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Gray Matter Alterations in Adults with Attention-Deficit/Hyperactivity Disorder Identified by Voxel Based Morphometry

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Abstract

Background—Gray and white matter volume deficits have been reported in many structural magnetic resonance imaging (MRI) studies of children with attention-deficit/hyperactivity disorder (ADHD); however, there is a paucity of structural MRI studies of adults with ADHD. This study used voxel based morphometry and applied an a priori region of interest approach based on our previous work, as well as from well-developed neuroanatomical theories of ADHD.

Methods—Seventy-four adults with DSM-IV ADHD and 54 healthy control subjects comparable on age, sex, race, handedness, IQ, reading achievement, frequency of learning disabilities, and whole brain volume had an MRI on a 1.5T Siemens scanner. A priori region of interest hypotheses focused on reduced volumes in ADHD in dorsolateral prefrontal cortex, anterior cingulate cortex, caudate, putamen, inferior parietal lobule, and cerebellum. Analyses were carried out by FSL-VBM 1.1.

Results—Relative to control subjects, ADHD adults had significantly smaller gray matter volumes in parts of six of these regions at $p < .01$, whereas parts of the dorsolateral prefrontal cortex and inferior parietal lobule were significantly larger in ADHD at this threshold. However, a number of other regions were smaller and larger in ADHD (especially fronto-orbital cortex) at this threshold. Only the caudate remained significantly smaller at the family-wise error rate.

Conclusions—Adults with ADHD have subtle volume reductions in the caudate and possibly other brain regions involved in attention and executive control supporting frontostriatal models of ADHD. Modest group brain volume differences are discussed in the context of the nature of the samples studied and voxel based morphometry methodology.

Keywords

Attention-deficit/hyperactivity disorder; caudate; cerebellum; prefrontal cortex; structural MRI; voxel based morphometry

Attention-deficit/hyperactivity disorder (ADHD) in adults has gradually become recognized as a valid and reliable disorder, sharing many features with the childhood syndrome (1). A substantial percentage of individuals diagnosed with ADHD in youth have symptoms persisting into adulthood (2,3) and epidemiologic data indicate that approximately 4% of adults in the United States suffer from ADHD (4,5). Adults with ADHD share similar clinical features, comorbidities (6,7), neuropsychological dysfunctions (8–10), and functional impairment with ADHD children (1,11–15). The persistence of ADHD into adulthood in two thirds of childhood cases (16) supports the hypothesis that structural brain abnormalities present in childhood will persist to adulthood (17,18).

Little is known about the neuroanatomy of adult ADHD (19,20). Whereas there are more than two dozen quantitative reports of structural neuroimaging using magnetic resonance imaging (MRI) in ADHD children from more than a dozen research groups (reviewed in [17]) and summarized in two meta-analyses (21,22), there are only a few structural imaging studies of adults with ADHD: two articles from one research group (23,24), an article by another group (25), and a number of articles from our group (18,26–28).

Hesslinger *et al.* (23) and Perlov *et al.* (24) reported a significant reduction of the left fronto-orbital cortex (FOC) (23) in a small sample, and after specifically testing for hippocampus and amygdala volume differences in a subsequent analysis with a larger sample, they reported a null finding compared with control subjects (24), similar to our negative results (18). Frodl *et al.* (25) reported no significant differences in hippocampus but found a bilateral reduction in amygdala compared with healthy control subjects. We found significant gray matter volume reductions in ADHD in dorso-lateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the cerebellum (18,28) compared with healthy control subjects. We also found significant cortical thinning in ADHD involving the inferior parietal lobule (IPL), DLPFC, and ACC in the sample (26) used in the Seidman *et al.* (18) volumetric study. We evaluated the structural connectivity network underlying attention and executive functions (EFs), demonstrating white matter abnormalities measured by fractional anisotropy in the cingulum bundle and the superior longitudinal fasciculus II in a completely independent sample of ADHD adults (27). These findings largely emphasize cortical circuits (DLPFC, ACC, and IPL) and subcortical circuits with reciprocal connections to DLPFC, including the caudate, putamen, and cerebellum (29).

Our empirical work has been guided by a conceptual model of the core neurocognitive deficits in ADHD, including attention and EFs (30), and the functional neuroanatomy of neural circuits hypothesized to underlie these functions (17,18,26–29,31). The likely persistence of structural abnormalities is supported by the continued deficits in attention and EFs in adults with ADHD, reflected in many neuropsychological studies (8–11,32,33) and growing numbers of functional MRI studies in ADHD adults showing abnormalities in prefrontal cortex, ACC, and other regions of the network for attention and EFs (34–36). Thus, many investigators have conceptualized the neurobiology of ADHD as involving structural and functional brain abnormalities in frontal-striatal circuitry that governs attention and EFs (37–42), and we have utilized this model to guide our work.

