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Brain development and ADHD

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by excessive inattention, hyperactivity, and impulsivity, either alone or in combination. Neuropsychological findings suggest that these behaviors result from underlying deficits in response inhibition, delay aversion, and executive functioning which, in turn, are presumed to be linked to dysfunction of frontal–striatal–cerebellar circuits. Over the past decade, magnetic resonance imaging (MRI) has been used to examine anatomic differences in these regions between ADHD and control children. In addition to quantifying differences in total cerebral volume, specific areas of interest have been prefrontal regions, basal ganglia, the corpus callosum, and cerebellum. Differences in gray and white matter have also been examined. The ultimate goal of this research is to determine the underlying neurophysiology of ADHD and how specific phenotypes may be related to alterations in brain structure.

Keywords: ADHD; Development; Brain; Magnetic resonance imaging; Phenotypes; Basal ganglia; Cerebellum

According to the DSM-IV-TR, Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by excessive inattention, hyperactivity, and impulsivity, either alone or in combination (American Psychiatric Association, 2000). Neuropsychological findings suggest that these overt behavioral signs result from underlying deficits in response inhibition, delay aversion, and executive functioning. In turn, these hypothesized psychological deficits are presumed to be linked to dysfunction of frontal–striatal–cerebellar circuits. In particular, much attention has been paid to the neural circuits connecting the prefrontal cortex and the basal ganglia, which likely modulate response inhibition. Further, the cerebellum, which has traditionally been viewed as a motor coordination center, has also been shown to be closely linked to non-motor regions of the cerebral cortex and to play a role in executive functions such as cognitive planning. Over the past decade, magnetic resonance imaging (MRI) has been used to examine anatomic differences in these regions between ADHD and control children. In addition to quantifying differences in total cerebral volume, specific areas of interest have been prefrontal regions, basal ganglia, the corpus callosum, and cerebellum. Differences in gray and white matter have also been examined. The ultimate goal of this research is to determine the underlying neurophysiology of ADHD and how specific phenotypes may be related to alterations in brain structure. The findings of these studies will be discussed in the following review.

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ADHD is most often diagnosed during childhood and therefore, we will limit our discussion to recent MRI studies of children and adolescents diagnosed with this common psychiatric condition. Anatomic MRI is the principal technology used to examine the pediatric brain because it provides excellent spatial resolution and does not use ionizing radiation. Although other approaches such as computed axial tomography, positron emission tomography, and single photon emission computed tomography also inevitably contribute to our understanding of the pathophysiology of ADHD, they will not be discussed in detail here. Despite the significant advances made by MRI, there are some limitations which require mention when evaluating the available data. First, the substantial cost of obtaining MRI scans usually results in small sample sizes, which tend to yield insufficient statistical power. As Rossi (1990) pointed out, when most studies in a field have statistical power in the range of 50%, then inconsistent results, largely representing type I error, are to be expected. The cost of MRI studies of ADHD can also be increased by loss of scans due to excessive motion, which is to be expected, given that hyperactivity is one of the defining features of ADHD. Second, ADHD is characterized by symptoms that vary depending upon subtype, age, sex, and clinical setting. This heterogeneity makes comparisons across studies difficult, particularly when sample sizes are small. Further complications arise when one considers the widespread use of stimulant medications to treat ADHD. It is difficult to recruit a sample that is medication-naïve in North America. Therefore, studies often include children who are taking medications, those who have been exposed previously to medications, and those who are unmedicated. Third, the field has not yet adopted standard quantitative analytical methods which would improve comparisons across studies. Current methods include hand-tracing of individual regions of interest, which tends to optimize validity at the expense of reliability; fully automated methods, which maximize test–retest reliability but are best applied to large well-defined brain regions; and semi-automated methods, which combine the strengths and weaknesses of the other two alternatives. Finally, another source of inconsistencies in the anatomical literature has derived from a focus on lateralization and indices of asymmetry (Castellanos et al., 1994). Given the compelling evidence of lateralization of language and increasing evidence of lateralization of some aspects of attention, interest in obtaining asymmetry measures is understandable. Unfortunately, asymmetry measures are intrinsically less reliable than the volumetric measures from which they are constructed, with reliability decreasing inversely with the degree of similarity between the right and left sides (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991; Bullmore, Brammer, Harvey, & Ron, 1995). Despite these concerns, the field continues to conduct MRI studies with the ultimate goal of delineating the brain anatomy of ADHD.

