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ORIGINAL ARTICLE

What can Cortical Development in Attention-Deficit/Hyperactivity Disorder Teach us About the Early Developmental Mechanisms Involved?

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Abstract

Studies of Attention-Deficit/Hyperactivity Disorder (ADHD) have shown developmental changes in the cortical mantle. Different dimensions of cortical morphology, such as surface area and thickness, relate to different neurodevelopmental mechanisms. As such, studying multiple dimensions may inform us about the developmental origins of ADHD. Furthermore, results from existing longitudinal samples await replication. Therefore, we conducted a longitudinal study of multiple cortical dimensions in a sizable, independent ADHD sample. We analyzed 297 anatomical MRI scans from two matched groups of 94 subjects with ADHD and 94 controls, aged 6–28 years. We estimated the developmental trajectories of cortical volume, surface, thickness and gyrification for 68 regions using mixed-effects regression analysis. Subjects with ADHD had smaller overall cortical volume, predominantly driven by decreases in frontal lobe volume that were associated with reduced surface area and gyrification. Nearly all decreases were stable across development. Only a few decreases survived stringent Bonferroni correction for multiple comparisons, with the smallest detectable Cohen's d |0.43|. There were no between-group differences in cortical thickness, or in subcortical volumes. Our results suggest that ADHD is associated with developmentally persistent reductions in frontal cortical volume, surface area, and gyrification. This may implicate early neurodevelopmental mechanisms regulating cortical expansion and convolution in ADHD.

Key words: ADHD, brain development, cerebral cortex, cortical dimensions, structural MRI

Introduction

Studies of brain development in Attention-Deficit/Hyperactivity Disorder (ADHD) have shown developmental changes in volume of cortical and subcortical areas (Valera et al. 2007; Durston et al. 2009a; Nakao et al. 2011; Frodl and Skokauskas 2012; Greven et al. 2015; Vilgis et al. 2016; Hoogman et al. 2017). However, the developmental mechanisms underlying these changes are still unclear. Relatively new analysis approaches may provide the opportunity to address these mechanisms: distinct dimensions of the cortex, such as surface area and thickness, relate to different cytoarchitectonic properties, which in turn are hypothesized to be determined by partially

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distinct neurodevelopmental mechanisms (Rakic 1995; Panizzon et al. 2009; Chen et al. 2013). For example, the radial unit hypothesis of early development (Rakic 1995) postulates that cortical surface area is related to the number of columnar units (Mountcastle 1997; Jones 2000), which is regulated by the number of neural progenitor cells dividing symmetrically during early phase of neuronal proliferation: at each round of symmetric division, each progenitor generates 2 progenitor cells, with exponential increase of the founders of cortical columns. In contrast, cortical thickness is hypothesized to be regulated by the number of postmitotic neurons that arise from asymmetric cell division and then migrate within a column during embryonic neurodevelopment (Rakic 1995, 2000). Therefore, the symmetric cell proliferation would relate to the expansion of cortical surface area, whereas asymmetric division would determine its thickness. As such, studying these markers of cortical morphology, for example, cortical surface area and thickness, separately in ADHD may potentially inform us on the developmental stage at which early cortical changes occur.

There have been numerous studies on brain development in ADHD, with those from the research group at National Institute of Mental Health (NIMH) perhaps being the most prolific. They have reported reductions in cortical thickness (Shaw et al. 2006) that have been (partially) replicated (Sowell et al. 2003; Narr et al. 2009; Batty et al. 2010; Schweren et al. 2015) but not always (Wolosin et al. 2009; de Zeeuw et al. 2012). The first studies to investigate different dimensions of cortical morphology (surface area and gyrification) have reported either reduced (Wolosin et al. 2009) or delayed (Shaw et al. 2012) cortical surface expansion in ADHD, whereas results for gyrification have been less unequivocal (Li et al. 2007; Shaw et al. 2012). The findings from NIMH of a simultaneous delay in the development of cortical thickness (Shaw et al. 2007) and surface area (Shaw et al. 2012) suggest that there may be a global perturbation of cortical maturation in ADHD (Shaw et al. 2012). To date, no studies have assessed all relevant cortical markers simultaneously (cortical volume, thickness, surface area and gyrification) in a single, longitudinal sample. Doing so may permit a more refined characterization of cortical development in ADHD, as it will permit us to assess the interplay between multiple architectonic features that represent different aspects of early development. Furthermore, studies of longitudinal brain development in ADHD are scarce and often come from overlapping samples (Castellanos et al. 2002; Shaw et al. 2007, 2012). Therefore, there is a call in the field for replication in other, independent longitudinal samples (Horga et al. 2014).

In the current study, we investigated brain development in ADHD, using comprehensive markers of cortical development, in a European, longitudinal sample. We hypothesized that subjects with ADHD would show decreases in cortical volume, in particular in frontal areas. We had no specific expectations regarding which aspects of cortical morphology (e.g., thickness or surface area) would be most affected.

Materials and Methods

The Institutional Review Board of the University Medical Center Utrecht, the Netherlands, approved the study and its procedures. For subjects under the age of 18 years, written informed consent was obtained from the parents after full disclosure of the study purpose and procedure. Children provided written and/or verbal assent. Subjects aged 18 years or above gave written informed consent themselves.