One of the most replicated alterations in ADHD in childhood is a significantly smaller volume in the caudate (43–45) and a smaller putamen-pallidum region, identified by voxel

based morphometry (VBM) meta-analysis (22). The caudate, along with the putamen, and globus pallidus are part of discrete, somatotopically distributed circuits essential for EFs, including prefrontal–basal ganglia–thalamic loops (46). Damage to the striatum has been hypothesized to be associated with ADHD (47). Striatal lesions in animals produce hyperactivity and poor working memory and response inhibition performance (46), and the striatum has one of the highest densities of dopaminergic synapses in the brain (48). Finally, stimulant medications, commonly used to treat ADHD, increase synaptic dopamine by blocking the dopamine transporter in striatum (49). Because Castellanos *et al.* (45) demonstrated that significant differences in caudate volume between children with ADHD and control subjects diminished by the oldest age studied (19 years), it is possible that this region normalizes over time. It is also possible that the absence of caudate differences in our sample of 24 adults with ADHD compared with 18 control subjects (18) was due to small samples sizes. This suggests that larger studies of ADHD adults are needed to determine whether there are persistent caudate or other striatal alterations.

Finally, we addressed the cerebellum, given its involvement in a number of cognitive and affective processes beyond simple motor functions (50). Middleton and Strick (51) demonstrated cerebellar–cortical connections that provide an anatomical substrate for a possible cerebellar–prefrontal dysfunction in ADHD (17,52). Many researchers studying the cerebellum in ADHD children have observed structural abnormalities, including volume reduction in specific regions of the vermis. For example, reductions in the posterior inferior lobules, VIII to X, of the cerebellar vermis have been found for ADHD boys (43–45,53–56). Durston *et al.* (56) found smaller overall right cerebellar volumes in a group of 30 ADHD children. In a study of 152 children and adolescents with ADHD and 139 control subjects, after adjusting for total cerebral volume, only the difference for the cerebellar volume remained significant (45). Thus, cerebellar gray matter is hypothesized to be an important part of the brain affected in ADHD.

Based on this prior work and conceptual model, we hypothesized that ADHD adults would have smaller volumes in DLPFC, IPL, ACC, caudate, putamen, and cerebellar gray matter. Because these a priori regions of interest (ROIs) have strong theoretical and empirical support, they are appropriate for directional hypothesis testing. Second, we conducted exploratory analyses on these ROIs to assess whether any of these regions were significantly larger in ADHD and on other ROIs not specifically predicted to be part of ADHD. To the best of our knowledge, this is the first VBM study of the brain in adults with ADHD.

Methods and Materials

Subjects

Male and female subjects between the ages of 18 and 59 participated in the study. Attention-deficit/hyperactivity disorder ($n = 74$) and control ($n = 54$) adults were group matched to be comparable on age, sex, handedness, and race. A preliminary imaging study of 32.8% of these subjects (24 ADHD, 18 control subjects) has been previously published (18,26) utilizing volumetric and cortical thickness analyses, respectively, and a slightly larger (38.3%) sub-sample (26 ADHD, 23 control subjects), including all those in the original sample, was used in a volumetric analysis of the effects of comorbidity of bipolar disorder and ADHD (28). This is the first report of the complete dataset of adults 18 or older, using subjects in which we extend matching of cases and control subjects on the same characteristics as in the first sample by Seidman *et al.* (18) and excluding subjects with bipolar disorder comorbidity previously reported (28). Exclusion criteria were deafness, blindness, psychosis, neurological disorder, sensorimotor handicaps, inadequate command of the English language, current alcohol or substance abuse or dependence defined by DSM-IV or a chronic history of abuse or dependence as defined by clinician review, or a full-scale

IQ less than 80 as measured by the Wechsler Adult Intelligence Scale-Third Edition (57). Socioeconomic status was assessed with the Hollingshead Four Factor Index of Social Status scale (58).

Regarding lifetime medication history for ADHD participants, 23 had never been prescribed psychotropic medications, 22 had received stimulants, 17 had received stimulants and antidepressants, 3 had received antidepressants only, and 9 had received a combination of other psychotropic medications. For control participants, 47 had never been prescribed psychotropic medications, 5 had been prescribed antidepressants, 1 had received both stimulants and antidepressants, and 1 had received other psychotropic medications. Patients with ADHD who were currently being treated with stimulants underwent a 24-hour washout period before scanning ($n = 21$).