1. Normal brain development

Over the past 20 years, converging studies have shown that over 90% of a young adult's total brain volume is attained by age 5 (Giedd et al., 1996) and that total cerebral volume (TCV) reaches its maximum volume by early adolescence (Courchesne et al., 2000; Giedd, Blumenthal, Jeffries, Castellanos et al., 1999). A recent study of 45 children who received MRI scans 2 years apart between the ages of 5 and 11, showed expansion of the brain to be approximately 1 mm per year, predominantly in the prefrontal cortex (Sowell et al., 2004). More specifically, cross-sectional analyses have shown significant age-related decreases in the thalamus and lenticular nucleus, and increases in ventricular size after controlling for TCV (Sowell, Trauner, Gamst, & Jernigan, 2002). Sex differences are prominent. Both the cerebrum and the cerebellum are significantly larger (by 7–10%) in boys than girls (Giedd et al., 1996; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell et al., 2002). Consistent with this, the absolute size of cortical gray matter is nearly 10% larger in boys than in girls. Subcortical regions such as the putamen and globus pallidus are also significantly larger in boys, even after controlling for total cerebral volume (Giedd et al., 1996). Conversely, the caudate is larger in girls than boys, after controlling for TCV (Giedd et al., 1996; Sowell et al., 2002). There is also some inconsistent evidence of sex differences in developmental patterns. In a cross-sectional study of 104 children between the ages of 4 and 18, Giedd and colleagues (1996) found age-related decreases in caudate and putamen volumes in boys only.

1.1. White and gray matter development

The lack of total brain volume changes during late childhood and adolescence masks complex changes in gray and white matter. Cross-sectional (Courchesne et al., 2000; Reiss et al., 1996; Sowell et al., 2002) and longitudinal (Giedd,

Blumenthal, Jeffries, Castellanos et al., 1999) studies have shown increases in white matter volumes during the pediatric age range, reflecting increasing myelination during this time. This increase appears to be greater in males than females (Giedd, Blumenthal, Jeffries, Castellanos et al., 1999; Reiss et al., 1996). Maturational increases in white matter are assumed to be present globally, with specific increases shown in the frontal, parietal, and occipital lobes (Sowell et al., 2002). A cross-sectional study of 111 children and adolescents (ages 4–17) examining age-related changes in neural tracts found significant increases in white matter in the internal capsule and posterior portion of the left arcuate fasciculus (Paus et al., 1999). Specific patterns of white matter development have also been noted in the corpus callosum, the anterior cross-sectional area of which increases first, followed by posterior growth through late adolescence (Giedd, Blumenthal, Jeffries, Rajapakse et al., 1999).

Gray matter shows a more heterogeneous overall growth pattern throughout the cerebrum (Sowell et al., 2003). Overall, gray matter decreases from early childhood to post-adolescence but this effect is non-linear, likely reflecting selective pruning of neuronal connections (Courchesne et al., 2000; Huttenlocher, 1979; Reiss et al., 1996). More specifically, there is a 13% increase in gray matter from early childhood to later childhood (6–9 years), after which it decreases about 5% per decade throughout life (Courchesne et al., 2000). Regional analyses have found that gray matter volumes peak at about age 12 in frontal and parietal lobes and then decline post-adolescence resulting in a net decrease (Giedd, Blumenthal, Jeffries, Castellanos et al., 1999). Significant decreases in gray matter have been found in right dorsolateral frontal, bilateral occipitoparietal, and anterior and posterior–inferior temporal cortices (Sowell et al., 2004). Increases in cortical thickness are restricted to classical language areas such as left anterior and posterior perisylvian regions. The maximum gray matter volume is reached somewhat earlier in girls than boys in each of these regions, corresponding with the earlier attainment of developmental milestones including puberty. However, preliminary findings suggest that brain maturation appears to be age-dependent rather than reflecting pubertal development (Dr. Jay Giedd, personal communication, 2003). Temporal lobe gray matter also follows a nonlinear developmental course with maximum size at about age 16 across genders, followed by a slight decline, while gray matter in the occipital lobe appears to continue increasing through age 20. Gray matter volumes in the anterior and posterior cingulate, basal ganglia, and high-parietal regions have been shown to be highly variable in older children (Wilke & Holland, 2003) which is consistent with specific gray matter volume reductions during this age range reflecting individual adaptive and remodeling processes.

