows the estimated source distribution projected to the surface of the brain. One brain volume indicated with solid white circle in the right occipito-temporal border was more strongly activated to NoGo correct than Go correct trials in both subject groups. In the left hemisphere somatosensory cortex was more activated to Go correct trials (associated with the button press) than to NoGo correct trials. The dashed circles indicate statistically non-significant differences between the two trials.

MCE analysis around the peak of the LPC (475–575 ms), calculated across all subjects, revealed enhanced activation in the bilateral posterior temporal cortex to NoGo correct (5.3 ± 4.9 nAm in the left and 6.8 ± 3.3 nAm in the right hemisphere) compared to Go correct trials (3.7 ± 3.6 nAm in the left and 3.4 ± 1.4 nAm in the right hemisphere, paired t -test between Go correct and NoGo correct trials $p < .03$ in the left hemisphere and $p < .001$ in the right hemisphere) (Fig. 5). In the right posterior temporal cortex, activation to NoGo correct trials was enhanced in both subject groups (control group $p < .001$, ADHD group $p < .02$), but in the left hemisphere, a statistically significant difference between trials was detected only in the control group (control group $p < .01$, ADHD group $n.s.$). Also in this time window, the motor responses elicited stronger activation to Go correct than to NoGo correct trials in the left motor area (across all 23 participants 4.1 ± 2.9 nAm vs. 2.9 ± 1.8 nAm, respectively; paired t -test $p < .05$). The overall level of activation to Go correct and NoGo correct trials in the left and right ROIs was comparable between control and ADHD participants.

3.3. ECD analysis of the stimulus-locked MEG data

Fig. 6 shows the distribution and time behavior of those equivalent current dipoles across control and ADHD participants that centered in the left and right posterior temporal areas. The mean signal strength of these ECDs during the LPC activation (475–575 ms) was stronger to NoGo correct than to Go correct trials (i.e., the difference between categories was at least 1.96 times

the baseline period 200 ms prior to the stimulus) in 10/13 control subjects in the left and in 11/13 control subjects in the right hemisphere. In these same dipoles the mean activation to NoGo correct trials also exceeded 1.96 times the baseline activation. Similar significant ECD activation, stronger for NoGo correct than Go correct trials, was detected in 5/10 ADHD participants in the left and in 7/10 ADHD participants in the right hemisphere.

Around the peak of the LPC (475–575 ms) the mean activation elicited by NoGo correct trials (across all 23 participants 14.6 ± 11.9 nAm in the left and 16.1 ± 11.5 nAm in the right hemisphere) was stronger than activation elicited during this time window by Go correct trials (6.3 ± 6.3 nAm in the left and 6.4 ± 6.0 nAm in the right hemisphere, paired t -test $p < .001$ in both hemispheres). We also calculated the size of the LPC effect in the bilateral temporal areas as the difference between the NoGo correct and Go correct trials. The 2 (right hemisphere, left hemisphere) \times 2 (controls, ADHD) ANOVA revealed that the size of the LPC effect differed between the subject groups ($F(1,21) = 4.6$, $p < .05$). Further analysis showed that the LPC effect size difference between the two groups approached significance in the left hemisphere ($p < .07$).

4. Discussion

Human visual cortical areas are segregated into dorsal and ventral processing streams (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). The ventral visual stream originates from primary visual cortex and is directed towards temporal cortex. This

