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Regional Gray Matter Volume Differences Between Adolescents With ADHD and Typically Developing Controls: Further Evidence for Anterior Cingulate Involvement

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Abstract

Objective: The present study investigated structural brain differences between adolescents with ADHD and matched control participants. **Method:** Voxel-based morphometry (VBM) using the DARTEL approach was performed to assess regional gray matter (GM) volumes. Additionally, individual performance on tests of attention was recorded to correlate ADHD related cognitive impairments with regional gray matter abnormalities. **Results:** We found significantly smaller GM volume in subjects with ADHD compared to their matched controls within the anterior cingulate cortex (ACC), the occipital cortex, bilateral hippocampus/amygdala and in widespread cerebellar regions. Further, reductions of the ACC gray matter volume were found to correlate with scores of selective inattention. **Conclusion:** These findings underline that structural alterations in a widespread cortico-subcortical network seem to underlie the observable attention problems in patients with ADHD. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

adolescent ADHD, ACC, voxel-based morphometry

Introduction

ADHD is one of the most prevalent psychiatric disorders of childhood (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Its prevalence has been estimated to be around 4% (Costello et al., 2003); it is characterized by developmentally excessive levels of inattention, impulsivity, and hyperactivity (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). In the past, functional magnetic resonance imaging (fMRI) studies have been used to gain insights into the pathophysiology of ADHD and to identify brain regions that are associated with symptoms of attentional deficits, insufficient encoding of reward or motivational goals, and inadequate motor control (Bush, Valera, & Seidman, 2005; Christakou et al., 2013; Cubillo et al., 2014; Edel et al., 2013; Morein-Zamir et al., 2014; Mostofsky et al., 2006; Rubia et al., 2009; Rubia et al., 2006; Schulz et al., 2004; Smith, Taylor, Brammer, Toone, & Rubia, 2006). Among other regions, the anterior cingulate cortex (ACC) has been implicated repeatedly in the lack of attentional control ADHD participants display (Bush, 2011; Kessler, Angstadt, Welsh, & Sripada, 2014; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006).

Previous imaging studies on cognitive control provide evidence that the ACC plays a key role in several processes such as reward based (Bush et al., 2002; Gehring & Willoughby, 2002) and simple decision making (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006). Most notably, it was found to play an important role in error monitoring (Botvinick, Cohen, & Carter, 2004; Kiehl, Liddle, & Hopfinger, 2000; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001) with either up or down regulation of attention in subsequent performance (Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003; Weissman, Gopalakrishnan,

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Hazlett, & Woldorff, 2005) or strategic adjustments to prevent subsequent conflict processing (Kerns et al., 2004). Particularly, the ACC is strongly associated with selective attention processes, in particular with stimulus selection due to the appearance of additional distracting events (Weissman et al., 2003; Weissman et al., 2005).

ADHD has also been associated with structural differences in several brain regions, including occipital, cerebellar, temporal, frontal, and subcortical regions (Bush, 2011; Frodl & Skokauskas, 2012; Narr et al., 2009; Pironti et al., 2014; Seidman, Valera, & Makris, 2005; Seidman et al., 2006; Shaw, De Rossi et al., 2014; Shaw et al., 2007; Shaw et al., 2011; Shaw et al., 2009; Shaw et al., 2006; Shaw et al., 2012). Again, one of the most consistently reported brain regions to show ADHD-related reductions in gray matter (GM) volume from childhood to adulthood is the ACC (Frodl & Skokauskas, 2012).

In recent years, voxel-based morphometry (VBM; Ashburner & Friston, 2005) has been used to identify localized differences in GM volume between controls and patients with many different disorders. This method relies on algorithms that partition the human brain into GM and white matter and cerebrospinal fluid (CSF), as well as several other (nuisance) tissue classes. The classification can be based on voxel intensity as well as on voxel location (Ashburner & Friston, 2005). The available volumetric neuroimaging studies in patients with ADHD mostly provide region-of-interest analyses based on a priori hypotheses rather than unbiased whole-brain assessments using automated techniques such as VBM. Recently, a structural magnetic resonance imaging (MRI) study (Semrud-Clikeman, Fine, Bledsoe, & Zhu, 2014) examining the ACC observed a correlation between parent-reported inattention in participants with ADHD and regional reductions in volume of the ACC. So far, however, there is only limited evidence of a direct association between ADHD-related symptoms (such as inattention, impulsivity, or hyperactivity) and reduced ACC GM volume in participants with ADHD.