1.2. Symmetry in normal development

As noted earlier, measures of symmetry of brain regions are markedly less reliable than direct volumetric measures and should be interpreted with caution. However, a number of findings have been consistent across the pediatric and adult literatures. For example, the right cerebral hemisphere, and more specifically the right prefrontal cortex, has been shown to be significantly larger than the left side (Giedd et al., 1996; Reiss et al., 1996; Watkins et al., 2001). Consistent with this, lateral ventricle and CSF volumes are larger on the left side. Subcortical findings are less consistent. The caudate nucleus has shown right greater than left asymmetry (Giedd et al., 1996; Reiss et al., 1996; Watkins et al., 2001) as well as left greater than right asymmetry (Pineda et al., 2002; Semrud-Clikeman et al., 2000). Studies of the putamen and lenticular nucleus (globus pallidus and putamen) have found left-sided (Giedd et al., 1996; Watkins et al., 2001), and right-sided laterality (Reiss et al., 1996).

2. Neuroanatomical correlates of ADHD

As described earlier, MRI studies of children with ADHD must be considered in light of several potential limitations including sample heterogeneity, small sample sizes, and the lack of consistency in MRI methodology (see Table 1). Despite this, there is consistent evidence that the brains of children with ADHD are significantly smaller, on average, than the brains of healthy comparison children throughout childhood and adolescence (Castellanos et al., 2002; Durston et al., 2001, 2004). Beyond this, there is more conflicting evidence in support of a distributed circuit, the disruption of which likely underlies ADHD symptoms (Durston, 2003). At least in boys, this circuit appears to include frontal brain regions, the basal ganglia, the cerebellar hemispheres, and a sub-region of the cerebellar vermis. The distribution of gray and white matter may also be altered in ADHD in the frontal lobes. We will discuss these abnormalities in turn.

Table 1
Summary of MRI studies of ADHD

Study[a]	*N*	Diagnostic protocol	Magnet	MRI protocol/sequence	TR/TE (ms)	Measurement protocol[a]	Orientation	No. of slices/ thickness
Aylward et al., 1996	16 TS and ADHD, 10 ADHD, 11 NC	Clinical interview	1.5 T	Inversion recovery	3000/20	M	Axial	Contiguous/3.0 mm
Berquin et al., 1998	46 ADHD, 47 NC	DICA-P	1.5 T	3D-SPGR	24/5	SA, M	Axial	Contiguous/1.5 mm
Castellanos et al., 1996	57 ADHD, 55 NC					A	Coronal	Contiguous/2.0 mm
Castellanos et al., 2001	50 ADHD, 50 NC (girls only)							
Castellanos et al., 2002	152 ADHD, 139 NC							
Bussing et al., 2002	7 ADHD and CD, 5 ADHD, 19 NC	DICA-P	1.5 T	3D-MPRage Turboflash	10/4	M	Sagittal	Contiguous/1.25 mm
Durston et al., 2004	30 sib pairs discordant for ADHD, 30 NC	DISC-P	1.5 T	T1 fast field echo	30/4.6	A	Coronal	130–150/1.5 mm
				T2 dual echo turbo spin-echo	6350/1480		Coronal	65–75/3.0 mm
Filipek et al., 1997	15 ADHD, 15 NC	K-SADS	1.5 T	3D-SPGR	40/5	SA	Coronal	Contiguous/3.0 mm
Semrud-Clikeman et al., 1994	10 ADHD, 11 NC			Dual-echo (T2)	2250/TE_1=30, TE_2=80		Coronal	5.0 mm with 2.5 mm interslice gap
Semrud-Clikeman et al., 2000	15 ADHD, 15 NC							
Hesslinger et al., 2002	8 ADHD adults, 17 NC adults	Clinical interview	2.0 T	T1-weighted 3D-dataset using MDEFT	17/5.5	M	NA	NA
Hill et al., 2003	23 ADHD,24 NC	Clinical interviews (DSM-IV)	1.5 T	T1 weighted (fast-SPGR)	17.7/6.9	SA	Axial	Contiguous/3.0 mm
Hynd et al., 1991	7 ADHD, 10 NC	K-SADS	0.6 T	Sequential T1	690/32	M	Sagittal	15/7.5 mm
Hynd et al., 1993	11 ADHD,11 NC				500/32		Axial	11/5.0 mm
Hynd et al., 1990	10 dyslexic, 10 ADHD, 10 NC							
Kates et al., 2002	13 TS, 13 ADHD, 13 NC	DICA-P	1.5 T	3D-SPGR	35–45/5–7	SA	Coronal	124/1.5 mm
Mostofsky et al., 1998	12 ADHD,12 NC					A, M		
Mostofsky et al., 2002	12 ADHD,12 NC							
Mataró et al., 1997	11 ADHD, 19 NC	Family interview (DSM-III-R)	1.5 T	Inversion–recovery sequence	1800/20 (TI=650)	SA	NA	15/5.0 mm with 2.5 mm gap
Overmeyer et al., 2001	18 ADHD, 16 NC–4 siblings of ADHD in study	Parental and psychiatric interview	1.5 T	Dual echo, fast spin	400/TE1=20, TE2=100	A	Sagittal	50/3.0 mm
Pineda et al., 2002	15 ADHD-C, 15 ADHD-I, 15 NC	Clinical interview	1.5 T	T1-weighted	519/12	M	Axial	NA/5.0 gap 0.5
				3D-T1-weighted	40/5		Coronal	1.8 mm
				T1-weighted	485/14		Sagittal	5.0 gap 0.5
Yeo et al., 2003	23 ADHD, 24 NC	Clinical interview	1.5 T	Single voxel proton MRS using steam pulse sequence	2000/30	A, M	Sagittal Axial	Single voxel/ 12.6 cm^3