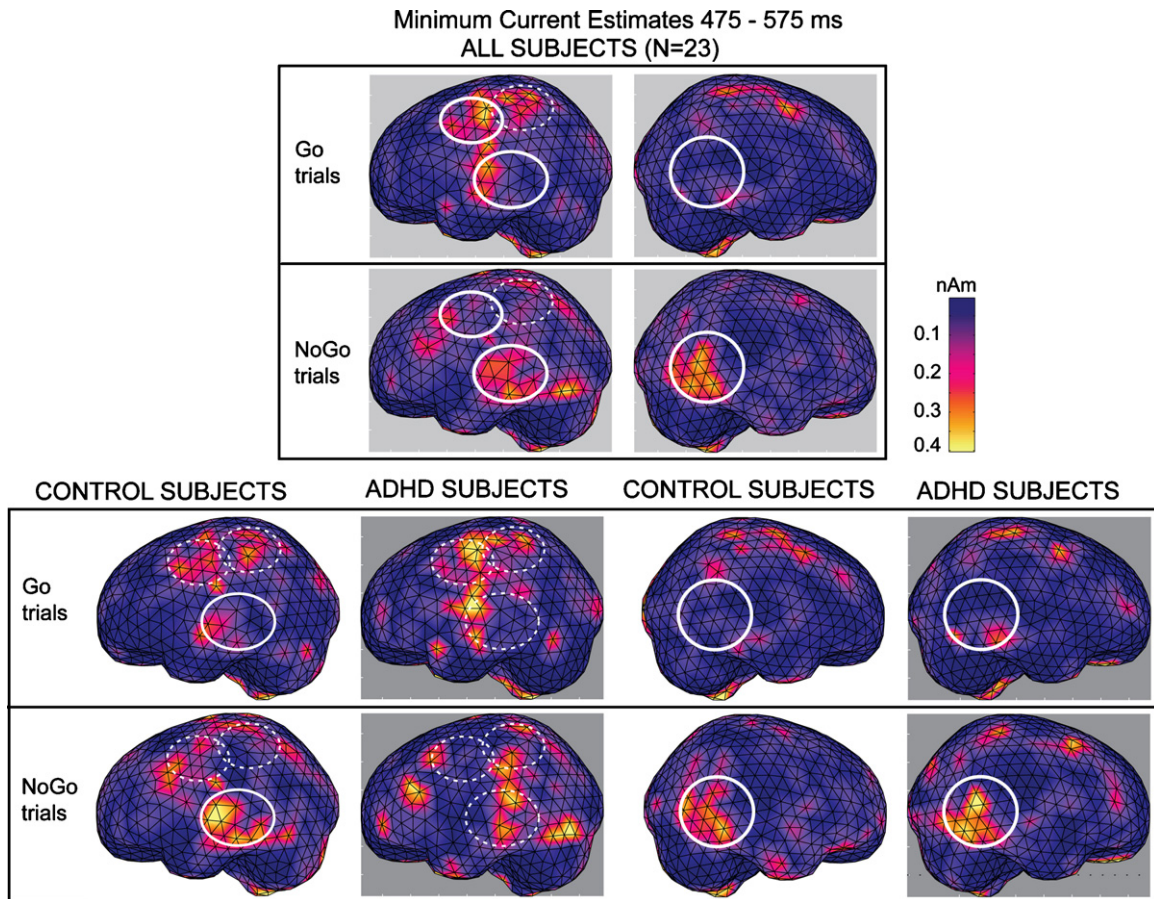


Fig. 5. Minimum current estimates for Go correct and NoGo correct trials during the LPC peak across all subjects ($n=23$) and separately for control ($n=13$) and ADHD subjects ($n=10$). Activation is integrated over 475 and 575 ms. The brain volumes in the right posterior temporal cortices showed stronger activation to NoGo correct than Go correct trials in both subject groups (solid white circles) but in the left hemisphere similar modulation was detected only in control subjects. The dashed circles indicate statistically non-significant differences between the two trials.

pathway is crucial for visual recognition of objects. The dorsal system oriented towards parietal cortex is responsible for grasping spatial information. The neuroanatomical model of attention by Corbetta and Shulman (Corbetta et al., 2008; Corbetta & Shulman, 2002) builds upon this framework by postulating a

neuroanatomical model of attention with ventral stimulus-driven attention and dorsal goal-directed attention. The ventral attention system is recruited when reorienting is necessary due to, for instance an unexpected but important event (Corbetta et al., 2008).

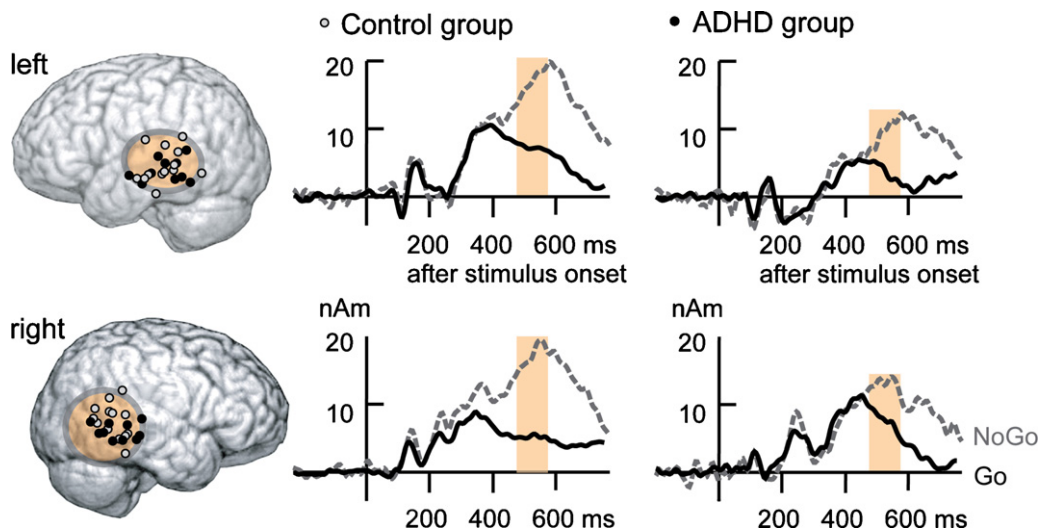


Fig. 6. Left: The distribution of equivalent current dipoles across all participants (control individuals grey circles, ADHD individuals black circles) in the left and right temporal cortex shown on an atlas brain. Right: Mean time course of activation averaged across subjects for correct Go and correct NoGo trials in the left and right temporal areas. The time window of the LPC peak (475–575 ms) is indicated with shading.