We recruited ADHD subjects from referrals to psychiatric clinics at the Massachusetts General Hospital (MGH) and advertisements in the greater Boston area and control subjects through advertisements in the same geographic areas. After a complete description of the study, written informed consent was obtained, and all participants received an honorarium for participating. The study was approved by the MGH Human Subjects committee.

Clinical Assessment

Attention-deficit/hyperactivity disorder adults were included if they met full criteria for ADHD according to the DSM-IV, with childhood onset and persistence into adulthood. We conducted direct interviews with all subjects. Trained, lay interviewers, blind to ascertainment status, interviewed all adults with the Structured Clinical Interview for DSM-IV (59) supplemented with modules from the Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiological Version (60) to cover ADHD and other childhood disorders. Throughout the study, they were supervised in weekly meetings by board-certified child and adolescent psychiatrists and experienced licensed psychologists, who formed the Diagnostic Committee. During the study, all interviews were audiotaped for random quality control assessments.

The interviewers' data were reviewed by the Diagnostic Committee so that a DSM-IV consensus diagnosis (61) could be made. The Diagnostic Committee was blind to the subject's ascertainment group, all data collected from other family members, and all nondiagnostic (e.g., brain imaging) data. Diagnoses were made for two points in time: lifetime and the month before the interview.

We computed kappa coefficients of diagnostic agreement by having experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses included: ADHD (.88), conduct disorder (1.0), major depression (1.0), and multiple anxiety disorders (separation anxiety [1.0], agoraphobia [1.0], and panic disorder [.95]).

For this article, we include estimates of IQ and academic achievement tests to demonstrate comparability of the two groups on overall intellectual potential and achievement. The IQ was estimated from the block design and vocabulary subtests of the Wechsler Adult Intelligence Scale-Third Edition (57). Academic achievement was assessed with the reading and arithmetic tests of the Wide Range Achievement Test-Third Edition (WRAT-III) (62). Learning disability (LD) was defined by a score less than or equal to 85 on the WRAT-III reading and/or arithmetic scaled scores.

MRI Protocol

Whole-brain magnetic resonance images were collected on a Siemens 1.5 Tesla scanner (Siemens Medical Systems, Erlangen, Germany) at the MGH Martinos Center (Charlestown, Massachusetts). A sagittal localizer scan was performed for placement of slices, followed by a coronal T2-weighted sequence to rule out unexpected neuropathology. Two sagittal three-dimensional magnetization-prepared rapid gradient-echo imaging (T1-weighted, nonselective inversion-prepared spoiled gradient echo pulse) sequences were collected (repetition time/echo time/T1/flip = 2.73 sec/3.39 msec/1.0 sec/7, bandwidth = 190 Hz/pixel, sampling matrix = 256×192 pixels, field of view = 256×256 mm, effective slice thickness = 1.33 mm on a 170 mm slab of 128 partitions) and used for analyses conducted at the MGH Center for Morphometric Analysis (CMA).

Data Analyses

We compared the ADHD and control groups on demographic, psychiatric, and cognitive factors, using the chi-square test and *t* test for categorical and dimensional variables, respectively.

VBM Methods—Structural scans were transferred to the CMA and coded and catalogued for blind analysis using VBM. Structural data were resampled to $2 \times 2 \times 2$ mm and were analyzed with FSL-VBM 1.1 (<http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html>; Oxford University, Oxford, United Kingdom), a VBM style analysis (63,64) carried out with FSL tools (65). First, structural images were brain-extracted using the Brain Extraction Tool (66). Next, tissue-type segmentation was carried out using FAST4 (67). The resulting gray-matter partial volume images were then aligned to Montreal Neurological Institute (MNI) 152 standard space using the affine registration tool FLIRT (68,69). The resulting images were averaged to create a study-specific template, to which the native gray matter images were then nonlinearly reregistered using FNIRT (70,71), which uses a B-spline representation of the registration warp field (72). The registered partial volume images were then modulated, to correct for local expansion or contraction, by dividing the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (full width at half-maximum = 7.05 mm).

Voxelwise general linear model was applied using permutation-based nonparametric testing (5000 permutations). We also used analysis of covariance with the total intracranial volume (TIV), gender, and presence/absence of lifetime psychotropic medications as covariates. Total intracranial volume was calculated as the sum of gray matter, white matter, and cerebrospinal fluid volumes, from FSL Brain Extraction Tool segmentations. As we did not see a difference between the two models (*t* test vs. analysis of covariance), only *t* test results are reported. After whole-brain analysis, we performed ROI VBM analysis by creating a mask for each of the six a priori ROIs, based on the CMA adaptation of the MNI atlases. The mask was then inserted as an explicit mask into VBM analysis. The ROI VBM is more sensitive than the whole-brain VBM used for testing a priori hypotheses.