[a] Studies grouped in rows follow the same diagnostic and imaging protocols, except where noted. DICA-P=Diagnostic Interview for Children and Adolescents–Parent Interview, DISC-P=Diagnostic Interview Schedule for Children, K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; 3D-SPGR=three-dimensional spoiled gradient recalled echo; 3D-MPRAGE=three-dimensional magnetization prepared rapid gradient echo imaging; MDEFT=modified driven equilibrium Fourier transfer sequence M=manual, SA=semi-automated, A=automated; NA=information not available; ADHD=subjects with Attention-Deficit/Hyperactivity Disorder; ADHD-C=Combined type ADHD; ADHD-I=Inattentive type ADHD; NC=normal (healthy) controls; TS=subjects with Tourette syndrome.

2.1. Decreased global brain volume

Most studies of ADHD anatomy have found overall reductions in total brain volume compared to age- and sex-matched controls. In a meta-analysis of published volumetric studies in ADHD, we found a highly significant overall effect ($Z=22.16$; $p<.0001$; 95% CI: 11.23 to 33.09) (Castellanos & Acosta, 2004), which remained significant even when the largest study (Castellanos et al., 2002) or the study with the largest effect size (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002) was excluded. The largest study to date examined 152 children and adolescents with ADHD and 139 controls, and analyzed the results using fully automated methods. Children with ADHD showed overall cerebral volumes that were 3.2% smaller than controls, adjusted for significant covariates ($p=.004$). All four major lobes (frontal, parietal, temporal, and occipital) were comparably affected. These volume reductions were not likely attributable to stimulant treatment as they were at least as pronounced in the 49 medication-naïve children with ADHD as in the 103 children with ADHD who were being treated with stimulants. Further confirmation was obtained in an ingenious study that compared 30 boys with ADHD to their unaffected siblings ($n=30$), and to matched healthy controls. Compared to the controls, the boys with ADHD had a 4% reduction in intracranial volume, which is a surrogate for total cerebral and cerebellar volume ($p=.03$), with a similar, although less robust, effect ($p=.07$; 3.4% reduction) in the unaffected siblings (Durston et al., 2004).

2.2. Frontal cortex

Anatomic hypotheses of the substrates of ADHD have generally focused on the role of frontal brain. In one sample of 12 boys with ADHD and 12 age-matched controls, decreased size of the frontal lobe in children with ADHD was shown to account for 48% of the reduction in total cerebral volume (Mostofsky et al., 2002). More specifically, the prefrontal cortex (PFC) has been shown to be significantly smaller in ADHD children than controls (Castellanos et al., 1996; Durston et al., 2004; Filipek et al., 1997; Kates et al., 2002; Mostofsky et al., 2002) and in their unaffected siblings (Durston et al., 2004). These effects are relatively specific to frontal regions; no diagnostic differences were found for the parietal, temporal, or occipital lobes (Mostofsky et al., 2002), although in the sibling study, both boys with ADHD and their brothers had decreased left occipital gray and white matter volumes (Durston et al., 2004). Differences in the symmetry of the prefrontal regions have also been found. As reported earlier, there is normally a right greater than left asymmetry of the prefrontal cortex. This asymmetry is reduced in ADHD children due to a significant decrease in right prefrontal regions (Castellanos et al., 1996; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Reiss et al., 1996; Shaywitz, Shaywitz, Byrne, Cohen, & Rothman, 1983). However, the inherently lower reliability of asymmetry indices (Arndt et al., 1991) must be taken into account when examining these data.

