Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder

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Background: Although there are many structural neuroimaging studies of attention-deficit/byperactivity disorder (ADHD) in children, there are inconsistencies across studies and no consensus regarding which brain regions show the most robust area or volumetric reductions relative to control subjects. Our goal was to statistically analyze structural imaging data via a meta-analysis to help resolve these issues.

Methods: We searched the MEDLINE and PsycINFO databases through January 2005. Studies must have been written in English, used magnetic resonance imaging, and presented the means and standard deviations of regions assessed. Data were extracted by one of the authors and verified independently by another author.

Results: Analyses were performed using STATA with metan, metabias, and metainf programs. A meta-analysis including all regions across all studies indicated global reductions for ADHD subjects compared with control subjects, standardized mean difference = .408, p < .001. Regions most frequently assessed and showing the largest differences included cerebellar regions, the splenium of the corpus callosum, total and right cerebral volume, and right caudate. Several frontal regions assessed in only two studies also showed large significant differences.

Conclusions: This meta-analysis provides a quantitative analysis of neuroanatomical abnormalities in ADHD and information that can be used to guide future studies.

Key Words: ADHD, meta-analysis, structural imaging, MRI, cerebellum, corpus callosum

ttention-deficit/hyperactivity disorder (ADHD) is characterized by age inappropriate symptoms of inattention and/or hyperactivity or impulsivity which occur for at least 6 months in at least two domains of life and begin prior to the age of 7 (American Psychiatric Association 1994; Faraone 2005). It is estimated that ADHD affects approximately 8% to 12% of school-aged (6-12 years) children (Faraone et al 2003) and 5% of adults (Faraone and Biederman 2005; Faraone et al 2006; Kessler et al 2006). Impairments associated with ADHD have been found across the life span in areas such as academics (Biederman et al 1993; Seidman et al 1998), socioeconomic status and employment (Borland and Heckman 1976; Murphy and Barkley 1996a, 1996b), family life (Murphy and Barkley 1996a), and mental health, including greater rates of disruptive behaviors, oppositional and conduct disorders, and substance use disorders (Biederman et al 1993; McGough et al 2005).

There is now a plethora of psychopharmacological, genetic, neuropsychological, structural, and functional imaging data that provide a strong foundation for a network, or possibly several networks, of neurobiological abnormalities resulting in ADHD symptomatology. For example, imbalances in the noradrenergic and dopaminergic systems are the targets of pharmacological treatment of ADHD symptoms (Pliszka 2005). Also, ADHD is a highly heritable disorder and several genes have been implicated

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in its etiology (Faraone 2004a; Faraone et al 2005). Performance on neuropsychological tasks has been largely suggestive of fronto-subcortical abnormalities, often demonstrating executive dysfunctions (Hervey et al 2004), and as reviewed recently (Bush et al 2005; Seidman et al 2005), structural and functional neuroimaging data show abnormalities throughout the ADHD brain. In short, ADHD has been increasingly recognized as a neurobiological disorder. In light of these data, increasing our understanding of the overall neurobiology, including the neuroanatomical correlates, of ADHD is important. Some studies have already demonstrated that structural abnormalities are related to functional impairments (Casey et al 1997; Castellanos et al 2002), and other studies have demonstrated that treating biological abnormalities can lead to improvements in such functional impairments (Mehta et al 2004; Turner et al 2004). Using converging data from structural, functional, and other experimental studies of ADHD will help us pinpoint problematic brain regions and focus treatment approaches on regions that appear to be most abnormal.

There are now a number of published structural imaging studies assessing volume or area differences of brain regions between ADHD and control individuals. Notably, only one of these studies includes adults and the rest include children and adolescents. Although many of these studies indicate that there are significant reductions in ADHD brain regions, there are inconsistencies across studies such that one study finds an ADHD brain region to be smaller but another study does not (Seidman et al 2005). For example, whereas Semrud-Clikeman et al (1994) found smaller area measurements for the splenium of the corpus callosum for ADHD individuals relative to control subjects, Giedd et al (1994) found no splenium differences. Inconsistencies across studies are also notable for the caudate, with individual studies finding either equal (Hill et al 2003), larger (Mataro et al 1997), or smaller (Hynd et al 1993) caudate measurements in ADHD individuals relative to control subjects. Furthermore, it is unclear which brain regions may have the greatest differences relative to control subjects. More specifically, structural studies indicate that the four major lobes (frontal, parietal, occipital, and temporal) (Castellanos et al 2002), caudate (Castellanos et al 2002; Filipek et al 1997), cerebellum (Berguin et al 1998;

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2 BIOL PSYCHIATRY 2006;xx:xxx

Castellanos et al 2001), and regions of the corpus callosum (CC) (Giedd et al 1994; Hynd et al 1991), among other regions, are smaller in ADHD children and adolescents compared with control subjects. However, it is unclear whether all of these structural reductions are equal in magnitude or whether some reductions are larger than others. Given the numerous regions within the ADHD brain that have been found to be abnormal (e.g., total cerebrum, all four major lobes, cerebellum, caudate, globus pallidus, CC), it is important to gain a knowledge of which brain regions may be most abnormal (i.e., have greatest differences from normal control subjects) to focus research and clinical treatment efforts on brain regions that are likely to have the greatest impact in terms of understanding or effectively treating ADHD symptoms. A meta-analysis can help answer what brain regions these may be and help resolve the inconsistencies noted above.