Voxel-based thresholding, both uncorrected and corrected, for multiple comparisons was adopted. The significance level with the familywise error (FWE) corrected was set at $p < .05$ for both whole brain and six ROI analyses and the uncorrected significance level was set at $p < .01$, for preliminary identification of gray matter volume reductions or increases. Statistical maps were thresholded at $p < .01$ (uncorrected) using a minimum cluster size of three or more voxels. Threshold free cluster enhancement (73) was used to control FWE.

Anatomical localization was defined by the CMA parcellation unit system for cortex (74) and cerebellum (75). A priori ROI predictions for VBM included volume reductions in: 1)

DLPFC—Brodmann areas (BAs) 8, 9, and 46, represented by parcellation units F1 (superior frontal gyrus; BA 8, 9), F2 (middle frontal gyrus; BA 9), and F3 (inferior frontal gyrus; BA 46); 2) the ACC (anterior cingulate cortex, BA 24) and paracingulate gyri (paracingulate cortex, BA 32); 3) the IPL, comprising the angular (angular gyrus, BA 39) and supramarginal (supramarginal gyrus, BA 40) gyri; 4) the caudate—head and body of the caudate nucleus; 5) the putamen; and 6) the cerebellum. The clusters of significance were localized using a CMA adaptation of the MNI and Talairach atlases and reviewed by N.M. (26).

Results

Demographic Characteristics, Intellectual Functioning and Symptoms

As Table 1 shows, adults with ADHD were not significantly different than control subjects on the matching variables of age, sex distribution, handedness, or race. They were also statistically comparable on IQ, reading achievement, rates of LDs, and whole brain volume. Both groups had above average IQ. The only significant differences were in social class, which is consistent with the ADHD association with underachievement (76), Global Assessment of Functioning scores, and on the WRAT-III arithmetic test, which is commonly abnormal in ADHD and considered to be an effect of the disorder (77,78). There were no significant differences between groups on rates of major depressive, anxiety, combined substance use, or antisocial disorders; the rates of these comorbidities were very low in both groups at the most recent interview.

VBM Results in A Priori ROIs

In all six ROIs, compared with control subjects, adults with ADHD had at least one area of significantly smaller gray matter volumes (Table 2, and Figures 1, 3, and 4). These smaller regions included the 1) DLPFC—an area corresponding to lateral BA 8 in the left and right hemispheres; 2) ACC—an area corresponding to BA 24/32 in the right hemisphere; 3) IPL—an area in the left hemisphere corresponding to BA 40 (supramarginal gyrus); 4) caudate—an area involving the head and body in the left hemisphere; 5) putamen—left hemisphere; and 6) cerebellum—areas in the left cerebellum corresponding to regions culmen superior, culmen inferior, simplex, hemispheric zone of lobule X (X-h), biventer (pars paraflocculus dorsalis), and tonsil (Makris *et al.* [75]) and areas in the right cerebellum corresponding to culmen superior, superior semilunar lobule, biventer (pars paraflocculus dorsalis), and tonsil. No significant differences were identified at the FWE correction in these ROIs or the rest of the brain when the FWE correction ($p < .05$) was applied to the whole brain. Using ROI-VBM for the six regions individually, a t test was significant at the FWE for the caudate (Table 3). Results did not change when covarying sex, TIV, and presence/absence of medications; nor were there significant differences between ADHD individuals with versus without lifetime psychotropic medication exposure.

In two of the six ROIs, there were differences between ADHD and control groups in which the ADHD group had larger gray matter volumes at $p = .01$ (DLPFC and IPL) (Table 2 and Figure 2).

VBM Exploratory Results

Here, we report any nonpredicted findings in which there was smaller or larger gray matter in ADHD than control subjects in other ROIs at $p = .001$. A number of areas in the left and right frontal lobe, left hippocampus/parahippocampus, right temporal cortex, left and right occipital cortex, and right thalamus were significantly smaller in ADHD at this threshold (Table S1 in Supplement 1). A number of areas were larger in ADHD than control subjects at this threshold, including a large area in FOC bilaterally and a large area in the left

temporal cortex and anterior parahippocampus. Some areas of left and right occipital cortex were also larger in ADHD than control subjects (Table S1 in Supplement 1). No statistically significant differences were found at the FWE at the whole brain.