Another recent development has been the quantification of PFC subregions. Yeo et al. (2003) reported that right dorsolateral prefrontal volume, measured as a block, was significantly smaller in 23 children with non-comorbid ADHD as compared to 24 controls. Hesslinger and colleagues (2002) found that eight adult patients with ADHD who had never been medicated had significantly smaller left orbital–frontal cortical gray and white matter volumes than did 17 comparison subjects (−12%, $p=.04$). Decreases in right-sided volumes were not significant. Sowell and her colleagues (2003) recently conducted an innovative morphological study comparing the cortical surfaces of children and adolescents with ADHD ($n=27$) to healthy controls ($n=46$). This study allowed more specific analyses of brain size reductions in children with ADHD, by analyzing distances between the center of the brain and cortical surface. Brain surface of ADHD subjects was reduced up to 4 mm bilaterally in the lateral anterior temporal cortices and in the inferior portion of dorsolateral prefrontal cortices. Some reduction in brain size was also seen in right parietal cortex of the ADHD group. In these regions, the cortical surface is closer to the center of the brain in children with ADHD, possibly because there has been less local growth. These reports are currently difficult to integrate because of many differences in methods and subjects. However, automated image analysis techniques should alleviate these problems in the future.

2.3. Basal ganglia

Along with the prefrontal cortex, the caudate nucleus and its associated circuits have long been implicated in ADHD (Pontius, 1973). The caudate nucleus and the putamen serve as the entry point to the basal ganglia, and abnormalities of

both structures have been reported in this disorder. Researchers have shown both volumetric and asymmetry differences in the caudate between ADHD and control groups, but these findings have not been consistent across studies. For example, while several groups found a decrease in caudate volume in children with ADHD (Aylward et al., 1996; Castellanos et al., 2002; Hill et al., 2003), others have not (Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Pineda et al., 2002). Mataró found larger caudate area in ADHD children although the use of a single section makes it difficult to interpret this result (Mataró, García-Sánchez, Junqué, Estévez-González, & Pujol, 1997). When total caudate volume was analyzed in a mixed cross-sectional/longitudinal design with fully automated measurements, decreased volumes were detected in the group with ADHD for ages below 16, but not beyond that age (Castellanos et al., 2002). Around age 16, caudate volumes appeared to normalize: there was a decrease in caudate volumes in the normal controls, making them more consistent with the caudate volumes in the ADHD group which did not demonstrate as large a decrease from maximal values. Such transient abnormalities may relate to the diminishment of motoric symptoms in ADHD with increasing age, but this speculation should be tested directly. In a study of 19 children with ADHD, Bussing found caudate differences between children who were exposed to methylphenidate and those who were not (Bussing et al., 2002). The treated group demonstrated smaller left and total caudate volumes than their untreated peers. This finding was not supported by a larger comparison of 49 unmedicated and 103 medicated ADHD patients, although a possible association between stimulant effects and smaller caudate volume should not be ruled out (Castellanos et al., 2002).

Studies have also found alteration of the normal symmetry of the caudate in children with ADHD. As reported earlier in this manuscript, it is still unclear whether the normal caudate is asymmetric. However, when caudate asymmetry is found, it most often indicates greater left than right volumes (Castellanos et al., 2001; Filipek et al., 1997; Giedd, Blumenthal, Jeffries, Castellanos et al., 1999; Hynd et al., 1993; Mataró et al., 1997; Pineda et al., 2002). Studies of ADHD children have shown a decreased left caudate, making the caudate more symmetrical than in the normal control children who showed a left greater than right asymmetry (Hynd et al., 1993; Filipek et al., 1997; Semrud-Clikeman et al., 2000). Findings regarding the right caudate have been varied. One study found a decrease in the right caudate in ADHD children (Castellanos et al., 1996) while another reported an increase (Mataró et al., 1997). In a community sample of 27 children (12 girls; ages 7 to 16) that included one child whose ratings were consistent with ADHD, greater right than left caudate asymmetry uniquely accounted for 17% of the variance in parent ratings of inattention and only 4% of the variance in ratings of hyperactivity/impulsivity (Schrimsher, Billingsley, Jackson, & Moore, 2002). Overall, the inconsistency of these data highlights the limitations of symmetry measures in neuroimaging research.