There have been a number of reviews on structural imaging findings in ADHD (Durston 2003; Seidman et al 2005) but there have been no meta-analyses. A meta-analysis has advantages over qualitative reviews or individual study results because the magnitude of differences within each study can be pooled across all studies assessing that region while using variables such as sample size to weigh the degree to which each study contributes to an overall difference score. Therefore, results for regions whose findings have been equivocal can be quantitatively combined to create a weighted best estimate of the true difference between groups for that region. Since the results for each region are in a common metric (i.e., an effect size), one can then compare across regions to determine which ones show the greatest differences between groups. Thus, we performed a meta-analysis of structural neuroimaging data in ADHD to help clarify inconsistent findings and determine which brain regions show the most robust structural differences between ADHD and control groups. When possible, we also assessed for potential sources of heterogeneity (e.g., age) that might be influencing the meta-analyses effect sizes.

Methods and Materials

We searched the MEDLINE (PubMed) and PsycINFO databases, using the key words ADHD, attention-deficit/hyperactivity disorder, attention deficit disorder, hyperkinetic disorder, neuroimaging, structural imaging, imaging, magnetic resonance imaging, and MRI. Citations from identified articles were also searched for relevant studies. We placed no limit on year of publication and the search was completed in January of 2005. To be included, studies must have been written in English, used magnetic resonance imaging (MRI) (e.g., computed tomography scan studies were not included because of the relatively poor spatial resolution of the images), and must have presented the volume or area means and standard deviations of the regions of interest (ROIs) assessed in both the ADHD and control groups. Studies were excluded if they: 1) only included structural data that was also included in a larger published study; 2) only included brain ratios or only assessed structure widths; 3) had brain regions delineated by voxel based morphometry (VBM); or 4) included twins or siblings as the only control group. Also, since there was only one study of adults (Hesslinger et al 2002) with a small sample, and all other studies were of children and adolescents, this study was not included in the analyses. After excluding studies based on these criteria, 21 studies were identified as being appropriate for inclusion in the meta-analysis. One of these studies (Pineda et al 2002) provided data for two samples of ADHD children resulting in a total of 22 samples for which ROIs were compared between ADHD and control groups. Data were extracted by one of the authors (K.E.M.) and independently verified by another author (E.M.V.).

Analyses were performed using STATA, version 8 (Stata Corporation, College Station, Texas, 2003) by means of the metan, metabias, and metainf programs. Effect sizes for each dependent measure in each study were expressed as the standardized mean difference (SMD) between the ADHD and control area or volume for each region. Standardized mean differences were computed using Cohen's (1988) method as the difference between means divided by the pooled standard deviation. We did not use Hedge's correction for small samples because Cohen's d is more widely understood and the samples were sufficiently large according to the criteria of Green and Hall (1984) (see also Hunter and Schmidt 2004). We used the q-statistics to assess heterogeneity among studies for all ROIs in every study, as well as for each ROI individually, to determine the likelihood that the differences between studies could occur by chance alone. The meta-analyses were performed using the random effects model of DerSimonian and Laird (1986). Under this model, the effects are assumed to have a normal distribution with the mean equal to the pooled effect size and a variance estimated from the data as a function of the number of studies, the q-statistic, and the weight for each study. Studies were weighted by the precision of their SMD estimate (which is proportional to the study sample size). To determine if the results of the meta-analysis were unduly influenced by one study, we conducted a sensitivity analysis by recomputing the pooled SMD after deleting each study observation of volumetric or area differences one at a time. We assessed publication bias (i.e., whether the available literature is biased toward excluding negative studies) using the method of Egger et al (1997). This method regresses the effect size (the effect size divided by its standard error) against the precision of the SMD (the inverse of its standard error). We conducted Egger's tests and influence analyses on meta-analyses with at least three studies. Finally, when possible (i.e., enough studies were present to generate reasonable power), meta-analytic regression (using metareg) was used to test whether effect sizes were influenced by specific study design features (e.g., age of sample).

Listed in Table 1 are demographic and other descriptive data for each of the 21 studies. Across the 21 studies included in this meta-analysis, there were a total of 565 ADHD subjects and 583 control subjects. The mean and modal Ns across the studies were 25.7 and 15, respectively, for the ADHD subjects and 27.8 and 15 for the control subjects. The mean age and age range were 11.0 (9.08-14.6) for ADHD and 11.3 (9.3-14.8) for control subjects. The majority of subjects studied were male. Half (11 of 22) of the ADHD samples were 100% male and 10 of the 22 control samples were 100% male. Across studies, the mean percentage of male ADHD and control subjects was 81.2% and 81.3%, respectively. A 1.5 Tesla magnet was used in all studies except for those of Hynd et al (1990, 1991, 1993), for which a .6 Tesla magnet was used. For ADHD diagnoses, 9 samples used DSM-IV criteria, 12 samples used DSM-III-R criteria, and 1 sample used both DSM-IV and DSM-III-R criteria. Lyoo et al (1996) presented two sets of data. One included subjects who were diagnosed using DSM-III-R criteria via the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al 1985) and another included subjects who were diagnosed based on chart review and/or DISC-C diagnoses. We only included the sample that included all subjects diagnosed via the DISC-C. Ten studies used only