Discussion

This VBM study of brain structure in ADHD adults partially supported the hypothesis that ADHD adults have subtle brain volume reductions in a priori predicted ROIs (DLPFC, ACC, IPL, caudate, putamen, and cerebellum), a network of structures involved in attention and EFs (cf. 29). However, the results were only robust with respect to the caudate, the only ROI that met FWE threshold for significance using ROI-VBM. Results were not significantly influenced by sex, TIV, or medication status. These results extend to adults with ADHD the previously reported findings in the literature on children with ADHD. They provide support for the validity of ADHD in adults and for the syndromic continuity into adult life of biological features found in ADHD children.

It is notable that brain differences were detectable in the absence of significant differences in demographic, psychiatric, or cognitive variables used to group match. Both groups were highly educated and were above average in general intellectual ability. Moreover, there were no meaningful differences between groups on rates of mood, anxiety, substance or antisocial disorders, or learning disabilities, comorbidities that are typically significantly more common in adult ADHD than control subjects (20). The differences in social class, a variable comprised of occupation and education of the participants (not of the family of origin), the Global Assessment of Functioning, and WRAT-III arithmetic are strongly associated with the disorder and were not matching variables. Thus, the significant structural reduction in the ADHD group can be attributed to having ADHD and not to co-occurring current psychiatric or cognitive comorbidity or medications.

The larger FOC observed in our study is notable in that Hesslinger *et al.* (23) used an ROI analysis to examine the FOC and found a significant volume reduction of the left FOC. In contrast, our initial morphometric ROI analysis (18) found no FOC volume reductions in adult ADHD and in prior work found volumetric reductions in FOC in a study of adults with comorbid ADHD and bipolar disorder (28), suggesting that reductions of FOC may be a correlate of comorbidity with mood disorders rather than a correlate of ADHD. More work is needed to clarify these differences, as the studies differ substantially in sample size and methods. Moreover, the role of the FOC in ADHD needs to be clarified, as its dysfunction in ADHD has been hypothesized by a number of investigators (30) due to its importance in task coordination and control of emotional behavior. The larger volumes of FOC and of other ROIs in our sample were not predicted, require further study, and must be viewed cautiously until replicated.

Our ROI findings are generally consistent with the pediatric literature (17,20–22) with one major exception: our adult data indicate comparability of overall cerebral volume, whereas the pediatric literature consistently reports smaller overall brain volume in ADHD than control subjects. One possible explanation for this difference is that our adult ADHD sample is relatively high functioning (mean IQ of 116) with few comorbidities, either psychiatric or LDs, and thus, a higher functioning subgroup of the distribution of cases than those typically seen in pediatric samples. Moreover, there were no meaningful sociodemographic and cognitive differences from control subjects. The ADHD samples typically have lower IQs (on average by about nine points, Cohen's $d = -.61$), as reflected in a meta-analysis of 137 studies (79) and in frequency of comorbid LD (77,78), whereas this adult ADHD sample did not. While the ADHD features of high IQ patients parallel those seen in lower IQ patients for both children (80) and adults (81) with the disorder, it is possible that higher IQ in

ADHD is associated with fewer structural brain differences from control subjects. Another explanation is that developmental differences that are present in childhood diminish in adulthood, a hypothesis that has some traction based on results by Shaw *et al.* (82). Their work demonstrated a developmental lag in cortical thickness of between 3 and 5 years, depending on the ROI, in children entering their early teen years. In contrast, our sample ranges from ages 18 to 59, with means of approximately 35 years of age in the two groups. This issue can only be resolved by long-term follow-up study of children diagnosed with ADHD in childhood who retain their ADHD diagnoses and receive brain imaging in their adult years. Another possibility requiring further research is that stimulant medications may have normalized brain volumes in ADHD (83).

Limitations

This study has a number of limitations. We conducted a number of statistical tests on six ROIs that vary in size, and thus we are vulnerable to making a type I error, given the nonsignificant findings at the FWE threshold for the whole brain. However, our main findings were in the predicted direction, were consistent with a priori hypotheses and with the bulk of the literature in children with ADHD, and were robust in the caudate at the a priori hypothesis testing FWE. Moreover, there were no significant differences in the opposite direction in these ROIs. These results were observed in the context of a very tightly matched control group and an ADHD group with relatively high IQs, few LDs, and few psychiatric comorbidities. Thus, this study may have been less likely to find significant results than many in the literature, assuming that brain volume differences are associated with IQ, LDs, and psychiatric comorbidities.