Studies of the putamen, a region associated with primary and supplementary motor areas that may contribute to the motoric symptoms of ADHD, have yielded equally ambiguous results. Investigators examining putamen volumes as regions of interest have not detected significant differences (Aylward et al., 1996; Castellanos et al., 1996). On the other hand, a preliminary functional imaging study found decreased blood flow in the putamen of objectively hyperactive boys with ADHD compared to those boys whose activity level resembled that of controls (Teicher et al., 2000). Lastly, the globus pallidus, which receives input from caudate and putamen, has been examined. Although it is difficult to measure reliably, it was found to be significantly smaller in boys with ADHD (Aylward et al., 1996; Castellanos et al., 1996). However, the two studies differed as to whether the size reduction was greater in the left or right side. In another study, the globus pallidus was smaller in children with ADHD and Tourette Syndrome than those with Tourette alone or no diagnosis (Singer et al., 1993).

In addition to comparisons between children with ADHD and controls, investigators have examined the effects of head trauma and damage to the basal ganglia, on the secondary development of ADHD (S-ADHD). ADHD is the most common psychiatric disorder to develop after brain injury (Max et al., 1997) or stroke (Max et al., 2002) in childhood, and its occurrence is correlated with severity of injury (Max et al., 1998). Two instructive cases of severe ADHD associated with a traumatic amniocentesis at 17 weeks gestation revealed complete elimination of the right basal ganglia (DeLong, 2002). More specifically, lesions of the right putamen and posterior ventral putamen have been associated with a higher incidence of S-ADHD and ADHD respectively (Herskovits et al., 1999; Max et al., 2002). One study followed 99 children, ranging in age from 4 to 19 years, who suffered closed head injury over the course of a year. During this time, the odds of developing S-ADHD were 3.6 times higher among children with thalamus injury and 3.2 times higher in children with basal ganglia injury (Gerring et al., 2000). Further brain injury studies, especially those using imaging techniques, should shed further light on neurodevelopmental susceptibilities.

2.4. Cerebellum

In recent years, more attention has been paid to the role of the cerebellum in ADHD. The cerebellum is associated with coordination of motor movements but is also known to be involved in non-motor functions such as timing and attentional shifting through connections with frontal regions (Allen, Buxton, Wong, & Courchesne, 1997; de Zubicaray, Zelaya, Andrew, Williams, & Bullmore, 2000; Desmond, Gabrieli, & Glover, 1998; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Rao et al., 1997; Thomas et al., 1999; Tracy, Faro, Mohamed, Pinsk, & Pinus, 2000). Similar to the cerebral cortex, anatomic MRI studies of the cerebellum have measured the total volume as well as volume and area measurements of its primary components: the cerebellar vermis and lobes. MRI studies of the cerebellum in ADHD have detected smaller cerebellar hemispheric volumes (by up to 6%) which are sustained throughout adolescence (Berquin et al., 1998; Durston et al., 2004; Hill et al., 2003) and remain significant even after adjusting for TCV (Castellanos et al., 2002). Vermal volume has also been shown to be smaller in ADHD children than controls, even after controlling for total cerebral volume and vocabulary scores (Berquin et al., 1998). The most robust cerebellar finding is decreased size of the posterior inferior lobe of the cerebellum (lobules VIII–X) in ADHD subjects, as compared to controls (Berquin et al., 1998; Bussing et al., 2002; Hill et al., 2003; Mostofsky, Reiss, Lockhart, and Denckla, 1998). This decrease in size in ADHD subjects is specific to lobules VIII–X as most studies, with the exception of one (Hill et al., 2003), have failed to find decreases in other cerebellar lobules (Berquin et al., 1998; Mostofsky et al., 1998). In light of these consistently significant findings, the cerebellar hemispheres and the posterior–inferior cerebellar vermis are becoming increasingly incorporated into hypotheses of ADHD (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002; Castellanos & Tannock, 2002).

2.5. Gray and white matter

Recently, due to more sophisticated measurement techniques and an increased interest in the ratios of gray to white matter in the developing brain, a number of studies have examined gray–white matter segmentation in ADHD populations. Reductions in both gray and white matter have been reported for the right PFC (Filipek et al., 1997; Overmeyer et al., 2001), and left PFC (Kates et al., 2002). These latter findings were confirmed by Mostofsky et al. (2002) who reported significant white matter reduction confined to the left PFC, with gray matter reduced in both hemispheres but more so in the right. Overmeyer and his colleagues (2001) also noted reduced gray matter primarily in right side in the posterior cingulate gyrus, superior frontal gyrus, and putamen, and bilaterally in the globus pallidus in children diagnosed with hyperkinetic disorder, when compared to normal controls. Reductions in white matter were predominantly in the left hemisphere. In contrast to these studies of prefrontal gray and white matter volumes, Sowell and colleagues (2003) found gray matter density to be increased by 15–30% in the posterior temporal lobes and inferior parietal lobes bilaterally in ADHD subjects. There was also evidence of a significant increase in gray-matter density in the right occipital lobe of the ADHD children. Consistent with previous studies, white matter volumes were significantly reduced in the ADHD group.

