Dysfunctional Attentional Networks in Children with Attention Deficit/Hyperactivity Disorder: Evidence from an Event-Related Functional Magnetic Resonance Imaging Study

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Background: *Although there is evidence for attentional dysfunction in children with attention deficit/hyperactivity disorder (ADHD), the neural basis of these deficits remains poorly understood.*

Methods: *We used event-related functional magnetic resonance imaging (fMRI) to investigate brain activations related to three particular aspects of attention: alerting, reorienting, and executive control. Sixteen medication-naive boys with ADHD and 16 healthy boys, aged 8 to 12 years, were studied.*

Results: *Behaviorally, children with ADHD showed a significant impairment only in their executive control system compared to healthy subjects. Neurally, children with ADHD (relative to controls) recruited deviant brain regions for all three attentional networks: less right-sided activation in the anterior cingulate gyrus during alerting, more fronto-striatal-insular activation during reorienting, and less fronto-striatal activation for executive control. ADHD symptom severity was associated with dysregulation of the blood oxygen level dependent (BOLD) signal within the putamen during reorienting and executive control.*

Conclusions: *Our results demonstrated altered brain mechanism in ADHD associated with all three attentional networks investigated. For alerting and executive attention, our data indicate a deviant mechanism of cortical control, while ADHD children may have adopted altered strategies for reorienting of attention. Our results also stress the etiological role of functional abnormalities in the putamen in medication-naive ADHD.*

Key Words: ADHD, event-related fMRI, alerting, reorienting, executive attention, putamen

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood. The core behavioral symptoms of ADHD are inappropriate patterns of inattentiveness, impulsivity, and hyperactivity. Although the diagnosis of ADHD implies deficient attentional functions, the concept of attention within the diagnostic criteria of the DSM IV (American Psychiatric Association 1994) is not formally defined in cognitive terms. By contrast, behavioral ratings from parents and teachers differentiate between the two symptom domains of inattentiveness and hyperactivity/impulsivity (McBurnett et al 1999). It has been suggested that behavior which appears "inattentive" may not necessarily be traceable to dysfunction in attentional processes or their underlying neural networks (Konrad et al 2005). However, recent neuroscientific models which emphasize different attentional processes have stimulated the search for cognitive and neural markers or endophenotypes that help to identify etiologically important dysfunction of ADHD (Castallanos and Tannock 2002).

One influential model of attentional functions has been developed by Posner and Petersen (1990). This model assumes independent neural networks and neuromodulators to subserve different attentional functions, such as alerting, orienting/reorienting, and executive control. Alerting is defined as achieving and maintaining an alert state, orienting and reorienting is required when stimuli occur outside the current focus of attention, and executive control is defined as resolving conflicts between responses. While the alerting system has been associated with right hemisphere frontal and parietal regions modulated by norepinephrine, attention orienting and reorienting is thought to be achieved by a network lateralized to the right temporo-parietal cortex and to the right inferior frontal gyrus and to be modulated by the cholinergic system. The executive control network is assumed to include the anterior cingulate and lateral prefrontal cortex and is modulated by dopamine (Marrocco and Davidson 1998).

A number of behavioral studies have investigated attentional dysfunction in ADHD. It has been shown for the alertness system that, in comparison to healthy subjects, ADHD children have slower reaction times (RTs) and tendentially larger within-subject variability of responses, although a recent meta analysis suggests that these effects are small (Huang-Pollock and Nigg 2003). Evidence has been found for the orienting/reorienting system of a specific deficit in disengaging attention, as reflected by increased RTs to invalidly cued targets (Nigg et al 1997). The strongest deficits, however, have been reported in the executive control system, particularly, when interference control or motor inhibition is involved (Sergeant 2003). These behavioral findings on executive control dysfunction are in line with recent functional neuroimaging data that indicate fronto-striatal dysfunction during inhibitory control tasks in ADHD (Vaidya et al 1998; Durston et al 2003; Schulz et al 2004; Rubia et al 1999). However, in all these studies ADHD subjects who had been previously treated with stimulants were included.

When focusing on aspects of inhibition only, pathological attentional mechanisms outside the fronto-striatal circuitry may go unnoticed in children with ADHD. This issue is of particular interest since recent morphometric studies have reported widespread reductions in volume throughout the cerebrum and

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cerebellum, with comparable anatomical abnormalities in all four cerebral lobes (Castellanos et al 2002; Sowell et al 2003). In line with these more widespread anatomical abnormalities, two recent functional imaging studies also reported a reduced activation in the the middle temporal gyrus (Shafritz et al 2004) and in the superior parietal lobule (Booth et al 2005) in ADHD during selective attention tasks.

Thus, there is presently an insufficient understanding of the neurobiological basis of attentional dysfunction in ADHD. In the present study, we therefore used event-related functional imaging and a modified version of the Attention Network Test (ANT; Fan et al 2002) to investigate three different attentional networks associated with alertness, reorienting, and executive control of attention in children with ADHD and in healthy subjects. Since previous functional imaging studies included ADHD patients who had been treated with stimulants, it is not possible to conclude whether the reported neural differences were also related to drug effects or only to ADHD itself. Therefore, our current study included only drug-naive right-handed boys aged 8 to 12 years. Based on effect sizes derived from recent meta-analyses, we expected significant group differences on the behavioral level only in the executive attentional system with an increased interference effect in children with ADHD compared to controls. However, since brain abnormalities in children with ADHD occur not only within but also outside the frontostriatal circuitry, we hypothesized that neurally the largest deficits of attentional dysfunction would be observed in the executive system but that the alerting and reorienting system would also be affected. In addition, since recent imaging studies also suggest an association between severity of clinical symptom expression, neuropsychological attention impairments and changes of brain activation patterns within the dorsolateral prefrontal cortex and the basal ganglia (Teicher et al 2000; Spalletta et al 2001), we also expected larger functional brain abnormalities in the frontostriatal circuitry associated with more severe ADHD symptoms.