Participants and Clinical Measures

We acquired 410 whole-brain MRI scans from 260 subjects (129 with ADHD and 131 typically developing controls). We used propensity score matching (PSM) to equalize gender, socioeconomic status (SES), and the number of longitudinal scans between groups. We chose not to match the groups for intelligence quotient (IQ) as changes in IQ are intrinsically related to ADHD (Frazier et al. 2004). Therefore, matching for IQ would have led to unrepresentative samples of both the ADHD and control populations (i.e., selection bias). Such bias would likely remove variability in the dependent variables of interest (e.g., brain volume) and possibly generate anomalous findings (Dennis et al. 2009). PSM resulted in a sample of 188 closely matched subjects (94 in each group), aged between 6 and 28 years. There were a total of 297 MRI scans available, with 73 participants (34 subjects with ADHD; 39 controls) scanned twice or more. There was no difference in mean age between groups at each wave of scanning. Longitudinal scans were acquired with a similar average interval in both groups (ADHD: M (SD) = 3.6 (2.0) years, controls: M (SD) = 3.4 (2.3) years; $P = 0.739$).

The Diagnostic Interview Schedule for Children (DISC, version 2.3 or IV), parent version (Shaffer et al. 2000), was administered to parents in order to confirm the clinical diagnosis of ADHD or to exclude psychiatric comorbidity in controls at study entry. Parents and teachers completed broadband psychiatric screeners at each time point: Child Behavior Checklist (CBCL) and Teacher Report Form (TRF) respectively, to provide a dimensional measure of behavioral symptoms (Verhulst et al. 1996, 1997). Total IQ was estimated using a short form of the Dutch version of the Wechsler intelligence scales (WISC-R/WISC-III or WAIS-III as appropriate), including the subtests Vocabulary, Block Design, Similarities, and Object Assembly (Wechsler 2005).

Controls were excluded in case of psychiatric morbidity or first-degree relatives with a history of psychiatric problems. Children with ADHD were excluded if they met DSM criteria for any co-morbid disorder other than Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) on the DISC at study entry. In both groups, additional exclusion criteria were IQ below 70, any major physical or neurological illnesses or the presence of metals in the body that precluded the MRI session. Table 1 lists participant characteristics for both samples. Medication status based on parental- and self-report could reliably be assessed at study entry for 89% of ADHD cases. At study entry, 75% of the subjects with ADHD were using psychostimulant medication. The vast majority (94%) was taking methylphenidate preparations. The proportion of medicated subjects declined slightly at follow-up: 73% of subjects with ADHD were medicated at the time of their second scan, 67% were medicated at scan 3.

Prior to the MRI scan, children under 13 years of age were acclimated to the MRI procedure in a practice session using a dummy scanner as described previously (Durston et al. 2009b); children over 13 years were also offered the opportunity to do a practice session.

Propensity Score Matching

PSM is a statistical matching technique that pairs cases and controls with similar values on a propensity score (PS) from a pool of participants. The PS is the probability of group membership conditional on a set of observed non-random confounders. PSs were estimated using logistic regression, including gender, SES, and a dummy variable for the presence of longitudinal scans as covariates, implemented in SPSS 20.0.0 and R 3.0.2 (Thoemmes

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Table 1 Demographic and clinical characteristics of the sample

		ADHD (N = 94)	Controls (N = 94)	Group differences[a]
Gender	N Male–Female	78–16	80–14	ns
Age at scan	N scans Wave 1/years M (SD)	94/11.4 (2.9)	94/11.2 (4.0)	ns
	N scans Wave 2/years M (SD)	34/15.1 (2.6)	39/14.5 (3.4)	ns
	N scans Wave 3+/years M (SD)	13/18.5 (2.7)	23/18.1 (2.7)	ns
Hand preference	N Right-handed/other	70/24	77/17	ns
SES	Parental education years M (SD)	12.8 (2.2)	13.1 (2.0)	ns
Total IQ	M (SD) at baseline*	100.9 (16.8)	109.8 (16.8)	*
DISC[b]	N ADHD-I	23	0	—
	N ADHD-HI	16	0	—
	N ADHD-C	55	0	—
	N ODD	34	0	—
	N CD	1	0	—
CBCL[c]	Internalizing raw score M (SD)	9.3 (5.6)	4.4 (4.9)	**
	Externalizing raw score M (SD)	16.6 (9.5)	4.5 (5.0)	**
	Attention problem raw score M (SD)	9.2 (4.0)	3.1 (2.5)	**
TRF[d]	Internalizing raw score M (SD)	7.5 (5.9)	3.5 (4.6)	**
	Externalizing raw score M (SD)	13.1 (10.6)	3.0 (5.0)	**
	Attention problem raw score M (SD)	16.9 (9.4)	6.0 (7.0)	**
Medication	N Medicated/unmedicated/no reliable Info Available at			
	Wave 1	64[e]/20/10	0/94/0	**
	Wave 2	22/12/0	0/39/0	**
	Wave 3+	6/4/3	0/23/0	*

Note: I, inattentive type; HI, hyperactive/impulsive type; C, combined type; N, number; M, mean; SD, standard deviation; DISC, Diagnostic Interview Schedule for Children.
[a]t-Test for age at scan at each wave of scanning and total IQ; X2 for Gender and Handedness; nonparametric statistical test for SES, CBCL and TRF; Fisher's exact test for Medication status at each wave of scanning; ns, not significant.
[b]DISC repeated at follow-up for 36% of the subjects.
[c]CBCL unavailable for 9 controls and 13 ADHD subjects.
[d]TRF unavailable for 19 controls and 30 ADHD subjects.
[e]63 subjects on psychostimulants (59 on methylphenidate, 3 on dexamphetamine, 1 on atomoxetine), 1 subject on desipramine.
*$P < 0.001$; **$P < 0.0001$.