Based on these previous findings, we hypothesized that adolescents with ADHD would have smaller volumetric measures for the ACC. We further hypothesized that measures of inattention would be related to ACC volume.

Method

Participants and Measures

Thirty-six adolescents (all male, M_{age} = 13.7 years, SD = 1.5 years, range = 11-17 years) participated in the current study. Participants with an ADHD diagnosis (n = 18) were recruited from the Department of Child and Adolescent Psychiatry at the University of Magdeburg, Germany. Typically developing healthy control participants (n = 18) were recruited via advertisements in local newspapers. In-person interviews with all participants using the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL; Delmo, et al. 2000) were conducted by three board-certified child psychiatrists (K.K., B.B., and J.T.). The Child Behavior Checklist (CBCL) and the Youth Self-Report (Y-SR) were used as additional measures. Diagnostic criteria for ADHD were fulfilled in all patients (n = 11 combined type, n = 6 inattentive, n = 1 with comorbid oppositional defiant disorder [ODD]) according to *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994). Participants with ADHD who met criteria for any comorbid psychiatric disorder other than ODD were excluded from the current study. Healthy control participants were included if they did not report previous or current psychiatric disorder. A clinical meeting to review all participants in this study was performed, and all diagnoses were confirmed during this meeting via clinician consensus (B.B., K.K., H.H.F., J.T.). Most ADHD participants had a medication history with current (n = 10) or past (n = 4) intake of methylphenidate (MPH). All participants completed the Culture Fair Intelligence Test (CFT 20 R; Weiss, 1997) and the d2-test (Brickenkamp et al., 2002) as a standardized instrument to assess selective attention performance. The total score of the d2-test reflects the accuracy of attentional performance by relating the overall number of processed stimuli to the number of errors of commission and omission. participant's hand preference was assessed using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). Informed assent/consent was obtained from all participants and their parents in accordance with requirements set forth by the local ethics committee at the University of Magdeburg, Faculty of Medicine, which approved the study. Participants were reimbursed for their participation.

MRI Data Acquisition and Processing

All participants underwent MRI scanning on a whole body Siemens 3 T Trio-scanner (Siemens Magnetom Trio, Erlangen, Germany) using an eight-channel phased-array head coil. A T1-weighted three-dimensional data set was obtained using a magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence (TR/TE/TI = 2,500 ms/4.77 ms/1,100 ms, flip angle = 7°, field of view = 256 mm, 192 slices, voxel size 1 × 1 × 1 mm^3). MRI data were pre-processed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/), including the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm), running on Matlab (The Mathworks, Natick, MA).

Initially, all individual anatomical scans were segmented into tissue classes. Importantly, this was achieved without using information from anatomical priors which may bias the estimation (Wilke, Schmithorst, & Holland, 2003). Using a customized pediatric template (Wilke, Holland, Altaye, & Gaser, 2008) created by the TOM8 toolbox (http://dbm.neuro.uni-jena.de/software/tom/), individual GM scans

Table 1. Demographic and Clinical Characteristics of Our Sample.