Methods and Materials

A total of 16 boys with ADHD and 16 healthy male controls all aged between 8 and 12 years participated in this study. All children in the ADHD group met the DSM-IV criteria for ADHD and were recruited from our Outpatient Unit at the Department of Child and Adolescent Psychiatry. Unrelated healthy boys were recruited from the community. Prior to scanning, all children underwent an extensive psychiatric examination conducted by an experienced child psychiatrist. Their psychiatric classification according to DSM-IV was then determined on the basis of a semi-structured diagnostic interview (Kaufmann et al 1997; German translation: Delmo et al 2001) performed by a second independent rater. In addition, information on the developmental history, on playroom observations, neurological and pediatric examinations, cognitive testing and test of handedness, and on evaluations with the German Parental and Teacher Report on ADHD symptoms (FBB-HKS; Döpfner and Lehmkuhl 1998) was obtained for all children. The number of items from this questionnaire equates to the number of DSM-IV items and also provides a severity score for each symptom.

All children were screened for any contraindications for MRI. Only children without a prior history of stimulant treatment were included in the study protocol. Further exclusion criteria were general IQ below 80 (Wechsler Intelligence Scale for Children-III [WISC III]), any potentially confounding diagnoses such as psychosis, mania, major depression, substance abuse, pervasive developmental disorders or receptive language disorders, and any kind of additional medication (including selective serotonin reuptake inhibitors, neuroleptics or anticonvulsants). All children were trained in a mock fMRI to familiarize them with the scanner environment prior to scanning. The study was approved by the Medical Ethics Committee of the University Hospital of Aachen, and informed parental consent was obtained for all participants. Table 1 summarizes the major clinical and demographic data. The groups did not differ with respect to age, full scale IQ, handedness or oppositional or anxious symptoms.

Table 1. Characteristics of the Patient and Control Groups

	Healthy Children M (SD)	ADHD Children M (SD)	*p*
Age	10.1 (1.3)	10.2 (1.9)	.9[a]
Full-Scale IQ (WISC-III)	105 (10)	103 (12)	.8[a]
FBB-HKS (total score of symptom severity)	6.3 (2.1)	32.1 (8.7)	<.001
	n	*n*	*p*
Handedness	16 R	16 R	>.99[b]
DSM IV Diagnoses of ADHD	0	16	<.001[b]
ADHD Combined	0	9	
ADHD Inattentive Subtype	0	6	
ADHD Hyperactive/Impulsive Subtype	0	1	
ODD	2	5	.45[b]
Anxiety Disorders	3	3	>.99[b]

WISC-III, Wechsler Intelligence Scale for Children-III edition; FBB-HKS, German Parental and Teacher Report on ADHD symptoms; R, right-handed; ODD, Oppositional Defiant Disorder; ADHD, attention deficit hyperactivity disorder.

[a] *P* values are for 2-tailed *t* tests.

[b] *P* values are for χ^2.

Experimental Task

We used a modified version of the Attention Network Test originally developed by Fan et al (2002). The ANT requires the participant to determine whether the middle arrow of 5 vertically arranged arrows is pointing left or right. The efficiency of the different attentional networks is assessed by measuring how response times are influenced by alerting cues, spatially valid and invalid cues, and flankers. In order to make the task more comparable with other cueing paradigms and to include a condition that requires attention reorienting, we modified the task by having the targets appear peripherally (instead of centrally) and by including invalid cues in 20% of all spatially cued trials. Figure 1 illustrates the time course of the different trial types.

Stimuli were presented on a screen facing the participant in the MRI scanner. Responses in the scanner were collected via two push-buttons on a keyboard resting in the subject's lap. The viewing distance was approximately 29 cm. Each stimulus consisted of a vertical row of five black arrows pointing to the left or to the right shown against a white background. The target was the middle arrow which was flanked by two arrows above and two arrows below pointing in the same (congruent condition) or in the opposite (incongruent condition) direction. Participants were required to indicate the direction of the target arrow by pressing the left key for the target pointing left and the right key for the target pointing right. Each trial consisted of five events. The first was a 400 msec fixation period. Next, a 150 msec warning cue was presented. This was either a double cue, a spatial cue (either valid or invalid), or no cue. This warning cue

