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Brain Gray Matter Deficits at 33-Year Follow-Up in Adults with Attention-Deficit/Hyperactivity Disorder Established in Childhood

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Abstract

Context—Volumetric studies have reported relatively decreased cortical thickness and gray matter volumes in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) whose childhood status was retrospectively recalled. We present the first prospective study combining cortical thickness and voxel-based morphometry (VBM) in adults diagnosed with ADHD in childhood.

Objective—In adults who had Combined Type ADHD in childhood, to 1) test whether they exhibit cortical thinning and decreased gray matter in regions hypothesized related to ADHD, and 2) test whether anatomic differences are associated with current ADHD diagnosis, including persistence versus remission.

Design—Cross-sectional analysis embedded in a 33-year prospective follow-up at mean age 41.

Setting—Research outpatient center.

Participants—ADHD probands were from a cohort of 207 6–12 year old Caucasian boys; male comparison subjects (n=178) had been free of ADHD in childhood. We obtained MRI scans in 59 probands and 80 comparisons (28% and 45% of original samples, respectively).

Main Outcome Measure—Whole-brain VBM and vertex-wise cortical thickness analyses.

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Results—Cortex was significantly thinner in ADHD probands than comparisons in the dorsal attentional network and limbic areas (FDR<0.05, corrected). Additionally, gray matter was significantly decreased in probands in right caudate, right thalamus and bilateral cerebellar hemispheres. Probands with persistent ADHD (n=17) did not differ significantly from remitters (n=26) at FDR<0.05. At uncorrected p<0.05, remitters had thicker cortex relative to those with persistent ADHD in medial occipital cortex, insula, parahippocampus, and prefrontal regions.

Conclusions—We observed anatomic gray matter reductions in adults with childhood ADHD, regardless of current diagnosis. The most affected regions underpin top-down control of attention and regulation of emotion and motivation. Exploratory analyses suggest that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry.

CONTEXT

Volumetric studies in children with Attention-Deficit/Hyperactivity Disorder (ADHD) have consistently found global reductions of total brain volume with prefrontal cortex, anterior and posterior cingulate cortex, basal ganglia, cerebellum and parieto-temporal regions particularly affected relative to typically developing subjects.[1–4] These findings are consistent with a model of ADHD as a disorder of frontal-striatal-cerebellar circuitry. The diagnosis of ADHD requires onset in childhood, but persistence of ADHD into adulthood is now well documented.[4, 5] This longitudinal course together with smaller brain volumes in children with ADHD has raised questions about brain development into adulthood.

A sparse literature on brain anatomy in adults with ADHD also reports decreased volumes in orbitofrontal cortex,[6] anterior cingulate cortex (ACC),[7, 8] dorsolateral prefrontal cortex (DLPFC),[9] superior frontal cortex and cerebellum.[10] Complementary analyses of cortical thickness[11] reveal overall decreased cortical thickness in children[11–14] and adults with ADHD with reductions in ACC, medial frontal regions and parieto-temporo-occipital cortex.[12–14] Recently, Almeida et al.[15] found cortical thinning in right frontal lobe of children, adolescents and adults with ADHD.

Faute de mieux, investigations of structural brain abnormalities in adults have relied on adults' retrospective recall of their childhood status.[8, 9, 16–22] The documented inaccuracies of such reports[23] highlight the advantage of assessing brain anatomy in individuals with established childhood-onset ADHD prospectively followed into adulthood. Additionally, clinical ADHD remits in a substantial proportion of individuals followed into adulthood,[24, 25] but the neurobiology of remission has not been previously examined in middle adulthood.

We report cortical thickness and voxel-based morphometry (VBM) analyses on the largest sample to date of adults with childhood ADHD diagnoses (mean age 8) consistent with DSM-IV. Follow-up assessments occurred at mean ages 18, 25 and 41 (18FU, 25FU, and 41FU, respectively). At 18FU, a comparison group free of childhood ADHD, matched for age, sex, ethnicity, and childhood social class was recruited.[26–30] Systematic diagnostic assessments at each follow-up were conducted by interviewers "blind" to past history and group membership. At 41FU, we conducted anatomic brain magnetic resonance imaging in probands with childhood ADHD and comparisons. We performed analyses based on childhood diagnosis as well as on current diagnostic status in adulthood. Primary aims were to: (1) test whether adults with a childhood diagnosis of Combined Type ADHD (probands), relative to comparisons, exhibit cortical thinning and decreased gray matter in regions hypothesized to be related to ADHD,[12–14, 31] and (2) assess whether anatomic differences are associated with current ADHD diagnosis.

METHODS

PARTICIPANTS

The ADHD group originally comprised 207 6 to 12 year-old Caucasian boys referred to a research clinic from 1970 to 1977 (mean age 8.3 years). Briefly, they were referred by schools because of behavioral problems, had elevated parent and teacher ratings of hyperactivity, IQ≥85, and a diagnosis of Hyperkinetic Reaction of Childhood.[32, 33] Children with a pattern of aggressive or antisocial behavior were excluded to rule out comorbid conduct disorder. Further details of proband characteristics appear in previous publications.[30, 34] These subjects were assessed at mean ages 18.4±1.3, 25.0±1.3, and 41.2±2.7. Comparison male subjects (n=178) were recruited at 18FU. Medical center pediatric charts were reviewed for children seen for routine physical exams from 1970–1977 when they were 6 through 12 years-old, group-matched for probands' race, childhood socioeconomic status and geographical residence. Parents of suitable children (by then adolescents) were called, informed of the study and, if interested, recruited, provided parents reported that no teacher had complained about their child's behavior in elementary school. Refusal was low (circa 5%).

ADULT-FOLLOW UP ASSESSMENT (41FU)

On average 33 years after initial childhood diagnosis, clinical data were obtained on 135 male probands (65% of original sample, 69% of those living) and 136 male comparisons (76% of 178 recruited in adolescence, 77% of those living). Major DSM-IV disorders, as well as multiple aspects of function, were assessed for the interval between 25FU and 41FU by trained clinicians "blind" to all antecedent data. A special interview, Assessment of Adult Attention Deficit Hyperactivity Disorder, was developed for diagnosing DSM-IV ADHD in adults (see Author e-Methods and Author e-Instrument). Current ADHD was defined as meeting DSM-IV criteria during the preceding six months. Participants were invited to take part in an anatomical MRI study. Due to refusals and MRI exclusions (see Table 1), we obtained MRI scans in 59 ADHD probands and 80 comparisons. Nearly all probands (n=57; 97% of those scanned) were treated with methylphenidate in childhood between ages 6 and 12, for an average of 2.2 years.[35] (See Author e-Table 1 for further details of childhood medication treatment, including thioridazine.[30]) All participants provided written informed consent as approved by the NYU School of Medicine Institutional Review Board.