	ADHD (n = 18) $M \pm SD$	Controls (n = 18) $M \pm SD$	p
Age	13.6 (1.7)	14.1 (1.3)	.11
Gray matter volume	784 (49.6)	804 (49.5)	.24
IQ (CFT)	106.8 (11.6)	108.1 (12.9)	.76
Selective attention (d2)[a]	101 (8.9)	112.1 (11.7)	<.005
CBCL			
Attention problems	68.2 (5.7)	53.4 (3.9)	<.001
Delinquent rule-breaking behavior	61.7 (9.9)	51.4 (3.4)	<.01
Aggressive behavior	61.5 (6.2)	53.2 (5.7)	<.001
Internalizing	60.4 (7.1)	50.0 (7.4)	<.001
Externalizing	60.6 (5.6)	49.7 (6.8)	<.001
Y-SR			
Attention problems	60.5 (7.7)	53.2 (3.9)	<.001
Delinquent rule-breaking behavior	53.3 (5.0)	54.3 (4.8)	.51
Aggressive behavior	54.4 (6.8)	53.6 (4.9)	.66
Internalizing	52.1 (11.6)	48.2 (15.2)	.45
Externalizing	51.4 (8.2)	50.8 (7.9)	.84

Note. CFT = Culture Fair Intelligence Test; CBCL = Child Behavior Checklist; Y-SR = Youth Self-Report.
[a]Standard values: M = 100, SD = 15.

were first affine-registered and subsequently deformed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra approach (DARTEL; Ashburner, 2007). GM images were then smoothed (FWHM = 8 mm) and Jacobian scaled, reestablishing the original tissue volume before spatial transformation. Thus, each voxel of the resulting images reflects absolute regional GM volume.

Statistical Analysis

To identify GM volume difference between ADHD and healthy control participants, we conducted a two-sample t test with age as a covariate. To improve reliability of the results, statistical maps were thresholded at $p < .001$ (uncorrected on the voxel level) with more than 100 contiguous voxels, corresponding to a $p < .05$, cluster-corrected using the false discovery rate (FDR). Using the MarsBar toolbox (Brett, et al. 2002), we extracted the volume estimates from the resulting ACC cluster and imported these values into SPSS for a correlation analysis with the standardized individual score of selective attention (d2-test) across all participants. Demographic variables were assessed using Student's t test for continuous variables and Fisher's exact test for categorical variables. Significance was assumed at $p < .05$.

Results

Demographic Characteristics

As can be seen from Table 1, adolescents with ADHD did not show significant differences relative to control participants in age and IQ. Except for three participants (two ADHD, one control), all participants were right handed (Fisher's exact test, $p > .05$). Parents of the ADHD group reported more internalizing, $t(34) = 4.3$, $p < .001$, and externalizing, $t(34) = 5.3$, $p < .001$, symptoms as well as more attention problems, $t(34) = 9.0$, $p < .001$, for their children than parents of healthy control participants, whereas ADHD participants (relative to control participants) reported more attention problems, $t(34) = 3.6$, $p < .001$, but did not differ in number of reported internalizing, $t(34) = 0.8$, $p = .4$, and externalizing, $t(34) = 0.2$, $p = .84$, symptoms. Furthermore, Table 1 shows that selective attention scores of the d2-test revealed significantly higher values for healthy control participants than for ADHD patients, $t(34) = 3.0$, $p < .005$.

VBM Results of GM

Figure 1 indicates significant differences in regional GM measures in the cerebellum, the occipital region, the ACC, the hippocampus, and the amygdala. Table 2 lists all clusters showing lower GM volume in participants with ADHD; these were observed within the cerebellum not only with a strong tendency toward the right dorsal/posterior lobe but also with reduced GM measures within the anterior/inferior lobe of the right and left hemisphere as well as the left anterior/posterior lobe (Figure 1). No brain region showed increased GM measures in ADHD participants relative to the control group.

Correlation Analysis for ACC GM Measures and Selective Attention

Correlational analysis between measures of ACC GM volume and standardized measures of the d2-test (Figure 1)