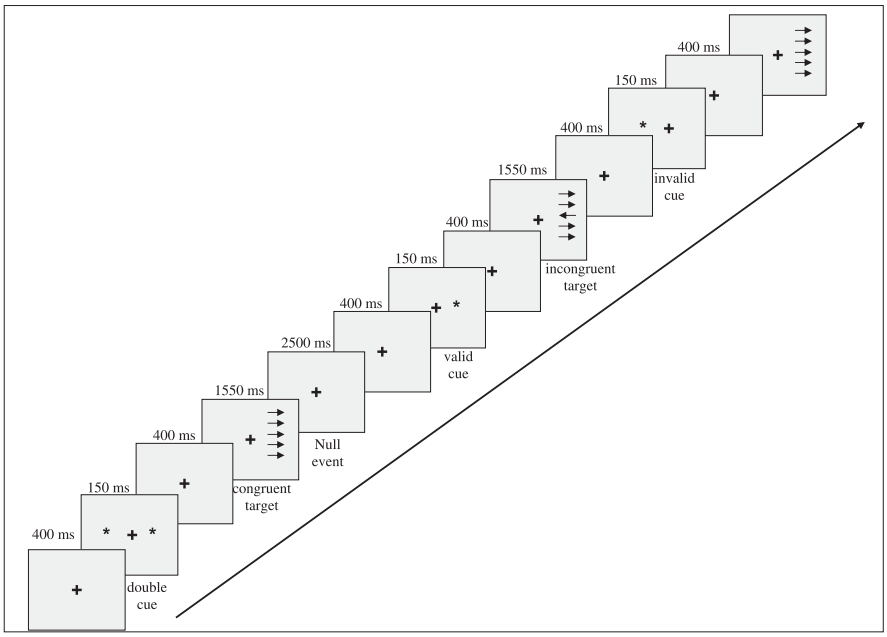

Figure 1. Experimental paradigm: modified version of the Attention Network Test (Fan et al 2002). Figure 1 illustrates the time course of the four different cue and the two target conditions.

was followed by another 400 msec fixation period. Finally, the target and flankers appeared simultaneously and were presented for 1550 msec. The stimuli (one central arrow plus the four flankers) produced a total visual angle of 4.34 degrees horizontally and 14.5 degrees vertically. Trials were presented every 2500 msec. Blank trials (with only the fixation cross presented on the screen) were included in 24% of all trials (Josephs and Henson 1999), leading effectively to variable stimulus-onset-asynchronies (SOAs). The order of trial types was randomized. Subjects were instructed to maintain fixation throughout the experiment and to covertly detect the peripheral target as quickly as possible. Prior to scanning, subjects were informed about the different trial types. They were told that spatial cues were highly informative and were encouraged to use these cues to improve performance. A 5-minute training session was performed before scanning.

Data Acquisition

Two hundred eighteen functional whole-brain images were acquired for each subject using a Siemens Sonata scanner (1.5 Tesla) and echo planar imaging (EPI) with the following parameters: TR (repetition time) = 3020 msec, TE (echo time) = 66 msec, thirty 4.0 mm-thick axial slices with an .4 mm gap, matrix size = 64 × 64, voxel size: = 3.125 × 3.125 × 4.0 mm^3, field of view (FOV) = 200 mm, flip angle = 90°. The first 5 volumes were discarded to allow for T1 equilibration effects. Images were spatially realigned to the first volume to correct for interscan movement, synchronized to the middle slice to correct for differences in slice acquisition time, and normalized to the standard EPI MNI template volume (resampled to 3 × 3 × 3 mm^3 voxel). Although the techniques presently available for normalizing children's brains are not ideal, it has recently been suggested that normalization to an adult template does not result in artifacts for children aged 6 and above (Muzik et al 2000). The data were then smoothed using a Gaussian kernel of 10 mm full-width-half-maximum to accommodate intersubject anatomical variability.

Statistical Analyses

Data were analyzed with Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London; Friston et al 1995) which used a random effects model. Nine event-types were defined at the first level. These consisted of eight effects of interest (double cue congruent/incongruent targets, no cue congruent/incongruent targets, valid cue congruent /incongruent targets, invalid cue congruent/incongruent targets) and one effect of no interest (missed responses/errors). Errors were excluded since it has previously been demonstrated that even a small number of errors might alter activation maps (Murphy and Garavan 2004) and that random effect analyses are relatively robust to differences in unequal trial numbers (Friston et al 2005). The event types were time-locked to the onset of the cue by means of a canonical synthetic hemodynamic response function (HRF) and its first-order temporal derivative. The 6 head movement parameters were included as confounds. Estimated motion parameters were examined on a subject-by-subject basis to ensure that the amount of absolute motion did not exceed 3 mm. All subjects exhibited less than 1 mm of absolute motion over the course of the experiment. The two groups did not differ in terms of estimated motion parameters (average movement in ADHD children = .27 mm, in controls = .21 mm; t [31] = .70, p = .49).

Data were globally scaled to 100 across scans and high-pass-filtered at 1/60 Hz. The parameter estimates for the canonical HRF and linear contrasts of these estimates made up the data for the second-stage analyses. Three planned t-tests were conducted at the second stage to identify neural correlates of 1) alerting [double - no cue trials], 2) reorienting [invalid - valid cue trials], and 3) conflict/executive control [incongruent - congruent trials]. Two-sample t-tests were performed on contrast images to investigate group differences in activation between ADHD children and controls. Activations are reported at a level of significance $p < .001$, uncorrected and a cluster threshold of greater than 10 voxels.