2012). Subjects were then matched using 1:1 nearest neighbor matching. The caliper width (maximum permitted difference between 2 subjects) was set to the recommended value (Austin 2011) of 0.20 standard deviations of the logit of the PS.

MRI Acquisition

All imaging was performed over the time span of 15 years using a 1.5-T MRI-scanner (Philips). A T1-weighted 3-dimensional fast field echo scan of the whole head was acquired with 130 to 150 1.5-mm contiguous coronal slices (earlier scans; 58 scans from subjects with ADHD and 51 scans from controls) or 160 to 180 1.2-mm contiguous coronal slices (later scans; 83 scans from subjects with ADHD and 105 scans from controls) (echo time 4.6 ms; repetition time 30 ms; flip angle 30°; field of view 256 mm; in-lane voxel size 1 mm × 1 mm). There were no major hardware upgrades during the study, and all the appropriate quality control procedures (e.g., use of phantoms) were applied on a regular basis, as well as before and after each software upgrade. Groups did not differ with respect to the distribution of scan acquisition date (Levene's test $P = 0.168$), or MRI protocols (slice thickness 1.5 vs. 1.2 mm), for either baseline ($P = 0.770$) or longitudinal measures ($P = 0.133$). Independent neuroradiologists evaluated all MRI scans and no gross morphological abnormalities were reported for any of the participants.

MRI Processing

All scans were coded in order to ensure rater blindness to subject identity and diagnosis at all times during analysis. The T1-weighted images were processed using FreeSurfer v5.1.0 (Fischl 2012), a well validated and widely used segmentation and image analysis software package (http://surfer.nmr.mgh.harvard.edu/fswiki).

The package contains a fully automated structural imaging pipeline for the quantitative assessment of brain anatomy including volumetry of subcortical structures and a complete assessment of cortical morphometry, along the entire surface and with accuracy comparable to manual methods (Fischl et al. 2002) and postmortem studies (Fischl and Dale 2000). The brain segmentation and cortical reconstruction pipelines in FreeSurfer have been described in more detail elsewhere (Dale et al. 1999; Fischl et al. 1999, 2002; Fischl and Dale 2000, 2004a, 2004b). In short, brain segmentation consists of registering the brain into Talaraich space (Talairach and Tournoux 1988), removing non-brain tissue using a deformable template model (skull stripping), and neuroanatomical labeling, based on both voxel intensity values and a probabilistic atlas (Fischl et al. 2002). The reconstruction of cortical surfaces involves the segmentation of white matter, used to derive a surface representing the gray-white matter boundary (white surface). The white surface is then refined and deformed to locate the pial surface (gray matter/cerebrospinal fluid boundary) (Dale et al. 1999). Finally, by incorporating both geometric information derived from the cortical model and standard neuroanatomical conventions (Desikan et al. 2006; Destrieux et al. 2010), the procedure automatically assigns a neuroanatomical label to each location on the cortical surface (cortical parcellation). The automated cortical reconstruction is described in more detail in the Supplementary Material.

The FreeSurfer pipeline requires that output is checked individually at multiple points during the processing stream, in

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order to correct errors, if necessary. Given the sensitivity of cortical markers to movement and other acquisition artifacts, this post-processing quality control procedure ensures robustness and reliability of the results across participants (Dewey et al. 2010; Ducharme et al. 2016). Accordingly, we inspected the Talaraich registration, tissue segmentations, surface reconstructions and cortical parcellation for accuracy. If necessary, manual edits were performed by experienced operators (S.A. and L.M.W.) following the standardized procedures documented on the FreeSurfer website (http://surfer.nmr.mgh.harvard.edu/fswiki). The types of errors that frequently required user editing were incomplete skull stripping and mis-classification of white matter.

We acquired the volume of 24 noncortical regions, including 6 subcortical structures per hemisphere (caudate, putamen, pallidum, accumbens, thalamus, and amygdala), the corpus callosum (anterior, mid-anterior, central, mid-posterior, and posterior segments), bilateral hippocampus, bilateral cerebellar gray and white matter and the brain stem. For simplicity, we refer to these as "subcortical" structures.

For cortical morphometry, we analyzed 34 regions per hemisphere from the Desikan-Killiany atlas (Desikan et al. 2006) (see Supplementary Material). The FreeSurfer outputs of interest were cortical volume (CV, mm^3), cortical surface area (CS, mm^2), cortical thickness (CT, mm), and local gyrification index (LGI, dimensionless) of the cortex as a whole and within the predefined areas (Fig. 1).

For each area, CS was measured along the white surface; CV and CT were measured as the volume and the average distance, respectively, between parcellated portions of white and pial surfaces (Fischl and Dale 2000). LGI is a measure of gyral complexity that is calculated at each point of the pial surface and was averaged across each area. LGI refers to the ratio between the surface of a circular patch of the pial surface and the corresponding patch on the outer smoothed surface of the brain (Schaer et al. 2008).

Total, left (lh) and right (rh) hemisphere values were obtained for cortical volume, surface, thickness and gyrification by summing or averaging each measure across all areas included. Average thickness throughout the cortex was computed applying the formula: Total CT = ((lh.CT × lh.CS) + (rh.CT × rh.CS))/lh.CS + rh.CS (http://surfer.nmr.mgh.harvard.edu/fswiki).

Statistical Analysis

SPSS Statistics 20.0.0 for Mac OS X (SPSS Inc.) was used to test for between-group differences in demographic and clinical data using parametric or nonparametric tests as appropriate.