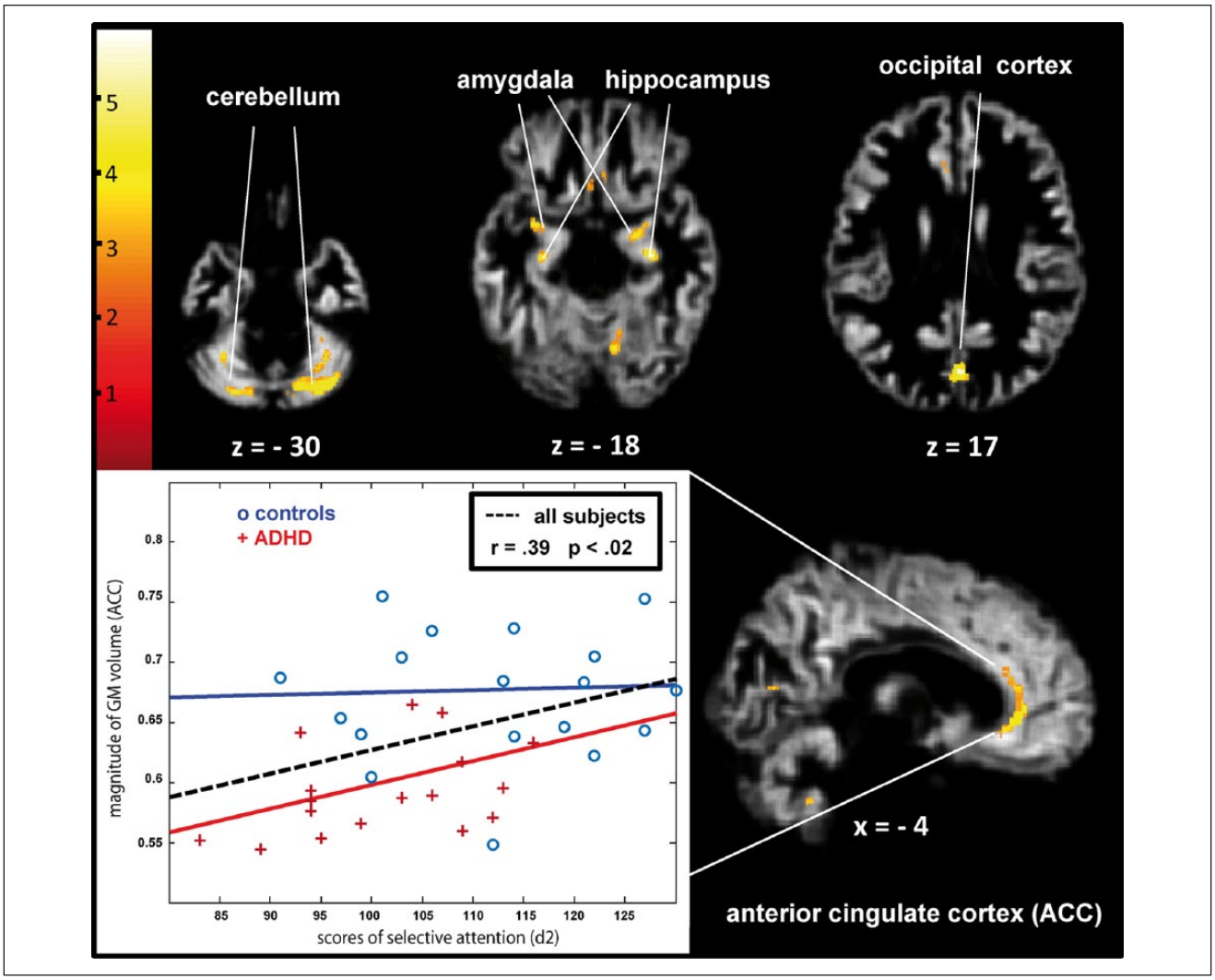

Figure 1. Voxel-based morphometry (VBM); regions with reduced gray matter measures in ADHD.
Note. $p = .05$ corrected for multiple comparisons on cluster level with more than 100 voxels per cluster. A positive correlation was found between measures of gray matter volume of the ACC and selective attention performance using the d2-test (correlation coefficient, $r = .39$, $p < .02$). ACC = anterior cingulate cortex.

revealed a significant positive correlation between ACC GM volume and the test scores of selective attention (Pearson's $r = .39$, $p = .02$; two-tailed) across all participants. However, separate analyses of both groups showed that this positive correlation was mainly driven by the ADHD participants (Pearson's $r = .38$; $p = .058$; one-tailed) and was not present in the healthy controls ($r = -.04$; $p = .44$; one-tailed). These results suggest that low performance in selective attention tends to be associated with lower GM volume within the ACC in participants with ADHD.