Additional group comparisons were computed separately for performance matched subgroups consisting of 8 subjects chosen

Table 2. Task Performance Separately for Children with ADHD and for Healthy Children

	Healthy Children (n = 16) M (SE)	ADHD Children (n = 16) M (SE)	t	p
Alerting [msec]	30 (17)	55 (21)	−.9	.38
Reorienting [msec]	93 (18)	138 (20)	−2.1	.08
Conflict [msec]	80 (9)	122 (13)	−2.9	.01
MRT [msec]	822 (26)	868 (48)	.84	.40
Total error [%]	4.45 (0.6)	8.44 (1.4)	−2.7	.02

MRT, Mean Reaction Time; ADHD, attention deficit hyperactivity disorder.

from each group to assess whether observed differences in brain activation patterns simply reflect performance differences across groups (Price and Friston 1999). Finally, correlation analyses were performed to examine the relationship between signal intensity and ADHD symptom severity in the ADHD group. Three correlation analyses (severity of hyperactive/impulsive symptoms, severity of inattentive symptoms, ADHD total severity score) were calculated for each of the attentional systems. Bonferroni corrections for inflated Type I error were applied in order to control for the number of analyses conducted**.**

Results

Behavioral Results

An exploratory analysis of the behavioral data across both groups showed no difference between left-pointing and right-pointing targets in any condition, so they were combined ($F(4,28) = .5$, $p = .5$). In addition, any incompatibility in terms of a conflict between arrow direction and side of arrow presentation was analyzed separately for congruent and incongruent targets, but no significant differences appeared (congruent: $F(2,30) = .3$, $p = .7$, incongruent: $F(2,30) = .9$, $p = .5$).

RTs for correct trials were submitted to a 2 × 4 × 2 analysis of variance (ANOVA) with group (ADHD versus healthy subjects) as a between subject factor and cue (double, no, valid, invalid) and target (congruent versus incongruent) as within subject factors. RTs varied as a function of both cue ($F(3,28) = 38$, $p < .001$) and target condition ($F(1,30) = 87$, $p < .001$), while no cue by target interaction ($F(3,28) = 1.2$, ns) and no cue by target by group ($F(3,28) = .22$, ns) interaction appeared. In addition, significant group by cue ($F(3,28) = 3.7$, $p = .03$) and significant group by target interaction ($F(1,30) = 3.9$, $p = .01$) were found.

The alerting effect was calculated by subtracting the mean RT of the double cue conditions from the mean RT of the no cue conditions. Children with ADHD showed a numerically but not significantly larger alerting effect (see Table 2), which resulted from numerically longer RTs within the non cued trials (ADHD: $RT_{no\ cue} = 910 \pm 18$ msec; Controls: $RT_{no\ cue} = 875 \pm 11$ msec, $p = .16$).

The validity effect was calculated as a measure of reorienting (invalidly cued trials minus validly cued trials). Reorienting was tendentially impaired in children with ADHD.

The conflict (executive control) effect was assessed by subtracting the mean RT of all congruent flanking trials conditions, summed across cue types, from the mean RT of incongruent flanking trials conditions. Children with ADHD showed a significantly larger interference effect compared to healthy controls.

Across all trials, children with ADHD showed numerically longer RTs and made significantly more errors. Error rates did not differ significantly between cueing conditions, but occurred more often in incongruent flanker trials across both groups.

Correlation Analyses of Behavioral Data

Correlation analyses using age and IQ across both groups revealed that the RT performance of the conflict (executive control) network was associated with IQ ($r = -.38$, $p = .04$). Thus, as already described in previous studies (Scheres et al 2004), interference susceptibility was larger the lower the child's general IQ. In contrast, overall RTs ($r = -.58$, $p < .01$) and the validity effect ($r = -.44$, $p = .01$) were found to be age dependent. Thus, the younger the children, the slower were their general RTs (Rueda et al 2004) and the larger was their validity effect (Wainwright and Bryson 2002). ADHD symptom severity did not correlate with any dependent variables of the ANT in the ADHD group.

Functional MRI Results

During alerting, healthy children (relative to ADHD children) activated the right anterior cingulate gyrus (ACC) to a significantly greater extent (x = 3, y = 15, z = 45, $Z = 3.79$, 13 voxel). Figure 2 shows the percentage signal change separately for both groups for the maximally activated voxel as a function of the cueing condition (collapsed over congruent and incongruent target presentation) and subjected to statistical analysis.

The plot reveals increased neural activity in the ACC for double cued trials relative to the no cue trials for the healthy children only. By contrast, a decrease of neural activity was observed in the ADHD group during double cued trials (relative to no cue trials), resulting in significant group × condition interaction ($F(1, 30) = 17.5$, $p < .001$). Interestingly, however, ADHD children showed significantly increased neural activity in the brainstem during alerting. The maximum brainstem activation was centered at × = −6, y = −33, z = −12 ($Z = 4.39$, 72 voxel) at the ponto-mesencephalic junction (and may thus correspond to or include the locus coeruleus). The differential effect in the brainstem resulted from a decrease in neural activity in double cue trials and increased neural activity in no cue trials in healthy children, while children with ADHD showed increased neural activity in double cued trials but no activation in no cue trials ($F(1, 30) = 19.3$, $p < .001$).

During reorienting, children with ADHD (relative to the controls) showed increased neural activation in the right putamen (x = 30, y = −6, z = 15, $Z = 4.22$, 91 voxel), in the right inferior frontal gyrus (x = 51, y = 6, z = 12, $Z = 4.35$, 15 voxels), and in the left insula (x = −42, y = 3, z = 12, $Z = 3.94$, 65 voxel). Figure 3 also depicts the percentage signal change at 30, −6, 15, separately for both groups.