The developmental trajectories of each measure were estimated using (generalized) Linear Mixed Models as implemented in the lme4 library (Bates et al. 2011) in the R statistical package (R Development Core Team, 2012). This method permits the inclusion of multiple scans per person, to combine both inter- and intra-individual differences in the growth parameters (i.e., intercepts and slopes), while accounting for unbalanced data structure due to irregular time intervals between scans and unequal numbers of scans between subjects.

The best-fit model was determined in 2 phases following the procedure described previously (Wierenga et al. 2014a, 2014b). First, a growth model was determined using a step-down selection procedure. Each brain measure of the ith individual at the jth time point was modeled using cubic, quadratic and linear age effects (with age centered around the mean of the whole group: 13 years), with gender as a covariate, according to the formula:

$$\begin{aligned}\text{Measure}_{ij} = \text{Intercept} + d_{ij} + \beta_1(\text{gender}) + \beta_2(\text{age}) \\ + \beta_3(\text{age})^2 + \beta_4(\text{age})^3 + e_{ij},\end{aligned}$$

where d_{ij} represents the within person dependence and the e_{ij} term is the residual error. Gender and age effects were fixed, while the intercept and the d_{ij} term were modeled as random effects. If the cubic age effect was not significant at $P < 0.05$, it was removed from the model in order to test the quadratic age effect and so on.

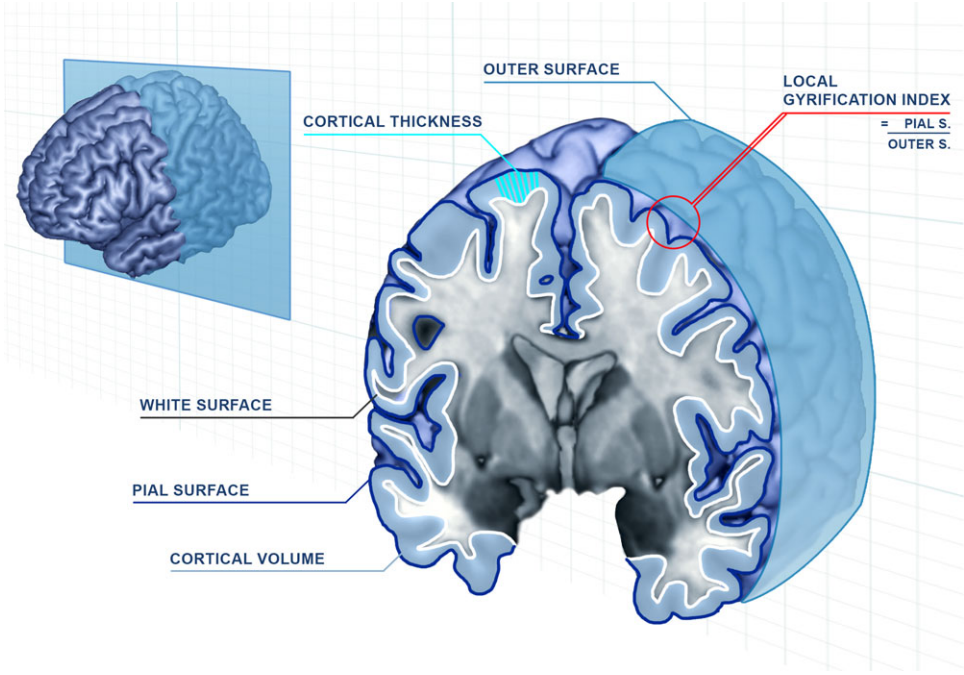

Figure 1. Morphometric parameters of the cerebral cortex. For every defined region of interest, cortical thickness was estimated as the average distance (in mm) between the white and pial surfaces; cortical surface was the area of the white surface (in mm^2); cortical volume was calculated as the volume contained between the white and pial surfaces (in mm^3); local gyrification index (dimensionless) was computed as the ratio between the pial and outer surface.

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Second, we examined whether the growth model differed between subjects with ADHD and controls. The selected growth model was expanded to include a dichotomous variable "ADHD" and its interaction with the age term(s) as fixed factors. For example, measures where the cubic model was appropriate were modeled as:

$$\begin{aligned}\text{Measure}_{ij} = {} & \text{Intercept} + dij + \beta_1(\text{gender}) + \beta_2(\text{age}) \\ & + \beta_3(\text{age})^2 + \beta_4(\text{age})^3 + \beta_5(\text{ADHD}) \\ & + \beta_6(\text{ADHD}) * (\text{age}) + \beta_7(\text{ADHD}) * (\text{age})^2 \\ & + \beta_8(\text{ADHD}) * (\text{age})^3 + e_{ij}\end{aligned}$$

We tested whether the full model fit the data better than a simpler model including only the main effects of the ADHD and age. If it did not (indicating that there was no group by age interaction), the simpler model was compared to the selected growth model including the age terms only (i.e., this would denote that ADHD had no effect at all). Coefficients were estimated using the full Maximum Likelihood criterion and models were compared using the Bayesian Information Criterion (BIC). If the difference between the BIC of 2 nested models was greater than 2, the model with the lower BIC was selected; if ($\Delta BIC \leq 2$), the simplest model was selected on the grounds of parsimony. This procedure permitted us to achieve a balance between model complexity and goodness of fit (Kass and Raftery 1995).

We calculated effect sizes for the ADHD predictor by dividing the fixed effect estimate by the square root of the variance at the within-subject level (Tymms 2004). This estimate of effect size is equivalent to Cohen's d (Cohen 1992).

We applied Bonferroni correction to control for multiple comparisons for ADHD main effects (adjusted P-value 0.00008). However, such correction is likely to be overly conservative given interdependency between brain regions and measures. Combined with the multidimensional nature of the data this makes it near impossible to compute the effective number of degrees of freedom in the data. Hence, we report both corrected and uncorrected results here.