Discussion

The present study investigated structural brain differences between adolescents with ADHD and matched control participants by using an optimized VBM approach. We found significantly lower GM volume in participants with ADHD (relative to their matched controls) in several brain regions, such as the ACC, the occipital cortex, and the hippocampus/amygdala complex, as well as in widespread cerebellar regions. Most interestingly, reductions in GM measures within the ACC seem to be related to attentional deficits in participants with ADHD.

ACC GM-Volume Reduction in ADHD

Previous studies consistently reported that ADHD-related structural abnormalities occur before the age of 10 (Shaw et al., 2007) and can persist into adulthood (Frodl & Skokauskas, 2012; Seidman et al., 2011). This has been

Table 2. Regions With Reduced Gray Matter Measures in ADHD Using Age as Covariate.

Brain regions included within significant cluster	Peak coordinate			*Z* score	Cluster size
	x	*y*	*z*		
Right cerebellum lobules Crus I, Crus II, VI	41	−72	−32	5.1	1,624
Right cerebellum lobules VIII, IX	23	−49	−56	5.3	288
Vermis	−2	−55	−41	5.1	117
Left cerebellum lobule Crus II	−42	−62	−45	4.6	124
Left cerebellum lobules VIII, IX	−36	−54	−53	4.6	294
Left cerebellum lobule VI	−35	−55	−30	4.2	126
Left cerebellum lobule Crus II	−24	−79	−42	4.1	116
Left cerebellum lobule Crus I	−29	−78	−30	4.0	110
Occipital cortex	3	−75	9	4.85	464
Right hippocampus–amygdala complex	33	−21	−15	4.4	279
Left hippocampus–amygdala complex	−27	−13	−23	4.3	261
Left anterior cingulate cortex	−5	38	11	3.4	241

Note. FDR-corrected with 100 as the cluster-level threshold at $p < .05$. FDR = false discovery rate.

suggested to be a consequence of a delay of, rather than a deviation from, normal brain maturation (Shaw et al., 2007). For example, consistent with results in our study, it has been shown that children with ADHD had significant cortical thinning within the ACC (Bledsoe, Semrud-Clikeman, & Pliszka, 2013). The authors reported that the cortical thickness of the right ACC predicts a significant amount of the variance in parent-reported symptoms of ADHD, but failed to show a relationship between this region and scores of a word-color inhibition subtest.

Also, it has been shown that a higher rate of cortical thinning in the cingulate gyrus during cerebral cortical development from childhood into adulthood is associated with higher levels of inattention in adults with ADHD (Shaw et al., 2012).

Recently it has been shown that parent ratings of attention significantly predicted the right volume of the ACC (Semrud-Clikeman et al., 2014). Importantly, our current results expand these previous observations, demonstrating a positive correlation between the GM volume of the ACC and test scores of selective attention. While observed over all participants, the association between reductions in ACC GM volume and scores of selective inattention was mainly driven by the ADHD participants. This is the first study to report a correlation between volumetric aberrations in the ACC and scores of selective attention. Interestingly, GM-volume reduction in the ACC has also been reported in adults with ADHD (Amico, Stauber, Koutsouleris, & Frodl, 2011; Matsuo et al., 2009; Seidman et al., 2011; Seidman et al., 2006) when compared with healthy control participants. Furthermore, Matsuo and colleagues (2009) reported that adult ADHD participants had a tendency of inverse correlation between ADHD-related reductions within the left ACC GM volume and the total score of the Barratt Impulsiveness Scale (BIS), so that higher impulsivity tended to be associated with smaller ACC GM volumes. This result is also well in line with the findings reported here.