While healthy and ADHD children showed comparable levels of neural activity in the putamen during the valid trials, only ADHD children showed an increase in neural activity during invalidly cued trials ($F(1, 30) = 17.8$, $p < .001$). The same activation pattern was observed for the insula and frontal gyrus (data not shown). No significant differential activations were found for the healthy children relative to the ADHD children.

During the conflict condition, healthy children differentially activated the following areas: the left frontal precentral gyrus (x = −51, y = −15, z = 30, $Z = 4.07$, 25 voxel) (Figure 4A) and the right putamen (x = 33, y = 3, z = 0, $Z = 3.68$, 20 voxel) (Figure 4B). In order to further explore these effects, percent blood oxygen level dependent (BOLD) signal changes were plotted and statistically analyzed as a function of target type for the maximally activated voxel.

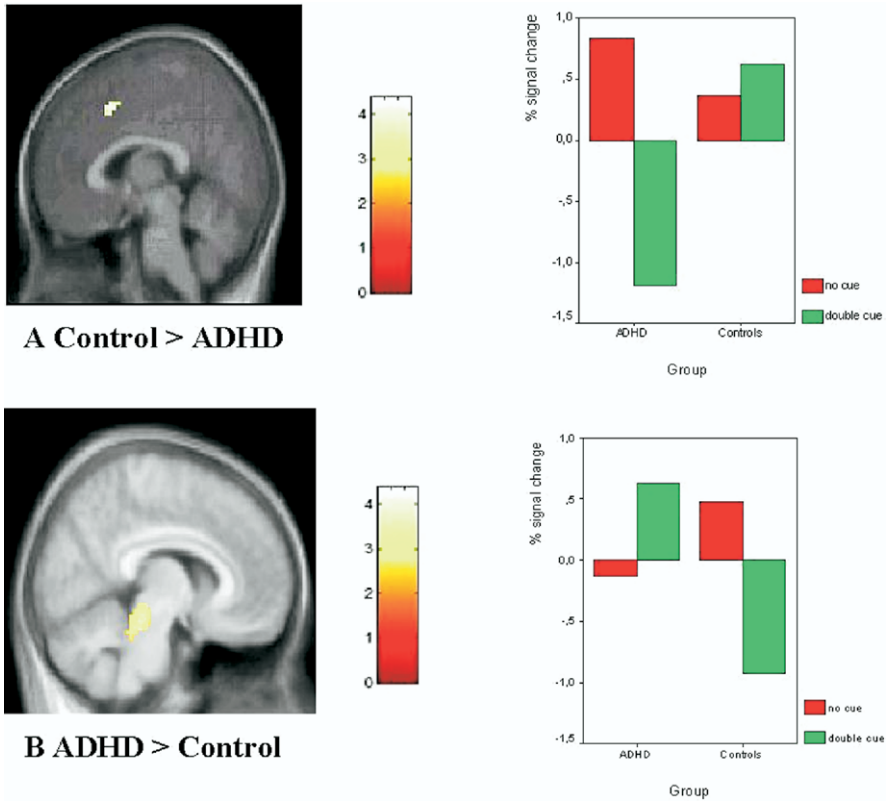

Figure 2. Differential activation of attention deficit hyperactivity disorder (ADHD) and healthy participants as identified in a two-sample-*t*-test for the alerting condition (thresholded at $p < .001$, uncorrected, extend threshold 10 voxel, shown on an averaged group T1 image). **(A)** Increased activation in the right anterior cingulate gyrus in healthy children compared to ADHD children. **(B)** Increased activation of the brainstem in children with ADHD compared to healthy children. Plots of the percentage blood oxygen level dependent (BOLD) signal change are shown separately for both groups as a function of trial type (pooled over congruent and incongruent targets) for the respective activation maximum.

While healthy children showed an increased BOLD signal in both areas during incongruent trials, children with ADHD showed a decrease in neural activity during incongruent trials, resulting in significant group × condition interactions (for putamen: $F(1, 30) = 24.1$, $p < .001$; for precentral gyrus: $F(1,30) = 16.0$, $p < .001$).

In the reverse comparison (ADHD children > controls), ADHD children activated the left medial superior parietal cortex (x = −3, y = −54, z = 66, $Z = 3.92$, 44 voxel) significantly more (Figure 4C). Analysis of the corresponding BOLD signal change revealed that this effect resulted from a relatively smaller decrease in activation in incongruent trials compared to congruent trials in children with ADHD.

Effects of Performance and ADHD Symptom Severity

Additional group comparisons were computed separately for performance matched subgroups. Because of the substantial overlap in performance between both groups, subgroups of 8 matched pairs were chosen for assessment of the reorienting and conflict systems, since tendential or significant group differences were found at the behavioral level in both networks. Note that these subgroups were not identical for the two conditions. However, we did not find any differences for both attentional networks between the results of these *t*-tests and the results of the *t*-tests reported above (the local maxima of significant BOLD signal change differed by less than 2 mm in each dimension from the local maxima obtained in group contrasts including the whole sample).