Because our sample was referred for ADHD, our results cannot be generalized to nonreferred samples. The diagnoses of adult ADHD relied entirely on the self-report of adult subjects. Thus, these findings may not generalize to diagnoses defined using data from informants. Another limitation to the generalizability of our results is that our sample was not representative of lower socioeconomic or all IQ strata and only included Caucasian participants. Although we had a relatively high IQ sample, we have shown elsewhere that ADHD features in high IQ ADHD adults parallel those seen in other adults with ADHD (81). While generalizability is limited until we learn whether these results are robust across samples, the relatively homogeneous nature of our sample and its tight matching with control subjects suggests that our findings do not result from these confounds. Finally, the effects on the brain of diverse medication histories are unknown, although presence or absence of lifetime medications did not significantly influence the results.

We used VBM, in part, to eliminate rater effects arising from manual morphometry, as this study was carried out over a 5-year period and involved a large sample. While VBM allows a large number of brains to be measured without the influence of raters, it suffers from its own intrinsic limitations (84,85), as do other automated measures, particularly the problem of co-registration, as we noted in detail in Makris *et al.* ([26] page 1372). Despite these limitations, the current methods of registration employed in this study represent state of the art technology in this domain. Finally, we identified a number of unpredicted results, and further work will be needed to replicate these findings (e.g., significantly larger FOC).

Conclusions and Future Directions

Despite these limitations, the results provide partial support for the hypothesis that some structural brain abnormalities persist into adulthood in ADHD, complementing studies demonstrating persistent neuropsychological and functional brain dysfunctions. Replication of these findings in adults is necessary to establish that the particular structures found to be abnormal are core components of the neurobiology of ADHD in adults. Moreover, future

studies should address these questions by studying psychotropically naïve individuals and studying the effects of substance use and medications on the brain in ADHD individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Voxel based morphometry control subjects > attention-deficit/hyperactivity disorder (ADHD): cortical regions that are smaller in ADHD compared with control subjects. Labels with arrows are those regions that are smaller in ADHD ($p < .01$) and correspond to those described in Table 2 for predicted regions of interest. Note those regions that are smaller at this threshold, which are considered exploratory findings outside of the predicted regions of interest, are in Table S1 in Supplement 1. Significant differences are displayed on the inflated surface of the Montreal Neurological Institute brain. AG, angular gyrus; Ant mACC, anterior middle cingulate cortex; BA, Brodmann area; CALC, calcarine area; CGp, posterior cingulate gyrus; F1, superior frontal gyrus; F2, middle frontal gyrus; F3o, inferior frontal gyrus, pars opercularis; FP, frontal pole; Lat, lateral; LG, lingual gyrus; OP, occipital pole; PHp, posterior parahippocampal gyrus; PO, parietal operculum; PP, planum polare; S-II, somatosensory area - II; SGa, anterior supramarginal gyrus; SGp, posterior supramarginal gyrus; SMC, supplementary motor cortex; VBM, voxel based morphometry.

Figure 2.

Voxel based morphometry control subjects < attention-deficit/hyperactivity disorder (ADHD): cortical regions that are larger in ADHD compared with control subjects. Labels with arrows are those regions that are larger in ADHD ($p < .01$) and correspond to those described in Table 2 for predicted regions of interest. Note those regions that are larger at this threshold, which are considered exploratory findings, outside of the predicted regions of interest are in Table S1 in Supplement 1. Significant differences are displayed on the inflated surface of the Montreal Neurological Institute brain. ACC, anterior cingulate cortex; AG, angular gyrus; BA, Brodmann area; CGp, posterior cingulate gyrus; CN, cuneus; F1, superior frontal gyrus; F3 or b, inferior frontal gyrus, pars orbitalis; FOC, fronto-orbital cortex; FP, frontal pole; Lat, lateral; Li, lateral inferior; LS, lateral superior; OLi, lateral occipital area, inferior part; OLs, lateral occipital area, superior part; PHa, anterior parahippocampal gyrus; PO, parietal operculum; PP, planum polare; PRG, precentral gyrus; SCLC, supracalcarine cortex; TP, temporal pole; VBM, voxel based morphometry; VMPF, ventromedial prefrontal cortex.

Figure 3.

Cerebellar regions that are smaller in attention-deficit/hyperactivity disorder compared with control subjects on a flattened brain. Labels with arrows are smaller in attention-deficit/hyperactivity disorder ($p < .01$) and correspond to those described in Table 2. Significant differences are displayed on the flattened cerebellar surface of the Montreal Neurological Institute brain. ADHD, attention-deficit/hyperactivity disorder; IV-m, culmen superior; IX-m, tonsil; V-m, culmen inferior; VI-m, simplex; VIIA_crusl-m, superior semilunar lobule; VIIIB-m, paramedian/gracilis; VIIIA-m, biventer (pars copularis); VIIIB-m, biventer (pars paraflocculus dorsalis); X-h, hemispheric zone of lobule X; X-m, flocculus; VBM, voxel based morphometry.