To test whether cortical thickness differed as a function of current ADHD, we subdivided probands into three subgroups: 1) those who met diagnostic criteria for DSM-IV ADHD at 41FU ("persistents" n=17, including seven Predominantly Inattentive, six Predominantly Hyperactive/Impulsive, and four Combined Type); 2) those who did not ("remitters" n=26); and 3) those diagnosed with ADHD Not Otherwise Specified ("ADHD-NOS" n= 16; see Author e-Methods). Comparisons were dichotomized into subjects who did not meet criteria for any type of ADHD ("non-ADHD comparisons" n=57) and those who were diagnosed with ADHD-NOS ("comparisons with ADHD" n=23). Although all probands and all comparisons were included in initial vertex-wise and VBM analyses, subgroup analyses focused on current diagnostic status. Accordingly, probands and comparisons with current ADHD-NOS, which is not well-defined and did not differ between groups (27% and 29%, respectively), were excluded from subgroup analyses.

IMAGING

Anatomic T1-weighted images were obtained on a 3T Siemens Trio with an 8-channel Siemens head coil (41 scans; 20 ADHD probands, 21 comparisons) and a 3T Siemens Allegra with a Siemens single channel head coil (98 scans; 39 ADHD probands, 59 comparisons; proportions did not differ significantly across scanners, $(\chi_{(1)}^2=0.96$, $p=0.33)$

with the following parameters: TR=2100ms; flip angle=12; slice thickness=1.5mm; inversion time=1100ms; matrix=192×256; FOV=172.5mm. The only parameter that differed was TE, which was 3.87ms on the Trio and 3.90ms on the Allegra.

Structural MRI scans were preprocessed through the fully automated CIVET-MNI pipeline.[36–39] The initial preprocessing step was to mask MRI native images using an automated brain extraction method.[40] Data were corrected for non-uniformity artifacts and registered to stereotaxic space (MNI152) using a 9-parameter linear transformation. Voxel-wise tissue type classification was performed using a neural network classifier followed by a partial volume estimation step.[38, 41]

For VBM, the classified tissue maps were blurred with a Gaussian kernel of 10mm full width at half-maximum. Cortical thickness measures were assessed using a fully automated algorithm which defines the distances between a set of vertices at the white matter (WM) surface and then expands outward to find the intersection with GM in order to generate surface meshes that represent WM and GM interfaces.[42] A total of 40,962 linked vertices were calculated per hemisphere. Each individual cortical thickness map was blurred using a 30mm surface-based diffusion-smoothing kernel to reduce noise while preserving anatomical location, as this method produces less volumetric blurring than the equivalent Gaussian kernel.[43]

STATISTICAL ANALYSES

Global cortical thickness—We obtained a single global cortical thickness value for each subject by averaging across all 81,924 vertices. Linear regression models controlled for age at time of scan and scanner model (Trio vs. Allegra).

Vertex-wise and voxel-based morphometry analyses—Following the study aims, group analyses tested for regional differences in cortical thickness and GM density between (1) all adults with a childhood diagnosis of Combined Type ADHD and all comparisons; (2a) persistents versus non-ADHD comparisons; (2b) remitters versus non-ADHD comparisons; and (2c) persistents versus remitters. For each comparison, we regressed cortical thickness at each of 81,924 vertices or whole-brain GM density on group, controlling for age at time of scan and scanner model. The software package ‘mni.cortical.statistics’ (Brain Imaging Centre of the Montreal Neurological Institute) for the R environment[44] was used for cortical thickness analyses and the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk)tool Feat, for VBM. Results were thresholded using a false discovery rate (FDR) of 0.05.[45, 46] Maps of t-statistics for group effects on cortical thickness at each vertex or GM density at each voxel were projected onto an average brain template revealing clusters that differed significantly between groups. We retained clusters comprising at least 50 contiguous vertices for cortical thickness[47] and five voxels for VBM.

Region-based analyses of cortical thickness and voxel-based morphometry—To test whether childhood or current ADHD was associated with significant differences in specific regions, we performed *post-hoc* region-of-interest (ROI)-based analyses. For each participant, we computed mean cortical thickness or GM density within each cluster exhibiting significant (FDR<0.05) group differences in primary analyses by averaging across all vertices or voxels within each cluster. We then compared the diagnostic subgroups of probands (persistents, remitters) and the comparisons without current ADHD, Bonferroni corrected for the number of clusters. For completeness, Author e-Table 2 contains means and SD for the subgroups with current ADHD-NOS.

Exploratory analyses of cortical thickness—To further investigate primary hypotheses for which no FDR<0.05 vertices were found, we reexamined subgroup differences heuristically using an uncorrected p<0.05 threshold with a cluster threshold of 50 vertices.[47] Because of significant between-group differences in IQ, we confirmed cortical thickness results by also adjusting for IQ.

RESULTS

Table 1 summarizes the derivation of the sample. A larger proportion of comparisons (45% of originally enrolled participants) than probands (29%) had analyzable MRI scans. This discrepancy reflects a significantly higher rate of unavoidable factors in probands (27%) (i.e., deaths, incarcerations and MRI exclusions) than in comparisons (12%) ($\chi^2_{(1)}$=12.08, p<0.001). By contrast, rates of refusal, failure to schedule or to locate subjects did not differ significantly (45% of probands versus 43% of comparisons). Accordingly, results are based on anatomic images from 59 ADHD probands and 80 comparisons.

We compared diagnoses and demographic information at 18FU of subjects who were scanned and those who were not (data available for 57/59 probands and all comparisons; see Author e-Table 3). Within both proband and comparison groups, individuals scanned and those not scanned did not differ significantly on prevalence of ADHD, Antisocial Personality Disorder, mood or anxiety disorders, any DSM-III disorders, age at referral, IQ, socioeconomic status, or Teacher Conners Hyperactivity Factor score. However, scanned probands had significantly higher rates of alcohol substance use disorder (SUD), non-alcohol SUD, and any SUD than probands who were not scanned (Author e-Table 3)

DEMOGRAPHICS

Probands and comparisons did not differ significantly in age at scan, or in lifetime prevalence of substance abuse or dependence (see Table 1). As expected, probands and comparisons differed significantly in IQ in childhood and 41FU assessments. See Author e-Table 5 for demographics of subgroups based on current diagnosis. Current substance use and comorbid diagnoses are presented in Author e-Table 5.

GLOBAL CORTICAL THICKNESS

Surface-wide, mean cortical thickness was significantly lower in probands (n=59) than comparisons (n=80) (mean ± SD 3.18±0.11mm and 3.24±0.11mm, respectively; p<0.001 in regression controlling for age and scanner; Cohen's d=0.54). At 41FU, probands with persistent ADHD differed significantly from non-ADHD comparisons (3.14±0.13mm and 3.25±0.10mm, respectively; p=0.0005; d=1.02). The remitters (3.20±0.11mm) also differed from non-ADHD comparisons in overall cortical thickness (p=0.04, d=0.48). However, persistents and remitters did not differ significantly (p=0.10, d=0.51).