Table 1. Demographics

			D	Con	trol Subje	ects	Matching of ADHD	Magnet		
Study and Year	n	Mean Age	% Male	Dx System	n	Mean Age	% Male	and Control Samples ^a	Strength (Tesla)	Measure
Aylward et al 1996	10	11.3	100	DSM-III-R	11	10.7	100	1–3	1.5	Volume
Baumgardner et al 1996	13	11.3	100	DSM-III-R	27	10.8	78	1, 3	1.5	Area
Berquin et al 1998 ^c	46	11.7	100	DSM-III-R	47	11.8	100	1–3, 6–8	1.5	Both ^b
Bussing et al 2002	5	10.8	75	DSM-IV	19	9.8	74	1–3, 10–11	1.5	Volume
Castellanos et al 1996	57	11.7	100	DSM-III-R	55	12	100	1–3, 6–8	1.5	Both
Castellanos et al 2001	49–50	9.7	0	DSM-IV	49–50	10	0	1–4, 6–8	1.5	Volume
Castellanos et al 2002 ^d	152	10.0	59	DSM-IV	139	10.5	60	1–2, 12	1.5	Volume
Durston et al 2004	30	12.1	100	DSM-IV	30	10.7	100	1–7, 13	1.5	Volume
Filipek et al 1997	15	12.4	100	DSM-III-R	15	14.4	100	1, 3–4	1.5	Volume
Giedd et al 1994	18	11.9	100	DSM-III-R	18	10.5	100	1, 3, 6–8	1.5	Area
Hill et al 2003	23	9.4	74	DSM-IV	24	9.4	67	1, 4–5, 9	1.5	Both
Hynd et al 1990	10	10.1	80	DSM-III-R ^e	10	11.8	80	1–3, 10	.6	Area
Hynd et al 1991	7	9.1	71	DSM-III-R ^e	10	11.8	80	3, 10	.6	Area
Hynd et al 1993	11	11.1	73	DSM-III-R ^e	11	11.0	55	1, 3, 10	.6	Area
Kates et al 2002	13	9.4	100	DSM-IV	13	10	100	1–2, 4	1.5	Volume
Lyoo et al 1996	25	12.5	84	DSM-III-R	20	12.2	85	1–4	1.5	Both
Mataro et al 1997	11	14.6	73	DSM-III-R	19	14.8	84	1, 4	1.5	Area
Mostofsky et al 1998	12	11.3	100	DSM-III-R or DSM-IV	23	11.3	100	1–2, 4	1.5	Area
Mostofsky et al 2002	12	10.1	100	DSM-IV	12	10.2	100	1–2	1.5	Volume
Pineda et al 2002 Hyp/In ^f	15	9.3	47	DSM-IV	15	9.3	47	1–3, 5, 7–9, 14–15	1.5	Volume
Pineda et al 2002 Inat ^f	15	9.3	47	DSM-IV	15	9.3	47	1–3, 5, 7–9, 14–15	1.5	Volume
Semrud-Clikeman et al 1994	15	13.0	100	DSM-III-R ^e	15	14.5	100	1–4	1.5	Area

ADHD, attention-deficit/hyperactivity disorder; Dx, diagnostic; Hyp/In, combined inattentive and hyperactive sample; Inat, inattentive sample; IQ, intelligence quotient; ROI, region of interest.

^{*a*}Matching of ADHD and Control Samples = Demographic variables which were either explicitly stated as being matched or were assessed and showed no statistically significant differences between the ADHD and Control groups: 1 = age; 2 = sex; 3 = handedness; 4 = IQ or IQ estimate; 5 = SES; 6 = Tanner stage; 7 = height; 8 = weight; 9 = grade; 10 = race; 11 = poverty; 12 = birth weight; 13 = education level of mother and father; 14 = head circumference; 15 = encephalic index.

^bBoth = used both volume and area measurements.

^cThe 46 ADHD subjects included in the Berquin et al 1998 study were previously included in Castellanos et al 1996. However, since Berquin et al 1998 assessed additional ROIs, we have included the additional regions measured by Berquin et al 1998 in the meta-analysis.

^dCastellanos et al 2002 mean age is the mean age at initial scan.

^eSubjects met criteria for DSM-III and DSM-III-R ADHD.

^fThe Pineda (2002) study is listed twice, as there are two different samples from this study.

volumetric measurements, 8 studies used area measurements, and 4 studies used both volume and area measurements. With the exception of three studies, all area measurements were used for the CC, cerebellum, and caudate. Most ADHD and control samples were either matched explicitly on or showed no statistically significant differences between groups on age, sex, and handedness. Almost half of the samples were statistically matched on full or estimated intelligence quotient (IQ) and approximately 25% to 30% of the samples were matched on height, weight, or Tanner stage (a measure of physical development). Although several other matching criteria were used, they were used less frequently.

The divisions of the ROIs varied considerably across the 21 studies. For example, whereas one study (Mostofsky et al 2002) presented data for the total parietal lobe, other studies (Castellanos et al 2002; Durston et al 2004) presented data separately for left and right parietal lobe or parietal gray and parietal white. Since the divisions used to measure the ROIs are meaningfully different between studies, many of them could not be included in a meta-analysis to compute an SMD across studies. Nonetheless, 64 ROIs were assessed enough times (i.e., more than once) to be included in the meta-analyses. To present the data in the most comprehensive yet meaningful way possible, we ran two sets of meta-analyses. One set included ROIs that were assessed in at least three studies, and another set included ROIs that were

assessed in only two studies. We recommend that the metaanalyses of ROIs that include data from only two studies be interpreted cautiously. However, in an effort to be more inclusive and comprehensive, we felt it was important to include data for these ROIs. There were 33 ROIs that were assessed in at least three studies and 31 ROIs that were assessed in only two studies. We used Holm's (1979) method to correct for multiple comparisons.

There are two different segmentation methods that have been used for defining and measuring the different regions of the CC. The Witelson (1989) method divides the CC into seven ROIs: rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium. The O'Kusky et al (1988) method divides the CC into only five ROIs: genu, rostral body, midbody, isthmus/posterior body, and splenium. We therefore chose to analyze the CC data in two ways. One way was to conduct separate meta-analyses for each CC subsection for each method (i.e., measurements created using the Witelson [1989] method were not included in the meta-analyses of measurements created using the O'Kusky et al [1988] method). We also conducted meta-analyses that included both methods (i.e., all measurements of the splenium were included regardless of whether they were made using the O'Kusky et al [1988] or Witelson [1989] method) so that we could maximize the number of studies in a single meta-analysis for each region assessed.