In addition, we performed robustness analyses to assess the robustness of our findings in the face of potential confounders. First, a dummy variable for slice thickness (1.5 vs 1.2 mm) was included as an additional fixed term in the growth models. To enable inferences about local changes un-confounded by global brain measures, further analyses with intracranial volume (ICV), total cortical surface area, average cortical thickness, or average local gyrification to correct local measures of cortical and subcortical volumes, cortical surface area, cortical thickness, and local gyrification, respectively, were run. However, given collinearity between gender and ICV, any analysis including both measures must be interpreted with caution. We did not add IQ to the model due to the problems of controlling for characteristics that are intrinsic to the phenotype of interest (Dennis et al. 2009). Finally, since there were only few data points over age 25 years, we reran the analysis without older participants. Since this did not lead to any meaningful changes in the results and interpretation, we report the results from all participants here.

Results

Total Cortical Volume, Surface, Thickness, and Gyrification

The developmental trajectories of total cortical volume and its geometric properties (surface area, thickness, and gyrification) are shown in Figure 2. The regression coefficients are provided in the Supplementary Material Table S2. There was a quadratic effect of age and a main effect of ADHD on total cortical volume, but no interaction between ADHD and age. Mean total cortical volume was 5% smaller for subjects with ADHD than controls and this difference was stable across development. Total cortical surface area followed a cubic trajectory for the entire group; total cortical thickness and total gyrification both showed a linear decrease with age for the group as a whole. There were no main effects or interaction between age and diagnostic group for these measures.

The analysis for each hemisphere separately showed that there was a reduction of cortical volume in the left hemisphere for ADHD, and a reduction of cortical volume and surface area in the right hemisphere (see Supplementary Table S2).

Local Differences in Cortical Volume, Surface Area, Thickness, and Gyrification

Subjects with ADHD had reduced cortical volume in several areas throughout the cortex, predominantly in frontal lobes (caudal anterior cingulate and rostral middle frontal cortex of the left hemisphere, bilateral medial, and lateral orbitofrontal cortex, bilateral precentral cortex, right superior frontal, caudal middle frontal, and pars opercularis of the inferior frontal gyrus). There were no group by age interaction effects on regional cortical volumes, indicating that the main effects of diagnosis were stable across development. Surface area and gyrification were also reduced in a number of areas. There were no differences in thickness in any cortical area. Table 2 and Figure 3 summarize these differences; parameters for developmental trajectories and effect sizes are provided in the Supplementary Material Table S3.

Reductions in volumes were particularly pronounced in the caudal middle frontal and isthmus cingulate cortices of the right hemisphere, where volume reductions of more than 10% (>4 SD below the mean of the controls) were found. Effect sizes ranged from −0.43 to −0.78, and are therefore "small" to "medium" according to Cohen's criteria (Cohen 1992). In many regions, the reduction of surface area occurred together with a reduction of cortical volume (left caudal anterior cingulate, rostral middle frontal, and superior temporal cortices; right caudal middle frontal cortex, isthmus cingulate cortex, pars opercularis, and lateral occipital cortex). In 2 regions with decreased cortical volume and surface area, we also found reduced gyrification (left rostral middle frontal cortex and right pars opercularis).

For nearly all areas, there were no differences in the shape of developmental trajectories between the ADHD and control groups. As such, the reductions in cortical surface area and gyrification described above were stable over development. We found only 2 group by age interactions: for gyrification in the left cuneus and right pars opercularis. In these regions, the gyrification was reduced in the younger age ranges in ADHD, but declined less steeply in subjects with ADHD than controls, which led to convergence of the gyrification index at later age ranges (see Supplementary Fig. S3).

Subcortical Areas

There were no differences between groups in the developmental trajectories of any subcortical areas, nor were there any main effects of diagnosis.