VERTEX-WISE ANALYSES OF CORTICAL THICKNESS

Figure 1A displays the multiple clusters of vertices (detailed in Table 2) for which the cortex was significantly thinner (surface-wide FDR<0.05) in ADHD probands; the largest cluster extended from right precuneus to precentral gyrus. Other right hemisphere clusters were located in inferior parietal lobe, temporal pole, and insula. Left hemisphere clusters were located in superior frontal gyrus/frontal pole, precentral gyrus, insula, temporal pole, and cuneus. There was no instance in which cortical thickness was significantly increased in probands. As shown in eFigure 1 and Author e-Table 6, after covarying for IQ (in addition to scanner and age), significant cluster centers remained largely unchanged in location, but the clusters were less extensive.

In order to assess associations with current ADHD diagnosis, we performed vertex-wise comparisons among the different diagnostic subgroups. The 17 individuals with persistent ADHD differed significantly from the 57 non-ADHD comparisons in most but not all the regions identified in the initial inclusive analyses (see Table 2 and Figure 1B). Additionally, this analysis revealed thinner cortex related to persistent ADHD in the left medial occipital cortex and right subgenual ACC. Using FDR<0.05, remitters (n=26) did not differ significantly from non-ADHD comparisons; persistents and remitters also did not differ in any region at this threshold. There were no vertices at which cortical thickness was significantly associated with lifetime or current substance abuse diagnoses, dimensional measures of substance abuse, lifetime smoking history, or thioridazine treatment, nor were there any significant interactions between group and scanner for any cortical or VBM measures.

REGION-BASED ANALYSES OF CORTICAL THICKNESS

To examine potential differences associated with remission from childhood ADHD, we focused on the clusters in which ADHD probands exhibited significantly thinner cortex than comparisons (FDR<0.05). Both remitters and persistents had thinner cortex than non-ADHD comparisons, with medium to large effect sizes. Average effect sizes between persistents and non-ADHD comparisons (d=0.73) were larger than for remitters (d=0.52), although all confidence intervals overlapped (not shown); persistents and remitters did not differ significantly from each other in any cluster at FDR<0.05 (see Table 2).

EXPLORATORY VERTEX-WISE ANALYSES

When vertex-wise results were thresholded at p<0.05 (uncorrected), we observed thinner cortex for persistents versus remitters in insula, bilateral temporal cortex including right temporal pole and in left occipital Brodmann area (BA) 19, orbitofrontal cortex and medial ACC (see Figure 2, Author e-Table 7). There were no regions exceeding our cluster size threshold of 50 vertices in which remitters exhibited thinner cortex than those with persistent ADHD.

EXPLORATORY REGION-BASED ANALYSES

In the clusters that differentiated persistents from remitters in exploratory vertex-wise analyses, persistents differed markedly from non-ADHD comparisons (average d=0.75), whereas remitters did not (average d=0.03; $t_{(9)}$=8.26, p<0.0001). Relative to comparisons, remitters had (non-significantly) greater cortical thickness in left superior temporal gyrus extending to insula and orbitofrontal cortex, left parahippocampus, left ACC, and left medial occipital cortex (see Author e-Table 7).

VOXEL-BASED MORPHOMETRY

As shown in Table 3 and Figure 3, GM density was significantly greater (FDR<0.05) for comparisons than for probands in many of the same regions identified through cortical thickness analyses as well as in subcortical regions inaccessible to cortex-based measures. Figure 4 displays decreased GM in probands in right caudate, right thalamus and bilateral cerebellar hemispheres. VBM analyses of diagnostic subgroups or of medication treatment in childhood with methylphenidate or thioridazine did not yield significant results even with more lenient thresholds (FDR≤0.2).

COMMENT

In a prospective 33-year longitudinal follow-up of 59 probands (mean age 41 years) with established ADHD in childhood and 80 prospectively enrolled non-ADHD comparisons, we found an overall significant reduction in mean cortical thickness in probands. Beyond this

global difference, the greatest cortical thinning associated with childhood ADHD was located in bilateral parietal lobes, temporal poles, insula, precentral gyri, frontal poles, and right precuneus. No cortical region was significantly thicker in probands than comparisons. Although less sensitive,[48] VBM also revealed significantly decreased GM in probands versus comparisons in right precentral, bilateral parietal, left temporal, and right cuneus. Additionally, VBM detected decreased GM in probands in caudate, thalamus and cerebellar hemispheres.

With respect to current adult diagnosis, probands with persistent ADHD differed most from non-ADHD comparisons in the same cortical regions identified in our primary analyses, as well as in additional clusters in left medial occipital cortex and subgenual ACC. Probands with remitted ADHD did not differ significantly from persistents when analyses were corrected for full-brain comparisons. In exploratory uncorrected analyses, probands with persistent ADHD exhibited reduced cortical thickness relative to remitters in bilateral medial occipital lobes, temporal lobes extending to insula, and left parahippocampus.

Our results extend prior volumetric and cortical thickness findings in ADHD. First, consistent with decreased total cerebral volume in ADHD,[2–4] our observation of reduced global cortical thickness in probands with ADHD confirms prior reports.[13, 14, 20] Furthermore, although we found less frontal and prefrontal cortical thinning in ADHD than others,[12–15, 20, 49] we confirmed thinner cortical mantle in occipito-parietal,[12, 13, 20] temporal cortex and precentral regions[13, 14] in ADHD. In subcortical analyses, we also confirmed anatomic abnormalities in caudate,[3, 50, 51] thalamus[52, 53] and cerebellum[3] in ADHD.

Studies of cortical thickness in adults with ADHD have focused on specific regions associated with executive function and attentional control.[54, 55] Makris et al.[9] selected nine parcellation units (from 48) per hemisphere and found thinner cortex related to ADHD in prefrontal and cingulate cortex and inferior parietal lobe, albeit without correcting for multiple comparisons.[9] A cross-sectional study of children, adolescents and adults found that individuals with ADHD, regardless of age, had significantly thinner right superior frontal cortex than controls.[15] In the adults with ADHD, the specific reduction, with correction for multiple comparisons limited to the frontal lobe, was localized to BA9. In contrast, we did not find group differences in much of prefrontal cortex but found widespread cortical thinning in bilateral parietal-temporal cortex. We found similar results in analyses that included all participants as well as in those limited to probands with persistent ADHD versus non-ADHD comparisons. The latter contrasts are comparable to studies in adults that define group membership by current diagnostic status.[15, 20]

Studies of cortical thickness in children with ADHD are more numerous than those in adults,[12–14, 33, 47, 56, 57] and typically have examined the entire cerebrum, although nearly all (except[14]) report results uncorrected for multiple comparisons. Thinner cortex has been reported in children with ADHD in prefrontal and precentral regions[12, 14] parietal and temporal lobes[12, 13] and inferior frontal gyrus bilaterally.[58] In our main analyses, we applied FDR full-brain correction for multiple comparisons, and observed significant differences whether groups were defined by initial childhood history or by current adult diagnoses. We speculate that the robustness of our results reflects having established the diagnosis of ADHD in childhood as well as our medium to large sample sizes.