Two significant correlations emerged between ADHD symptom severity and MR signal change in the putamen in the ADHD group. First, the putamen MR signal change for invalid trials during reorienting correlated significantly negatively with ADHD symptom severity (for hyperactive-impulsive symptoms: $r = -.80$, $p < .001$; for inattentive symptoms: $r = -.30$, ns; for a total

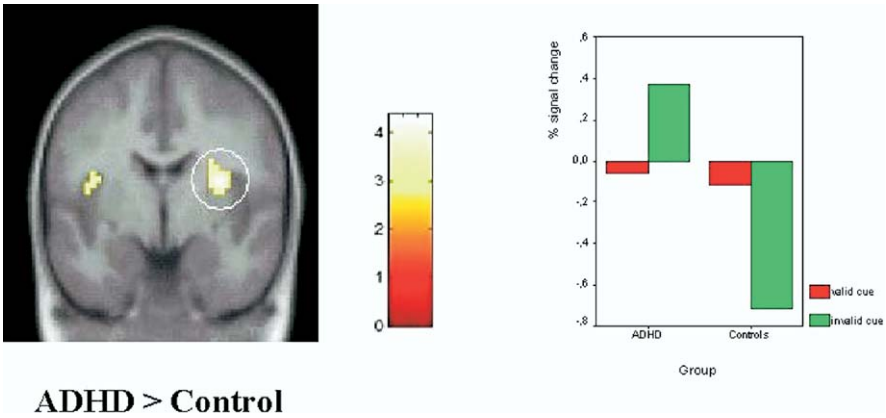

Figure 3. Differential activation of attention deficit hyperactivity disorder (ADHD) and healthy participants as identified in a two-sample-*t*-test for the reorienting condition (thresholded at $p < .001$, uncorrected, extend threshold 10 voxel, shown on an averaged group T1 image) showing increased activation in the putamen, inferior frontal gyrus and insula in children with ADHD compared to healthy children. Plots of the percentage blood oxygen level dependent (BOLD) signal change are shown separately for both groups as a function of trial type (pooled over congruent and incongruent targets) for the activation maximum in the putamen.

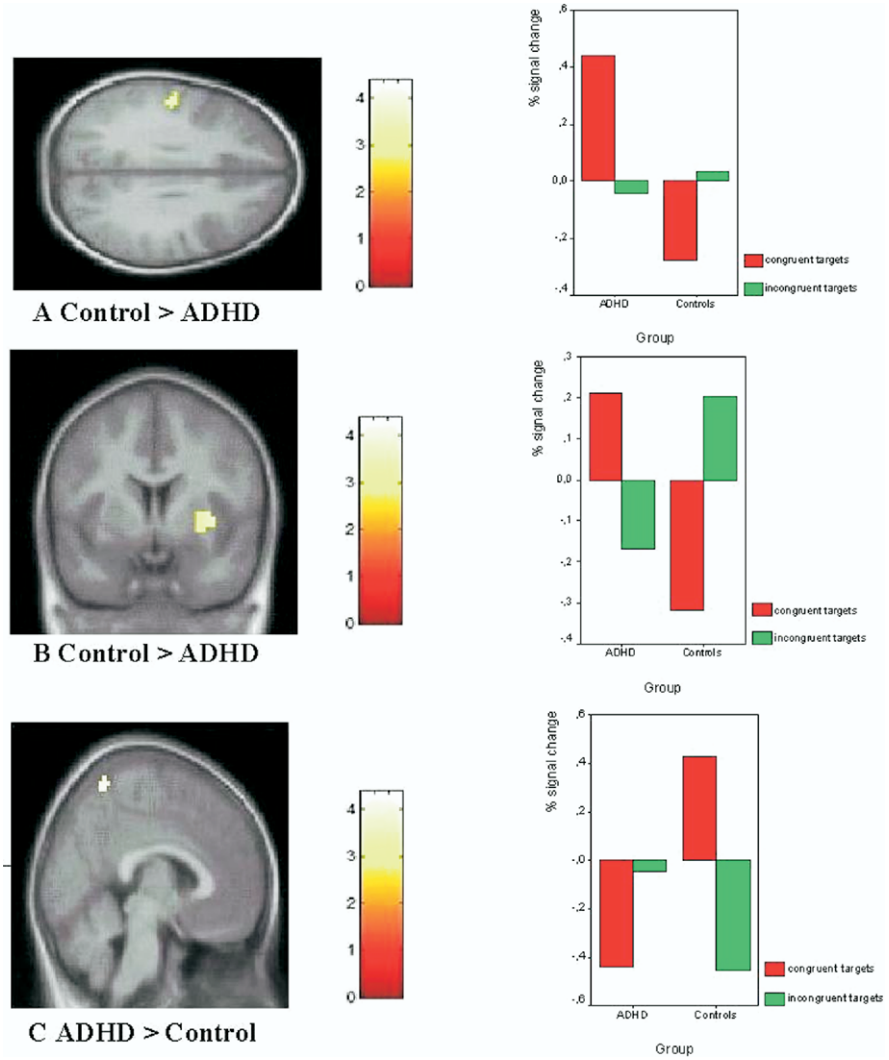

Figure 4. Differential activation of attention deficit hyperactivity disorder (ADHD) and healthy subjects as identified in a two-sample-*t*-test for the conflict condition (thresholded at $p < .001$, uncorrected, extend threshold 10 voxel, shown on an averaged group T1 image). **(A)** Increased activation in the left medial frontal gyrus in healthy children compared to ADHD children. **(B)** Increased activation in the right putamen in healthy children compared to ADHD children, and **(C)** increased activation in the left superior parietal cortex (BA 7) in children with ADHD compared to healthy children. Plots of the percentage blood oxygen level dependent (BOLD) signal change are shown separately for both groups as a function of target type (pooled over cueing conditions) for the activation maximum.

score of ADHD symptoms: $r = -.77$, $p < .001$) (Figure 5A). Secondly, ADHD symptom severity was negatively correlated with the putamen BOLD signal for incongruent trials for hyperactive-impulsive symptoms: $r = -.60$, $p = .01$; for inattentive symptoms: $r = -.06$, ns; for a total score of ADHD symptoms: $r = -.50$, $p = .05$) in the conflict contrast (Figure 5B).