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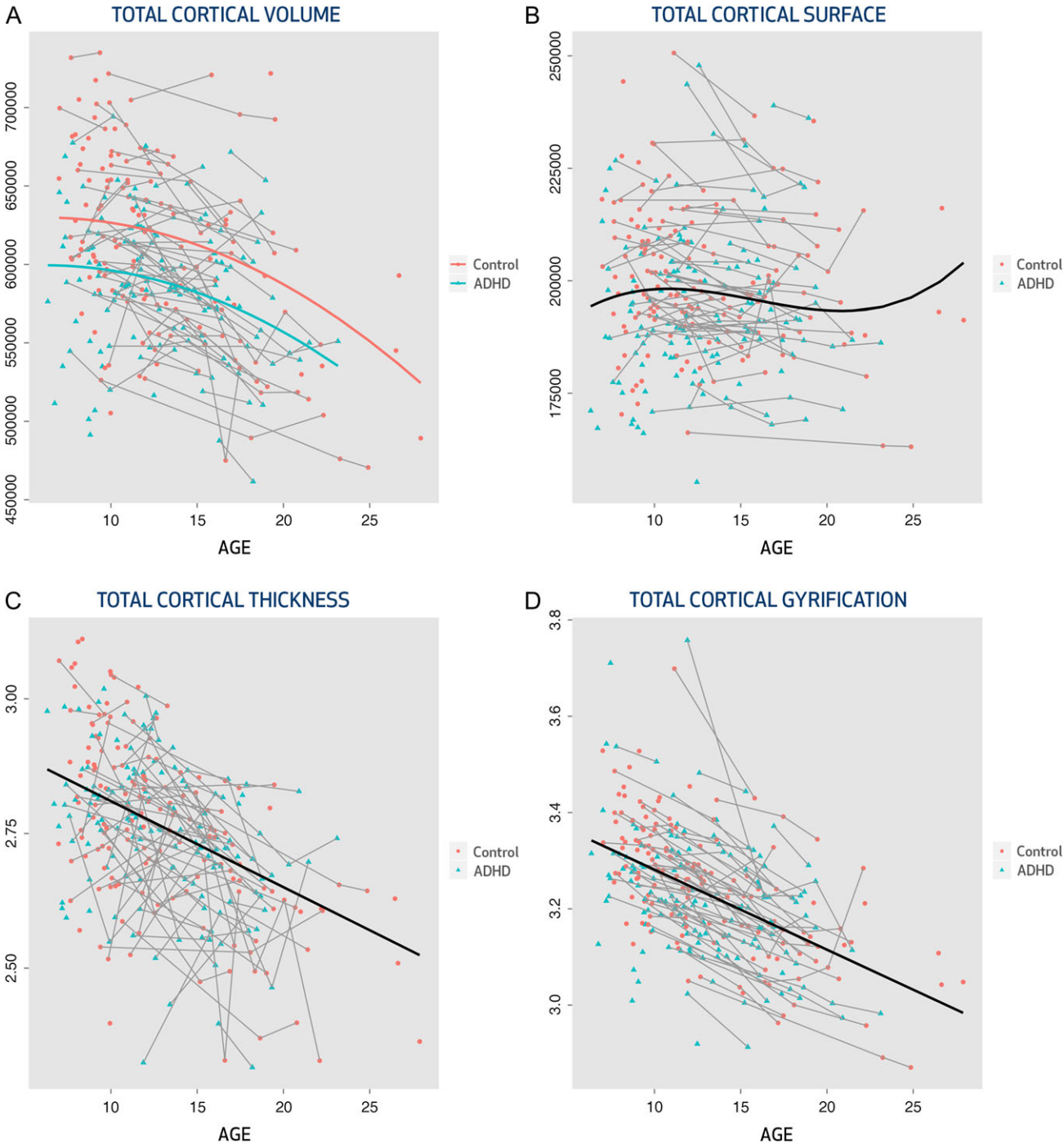

Figure 2. Developmental trajectories of total cortical volume (panel A, mm^3), total surface area (panel B, mm^2), total cortical thickness (panel C, mm), and total gyrification index (panel D, dimensionless).

Results with Stringent Bonferroni Correction for Multiple Comparisons and Robustness Analyses

Between-group differences in cortical volume reached Bonferroni-corrected significance for the following regions: left, right, and total cortical volume (see Supplementary Table S2), and locally for left rostral middle frontal cortex, left superior parietal, left superior temporal, left supra marginal cortices, right isthmus cingulate, and right lateral occipital cortices (Table 2 and Fig. 3; see Supplementary Table S3). These results were deemed robust, as they retained significance when slice thickness and ICV were included in the model as additional covariates, except for left cortical volume. Between-group differences in cortical surface area and gyrification failed to reach Bonferroni-corrected significance, or when total cortical surface area or average local gyrification (respectively) were added to the model (Supplementary Table S4). As such, they were deemed less robust.

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Table 2 Significant between-group differences for regional measures at the time of the first scan (baseline values).

	Left hemisphere						Right hemisphere				
Volume (mm^3)	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value	Volume (mm^3)	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value
Caudal anterior cingulate	2364.17 (620.95)	2131.25 (512.94)	9.85	−2.804	0.006	Caudal middle frontal	8693.085 (1611.33)	7785.415 (1416.34)	10.44	−4.102	<0.0001
Lateral orbitofrontal	9645.06 (1280.61)	9152.60 (1186.19)	5.11	−2.735	0.007	Cuneus	3895.93 (588.77)	3591.45 (634.43)	7.82	−3.411	<0.001
Medial orbitofrontal	6648.14 (942.18)	6231.90 (953.22)	6.26	−3.011	0.003	**Isthmus cingulate**	3460.10 (724.36)	3094.21 (509.83)	10.57	−4.005	<0.0001
Middle temporal	14 873.34 (2070.92)	14 144.67 (1836.65)	4.90	−2.552	0.012	**Lateral occipital**	14 491.13 (2097.74)	13 229.42 (1734.95)	8.71	−4.494	<0.0001
Precentral	16 023.61 (1836.40)	15 349.56 (1794.82)	4.21	−2.545	0.012	Lateral orbitofrontal	9458.86 (1279.44)	8952.87 (1146.93)	5.35	−2.855	0.005
Precuneus	13 796.31 (1792.36)	12 977.44 (1730.64)	5.94	−3.187	0.002	Medial orbitofrontal	6273.25 (848.37)	5873.16 (829.83)	6.38	−3.269	0.001
Rostral middle frontal	23 282.65 (3312.90)	21 494.06 (2341.65)	7.68	−4.274	<0.0001	Pars opercularis	5787.43 (963.86)	5300.62 (921.71)	8.41	−3.539	0.001
Superior parietal	18 177.81 (2473.67)	16 961.56 (2000.78)	6.69	−3.706	<0.001	Precentral	16 002.22 (1931.85)	15 119.47 (1740.48)	5.52	−3.291	0.001
Superior temporal	16 179.76 (1955.96)	15 048.86 (1788.64)	6.99	−4.137	<0.0001	Precuneus	14 164.17 (1972.88)	13 387.95 (1859.06)	5.48	−2.776	0.006
Supra marginal	15 878.93 (2151.64)	14 688.31 (2096.45)	7.50	−3.843	<0.001	Superior frontal	30 092.40 (3711.68)	28 745.44 (2876.46)	4.48	−2.781	0.006
						Superior parietal	18 074.09 (2442.41)	17 086.73 (2046.77)	5.46	−3.004	0.003
						Superior temporal	15 571.57 (1965.54)	14 801.53 (1580.31)	4.95	−2.960	0.003
Surface area (mm^2)	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value	Surface area (mm^2)	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value
Caudal anterior cingulate	705.61 (153.51)	645.12 (153.51)	8.57	−2.908	0.004	Caudal middle frontal	2692.20 (539.24)	2407.82 (439.15)	10.56	−3.965	<0.001
Rostral anterior cingulate	922.50 (156.31)	857.87 (179.75)	7.01	−2.630	0.009	Isthmus cingulate	1044.27 (185.54)	949.76 (174.11)	9.05	−3.601	<0.001
Rostral middle frontal	6791.60 (909.71)	6341.90 (906.39)	6.62	−3.395	0.001	Lateral occipital	5649.27 (755.85)	5291.44 (682.30)	6.33	−3.407	0.001
Superior temporal	4436.60 (487.06)	4180.88 (472.39)	5.76	−3.654	<0.001	Pars opercularis	1647.07 (273.67)	2407.82 (278.47)	9.57	−3.916	<0.001
Gyrification	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value	Gyrification	Controls M (SD)	ADHD M (SD)	Δ%	*t* (186)	*P*-value
Cuneus	3.03 (0.18)	2.99 (0.23)	1.29	−1.298	0.196	Pars opercularis	4.80 (0.34)	4.67 (0.32)	2.77	−2.775	0.006
Rostral middle frontal	3.01 (0.17)	2.93 (0.17)	2.60	−3.116	0.002	Transverse temporal	5.39 (0.36)	5.23 (0.38)	2.97	−2.953	0.004