Functional MRI studies have also repeatedly implicated the dorsal as well as the rostral ACC in patients with ADHD in a variety of cognitive tasks, irrespective of age. For example, a functional MRI study (Bush et al., 1999) revealed reduced BOLD responses in the ACC in adult participants with ADHD (relative to healthy controls) during an interference Stroop task, while Tamm, Menon, Ringel, and Reiss (2004) reported a decreased BOLD response of the anterior/mid-cingulate cortex during response inhibition in adolescents with ADHD. Furthermore, Konrad and colleagues (2006) observed less activation in the ACC during attentional alerting in children with ADHD. Importantly, Weissman et al. (2005) reported that the ACC plays a key role in directing attention toward task-relevant stimuli, especially when the task is complicated by distracting stimuli. These findings are therefore well in agreement with ours.

ADHD-related medication treatment might also influence the structural development of children with ADHD. Results from a volumetric MRI study (Pliszka et al., 2006) examining healthy control children, ADHD-treatment-naïve children, and chronically treated children with ADHD reported significantly smaller ACC volume for the ADHD-treatment-naïve group compared with the ADHD-treated and control group.

However, a study by Castellanos and colleagues (2002) reported no differences in GM or total brain volume between participants with and without medication history. Similarly, Makris and colleagues (2010) reported that ADHD-related volumetric deficits in the ACC persist into adulthood and are independent of medical treatment.

In line with this study, Castellanos and colleagues (2008) proposed that ADHD-related lapses of attention might be

associated with a decrease in the functional connectivity between the default-mode network-related structures, such as the ACC and parietal regions. Together, these results suggest a strong association of the ACC with ADHD-related dysfunctions in selective attention, which thus might be responsible for increased distractibility.

Amygdala/Hippocampus GM-Volume Reduction in ADHD

It was suggested that children and adolescents with ADHD suffer from a delay in cortical maturation and gyrification bilaterally in the medial temporal cortex, among other regions (Shaw et al., 2012). However, ADHD-related research focusing on temporal and subcortical brain regions found ambiguous results for the hippocampus, with higher, lower, or no brain volume differences (Amico et al., 2011; Plessen et al., 2006; Posner et al., 2014).

Our results of reduced GM volume within the hippocampus and the amygdala bilaterally, however, are in line with more recent findings. For example, Frodl and colleagues (2010) reported reduced GM volume within the amygdala in adults with ADHD relative to matched controls. The authors also reported that ADHD participants who have been treated with stimulants showed reduced GM volume within the left hippocampus relative to medication-naïve ADHD participants but failed to show significant differences in hippocampal volumes between patients with ADHD and healthy controls in general. Posner et al. (2014) compared medication-naïve children with ADHD with healthy control participants and also observed reduced volumes of the left hippocampus, as well as a reduced functional connectivity between the left hippocampus and the left orbitofrontal cortex (OFC). Furthermore, Das, Cherbuin, Anstey, Abhayaratna, and Easteal (2014) reported that a smaller volume of the left hippocampus was associated with greater hyperactivity symptoms but not inattention. Finally, Brieber and colleagues (2007) reported that children with ADHD showed a decrease of GM volume within the left hippocampus–amygdala complex. The authors proposed that this hippocampal GM reduction might be associated with the presence of the met allele of the brain-derived neurotrophic factor (BDNF) gene (Bueller et al., 2006), a polymorphism which has also been associated with ADHD-related symptoms (Friedel et al., 2005). Thus, Brieber and colleagues speculated that genetic variations in the BDNF gene might contribute to structural brain abnormalities in the hippocampal formation and might be thus the reason for impaired sleep-dependent memory consolidation in ADHD (Prehn-Kristensen et al., 2011). However, the picture is not coherent, with some studies even finding increased GM volume in mesial temporal lobe structures of children and adolescents with ADHD (Plessen et al., 2006). Also, no differences of amygdalar or hippocampal GM volume have been reported in adults with ADHD (Amico et al., 2011; Castellanos et al., 1996; Filipek et al., 1997; Perlov et al., 2008). One important explanation for these inhomogeneous results across studies may be the number of participants with a history of psychostimulant medication (Frodl & Skokauskas, 2012; Posner et al., 2014). Several studies have shown that MPH can modulate hippocampal physiology and/or functions, including long-term potentiation, learning, and memory (Bethancourt, Camarena, & Britton, 2009; Dommett, Henderson, Westwell, & Greenfield, 2008). Likewise, Verster and colleagues (2010) found that MPH significantly improves declarative memory functioning of adults with ADHD and speculated that MPH enhances the release of dopamine within the ventrolateral prefrontal cortex and the hippocampal formation that is involved in encoding and retrieval (Medin et al., 2013). In contrast to this, Lagace, Yee, Bolanos, and Eisch (2006) reported that juvenile MPH exposure leads to decreased long-term survival of new neurons in the adult hippocampus of rats. A study directly testing this hypothesis in a longitudinal design, however, is lacking.