Figure 4.

Cerebellar regions that are smaller in attention-deficit/hyperactivity disorder compared with control subjects as seen on an inflated brain. Labels with arrows are smaller in attention-deficit/hyperactivity disorder ($p < .01$) and correspond to those described in Table 2.

Significant differences are displayed on the inflated cerebellar surface of the Montreal Neurological Institute brain. ADHD, attention-deficit/hyperactivity disorder; IV-m, culmen superior; IX-m, tonsil; V-m, culmen inferior; VI-m, simplex; VIIA_crusI-m, superior semilunar lobule; VIIB-m, paramedian/gracilis; VIIIA-m, biventer (pars copularis); VIIIB-m, biventer (pars paraflocculus dorsalis); X-h, hemispheric zone of lobule X; X-m, flocculus; VBM, voxel based morphometry.

Table 1**Demographic Characteristics of Adults with ADHD and Control Subjects**

Demographic Characteristics	Control Subjects <i>n</i> = 54 Mean (SD) or Percentage	ADHD <i>n</i> = 74 Mean (SD) or Percentage	Test Statistic (<i>t</i> , <i>df</i>), <i>p</i> Value, and χ^2 and <i>p</i> Value
Age (in years)	34.3 (11.3)	37.3 (12.6)	$t = -1.4$ <i>df</i> = 126, $p = .161$
SES ^a	1.7 (.5)	2.0 (1.0)	$t = -2.2$ <i>df</i> = 123, $p = .033$
ADHD Symptoms	1.0 (1.7)	13.6 (2.9)	$t = -28.1$ <i>df</i> = 126, $p = .000$
Current GAF	68.0 (5.0)	60.5 (5.9)	$t = 7.63$, <i>df</i> = 126, $p < .001$
Whole Brain Volume–Voxels/cm ³	186947.7/1485	187656.6/1501	$t = -.24$ <i>df</i> = 126, $p = .817$
Full Scale IQ Estimate ^b	115.8 (12.1)	116.0 (12.6)	$t = -.1$ <i>df</i> = 124, $p = .925$
WRAT-III Reading SS ^c	109.4 (7.5)	107.4 (9.3)	$t = .2$ <i>df</i> = 126, $p = .186$
WRAT-III Arithmetic SS ^c	107.5 (11.8)	101.5 (11.7)	$t = 2.9$ <i>df</i> = 124, $p = .005$
Gender (Male)	25 (46%)	38 (51%)	$\chi^2 = .319$, $p = .572$
Handedness (Right)	48 (89%)	65 (88%)	$\chi^2 = .033$, $p = .855$
Race (Caucasian)	54 (100%)	74 (100%)	ns
Learning Disability ^d	3 (6%)	9 (12%)	$\chi^2 = 1.585$, $p = .208$
Major Depression ^e	1 (2%)	6 (8%)	$\chi^2 = 2.364$, $p = .124$
Multiple (2) Anxiety Disorder ^e	0 (0%)	0 (0%)	ns
Antisocial Personality Disorder ^e	0 (0%)	0 (0%)	ns
Substance Use Disorders ^e	0 (0%)	0 (0%)	ns

ADHD, attention-deficit/hyperactivity disorder; GAF, Global Assessment of Functioning; IQ, intelligence quotient; ns, nonsignificant; SES, socioeconomic status; SS, scaled score; WRAT-III, Wide Range Achievement Test, 3rd Edition.

^a Socioeconomic status (58).

^b Intelligence quotient, measured by Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale, Third Edition (57).

^c Wide Range Achievement Test, 3rd Edition, Reading Scaled Score and Arithmetic Scaled Score (62).

^d Learning disability is defined by a score less than or equal to 85 on the Wide Range Achievement Test, 3rd Edition, Reading Scaled Scores and/or Arithmetic Scaled Scores.

^e Rates of disorders at most recent interview.

Table 2

Voxel Based Morphometric Differences Between Adults with ADHD and Control Subjects in Six ROIs