Broadly, our results implicate disruptions in large-scale neural systems involved in the regulation of both attention and emotion in adults with childhood ADHD. We found convincing converging anatomic evidence implicating the dorsal attentional network[55] and distributed regions within limbic circuits that were thinner in ADHD probands than in

comparisons. Similar findings were obtained when we contrasted probands with persistent ADHD versus comparisons without ADHD. However, we failed to observe hypothesized group differences in prefrontal regions.[1, 3] Below we discuss our main findings and non-findings in turn.

First, we found widespread thinner cortex and decreased GM density in bilateral parietal and precentral regions, overlapping areas of the dorsal attentional network. The bilateral dorsal network, which mediates goal-directed, top-down executive control processes, interacts with a right-sided ventral system (stimulus-driven, bottom-up) during attentional functioning,[1, 55] particularly in redirecting attention. The core areas constituting the dorsal attentional network include the intraparietal sulcus and the conjunction of the precentral and superior frontal sulcus (frontal eye fields)[55] which were particularly affected in the ADHD probands. Strikingly, we also observed significantly thinner cortex in precuneus and superior parietal lobe, which along with the dorsal network core regions are implicated in top-down processing of shifting of attention.[59] These findings are consistent with studies of ADHD that report abnormal patterns of activation in parietal regions[52] during working memory,[60–62] attentional[63–65] or response inhibition tasks.[66, 67]

We also found occipital cortical thinning in probands with persistent ADHD versus non-ADHD comparisons. Occipital cortex has been recently found to interact with the dorsal network in maintaining attention[59] and in suppressing responses to irrelevant stimuli.[68, 69] Individuals with ADHD are easily distracted when required to ignore extraneous signals.[70, 71] Top-down control deficits when responding to irrelevant stimuli are associated with impaired working memory.[72, 73] Abnormal activation of occipital cortex has been found in youth[74] and adults[75–77] with ADHD during working memory tasks. Similarly, in a meta-analysis of functional imaging studies, children and adolescents with ADHD showed activation decreases in left middle occipital gyrus (BA19) compared to controls.[52] Additionally, a recent VBM study in adults with ADHD found significant bilateral reduction of GM volume only in early visual cortex.[78]

Our VBM analysis revealed cerebellar, thalamic and striatal GM deficits in ADHD. Cerebellar involvement in ADHD is well-established, with findings in children reported mostly in the vermis,[1–4, 79] and in the hemispheres in adults, as in this sample.[60, 80, 81] Early anatomical studies of ADHD did not specifically examine thalamic nuclei, although thalamic hypoactivation emerged in an unbiased meta-analysis.[52] Recently, several studies have identified thalamic abnormalities in children/adolescents[53, 82] and adults with ADHD.[83, 84]

Second, our analyses revealed thinner cortex in probands, and particularly those with persistent ADHD, across multiple limbic regions such as temporal poles (BA38), insula (BA13) and subgenual ACC (BA25). The insula and ACC play important roles in sensorimotor, emotional and cognitive function.[85, 86] Specifically, subgenual ACC is implicated in emotional processing and pain perception.[87] In humans, subgenual ACC is functionally connected with multiple limbic regions including temporal poles[88] and insula.[89] In turn, the insula, along with participating in performance of demanding tasks,[90] is clearly also related to affective processing.[91] Abnormal activations in insula and subgenual ACC were reported in a meta-analysis of ADHD functional imaging.[52]

Cortical thickness studies in ADHD have downplayed findings in the temporal pole, which have been reported but not discussed.[12–14] The temporal pole (BA38) is classified as a paralimbic region, based on its interconnections with both amygdala and orbitofrontal cortex, and is implicated in social and emotional processes.[92] Altered activation in temporal pole is associated with deficits in face recognition[93–100] and mentalizing, i.e., theory of

mind.[101–104] The temporal poles have been proposed as a channel for the integration of emotion and perception, playing an important role in both emotional and social functions.[92]

Our findings are consistent with pathophysiological models of ADHD highlighting not only cognitive executive functions ("cool" processes) but also emotion/motivational deficits ("hot" processes).[105] Anatomic "spiraling" circuits begin with emotion/motivation pathways which influence "cool" cognitive processes, which in turn control motor responses.[106] We observed thinner cortex in regions subserving both emotional regulation (temporal pole, insula, parahippocampus and subgenual ACC) and top-down attentional regulation (dorsal attentional network and medial occipital cortex). Further, our exploratory analyses suggest that thinner cortex and diminished gray matter in the dorsal attentional network and limbic relay regions is related to the trait of having had ADHD in childhood, regardless of current diagnostic status.

Third, the lack of proband-comparison differences in prefrontal cortex or ACC was unexpected.[8, 9, 17, 20, 21] To better understand possible differences between persistents and remitters, we performed uncorrected exploratory analyses. In regions in which we found suggestive differences, we observed remarkable congruence between remitters and controls in left superior temporal gyrus, ACC, parahippocampus, and occipital cortical thickness as well as in thalamus and cerebellum gray matter density. We cannot rule out that remitters may have differed from persistents in these regions since childhood, but the most parsimonious explanation is offered by the hypothesis that remission entails compensatory processes[12, 107] underpinned by prefrontal cortical maturation. While we found supporting evidence for ACC and orbitofrontal involvement in diagnostic remission of ADHD, our data also suggest superior temporal, medial occipital and thalamo-cerebellar involvement in remission.

Our findings must be interpreted in light of several limitations. First, despite our prospective longitudinal design, we examined brain imaging data only cross-sectionally in middle adulthood. Nevertheless, this is the largest sample of children with ADHD followed into adulthood, obviating the unreliability of retrospective recall of childhood symptoms. Additionally, we report on the largest sample to date of adults with confirmed childhood ADHD who had remitted. We were able to analyze imaging data from only 28% of initially diagnosed probands with ADHD and 45% of comparison subjects. However, these probands and comparisons did not differ from the original sample, and the probands studied did not differ significantly from those excluded on nearly all clinical and demographic variables, except for significantly higher rates of substance use disorders at 18FU in scanned probands. Nevertheless, we did not observe significant relationships between brain anatomic measures and substance use disorders. Finally, as is generally the case, our probands had significantly lower IQ than comparisons both in childhood/adolescence and adulthood. The issue of whether to covary for IQ in disorders such as ADHD is not settled.[108] As shown in eFigure 1 and Author e-Table 7, our principal findings of persistent differences in brain anatomy survived covarying for IQ even with conservative full-brain correction.