Discussion

As hypothesized, we found a significant deficit for the executive attentional system and an additional tendential deficit in the reorienting system on the behavioral level in ADHD children. On the neural level, we observed deviant brain activation patterns related to all three aspects of attention that were investigated. This apparent difference between behavioral and neural data fits with a recent discussion which states that differential patterns of neural activity might, in the absence of behavioral differences, be a result of using different task strategies, indicating that behavioral measures might be less sensitive than brain activation measures under some circumstances (Wilkinson and Halligan 2004; Fink et al 2002). Note, however, that all activations were reported on uncorrected *p*-values which might have contributed to more lenient fMRI results.

Within the alertness condition, healthy children activated the right ACC significantly more than ADHD children. It is often assumed that neural activity in subcortical regions is modulated in a "top-down" fashion (Sturm and Willmes 2001), facilitating processing of stimuli at attended locations and that parietal and frontal regions, in particular in the right hemisphere, are the source of such a top-down bias (Fink et al 1996; Kastner et al 1999). Children with ADHD, by contrast, showed increased brainstem activation, including the locus coeruleus. Analyses of the percentage signal changes revealed that healthy children showed an increased response during double cue trials in the ACC and a relative decrease of the BOLD signal in the brainstem, but that ADHD children showed the inverse activation pattern. These differential activations correspond well with recent models of an impaired top-down modulation process in ADHD and might also explain other phenomenons associated with the alerting system, such as the often reported higher within-subject variance (Teicher et al 2004) of reaction times or the poorer vigilance performance (Losier et al 1996) in ADHD. Since alerting is assumed to depend on the norepinephrinergic system, our results lend further support to the hypothesis that ADHD might be associated with noradrenergic dysregulation as suggested by recent pharmacological (Eiland and Guest 2004), neurobiochemical (Konrad et al 2003), and genetic data (Comings et al 2000).

Children with ADHD also showed decreased neural activity in

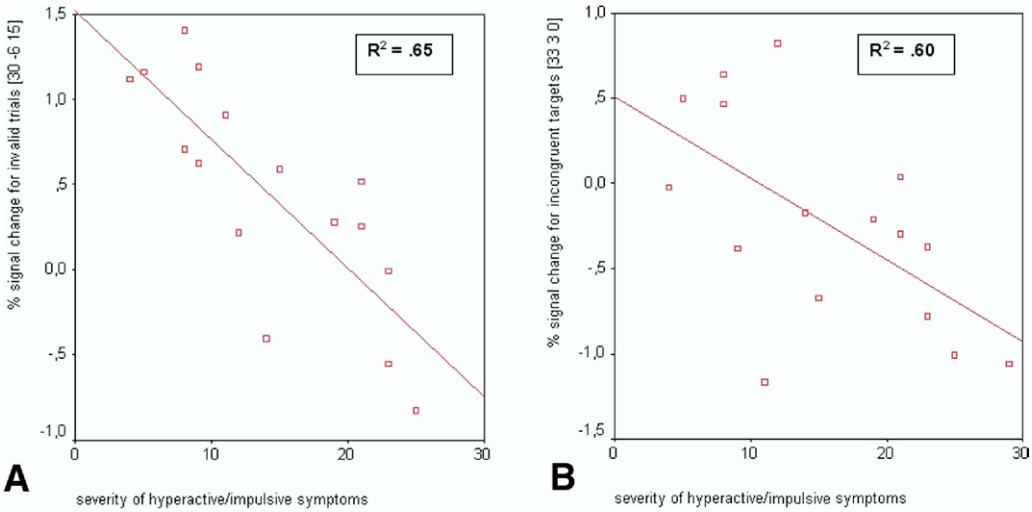

Figure 5. Scatterplots for the percentage blood oxygen level dependent (BOLD) signal change in the putamen and the severity of hyperactive/impulsive symptoms within the attention deficit hyperactivity disorder (ADHD) group: **(A)** for the maximally activated voxel found in the two-sample-*t*-test for the reorienting condition **(B)** for the maximally activated voxel found in the two-sample-*t*-test in the conflict condition.