Note: Between-group differences over development reaching Bonferroni-corrected significance are indicated in bold with underline. M, mean; SD, standard deviation; Δ%, percentage change, determined by dividing the difference of the ADHD and control values by the control value, multiplied by 100.

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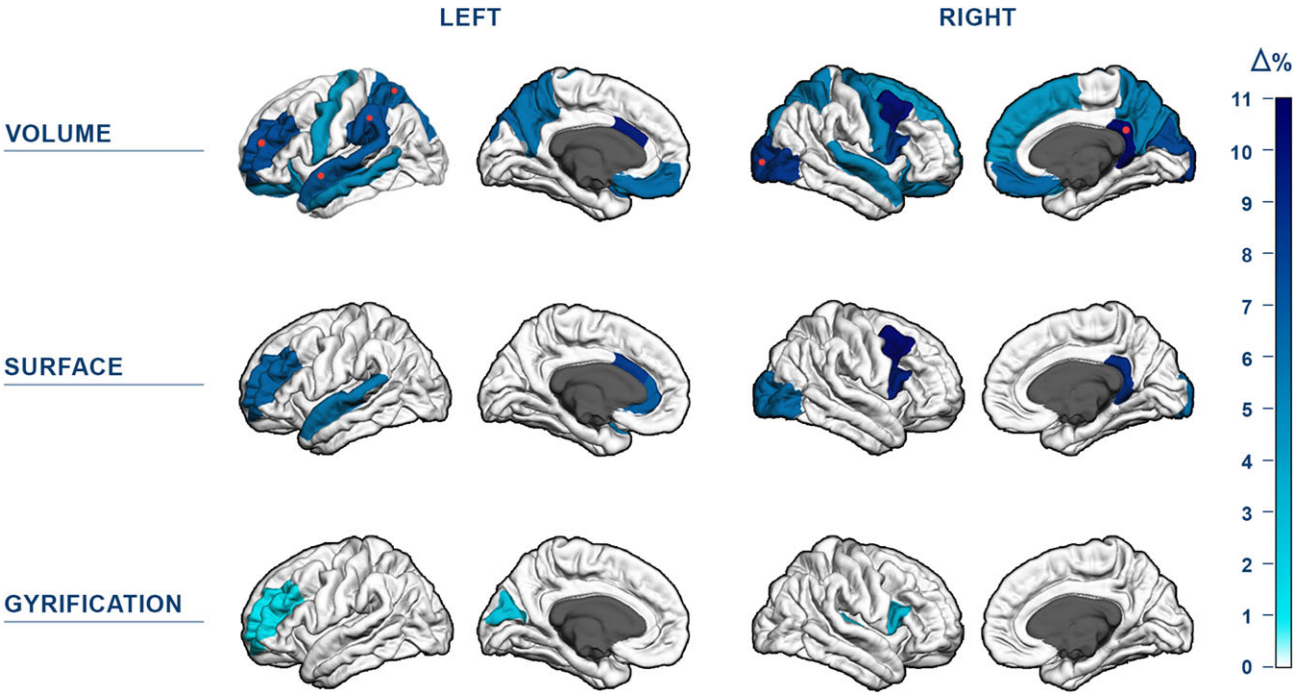

Figure 3. Group differences for regional measures. Note. The darker the color, the greater the reduction in ADHD compared with controls. References to color in this figure legend are provided in Table 2. The red dots indicate the findings significant at Bonferroni-corrected threshold (<0.00008).