4 BIOL PSYCHIATRY 2006;xx:xxx

Table 2. Regions of Interest Assessed in at Least Three Studies That Yielded Significant SMDs Between ADHD and Control Groups

	Number of	Number of Subjects		Volume or Area Difference					Heterogeneity Publication Bias Egger's				
Brain Region	Studies	ADHD Contro		SMD 95%		% Cl	Ζ	р	χ^2	р	Coef	р	Studies ^a
Posterior Inferior Vermis,													
Lobules VIII-X	5	135	163	.774	[.534	1.010]	6.31	<.001	1.22	.874	.946	.296	[3, 4, 6, 11, 18]
Cerebellar Vermis	3	107	119	.671	[.246	1.100]	3.10	.002	4.42	.110	2.520	.673	[3, 6, 18]
Splenium (W)	4	81	77	.593	[.272	.913]	3.62	<.001	2.46	.482	1.06	.877	[10, 11, 16, 22]
Splenium (Both)	6	101	114	.592	[.314	.871]	4.18	<.001	2.53	.772	.700	.747	[2, 10, 11, 13, 16, 22]
Total Cerebral Volume (R)	3	102	100	.500	[.219	.780]	3.49	<.001	.31	.858	.651	.648	[5, 8, 9]
Total Cerebral Volume ^b	8	251	256	.485	[.199	.772]	3.32	.001	11.38	.123	.405	.678	[4, 7, 11, 12, 15, 16, 17, 19]
Cerebellum (R)	3	137	135	.463	[.222	.704]	3.77	<.001	.16	.925	1.680	.158	[5, 6, 8]
Cerebellum (L)	3	137	135	.431	[.190	.673]	3.50	<.001	2.01	.366	-5.070	.457	[5, 6, 8]
Caudate (R)	6	160	174	.344	[.123	.565]	3.05	.002	5.04	.411	-1.680	.172	[1, 4, 5, 6, 9, 11]

Table is organized by size of SMD with the largest difference at the top of the table.

SMD, standardized mean difference; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; Coef, coefficient; W, only includes studies which used the Witelson (1989) method for segmenting the corpus callosum; Both; includes studies that used either the Witelson (1989) or O'Kusky et al (1988) method for segmenting the corpus callosum; R, right; L, left; ROI, region of interest.

^aStudies: [1] Aylward et al 1996, [2] Baumgardner et al 1996, [3] Berquin et al 1998, [4] Bussing et al 2002, [5] Castellanos et al 1996, [6] Castellanos et al 2001, [7] Castellanos et al 2002, [8] Durston et al 2004, [9] Filipek et al 1997, [10] Giedd et al 1994, [11] Hill et al 2003, [12] Hynd et al 1990, [13] Hynd et al 1991, [15] Kates et al 2002, [16] Lyoo et al 1996, [17] Mataro et al 1997, [18] Mostofsky et al 1998, [19] Mostofsky et al 2002, [22] Semrud-Clikeman et al 1994.

^bAlthough not explicitly stated in Castellanos et al 2002, personal communication with Dr. Castellanos (March 3, 2006) verified that subjects in the 1996 and 2001 reports were included in the 2002 report. Therefore, for the total cerebral volume ROI, only the value from the 2002 report was included in analyses since the values of the ROIs in the 1996 and 2001 reports were based on smaller samples than that of 2002.

Results

A meta-analysis including all brain regions measured across all studies indicated global reductions for the ADHD subjects compared with control subjects, SMD = .408, Z = 17.21, p <.001, 95% confidence interval (.361–.454). Not surprisingly, there was also significant heterogeneity across regions and studies, $\chi 2 = 437.09$, p < .001. Regions of interest that were assessed in at least three studies are shown in Tables 2 and 3. Table 2 presents ROIs that yielded significant SMDs between ADHD and control subjects. Table 3 presents ROIs that were assessed in at least three reports and failed to yield significant SMDs. Also included in those tables are the total *N*s across the studies for each ROI, the SMD statistics, and the results of the heterogeneity and publication bias tests.

In Table 2, the region assessed most frequently, with eight studies, was total cerebral volume. This was followed by regions of the CC, caudate, and cerebellum. The SMDs indicate that the largest significant differences between ADHD and control individuals are for cerebellar ROIs followed by the splenium, right and total cerebral volume, and the right caudate. Egger's tests for all ROIs found no evidence for publication bias, and influence analysis tests indicated that no single study accounted for the significant SMDs in any of the meta-analyses.

In Table 3, one can see that although other regions of the CC, as well as the total CC, are studied as frequently, or almost as frequently, as the splenium, they do not show significant differences between ADHD and control subjects. Additionally, although other cerebellar vermal regions have been studied with relative frequency, they do not show statistically significant differences, as does the posterior inferior region of the vermis. We also point out that there are a number of ROIs that have medium to large SMDs (according to Cohen's [1988] characterization of large effect = .80, medium effect = .50, and small effect = .20) and *p* values less than .05 (e.g., bilateral prefrontal gray and right globus pallidus) but did not remain significant once Holm's (1979) correction for multiple comparisons was applied. Despite medium SMDs for prefrontal white matter, there

is significant heterogeneity indicating that although there are modest differences between ADHD and control groups within one or more individual studies, there is also a large degree of variability in results across studies for that ROI. Finally, one can see evidence of publication bias for bilateral prefrontal white matter and left prefrontal gray matter.