Region of Interest CMA PU – BA	Clusters of Three Voxels or Larger at Statistical Threshold for Control Subject > ADHD			
	(Uncorrected) ^a			
Volume Reduction in ADHD	MNI Coordinates (x,y,z)	p = .01	p = .005	p = .001
DLPFC - Left Hemisphere				
F1/F2 - BA 8/LAT	–16, 28, 38	52	34	12
F2 - BA 9	–46, 16, 24	27	—	—
DLPFC - Right Hemisphere				
F2 - BA 8	26, 26, 32	30	17	—
F1 - BA 9/LAT	16, 38, 40	10	—	—
FP/BA 9/LAT	28, 42, 38	6	—	—
ACC - Right Hemisphere				
Ant mACC - BA 24/32	14, 20, 32	74	43	—
ACC - Left Hemisphere				
ACC/BA 24	–12, –22, 38	3		
IPL - Left Hemisphere				
SGp – BA 40	–64, –48, 36	7	3	—
SGp – BA 40	–58, 50, 50	20	12	—
PO - BA 40/S-II/SGa/BA 40	–60, –26, 20	122	60	—
AG/BA 39	–66, –56, 16	9	—	—
Caudate - Left Hemisphere	–16, 4, 12	334	215	44
Putamen - Left Hemisphere	–20, 6, 12	8		
Cerebellum – Left				
VIIA_crusI-m	–32, –82, –16	52	—	—
IV-m, V-m	–26, –32, –40	96	51	—
VI-m, X-h	–26, –32, –40	(96)	(51)	17
IV-m, V-m	–14, –54, –8	30	—	—
IX-m	–14, –44, –56	262	132	—
VIIIB-m	–14, –44, –56	(262)	(132)	24
Cerebellum – Right				
IV-m	20, –34, –24	30	3	—
V-m, VI-m, VIIIB-m	26, –36, –36	36	—	—
VIIA_crusI-m	56, –68, –32	56	28	—
VIIA_crusI-m	38, –86, 36	18	—	—
VIIA_crusI-m	44, –80, –30	41	17	—
VIIIA-m	20, –44, –54	74	—	—
VIIIB-m	20, –44, –54	(74)	21	—
VI-m	6, –74, –20	5	—	—
IX-m/VIIIB-m	6, –60, –58	89	17	—

Region of Interest CMA PU - BA	Clusters of Three Voxels or Larger at Statistical Threshold for ADHD > Control Subject (Uncorrected) ^b			
	MNI Coordinates (x,y,z)	<i>p</i> = .01	<i>p</i> = .005	<i>p</i> = .001
DLPFC - Right Hemisphere				
F1 BA 8/LAT	6, 30, 64	12	—	—
IPL - Right Hemisphere				
AG/BA 39	44, -62, 18	26	—	—

FSL-voxel based morphometry results comparing differences in gray matter volume thresholded to a probability of $p = .01$, $.005$, and $.001$ (uncorrected). Local maxima are reported, including cluster size and anatomical region. Locations for statistical findings are reported in the standard Montreal Neurological Institute coordinate space (x, y, z). Some clusters border on more than one region—those clusters are reported more than once with cluster size in parentheses (see also Figure 1). Parcellation units are regions of interest defined by the Center for Morphometric Analysis as in Caviness *et al.* (74) for the cortex and Makris *et al.* (75) for the cerebellum.

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; AG, angular gyrus; Ant mACC, anterior middle cingulate cortex; BA, Brodmann area; CMA, Center for Morphometric Analysis; DLPFC, dorsolateral prefrontal cortex; F1, superior frontal gyrus; F2, middle frontal gyrus; FP, frontal pole; IPL, inferior parietal lobule; LAT, lateral; m, medial; MNI, Montreal Neurological Institute; PO, parietal operculum; PU, parcellation units; ROI, region of interest; S-II, somatosensory area - II; SGa, supramarginal gyrus anterior; SGp, supramarginal gyrus posterior. Cerebellar areas: IV-m, culmen superior; IX-m, tonsil; V-m, culmen inferior; VI-m, simplex; VIIA_crusI-m, superior semilunar lobule; VIIIB-m, paramedian/gracilis; VIIIA-m, biventer (pars copularis); VIIIB-m, biventer (pars paraflocculus dorsalis); X-h, hemispheric zone of lobule X; X-m, flocculus (see also Figures 3 and 4).

^a All results are in the direction of smaller volumes in the ADHD group than in control subjects.

^b All results are in the direction of larger volumes in the ADHD group than in control subjects.

Table 3

Familywise Error Corrected p Values for Models Using Regions of Interest Hypothesized to be Significantly Smaller in ADHD Than Control Subjects

Regions of Interest	Group	Group, Sex, Total Brain Volume	Group, Medication Status	Group, Sex, Total Brain Volume, and Medication
DLPFC	.6510	.7510	.6464	.7352
IPL	.5160	.5250	.2094	.2426
ACC	.1580	.1650	.4112	.4404
Putamen	.4300	.4230	.3186	.2816
Cerebellum	.1300	.1110	.2240	.1500
Caudate ^a	.0130	.0130	.0292	.0394

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule.

^aStatistically significant at familywise error rate at $p < .05$.