We were surprised by the rate of ADHD-NOS diagnosed in comparisons, which was comparable to the rate in probands. We speculate that secular changes in the general public's awareness of ADHD may have contributed. While we cannot rule out instrument-related error (see Author e-Instrument), using similar approaches did not yield high rates of ADHD symptoms in comparisons in two previous "blind" assessments.[24, 26] Nevertheless, analyses excluding ADHD-NOS did not alter results appreciably.

Subjects were limited to Caucasian males, since the number of originally diagnosed females with ADHD was too small for meaningful statistical comparisons. Thus our results may not

generalize to ADHD in women or to other racial or ethnic groups. However, this constraint avoided potential confounds from possible sex, ethnic, or socioeconomic differences. Exclusion of conduct disorder comorbidity (see Author e-Text) in childhood also averted confusion as to the origin of the deficits found in cortical thickness or GM density.

We cannot comment on cortical thickness or GM density in ADHD in the absence of medication treatment, as all but four of the scanned probands were treated with methylphenidate as children. We also did not detect significant effects of childhood treatment with stimulants or thioridazine in cortical thickness or VBM analyses. Medication treatment has been reported to affect cortical thickness[47] although the durability of such effects is unknown, and treatment had been discontinued for all subjects for several decades.

For logistical reasons, we used two scanners. Fortunately, scans were approximately counterbalanced across probands and comparisons, and there were no significant main effects or interactions related to scanner type. Secondary analyses (see eFigure 2) also showed that we obtained comparable results when we examined only the 98 scans obtained on the Allegra scanner. Finally, the analyses presented here were limited to cortical thickness and VBM; ongoing analyses will examine white matter structure using diffusion tensor imaging.

In conclusion, in this first study of childhood ADHD prospectively examined in adulthood, we found thinner overall cortex in probands with childhood ADHD that was even more pronounced in those with persistent ADHD. Beyond this global effect, we also detected significant reductions in cortex thickness in parietal, temporal and posterior frontal regions corresponding to the dorsal attentional network and limbic areas. These findings were largely echoed by VBM, which additionally highlighted decreased GM in caudate. These regions underpin top-down control of attention and the regulation of emotion and motivation and were comparably diminished in probands with remitted ADHD or persistent ADHD. Thus these differences seem to primarily reflect the childhood diagnosis of ADHD. By contrast, remitters tended to differ from persistents in medial occipital cortex, temporal pole, insula, orbitofrontal cortex, parahippocampus, frontal pole, and subcortically in cerebellum and thalamus. This supports the suggestion that symptom amelioration and diagnostic remission may result in part from compensatory maturation of frontal thalamic cerebellar circuits.[107, 109]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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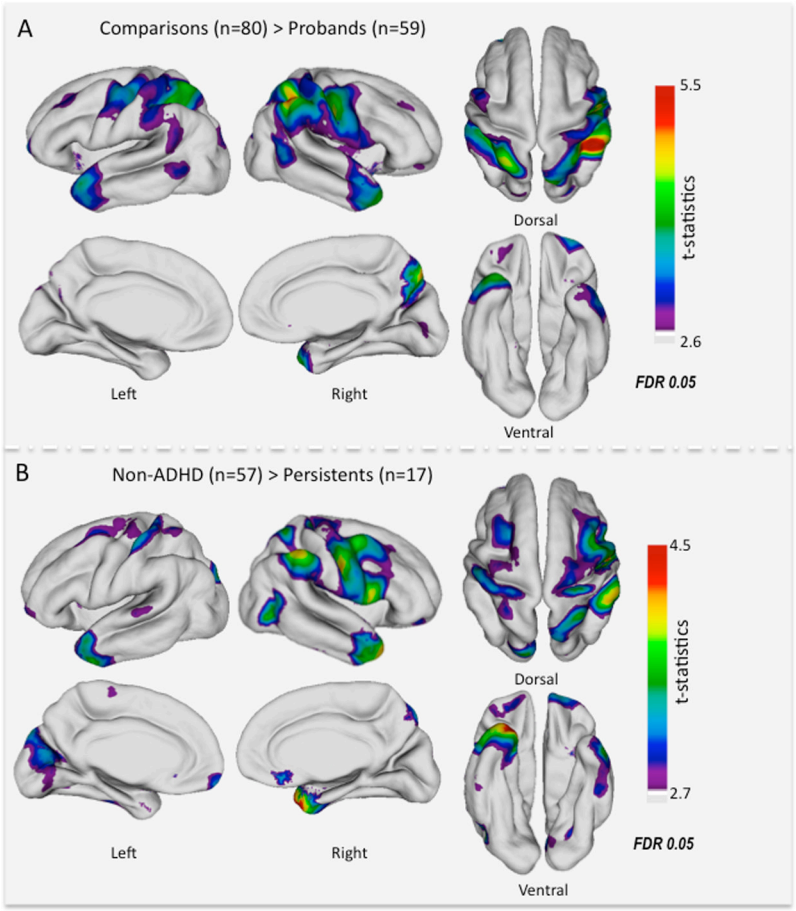

Figure 1.

(A) t-map of the significant cortical thinning in probands with ADHD (n=59) compared to comparisons (n=80). **(B)** t-map of the significant cortical thinning in probands with persistent ADHD (n=17) compared to non-ADHD comparisons (n=57). False Discovery Rate (FDR) threshold depends on the data and is different for the right and left hemispheres. Here the t-statistics at the lowest FDR threshold are projected across each hemisphere for each comparison.