Other explanations for divergent findings might be differences in age ranges, comorbid disorders, imaging methodologies as well as simply due to the fact that most studies did not focus on this complex when defining regions of interest (ROIs). Furthermore, Das and colleagues (2014) proposed that the hippocampal volume seems more associated with the hyperactivity score instead of the inattention score and might be therefore present only in the hyperactive- or combined, but not in the inattentive subtype of ADHD.

The amygdala is thought to be important in ADHD-related problems with hyperactivity (Frodl et al., 2010), impulsivity, and the regulation of emotion (Brotman et al., 2010; Posner et al., 2011). Several studies already reported reduced GM volume of amygdala in participants with ADHD (Frodl et al., 2010; Geurts, Ridderinkhof, & Scholte, 2013; Lim, Radua, & Rubia, 2014; Valera, Faraone, Murray, & Seidman, 2007), even after controlling for the confounding effect of comorbid ODD and conduct disorder (CD; Sasayama et al., 2010). Importantly, Frodl and colleagues (2010) also reported that more hyperactivity and inattention in participants with ADHD were associated with smaller right amygdala volumes. In addition, a resting-state fMRI study reported abnormal interregional connectivity of the frontal–amygdala–occipital network in young adults with ADHD (Cocchi et al., 2012).

To conclude, ADHD-related volumetric changes within the amygdala and the hippocampus have not been consistently reported in adolescents with ADHD and merit further investigation with optimized brain morphological approaches.

Cerebellar GM-Volume Reduction in ADHD

It has been shown repeatedly that the cerebellar volume is smaller in children and adolescents with ADHD compared

with healthy controls (Bledsoe, Semrud-Clikeman, & Pliszka, 2011; Carmona et al., 2005; Castellanos et al., 1996; Castellanos et al., 2002; Durston et al., 2004; Ivanov, Murrough, Bansal, Hao, & Peterson, 2014; Mackie et al., 2007; Montes et al., 2011; Yang et al., 2008). This ADHD-related volumetric abnormality of the cerebellum can even persist into adulthood (Castellanos et al., 2002; Makris et al., 2015). New findings have also found cerebellar vermis volume to be predictive of behavioral parent ratings of hyperactivity, attention, and restlessness/impulsivity (Bledsoe et al., 2011). Moreover, Mackie and colleagues (2007) examined children with ADHD who were divided into an ADHD group with better clinical outcomes and a group with worse outcomes, compared with matched healthy controls. The authors reported that ADHD participants with a worse clinical outcome show progressive neuroanatomical deficits in GM volumes of the right and left posterior inferior-cerebellar lobes during adolescence relative to both groups. Also, in a sibling study (Durston et al., 2004), the authors reported volumetric reductions in cortical GM and white matter in boys with ADHD as well as in their unaffected siblings relative to healthy controls. This suggests an increased ADHD-related familiar risk in general, although GM volume of the cerebellum seems unaffected in siblings without ADHD. Traditionally, cerebellum was associated with motor control, such as real-time fine tuning of movements (Allen & Tsukahara, 1974), but it has increasingly been associated with higher cognitive functions and emotion (Leiner, Leiner, & Dow, 1986; Stoodley & Schmahmann, 2010). It has further been shown that the cerebellum is also involved in multiple cerebro-cerebellar loops via thalamic regions. For example, Middleton and Strick (1994) observed that the cerebellum influences several areas of the prefrontal cortex via thalamic connections (Durston, van Belle, & de Zeeuw, 2011). Therefore, ADHD-related dysfunction might also be associated with an impaired interregional connectivity due to the loss of cerebellar GM and white matter volume (Castellanos & Proal, 2012; Makris et al., 2015; Rubia, Alegria, & Brinson, 2014).