Discussion

In this study, we investigated brain development in an independent, longitudinal sample of subjects with ADHD and matched, typically developing controls. We found reduced cortical volume in ADHD, predominantly in the frontal lobes, in line with previous studies (Castellanos et al. 2002; Wolosin et al. 2009; Durston et al. 2009a; Batty et al. 2010). More detailed examination of cortical markers suggested that the reductions in volume were primarily driven by a reduction in surface area, rather than thinning of the cortex, and that these differences persisted across development.

We found changes with development in cortical and subcortical areas for both controls and ADHD subjects, reflecting structural maturation of the brain. Furthermore, we observed different developmental trajectories for the different cortical dimensions (surface area, thickness, and gyrification), supporting earlier studies (Raznahan et al. 2011; Wierenga et al. 2014b) and suggesting that they may be driven, at least in part, by distinct regulatory processes (Panizzon et al. 2009; White et al. 2010).

Our data suggest that ADHD is primarily associated with developmentally stable changes in the volume of the cortical mantle as a whole and of specific cortical regions proportionally, as these changes did not seem to be driven by more global reductions in brain volume.

These changes appear to be mostly due to decreased surface expansion, as evidenced by reductions in surface area, and less convolution, as evidenced by reductions in gyrification. This pattern of results particularly implicates the neurodevelopmental mechanisms that govern the tangential growth and sulcation of the cortex in ADHD.

According to the radial unit hypothesis (Rakic 1995), cortical surface area is determined by the number of columns, which in turn depend on the number of neural progenitors within the proliferative zones. The proliferation phase of embryonic brain development is governed by mechanisms that either promote the number of neurons that can migrate to target cortical areas (neurogenesis) or restrict it (cell death) (Rakic 2000). Therefore, either lower production or excessive loss of cells during proliferation could lead to a lower degree of cortical expansion. Disorders of late neuronal proliferation have been associated with congenital anomalies such as primary microcephaly, characterized by small brain size with normal to thin cortex and simplified, but grossly conserved, gyral patterning (Barkovich et al. 2012). We speculate that a possible mechanism underlying the reduction in surface area with preserved cortical thickness in ADHD may represent a minor perturbation of late neuronal proliferation, leading to a subtle but stable reduction of cortical surface area, with largely preserved cortical layering. Any reflection on the mechanisms underlying such a perturbation is of necessity speculative. However, it is noteworthy that teratogenic substances targeting neuronal precursors, such as nicotine and alcohol have been linked to ADHD (Linnet et al. 2003; Banerjee et al. 2007), as have a number of genetic and molecular factors regulating neuronal proliferation and differentiation (e.g., *DIRAS2* (Reif et al. 2011), *CDH13* (Poelmans et al. 2011; Rivero et al. 2013), *UPF3B* (Jolly et al. 2013), BDNF (Shim et al. 2008), and other neurotrophins (Syed et al. 2007)).

Our results of decreases in cortical surface area and gyrification contrast with earlier findings of decreased cortical thickness (Sowell et al. 2003; Shaw et al. 2006; Narr et al. 2009; Schweren et al. 2015) and smaller striatum volume in ADHD (Durston et al. 2009a; Nakao et al. 2011; Frodl and Skokauskas 2012; Greven et al. 2015; Hoogman et al. 2017). Furthermore, we did not replicate longitudinal results showing delays in the maturation of cortical thickness and surface area in the NIMH longitudinal sample (Shaw et al. 2007, 2012). In the field, there

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is a call for replication in independent samples, particularly for longitudinal studies. As such, it is noteworthy that we do not fully replicate their findings, but rather report different ones in this independent sample. It underscores that earlier results do not necessarily generalize to other samples of subjects with ADHD, but that differences between ADHD and controls may vary as a function of sample characteristics. Important differences between the NIMH sample and ours are in geographical location, average IQ and SES. The NIMH studies have typically matched groups for IQ and SES (e.g., Shaw et al. 2007), whereas we matched for SES only. Demographic differences within and between studies are increasingly being recognized as an important caveat in conducting and comparing neuroimaging studies in developmental disorders (Horga et al. 2014). Another factor contributing to these differences might be methodology; the NIMH studies investigated between-group differences in the mean age of the peak of their developmental models. We applied a rigorous post-processing quality control procedure (Ducharme et al. 2016) and a stringent statistical method to determine the best developmental model for our data, resulting in different models than those used in the NIMH sample. Furthermore, we investigated cortical markers per area, rather than per vertex, to preserve statistical power. In doing so, we may have missed small effects in highly localized cortical areas.

There are some limitations to our study. First, a sensitivity analysis using G*Power (Faul et al. 2007) showed that the smallest effect size detectable with our data for 80% power was |0.43|, at the Bonferroni-corrected alpha-level. Therefore, although our sample was sufficiently sensitive to reasonably small to medium effects (Cohen 1992), we were unable to detect differences of the magnitude (≤–0.2) that have been reported previously in meta- and mega-analyses of cortical and subcortical measures in ADHD (Valera et al. 2007; Hoogman et al. 2017). Second, the majority of subjects with ADHD in our sample were using psychostimulants. There was insufficient power to statistically investigate the effect of medication on our results. Third, we could not examine developmental trajectories in more homogeneous clinical subgroups based on gender, IQ, subtype or severity of the clinical presentation.

In conclusion, our findings show developmentally persistent reductions in cortical volume, surface area, and gyrification in our sample of subjects with ADHD, particularly in frontal areas. These findings contrast with other studies in different samples and underscore the importance of replication in independent samples, particularly for longitudinal data. Furthermore, they suggest that, at least for some children with ADHD, the disorder may be associated with an early (prenatal) disruption of cortical development leading to changes in surface area and gyrification that are stable across development.

Supplementary Material

Supplementary data are available at *Cerebral Cortex* online.

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