Presented in Table 4 are ROIs that were assessed in only two studies and show significant SMDs between the ADHD and control subjects. The only ROIs with differences large and significant enough to withstand Holm's (1979) correction for multiple comparisons are several frontal ROIs and the cerebellum. Notably, although there are only two measurements for each region, the frontal SMDs are quite large (all greater than 1.0).

Table 5 indicates ROIs that were assessed in two studies and did not yield significant SMDs. Consistent with the lack of significant differences in all non-splenium CC measures using the Witelson (1989) method, the non-splenium CC regions using the O'Kusky et al (1988) method do not show significant reductions either. Although frontal gray and white matter and premotor ROIs show substantial SMDs ranging from .59 to .75, they also show statistically significant levels of heterogeneity, indicating rather variable results across the two studies in each meta-analysis. Due to the lack of power for the meta-analyses in this table, we need to interpret these results with caution. For example, the measures of intracranial volume, frontal lobe, right amygdala, and the splenium using the O'Kusky et al (1988) method failed to remain significant after correction for multiple comparisons. Similarly, the right putamen is at trend level significance and gray and white matter have medium-sized SMDs. Given that there were only two measures in these meta-analyses, we cannot rule out the possibility that the differences would be significant with adequate power. More studies would be needed to clarify these results.

We used meta-analytic regression to assess for the effects of certain study design features on the SMDs. We conducted this analysis only if the ROI had at least four measurements from different studies and had either a significant SMD or had signif-

E.M. Valera et al

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Table 3. Regions of Interest Assessed in at Least Three Studies That Did Not Yield Significant SMDs Between ADHD and Control Groups

	Number of	Number of Subjects		Volume or Area Difference				Heterogeneity Publication Bias Egger's				
Brain Region	Studies	ADHD	Control	SMD	95% CI	Ζ	р	χ^2	р	Coef	р	Studies ^a
Total Cerebral Volume (L)	3	102	100	.375	[.096 .653]	2.64	.008	.73	.695	.805	.723	[5, 8, 9]
Prefrontal Gray (L)	3	55	55	.845	[.154 1.540]	2.40	.017	5.33	.070	5.19	.002	[8, 15, 19]
Prefrontal White (L)	3	55	55	.681	[460 1.820]	1.17	.242	14.41	.001	8.45	.018	[8, 15, 19]
Prefrontal Gray (R)	3	55	55	.688	[.110 1.260]	2.34	.020	3.90	.142	3.45	.470	[8, 15, 19]
Prefrontal White (R)	3	55	55	.577	[212 1.370]	1.43	.152	7.25	.027	6.33	.028	[8, 15, 19]
Anterior Vermis, Lobules I–V	4	86	113	.400	[040 .840]	1.78	.075	5.77	.124	-1.43	.636	[3, 4, 11, 18]
Posterior Superior Vermis,												
Lobules VI–VII	4	86	113	.270	[327 .868]	.89	.375	10.45	.015	4.16	.180	[3, 4, 11, 18]
Rostrum (W)	3	58	53	.307	[113 .727]	1.43	.152	2.46	.292	5.83	.632	[10, 16, 22]
Genu (Both)	6	101	114	.243	[030 .517]	1.74	.081	3.39	.640	1.67	.485	[2, 10, 11, 13, 16, 22]
Rostral Body (Both)	5	78	90	.347	[112 .806]	1.48	.138	8.26	.083	.56	.916	[2, 10, 13, 16, 22]
Anterior Midbody (W)	3	58	53	.267	[109 .643]	1.39	.164	1.41	.495	6.30	.380	[10, 16, 22]
Posterior Midbody (W)	3	58	53	.245	[332 .823]	.83	.405	4.58	.101	3.57	.835	[10, 16, 22]
lsthmus (Both)	5	78	90	.356	[095 .807]	1.55	.122	7.93	.094	3.27	.471	[1, 10, 13, 16, 22]
Genu (W)	4	81	77	.186	[128 .500]	1.16	.246	2.31	.511	-3.91	.569	[10, 11, 16, 22]
Rostral Body (W)	3	58	53	.372	[336 1.080]	1.03	.303	6.76	.034	13.78	.381	[10, 16, 22]
lsthmus (W)	3	58	53	.367	[243 .977]	1.18	.238	5.06	.080	.26	.990	[10, 16, 22]
Corpus Callosum (Both)	4	108	121	.402	[.047 .758]	2.22	.027	4.73	.193	3.51	.095	[2, 5, 11, 22]
Corpus Callosum (W)	3	95	94	.430	[055 .916]	1.74	.083	4.65	.098	4.17	.182	[5, 11, 22]
Globus Pallidus (R)	3	117	115	.568	[.117 1.020]	2.47	.013	4.80	.091	1.58	.741	[1, 5, 6]
Globus Pallidus (L)	3	117	115	.479	[.057 .901]	2.22	.026	4.25	.120	3.50	.128	[1, 5, 6]
Caudate	4	190	193	.253	[188 .693]	1.12	.261	6.49	.090	94	.595	[1, 4, 7, 11]
Caudate Head (L)	5	67	75	.189	[373 .750]	.66	.510	10.87	.028	12.73	.268	[9, 14, 17, 20, 21]
Caudate Head (R)	5	67	75	.248	[661 .166]	1.17	.240	6.02	.198	-1.95	.878	[9, 14, 17, 20, 21]
Caudate (L)	6	160	174	.286	[019 .591]	1.84	.066	8.14	.149	-1.32	.435	[1, 4, 5, 6, 9, 11]

SMD, standardized mean difference; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; Coef, coefficient; L, left; R, right; W, only includes studies which used the Witelson (1989) method for segmenting the corpus callosum; Both, includes studies that used either the Witelson (1989) or O'Kusky et al (1988) method for segmenting the corpus callosum.