In the current experiment, we tracked electromagnetic signals while adults with ADHD and control participants were responding to frequent visual stimuli (Go) and withholding their response to infrequent stimuli (NoGo). The infrequent visual stimuli elicited two distinct activation patterns along the ventral visual and attentional streams; N2 followed by a LPC response in the ERP data, and right posterior occipito-temporal activation followed by bilateral posterior temporal activation in the MEG data. The latency of N2 and late positivities (P3) has been shown to covary with reaction time (Ritter, Simson, & Vaughan, 1983; Ritter, Simson, Vaughan, & Macht, 1982), and in the current experiment, using very complex visual stimuli, both responses were overall about 100 ms delayed compared to a previous ERP study using relative simple visual stimuli with comparable Go/NoGo probability (Nieuwenhuis, Yeung, Van den Wildenberg, & Ridderinkhof, 2003).

The N2 response and associated activation detected in the posterior occipito-temporal cortex 355–405 ms after stimulus onset is likely to reflect perceptual processes involved in the identification and discrimination of the complex visual stimuli (Helenius et al., 2010). The size of the N2 effect, calculated as the difference between frequent Go trials and infrequent NoGo trials, was comparable between the two subject groups based on both ERPs and the MEG data. Our ERP finding is in line with a previous ERP study using a visual Go/NoGo task in ADHD adults (Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006). Thus, the perceptual processes detected during the N2 response along the visual ventral stream seemed to be unaffected in adults with ADHD.

In the later phase of stimulus processing, during the LPC activation 475–575 ms after stimulus onset, difference between frequent Go and infrequent NoGo trials was abnormally small in ADHD group based on both ERPs and the MEG data. While many ERP studies, using a variety of visual tasks, have reported abnormal late positive components/P3 responses in ADHD (Brandeis et al., 1998; Holcomb et al., 1985; Jonkman et al., 1997; Klorman, 1991), such MEG studies have been nonexistent. In the current study, using an approach that maximizes the LPC (Helenius et al., 2010), we were able to detect abnormally small LPC fairly consistently in ADHD individuals and link the group difference seen in the ERP data to attenuated responding of the bilateral temporal cortices in ADHD adults. The responding of the left hemisphere, in particular, was abnormal based on both distributed and focal source analysis of the MEG data. We take this to indicate that ADHD is unlikely to be solely associated with impaired right hemisphere functioning, although lesions of the right hemisphere are particularly likely to lead to attentional deficits such as unilateral neglect (Vallar & Perani, 1987).

The ventral attention system is thought to interrupt and reset ongoing activity of the dorsal attentional pathway after an unexpected but important event (Corbetta et al., 2008). The P3 response peaks relatively late (well after 500 ms in the current study) suggesting that the underlying neural populations are not directly involved in task performance (whether to give or to withhold a response) within the particular event (Helenius et al., 2010; McCarthy & Donchin, 1981). Instead, by signaling that the current model of behavior must be updated, this activation facilitates more adaptive processing of the ensuing events, that is, switches from the dorsal expectation-guided mode to the ventral stimulus-guided mode (Corbetta et al., 2008). In the current study these signals of the ventral attentional pathway, bilateral temporal activation during the LPC response, were abnormally weak in ADHD participants, suggesting that switching to stimulus-based reacting could also be deficient. Behavioral data of stimulus-based reorienting in ADHD has been provided by Konrad, Neufang, Hanisch, Fink, and Herpetz-Dahlmann (2006). In their study, the participants had to determine whether the middle arrow of 5 vertically arranged arrows was pointing to left or right. The middle arrow could be preceded by spatially valid or invalid cues. In the task, the children with ADHD

tended to respond relatively slowly after an invalid cue which was suggestive of impaired reorienting. Future studies should evaluate whether the events following infrequent stimuli, and hence abnormal activation of the ventral attentional pathway, are associated with abnormal responses in behavioral or neurophysiological data.

In the current study, the participants were relatively highly functioning ADHD adults. Resembling previous studies (Biederman et al., 2006; Prox, Dietrich, Zhang, Emrich, & Ohlmeier, 2007; Wiersema, van der Meere, & Roeyers, 2009), their task performance in a visual Go/NoGo task or commonly used behavioral test of executive functioning did not markedly deviate from that of control subjects in this small sample. However, in children, particularly if they have ADHD, response errors are much more frequent (Wiersema, van der Meere, & Roeyers, 2005). Mulder et al. (2010) have recently demonstrated that children with ADHD display an overall preference for speed over accuracy in reaction time tasks. Such speed-accuracy tradeoff functions has not been tested in adults with ADHD, but based on their relatively accurate task behavior, it might be that they invest more effort on accurate task-related processing (for related discussions, see also Barry, Clarke, McCarthy, Selikowitz, Brown, & Heaven, 2009; Prox et al., 2007).

In the future studies MEG could be used to deepen our knowledge on visual attentional and executive processes and their dynamic interplay in children, with attentional and executive problems. Furthermore, the development of the ventral attentional network and the relative engagement of the left and right hemisphere could be investigated in more detail. These neurophysiological markers could complement behavioral measures and enhance our understanding of ADHD over the lifespan.

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