fronto-striatal areas during the conflict condition. Instead, ADHD children activated the left superior parietal cortex to a significantly greater extent. This result replicates the findings of previous fMRI studies employing response inhibition tasks in patients with ADHD (Durston 2003 for a review). Typically, fronto-striatal underactivation in ADHD is accompanied by an increased activation in more posterior parietal regions (Rubia et al 1999; Durston et al 2003). The posterior parietal cortex has also been associated with switching of attention in recent functional imaging studies (Sylvester et al 2003; Wager et al 2004) and thus might indicate a possibly "beneficial" compensatory process for the fronto-striatal hypoactivity in children with ADHD. Additionally, ADHD children in our study activated the fronto-striatal circuitry more during the reorienting condition. Thus, our data complement and extend previous studies by suggesting that children with ADHD do not suffer from a general fronto-striatal underactivation, but rather a dysfunction of this circuitry compared to controls. As a result of this dysfunction, our data suggest that the brain in ADHD children may have adopted an alternative strategy during reorienting which includes greater use of the putamen, insular cortex and dorsolateral prefrontal cortex. By strategy, we mean the tactic used by the brain to solve a problem and not necessarily to an overt or volitional approach used by the children. Bush et al (1999) also observed that adult patients, compared to healthy adults, showed increased activation of a fronto-striatal-insular network during a Counting Stroop Task. Such a compensatory recruitment of different brain areas has been demonstrated for a number of psychiatric disorders, such as autism (Hubl et al 2003; Schulz et al 2000) or tic-disorder (Gates et al 2004) during cognitive tasks.

Since the fronto-striatal-insular network is also implicated in various anxiety disorders and is associated with higher distress in normal subjects (Rauch and Savage 1997), one might argue that the activation of those structures does not reflect a compensatory mechanism but may rather result from higher distress in the ADHD group (when performing a task which was more difficult for them). However, two facts make this interpretation less probable: 1) we did not find any activation of the thalamus as is typically observed in distress; and 2) ADHD children did not activate the fronto-striatal-insular network during the conflict condition in which their performance, in comparison to the healthy boys, was even more impaired.

The results of our correlation analyses indicate that the relative deactivation of the putamen was associated with symptom severity, particularly with the severity of hyperactive/impulsive symptoms. This effect might be interpreted as follows: hyperactivity, in particular, has been shown to be associated with steady-state overactivation in the putamen in unmedicated children with ADHD (Teicher et al 2000). Thus, our data suggest that the more severe the ADHD symptomatology the less the ADHD children seem to be able to show a relative increase in their BOLD-signal, independently of the specific demands of the attentional network. For example, in the reorienting condition, the recruitment of the putamen might be a compensatory mechanism used only by ADHD children with lower symptom severity. In the conflict condition, however, ADHD children with more severe hyperactive/impulsive symptoms were even more impaired in showing the typical putamen activation to incongruent trials as is observed in healthy children.

Considering recent neuroimaging studies on attentional networks in normal adult subjects, one could have expected neural group differences betwen normal controls and children with ADHD in other brain areas of interest, such as in the parietal cortex for alerting (Sturm and Willmes 2001; Coull et al 2001), in the temporo-parietal junction for reorienting of attention (Corbetta and Shulman 2002) and in the ACC for executive control of attention (Botvinick et al 2001; Fan et al 2003). However, we previously demonstrated that even normal controls in the age range between 8 and 12 years differ neurally from young adults with regard to all three attentional networks investigated and did not show the typical brain activation patterns in these regions of interest as normal adults (Konrad et al, in press).

Our results support recent models of ADHD suggesting that the putamen is one of the primary structures involved in ADHD (Teicher et al 2000). This finding also fits well with some recent studies on the development of ADHD symptoms in children with focal brain lesions which have also demonstrated that lesions within the putamen tended to increase the risk of ADHD symptomatology (Max et al 2002).

In addition, our results demonstrate that both dopaminergic

and noradrenergic systems seemed to be involved in the pathophysiology of ADHD (see Solanto 2002, for a review). It has been suggested that the functional connectivity of the cortico-striatal circuitry is regulated by dopamine levels. The putamen projects somatotopically to the globus pallidus and to the substantia nigra pars reticulata (SNR). The SNR, in turn, regulates the dopaminergic inputs from the substantia nigra pars compacta back to the putamen and other striatal regions (Smith et a 1998). According to Tucker and Williamson (1984), the dopaminergic frontal modulation is balanced by arousal, which is primarily nordadrenergic. The observed deviant brain activation patterns in the brainstem and the fronto-striatal circuitry in children with ADHD found in our study are consistent with the above model of dopaminergic brainstem-basal ganglia-cortex interactions.

However, some limitations of our study have to be considered. First, the sample sizes for the analyses of DSM IV subtypes of ADHD were too small, thus subtype differences might be an issue investigated in further studies. Since over 80% of all ADHD children suffer from at least one comorbid diagnosis (Pliszka et al 1999), it did not seem appropriate to exclude all ADHD children with comorbid Axis I disorder according to DSM-IV. Secondly, although a connectivity analysis between ROIs in the brainstem, basal ganglia and frontal cortex might have been interesting, such an analysis remains, at the moment, mathematically problematical within an event-related design (Gitelman et al 2003). Thirdly, since we did not use cardiac gating techniques, the brainstem results should be considered with caution, given susceptibility to pulsatile motion. A further limitation of our study was that eye movements were not systematically assessed within the scanner.

However, taken together, our data do suggest that children with ADHD rely on deviant networks of neural systems during a task that taxes their attentional processes. The observed differences in brain activation patterns were independent of task performance and could not be a result of stimulant history, indicating neurally based attentional dysfunction in treatment-naive ADHD children. In the future, the use of neuroimaging procedures in larger samples of ADHD children might be a useful tool for identifying endophenotypes of ADHD which are closer to the primary dysfunctional neural basis of the disorder.

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