^aStudies: [1] Aylward et al 1996, [2] Baumgardner et al 1996, [3] Berquin et al 1998, [4] Bussing et al 2002 [5] Castellanos et al 1996, [6] Castellanos et al 2001, [7] Castellanos et al 2002, [8] Durston et al 2004, [9] Filipek et al 1997, [10] Giedd et al 1994, [11] Hill et al 2003, [13] Hynd et al 1991, [14] Hynd et al 1993, [15] Kates et al 2002, [16] Lyoo et al 1996, [17] Mataro et al 1997, [18] Mostofsky et al 1998, [19] Mostofsky et al 2002, [20] Pineda et al 2002 (combined inattentive and hyperactive sample), [21] Pineda et al 2002 (inattentive sample), [22] Semrud-Clikeman et al 1994.

icant heterogeneity in the absence of a significant SMD. This included total cerebral volume as well as cerebellar, CC, and caudate ROIs. We assessed for the effects of mean age (range from 9.4 to 14.6), diagnostic system used (i.e., what ADHD criteria were used), and IQ. There were no ROIs that showed significant effects for any of these variables. We also attempted to assess for the effects of either lifetime or current stimulant medication status. However, since a number of studies either had missing (e.g., Lyoo et al 1996; Baumgardner et al 1996; Giedd

et al 1994; Kates et al 2002) or ambiguous data (Hill et al 2003) pertaining to lifetime or current medication history, there were insufficient data for most ROIs to even conduct such analyses. For example, only total cerebral volume and the posterior inferior vermis had enough observations to conduct metaregression analyses and only to examine effects of stimulant medication history (but not current status). Neither of these ROIs showed effects of stimulant medication history, but given the general lack of medication data and the low power to

Table 4.	Regions of Interest	Assessed in Two	Studies That	Yielded Significant	SMDs Between	ADHD and Contr	ol Groups
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Brain Region	Number	of Subjects		Volume or Area	Heterogeneity				
	ADHD	Control	SMD	95% CI	Ζ	р	χ^2	р	Studies ^a
Prefrontal	25	25	1.364	[.742 1.986]	4.300	<.001	.420	.517	[15, 19]
Frontal Lobes	25	25	1.208	[.599 1.818]	3.890	<.001	.700	.404	[15, 19]
Deep frontal white matter	25	25	1.148	[.545 1.750]	3.730	<.001	.150	.694	[15, 19]
Deep frontal white matter (L)	25	25	1.140	[.536 1.743]	3.700	<.001	.740	.391	[15, 19]
Deep frontal white matter (R)	25	25	1.054	[.459 1.649]	3.470	<.001	.000	.993	[15, 19]
Cerebellum ^b	175	163	.452	[.236 .668]	4.10	<.001	.01	.918	[7, 11]

Table is organized by size of SMD with the largest difference at the top of the table.

SMD, standardized mean difference; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; L, left; R, right; ROI, regions of interest.

^aStudies: [7] Castellanos et al 2002, [11] Hill et al 2003, [15] Kates et al 2002, [19] Mostofsky et al 2002.

^bAlthough not explicitly stated in Castellanos et al 2002, personal communication with Dr. Castellanos (March 3, 2006) verified that subjects in the 1996 report were included in the 2002 report. Therefore, for the cerebellum, only the value from the 2002 report was included in analyses since the value of the ROI in the 1996 report was based on a smaller sample than that of 2002.

6 BIOL PSYCHIATRY 2006;xx:xxx

Table 5. Regions of Interest Assessed in Two Studies Which Did Not Yield Significant SMDs Between ADHD and Control Groups

	Number of Subjects			Volume or Area Diff	Heterogeneity				
Brain Region	ADHD	Control	SMD	95% CI	Ζ	р	χ^2	р	Studies ^a
Intracranial Volume	42	53	.502	[.086 .918]	2.370	.018	.000	.982	[8, 18]
Gray Matter	164	151	.607	[083 1.297]	1.720	.085	2.660	.103	[7, 19]
Cerebral Gray Matter (L)	45	45	.246	[169 .661]	1.160	.245	.100	.757	[8, 9]
Cerebral Gray Matter (R)	45	45	.372	[045 .790]	1.750	.081	.580	.445	[8, 9]
White Matter	164	151	.663	[138 1.464]	1.620	.105	3.360	.067	[7, 19]
Cerebral White Matter (L)	45	45	.196	[521 .913]	.540	.592	2.640	.104	[8, 9]
Cerebral White Matter (R)	45	45	.251	[488 .989]	.660	.506	2.770	.096	[8, 9]
Frontal Lobe (L)	60	60	.386	[.024 .748]	2.090	.037	.860	.355	[6, 12]
Frontal Lobe (R)	60	60	.365	[.004 .726]	1.980	.047	.010	.928	[6, 12]
Frontal Gray Matter	164	151	.752	[240 1.744]	1.490	.137	4.760	.029	[7, 19]
Frontal White Matter	164	151	.753	[290 1.796]	1.410	.157	5.200	.023	[7, 19]
Premotor	25	25	.586	[-1.118 2.289]	.670	.500	8.140	.004	[15, 19]
Total Midbody (O'K)	20	37	.307	[242 .856]	1.100	.273	.000	.952	[2, 13]
Genu (O'K)	20	37	.422	[132 .975]	1.490	.136	.560	.455	[2, 13]
Rostral Body (O'K)	20	37	.336	[361 1.032]	.950	.345	1.470	.225	[2, 13]
lsthmus (O'K)	20	37	.386	[616 1.388]	.750	.450	2.750	.097	[2, 13]
Splenium (O'K)	20	37	.592	[.034 1.150]	2.080	.038	.070	.794	[2, 13]
Putamen (R)	67	66	.339	[004 .682]	1.940	.053	.510	.477	[1, 5]
Putamen (L)	67	66	.492	[303 1.286]	1.210	.225	2.770	.096	[1, 5]
Amygdala (R)	72	70	.483	[.149 .817]	2.830	.005	.410	.522	[5, 9]
Amygdala (L)	72	70	.277	[054 .608]	1.640	.101	.440	.508	[5, 9]
Hippocampus (L)	72	70	051	[380 .278]	.300	.762	.030	.854	[5, 9]
Hippocampus (R)	72	70	129	[459 .200]	.770	.442	.160	.690	[5, 9]
Lateral Ventricles (L)	72	70	.234	[097 .564]	1.390	.165	.520	.470	[5, 9]
Lateral Ventricles (R)	72	70	.035	[294 .364]	.210	.835	.220	.641	[5, 9]