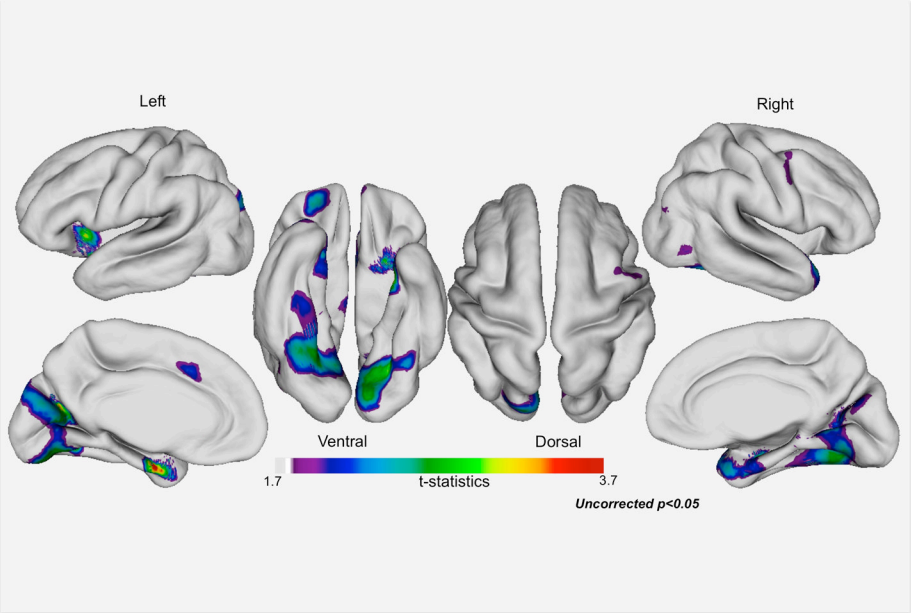

Figure 2.

Exploratory uncorrected analyses ($p<0.05$) reveal regions in which remitted probands (n=27) exhibit thicker cortex than probands with persistent ADHD (n=17). See Author e-Table 7 for peaks and coordinates of clusters.

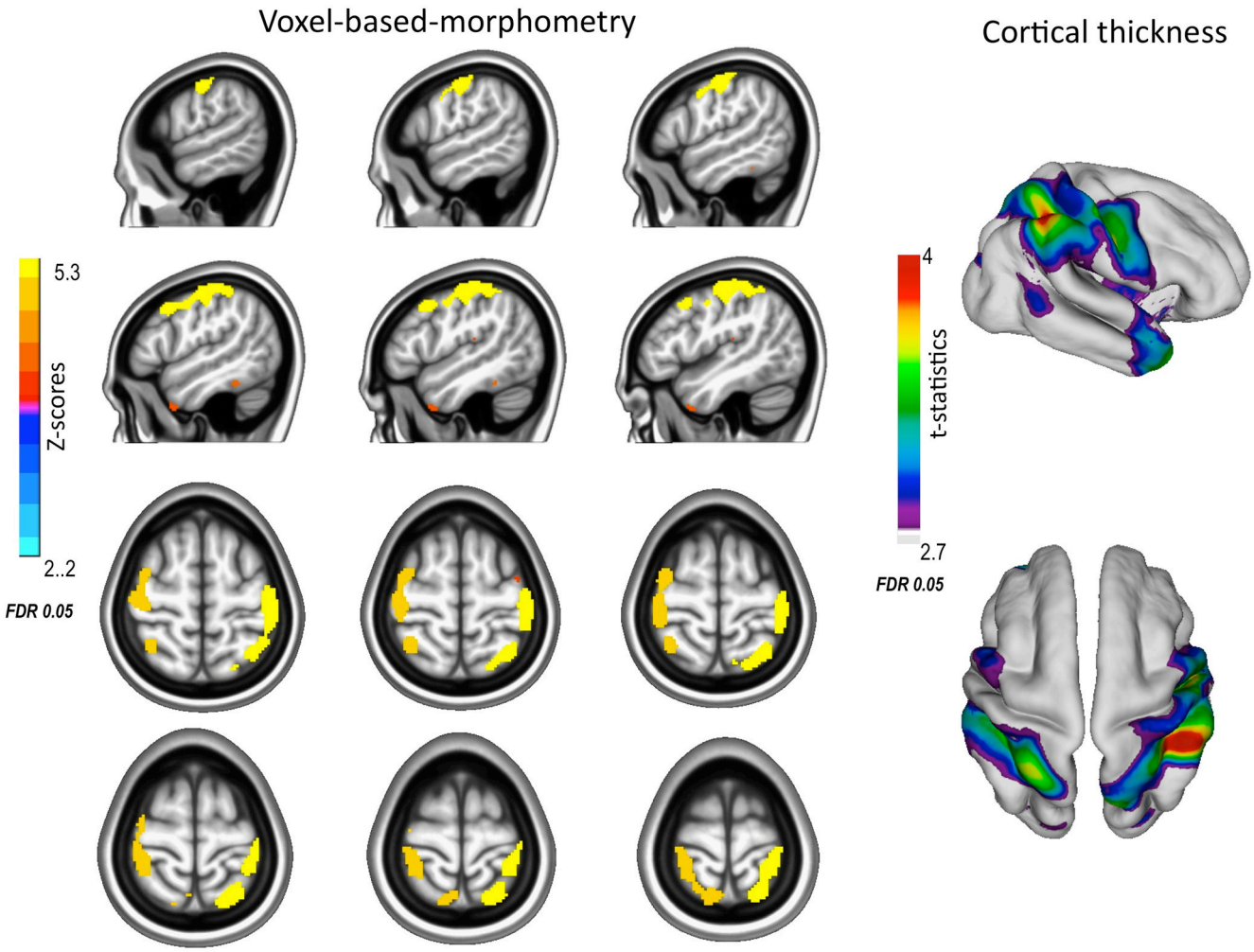

Figure 3.
Comparisons (N=80) exhibit greater gray matter density (left) and cortical thickness (right) in the bilateral dorsal attentional network than probands (n=59) with childhood combined type ADHD. Images are in radiological convention, right is left and left is right.