As a white matter structure, the corpus callosum has been examined and has been shown to be significantly smaller in ADHD children than controls (Hill et al., 2003; Hynd et al., 1991; Semrud-Clikeman et al., 1994). More specifically, subregions such as the genu and splenium are smaller in ADHD subjects. Giedd et al. (1994) also found smaller rostrum and rostral bodies in the ADHD group compared to controls. In contrast to these findings, Castellanos et al. (1996) failed to find diagnostic differences in overall corpus callosum area or its subdivisions.

2.6. Structural findings in girls with ADHD

Due to the greater apparent prevalence of ADHD in boys, most of the imaging studies described here utilized samples of boys or predominantly boys. Few studies have examined structural differences in girls. One study of 50 girls with ADHD and 50 female controls found total cerebral volumes to be smaller in girls with ADHD than controls, although these differences were no longer significant after controlling for vocabulary subscale score (Castellanos et al., 2001). After adjustment for TCV and vocabulary, girls with ADHD had significantly smaller volumes in the posterior–inferior lobules of the cerebellar vermis. No other brain regions, even those previously reported in boys, were found to be significantly smaller in ADHD girls after covariance. Exposure to stimulant medication was examined and found to have no relationship with regional brain volumes in the ADHD sample. In a more recent anatomical MRI study, no

interaction was found between sex and diagnosis for any anatomic measure, suggesting that diagnostic differences were consistent across boys and girls (Castellanos et al., 2002).

2.7. Association between brain structure and functioning

To better understand these structural differences between ADHD children and healthy controls, several studies have examined relationships between regional brain volumes and measures of functioning, such as behavioral rating scales and neuropsychological tests. Overall, findings suggest that smaller volumes are associated with greater ADHD symptom severity. Castellanos et al. (2002) found frontal and temporal gray, caudate, and cerebellar volumes to be significantly negatively correlated with global clinician ratings and parent ratings of child attention problems. Semrud-Clikeman et al. (2000) found smaller left caudate head and white matter volumes associated with higher Child Behavior Checklist (CBCL) Externalizing scores. Castellanos and his colleagues' study of ADHD girls also found smaller volumes to be associated with greater symptom severity (Castellanos et al., 2001). For example, smaller total cerebral volume was associated with greater attention problems and smaller posterior inferior vermal volumes were significantly correlated with global functioning and CBCL anxiety-depression scores. Gray matter density in the left occipital lobe has also been shown to be negatively correlated with inattention scores in children with ADHD (Sowell et al., 2003). In an early study, the size of the rostral body of the corpus callosum was negatively correlated with parent and teacher ratings of impulsivity and hyperactivity in children with ADHD and controls (Giedd et al., 1994).

Children with ADHD have been shown to have executive function deficits, particularly in response inhibition. Accordingly, several studies have examined the relationships between regional brain volumes and tests of neuropsychological functioning in children with ADHD. In a study of 26 ADHD and 26 control boys, ADHD task performance was positively correlated with prefrontal cortex, caudate, and globus pallidus volumes (Casey et al., 1997). More specifically, correlations between sensory selection task performance and prefrontal and caudate volumes were predominantly localized to the right, while response selection and response execution tasks were correlated with caudate symmetry and left globus pallidus size. Prefrontal volumes were correlated with performance on the inhibitory conditions, while basal ganglia volumes related to both control and inhibitory conditions. In contrast, in a study of 23 ADHD children and 24 normal controls, larger volumes in total superior prefrontal cortex and right superior prefrontal cortex were correlated with worse performance on a test of attention (Conners' Continuous Performance Test; CPT) (Hill et al., 2003). Similarly, a proton magnetic resonance spectroscopy study showed performance on the Conners' CPT to be significantly correlated with right dorsolateral volumes in a group of ADHD children. Larger volumes predicted poorer performance on the CPT composite, variability, and reaction time standard error scores. This result was not found in healthy controls, which suggests that the right dorsolateral region may be dysfunctional in ADHD and that the more tissue in this region leads to greater disruption in attention.