SMD, standardized mean difference; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; O'K, only includes studies which used the O'Kusky et al (1988) method for segmenting the corpus callosum.

^aStudies: [1] Aylward et al 1996, [2] Baumgardner et al 1996, [5] Castellanos et al 1996, [6] Castellanos et al 2001, [7] Castellanos et al 2002, [8] Durston et al 2004, [9] Filipek et al 1997, [12] Hynd et al 1990, [13] Hynd et al 1991, [18] Mostofsky et al 1998, [19] Mostofsky et al 2002.

detect differences, the findings need to be interpreted cautiously.

Discussion

This meta-analysis provides a quantitative analysis of the structural imaging findings for ADHD youth. By conducting meta-analyses for each ROI, we demonstrated that the brain regions most frequently assessed and showing the largest and most significant area or volumetric reductions relative to control subjects include cerebellar ROIs, in particular the posterior inferior vermis, as well as the splenium of the CC, total and right cerebral volume, and right caudate. Regions of interest assessed in only two studies but which show large significant differences between ADHD and control groups include prefrontal and other frontal lobe ROIs, as well as deep frontal white matter.

We also show that there are ROIs that have been assessed in at least three studies but do not show statistically significant differences relative to the control subjects. These include left cerebral volume, bilateral prefrontal gray and white matter, total and all non–splenium regions of the CC, anterior and posterior superior regions of the cerebellar vermis, bilateral globus pallidus and caudate head, caudate, and left caudate. Though some of these ROIs have medium to large effect sizes (e.g., bilateral prefrontal white and left prefrontal gray matter), they also show significant heterogeneity and/or publication bias. Other ROIs (e.g., right prefrontal gray, right globus pallidus) with reasonable effect sizes did not meet our more stringent alpha level when corrected for multiple comparisons. There are also a number of ROIs assessed in only two studies that did not show significant reductions in the ADHD groups relative to control subjects. However, these data should be interpreted with caution (especially if effect sizes are medium to large and there is no significant heterogeneity), as there was rather limited power to detect significant differences. More studies are needed to clarify these results.

The data in this meta-analysis add to previous qualitative reviews (Seidman et al 2005) by quantitatively combining findings from individual studies to provide a comprehensive summary of area and volumetric reductions in the ADHD brain. These results are particularly helpful in resolving inconsistent results across individual studies (e.g., inconsistent findings regarding CC subregions and the caudate) and also provide information about which ROIs show the greatest differences relative to control subjects. Results of our data extraction highlighted the tremendous variability in ROI measurements across studies, which limited our ability to perform more powerful meta-analyses on a number of ROIs. For example, as we can see from Tables 3, 4, and 5, although the frontal regions have been studied extensively, the tremendous diversity in how these frontal ROIs have been measured makes it impossible to combine all or even most studies in one meta-analysis. Diversity such as this consequently makes a meta-analysis of some ROIs impossible (i.e., if there is only one measurement) and also reduces the power of each meta-analysis, making it particularly more difficult to detect effects of methodological variations across studies.

Overall, the results of our study also emphasize the importance of measuring ROIs precisely and to question, when large

E.M. Valera et al

ROIs are measured, whether there are particular subunits that would be more meaningful to assess. For example, our findings show small and nonsignificant effect sizes for total CC reductions in ADHD individuals relative to control subjects. Theories about ADHD being a frontal-striatal disorder (Castellanos 1997) have led some researchers (Giedd et al 1994) to predict that the anterior or genu region of the CC would be affected, since it connects homologous regions of the frontal cortex. However, these meta-analysis data show that when measured in subunits, the only region within the CC that is different between ADHD and control subjects is the splenium located in the posterior region of the CC. Likewise, global measurements of the cerebellum in both individual studies and our meta-analysis show significant reductions relative to control subjects. However, our results indicate that not all cerebellar ROIs are equally reduced or reduced at all. For example, it is clear that the posterior inferior vermis is smaller in ADHD individuals. However, no differences were found for the posterior superior or anterior vermis.

In a related issue, all structural studies to date have used relatively crude segmentation techniques to examine the cerebellum. It is possible that differences in regions other than the posterior inferior vermis have been masked because ROIs were too large. Thus, measuring smaller ROIs could be useful in revealing potential differences embedded in larger regions. This issue can now be addressed with a novel method by Makris et al (2003) and Seidman et al (2005), in which the cerebellum is divided into 64 gyral-based units, 20 of which are within each of the cerebellar hemispheres. This type of fine-grained analysis of the cerebellum will help resolve this issue.