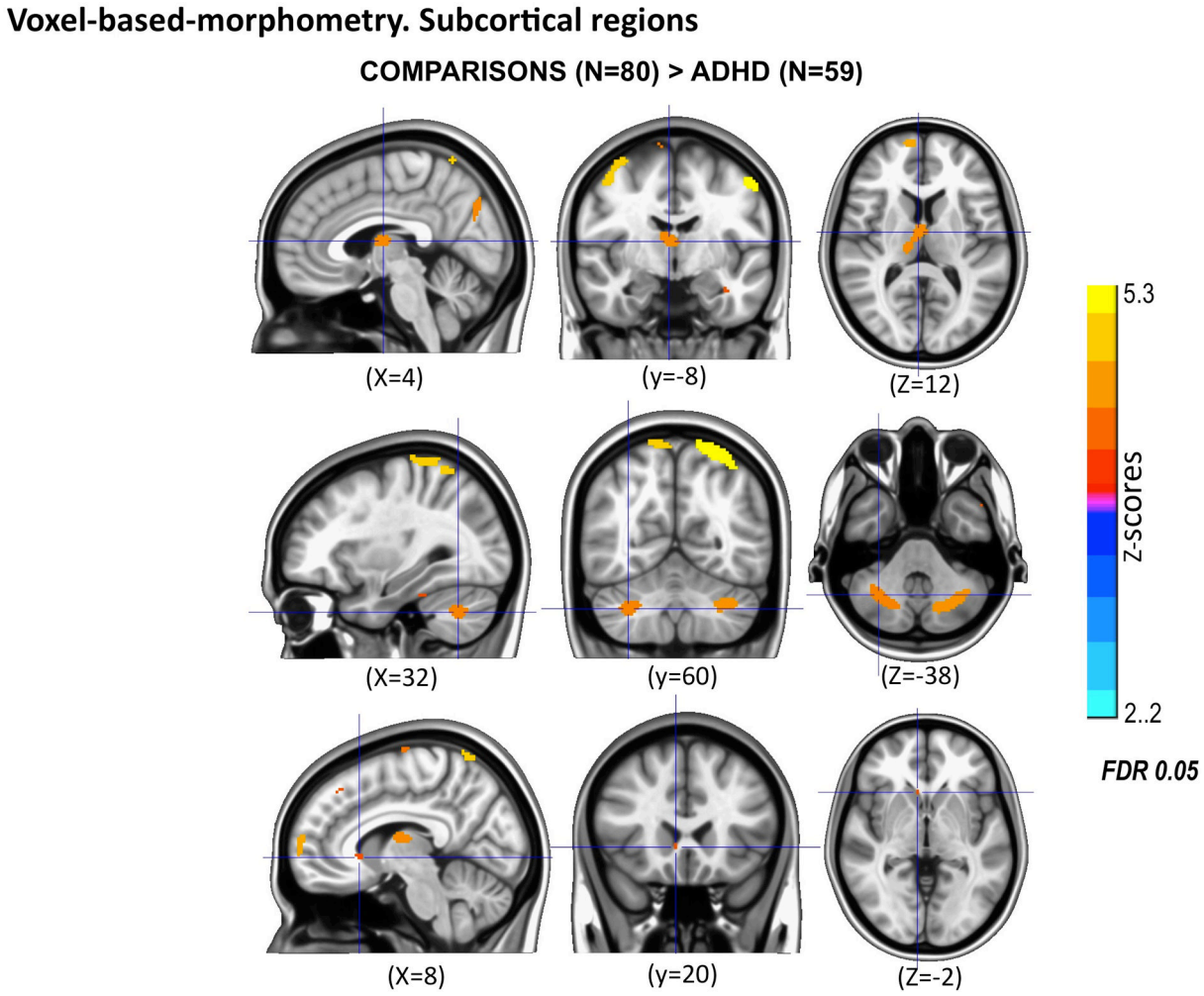

Figure 4.

Voxel-based morphometry reveals that comparisons (N=80) exhibit significantly greater gray matter density (FDR <0.05) in right ventral caudate, right thalamus, bilateral cerebellum than probands (n=59) with childhood combined type ADHD. Images are in radiological convention, right is left and left is right.

Table 1

Derivation of MRI Sample and Demographics

	ADHD Male Probands N (%)	Male Comparisons N (%)		
INITIAL SAMPLE	207 (100)	178 (100)		
Unable to locate	21 (10)	20 (11)		
Deceased	15 (7)	5 (3)		
Incarcerated	6 (3)	1 (1)		
Refused MRI	43 (21)	34 (19)		
Not evaluated prior to termination of funding	29 (14)	22 (12)		
SUBTOTAL-AVAILABLE FOR SCAN	93 (45)	96 (54)		
MRI Exclusions:				
Size (too large for scanner)	17 (8)	6 (3)		
Claustrophobic	7 (3)	3 (2)		
Metal contraindications	3 (2)	1 (1)		
Failed scan quality criteria	7 (3)	6 (3)		
TOTAL NUMBER WITH USABLE DATA	**59 (29)**	**80 (45)**		
DEMOGRAPHICS *	**Mean (SD)**	**Mean (SD)**	*t*	P (2-tailed)
Age at Follow-Up (Years)	41.1 (2.7)	41.3 (3.1)	0.51	0.61
Socioeconomic Status ** at Follow-Up	3.37 (1.1)	2.48 (1.0)	5.01	0.001
Educational Attainment †	13.5 (2.4)	15.6 (2.3)	5.31	0.001
WAIS Full Scale IQ at 18FU	104(13)	113(13)	3.58	0.001
WASI Full Scale IQ at 41FU	101 (13)	110 (15)	3.42	0.001
Global Assessment Scale Rating ***	63.4 (12.5)	71.4 (10.5)	4.05	0.001

* All ADHD probands and comparisons: Caucasian

** Hollingshead and Redlich (1958) scale, based on the participant's education and occupation.

† Highest Grade Completed WAIS: Wechsler Adult Intelligence Scale. Obtained for 39 (66%) of the 59 Probands and all Comparisons.

WASI: Wechsler Abbreviated Scale of Intelligence. Obtained on 54 (92%) of the 59 Probands and 73 (91%) of the 80 Comparisons.

*** Completed by the "blind" clinician that conducted the mental status and diagnostic assessments.

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Table 2

Cortical Thickness Values for Significant Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood.

Regions	MNI X, Y, Z (No. of vertices)	Non-ADHD Controls (n=57)		Probands w/ Persistent ADHD (n=17)		Remitted Probands (n=26)		Non-ADHD Controls vs. Persistents		Non-ADHD Controls vs. Remitters		Remitters vs. Persistents	
		mean	SD	mean	SD	mean	SD	p	ES	p	ES	p	ES
L Sup Parietal (BA7)	−26, −55, 68 (4,290)	2.97	0.13	2.85	0.17	2.86	0.13	0.004	**0.83**	**0.000**	**0.88**	0.978	0.01
L Precentral G (BA6)	−35, 37, 36 (784)	3.35	0.13	3.26	0.15	3.26	0.16	0.022	**0.65**	0.006	**0.67**	0.917	−0.03
L Sup Temp G (BA38)	−54, 10, −22 (915)	3.80	0.19	3.60	0.23	3.66	0.19	**0.001**	**0.98**	**0.002**	**0.75**	0.401	0.26
L Frontal Pole (BA10)	−31, 62, −6 (638)	3.23	0.18	3.06	0.18	3.11	0.23	**0.001**	**0.96**	0.010	**0.62**	0.453	0.24
L Cuneus (BA19)	−13, −91, 35 (618)	2.78	0.20	2.65	0.17	2.73	0.16	0.025	**0.63**	0.325	0.23	0.134	0.48
L Precuneus (BA31)	−6, −65, 30 (62)	3.35	0.20	3.23	0.19	3.26	0.15	0.028	**0.62**	0.029	**0.53**	0.630	0.15
R. Precuneus (BA7)	10, −73, 51 (1148)	3.23	0.16	3.12	0.13	3.15	0.15	0.010	**0.73**	0.040	0.49	0.430	0.25
R Inf Parietal (BA40)	49, −40, 50 (4836)	3.03	0.14	2.91	0.18	2.93	0.14	0.007	**0.77**	**0.002**	**0.74**	0.828	0.07
R Sup Temp G (BA38)	30, 15, −40 (1141)	3.87	0.27	3.62	0.25	3.75	0.22	**0.001**	**0.96**	0.044	0.48	0.080	**0.56**
R Temporal G extending to Insula (BA13)	48, −1, −3 (315)	3.81	0.21	3.69	0.24	3.72	0.21	0.049	**0.55**	0.053	0.46	0.747	0.10
R Precentral G (BA6)	58, 0, 36 (315)	3.41	0.15	3.27	0.19	3.35	0.18	**0.003**	**0.86**	0.109	0.38	0.207	0.40
R Frontal Pole (BA10)	27, 47, 32 (98)	3.37	0.16	3.28	0.17	3.27	0.18	0.057	**0.53**	0.021	**0.56**	0.907	−0.04
R Middle Frontal G (BA9)	25, 47, −14 (130)	3.36	0.20	3.19	0.18	3.33	0.17	**0.002**	**0.90**	0.497	0.16	0.011	**0.83**
R Occipital (BA19)	27, −87, 26 (210)	2.96	0.20	2.86	0.19	2.87	0.19	0.095	0.47	0.079	0.42	0.862	0.05
R Occipital (BA18)	10, −80, 10 (94)	2.79	0.20	2.69	0.21	2.71	0.19	0.079	0.49	0.080	0.42	0.776	0.09