One study comparing anatomic MRI measures with the performance of children with ADHD and normal controls on executive function tests found a relationship between reversed normal asymmetry of the caudate and poorer performance on the Stroop color–word test and Wisconsin Card Sorting Test (WCST) (Semrud-Clikeman et al., 2000). Reversal of normal left-greater-than-right asymmetry was related to greater disinhibition on the Stroop and a higher incidence of loss of set on the WCST. Further, the ability to name colors quickly was compromised in the ADHD group and was significantly related to smaller volumes of white matter of the anterior–superior region. Across groups, smaller volumes of this region were associated with worse performance on rapid naming. These findings suggest a role for these brain regions in maintaining attention, which is critical to successful performance on these tasks.

3. Conclusions

Overall, there is now conclusive evidence that ADHD is associated with globally decreased brain volumes relative to age- and sex-matched typically developing controls. This volumetric difference appears to represent a nonprogressive deficit presumably resulting from early genetic and/or environmental factors. These are likely to be equivalent across sex since when patient samples have been recruited to meet equivalent severity criteria (Sharp et al., 1999), results have been statistically comparable, if slightly less prominent, for girls as for boys (Castellanos et al., 2002).

Consistent with neuropsychological findings, the current structural neuroimaging literature implicates several key brain structures involved in ADHD. Evidence suggests decreases in frontal lobe volumes, with a tendency to locate these mostly on the right, although there are also several findings of decreases on the left. The same sort of inconsistency is reported for findings in basal ganglia structures. The safest conclusion, supported by cases of head trauma, is that basal ganglia are an important link in the circuits implicated in ADHD, but that we cannot specify whether such deficits are truly lateralized. At least for the caudate nucleus, the volumetric abnormalities seem to be age-dependent, as they are no longer detected after mid-adolescence (Castellanos et al., 2002, 1994).

The most robustly deviant region in brain associated with ADHD is the cerebellum, both when measured algorithmically as a single unit, which is mostly composed of the hemispheres (Castellanos et al., 2002), and even more so in hand-traced measurements of the posterior–inferior cerebellar vermis (Berquin et al., 1998; Bussing et al., 2002; Castellanos et al., 2001; Mostofsky et al., 1998). Thus, one of the most promising and unexpected frontiers of ADHD research is the exploration of the cerebellum's influence on cortico-striatal-thalamo-cortical (CSTC) circuits (Alexander, DeLong, & Strick, 1986), which choose, initiate, and carry out complex motor and cognitive responses (Graybiel, 1998). The posterior–inferior lobules of the cerebellar vermis appear to differ from the remaining cerebellar hemispheres and vermis in selectively containing dopamine-transporter-like immunoreactive axons (Melchitzky & Lewis, 2000). In light of the hypothesized role of dopamine in the pathophysiology of ADHD, these findings provide additional evidence for the involvement of these structures in this disorder.

The inconsistencies in current neuroanatomical findings, particularly regarding measures of basal ganglia asymmetry, likely result from methodological differences and low statistical power. As mentioned earlier, there is significant heterogeneity in sample characteristics such as age, gender, medication status, and inclusion of ADHD subtype, both within and across studies, which is likely to confound results. More specifically, it has been suggested that the inattentive subtype of ADHD may have a neural basis that is different from that of children with significant symptoms of hyperactivity and impulsivity (Solanto, 2000). MRI studies comparing children with each of these diagnostic subtypes will provide important information about the neural correlates of specific behavioral phenotypes or putative neurobiological endophenotypes (Castellanos & Tannock, 2002). Technical advances in MRI data acquisition and analytic procedures, such as voxel-based morphometry, will likely improve the reliability of anatomic measures. Also, the construction of a normative representative structural brain imaging data set of 433 individuals between the ages of 5 and 18 through the NIH Study of Normal Brain Development will allow us to test ever more sophisticated hypotheses regarding the structure of the brain in ADHD in the near future.

While the current literature reviewed here provides important information about possible neuroanatomical correlates of ADHD, it has not examined whether these structural differences cluster in specific meaningful ways. Are smaller volumes of cerebellum, basal ganglia, and frontal regions independent of each other, or do they reflect a single underlying process? Also, how do the changes in these brain regions correspond to behavioral, neuropsychological, and phenotypic measures of ADHD? These are the questions that the field is now ready to entertain, and which should lead to the formulation and evaluation of comprehensive conceptual models of ADHD and of its putative neurobiological subtypes.

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