Though it is common for ADHD research to focus on frontal or frontal-striatal regions, these meta-analysis results emphasize the need to provide equal attention to other regions such as the cerebellum and splenium. These data also provide additional support for the growing notion that ADHD pathophysiology may involve a cerebellar-prefrontal-striatal network (Giedd et al 2001). Several studies have reported hypofrontality and/or striatal abnormalities (Casey et al 1997; Lou et al 1989; Rubia et al 1999; Zametkin et al 1990; Zang et al 2005), and we found that relative to control subjects, ADHD adults showed reduced activation in the left cerebellum and a trend for reduced activation in the contralateral right prefrontal region during performance on a verbal working memory task (Valera et al 2005).

More direct support for involvement of this network comes from another recent study using diffusion tensor imaging (DTI). Diffusion tensor imaging is a newer imaging technique that can be used to assess fractional anisotropy (FA) of white matter tracts in the brain, with lower white matter (WM) FA values indicating alterations in WM fiber orientation and integrity (Makris et al 2002). In this first study of DTI in ADHD children, Ashtari et al (2005) found that relative to control subjects, ADHD children had decreased FA in several areas including right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, and left cerebellum. Additionally, they found that decreased FA values in the cerebellar region were associated with increased severity of inattentive scores of the Conners' Attention Deficit Scale. These data support the role of frontal-striatal and cerebellar abnormalities in the pathophysiology of ADHD.

Our meta-analysis also provides valuable information to guide future MRI studies of ADHD. For example, the anterior cingulate cortex, known for its role in cognitive control (Bush et al 2000), has only been assessed in one structural MRI study (Mostofsky et al 2002), despite information from functional MRI studies suggesting its potential importance in ADHD (Bush et al 2005). This would be a promising ROI for future structural studies to investigate.

The results of our study need to be viewed in light of the limitations of meta-analytic methods. There are other structural imaging studies of ADHD that we did not include because of different methodology that did not allow for reasonable comparison with more standard structural MRI studies. For example, Overmeyer et al (2001) conducted a VBM study and Sowell et al (2003) used a surface-based computational image analytic technique to map regional brain size and cortical gray matter abnormalities. Consistent with our meta-analysis results, Overmeyer et al (2001) found no statistically significant differences between ADHD/hyperkinetic children and normal control subjects for global measures of cerebral gray and white matter. They also found volumetric reductions on the right for the superior frontal and posterior cingulate gyrus and bilaterally for a "putamen/globus pallidus" ROI. These latter findings cannot be compared with our results, as there are not enough data to conduct meta-analyses for those ROIs. Interestingly, Sowell et al (2003) demonstrated both reductions and increases within different subregions of the frontal, temporal, and parietal cortices. Though not statistically significant, they found an increase in the superior frontal cortex, which was positively correlated with a measure of hyperactivity in the ADHD children. More studies using these newer methodologies are required to determine their consistency with more standard methodologies and the relative merits of each. Nonetheless, these findings highlight the importance of well-defined and smaller ROIs for future ADHD structural MRI studies.

The meta-analytic results also need to be viewed in the context of the restricted age range and gender composition of the individuals assessed across the structural imaging studies. The highest ADHD mean age studied was 14.6 and the mean age across all the studies was approximately 11 years old. As noted earlier, there is only one small study of adults (Hesslinger et al 2002). This lack of both adolescent and adult data is especially problematic in the context of gaining insight into the developmental course of ADHD over time (Faraone 2004b) and specifically in examining the potential effects of development on volumetric brain abnormalities in ADHD. It would have been particularly helpful to be able to replicate the pattern of caudate normalization by mid adolescence shown by Castellanos et al (2002). However, even with enough power, it would have been impossible to replicate this pattern of normalization in our meta-analysis, since the caudate only appears to begin to normalize by the age of 15 in the Castellanos et al (2002) study and the oldest ADHD mean age in any study in this meta-analysis was 14.6. Nonetheless, examining volumetric abnormalities from a developmental perspective is important for understanding ADHD from a life span perspective and should be considered in future reviews and meta-analyses when more data allow such analyses. Thus, there is a critical need for adolescent and adult structural imaging data.

Likewise, female subjects are extremely underrepresented in these studies. Only approximately 20% of the individuals studied were female and only 50% (11 of 22) of ADHD samples even included female subjects, whereas 95% (all but one) included male subjects. Structural imaging studies of female subjects will be required to examine potential gender effects in ADHD structural abnormalities. Finally, because of the combination of the limited number of measurements for most of the ROIs assessed and missing data for particular questions of interest, there was relatively little power to detect effects of methodolog-

8 BIOL PSYCHIATRY 2006;xx:xxx

ical variations on SMDs using meta-analytic regression. For example, it would have been informative to test for the effects of lifetime or current medication status on volumetric differences across structures. However, due to missing data on medication status for numerous studies (e.g., Baumgardner et al 1996; Giedd et al 1994; Kates et al 2002; Lyoo et al 1996), combined with the already low number of observations per ROI, we were only able to test for the effects of lifetime stimulant medication status for total cerebral volume and the posterior inferior vermis. Although our analyses did not detect any effect of stimulant medication status in the particular analyses we conducted, given the relatively low power and the fact that most ROIs could not even be tested, we cannot rule out the possibility that medication status might have affected ADHD brain volumes.

In sum, the results of this meta-analysis provide a significantly clearer picture of structural abnormalities in ADHD youth than had previously been available. The regions with the greatest significant reductions relative to control subjects are the cerebellum, in particular the posterior inferior vermis, the splenium of the CC, total and right cerebral volume, the right caudate, and various frontal regions. This meta-analysis also underscores the need for structural studies that include female subjects, ADHD individuals aged 15 and older, and analyses of structures that have been shown to be functionally abnormal in ADHD populations (i.e., the cingulate). These types of methodological advances will add to our growing knowledge of the neurobiological substrate of ADHD across the life span.

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BIOL PSYCHIATRY 2006;xx:xxx 9

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