Results for regions which survived FDR<0.05 and extent > 50 vertices in analyses of the entire sample (Figure 1a).

Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L.: Left; Sup.: Superior; Temp.: Temporal; G.: Gyrus; R.: Right; Inf.: Inferior. P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.

Table 3

Grey Matter Density within Clusters for Subgroups Defined by Current ADHD Diagnostic Status in Mid-Adulthood.

Regions	Maximum Z-scores	MNI Peak (No. of voxels)	Non- ADHD Controls (n=57)		Probands Persistent ADHD (n=17)		Probands Remitters ADHD (n=26)		Non-ADHD Controls vs. P-ADHD		Non-ADHD Controls vs. Remitters		Remitters vs. P-ADHD	
			mean	SD	mean	SD	mean	SD	p	ES	p	ES	P	ES
L Sup Parietal (BA7)	5.3	−28, −58, 66 (1747)	0.42	0.04	0.39	0.03	0.39	0.05	0.003	0.86	0.001	**0.78**	0.993	0
L Cerebellum	4.01	−14, −70, −34 (430)	0.57	0.15	0.51	0.14	0.56	0.16	0.146	0.41	0.821	0.05	0.279	0.34
L Inf Cerebellum	3.44	−32, −42, −58 (41)	0.41	0.17	0.28	0.15	0.34	0.18	0.009	0.74	0.116	0.38	0.27	0.35
L Middle Temp G (BA21)	3.32	−48, 10, −42 (32)	0.39	0.1	0.33	0.1	0.34	0.11	0.048	0.56	0.088	0.41	0.682	0.13
L Temp-occipital (BA37)	3.5	−50, −42, −22 (17)	0.6	0.08	0.55	0.09	0.54	0.07	0.024	0.64	0.002	**0.78**	0.724	−0.1
Brainstem extending to Cerebellum	3.37	0, −44, −48 (16)	0.36	0.14	0.3	0.12	0.32	0.11	0.1	0.46	0.148	0.35	0.653	0.14
L Temp-parahippocampal (BA35)	3.33	−34, −10, −22 (13)	0.75	0.06	0.73	0.06	0.72	0.07	0.117	0.44	0.027	**0.53**	0.727	−0.1
L Frontal pole (BA10)	3.31	−16, 52, 32 (9)	0.45	0.05	0.43	0.06	0.43	0.06	0.062	0.52	0.035	**0.51**	0.972	0.01
R Parietal Postcentral (BA3) extending to BA6	4.7	48,−18, 56 (1196)	0.41	0.04	0.37	0.04	0.38	0.05	0	1.04	0.003	**0.72**	0.444	0.24
R Cerebellum	3.84	32, −60, −38 (235)	0.51	0.17	0.44	0.14	0.53	0.17	0.146	0.41	0.581	−0.1	0.078	**0.56**
R Thalamus	3.94	4, −8, 12 (170)	0.73	0.1	0.7	0.09	0.74	0.07	0.202	0.36	0.541	−0.2	0.065	**0.59**
R Occipital, Cuneus (BA18/19)	3.88	2, −76, 36 (122)	0.67	0.05	0.63	0.06	0.65	0.05	0.005	0.79	0.082	0.42	0.2	0.41
R Sup Frontal G (BA10)	4.25	12, 64, 12 (68)	0.47	0.06	0.45	0.04	0.46	0.05	0.261	0.31	0.398	0.2	0.696	0.12
R Frontal lobe (BA6)	3.66	12, −12, 78 (32)	0.46	0.11	0.41	0.11	0.45	0.14	0.107	0.45	0.75	0.08	0.319	0.31
R Middle Frontal G (BA10) extending to OFC (BA11)	3.41	24, 38, −18 (23)	0.51	0.06	0.45	0.05	0.47	0.06	0.001	0.96	0.005	**0.69**	0.434	0.25
R Temp Fusiform (BA36)	3.23	34, −34, −26 (13)	0.63	0.08	0.58	0.05	0.6	0.07	0.014	0.69	0.062	0.45	0.423	0.25
R Caudate	3.3	8, 20, −2 (5)	0.51	0.09	0.49	0.07	0.48	0.1	0.41	0.23	0.18	0.32	0.715	−0.1
R Middle Temp (BA21) extending to (BA38)	3.16	52, 6, −32 (5)	0.55	0.06	0.52	0.05	0.51	0.08	0.063	0.52	0.009	**0.63**	0.614	−0.2
R Middle Temp (BA21) extending to (BA38)	5.3	46, 8, −42 (5)	0.52	0.06	0.51	0.08	0.51	0.05	0.557	0.16	0.561	0.14	0.894	0.04
Anterior Cingulate/limbic (BA24)	3.53	0, 44, −10 (20)	0.82	0.04	0.79	0.04	0.81	0.04	0.016	0.68	0.248	0.28	0.246	0.37

Results for regions which survived FDR<0.05 and extent > 5 voxels in analyses of the entire sample (Figures 3 and 4). Non-ADHD Controls: comparisons who did not meet criteria for any type of ADHD at 41FU longitudinal assessment; ES: Effect Size; BA: Brodmann area; L: Left; Sup: Superior; Temp: Temporal; G: Gyrus; R: Right; Inf: Inferior. OFC: Orbitofrontal cortex; P-values surviving Bonferroni correction for multiple comparisons or ES>.50 are indicated in bold.