Interestingly, similar to a current study on medication-naïve ADHD adults (Makris et al., 2015), our findings show consistent results of ADHD-related volume reduction within cerebellar regions (Crus I and Lobule VI) that are associated with executive functions (Stoodley & Schmahmann, 2009). It is known that the cerebellum is not only interconnected to motor areas but also to non-motor areas of the cerebral cortex, including frontal, parietal, temporal, and occipital cerebral regions (Strick, Dum, & Fiez, 2009), a cortical network involved in executive functions such as attention and impulsive control, core symptoms of ADHD. These results support the idea that not only cerebral- (Frodl & Skokauskas, 2012; Seidman et al., 2011; Shaw et al., 2007) but also cerebellar cortical developmental dysfunction from childhood into adulthood is associated with ADHD-relevant symptoms.

Occipital Cortex GM-Volume Reduction in ADHD

In addition, in the present study we also found reduced GM volume within occipital cortex for adolescents with ADHD relative to healthy controls. These results are in line with previous studies on ADHD-related volumetric abnormality (Ahrendts et al., 2011; Castellanos et al., 2002; Durston et al., 2004; Makris et al., 2012; Proal et al., 2011; Sasayama et al., 2010; Seidman et al., 2011). The occipital cortex is involved in the well-known attentional network to maintain, suppress, and shift attention (Corbetta & Shulman, 2002; Kanwisher & Wojciulik, 2000), and is thus relevant for ADHD-related aspects. Shaw and colleagues (2007) observed that cortical development in children with ADHD lagged behind that of typically developing children by several years, particularly in prefrontal, middle, and superior temporal, and also in occipital regions. In addition, the occipital cortex of ADHD participants has also been associated with abnormalities of interregional connectivity in distinct networks, such as fronto-occipital and temporo-occipital circuits (Cocchi et al., 2012; Lei et al., 2014; Shaw, Sudre et al., 2014). Together, these findings suggest that occipital brain regions and their relevance for the regulation of attentional processes warrant further studies in participants with ADHD.

Limitations

Our study results differed from results of earlier structural brain studies on participants with ADHD (meta-analysis; Frodl & Skokauskas, 2012) in that we did not observe GM reductions in subcortical regions, such as the striatum, the putamen, and the pallidum. Frodl and Skokauskas (2012) suggested that changes in the basal ganglia seem to diminish over time from child to adulthood; however, ADHD-related adulthood seems to be characterized by decreased GM volume in the ACC. Our sample, with a mean age of 13.7 years, may thus already show features more of the adult, rather than the pediatric, structural phenotype. Furthermore, it is also possible that findings of reduced basal ganglia volume in children and adolescents of earlier studies that have used manual tracing segmentation techniques or ROI-based approaches are biased, and thus overestimated. A further limitation of this study is the exclusive presence of male participants, due to the absence of female patients to which our control group was matched. In general, clinical studies have shown that ADHD predominantly affects males and exhibits a male-to-female sex ratio of 4:1 (Faraone et al., 2015; Polanczyk et al., 2007). Our results may therefore not be generalizable to a female ADHD sample. Also in the present study we did not consider participants' medication history as a study by Castellanos and colleagues (2002) reported no differences in GM or total brain volume between participants with and without medication history.

The small sample size used in this study is another limitation. Future studies with larger sample sizes are needed to confirm relationship between ADHD-related structural brain changes and ADHD-related behavioral outcomes.

Conclusion

Our results provide support for several brain regions being abnormally smaller in participants with ADHD. In particular, we suggest that reduced GM volume in the ACC is directly associated with ADHD-related attentional impairments.

Declaration of Conflicting Interests

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