

Longitudinal Mapping of Cortical Thickness and Clinical Outcome in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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Context: Data from a previous prospective study of lobar volumes in children with attention-deficit/hyperactivity disorder (ADHD) are reexamined using a measure of cortical thickness.

Objective: To determine whether regional differences in cortical thickness or cortical changes across time characterize ADHD and predict or reflect its clinical outcome.

Design, Setting, and Participants: Longitudinal study of 163 children with ADHD (mean age at entry, 8.9 years) and 166 controls recruited mainly from a local community in Maryland. Participants were assessed with magnetic resonance imaging. Ninety-seven patients with ADHD (60%) had 2 or more images and baseline and follow-up clinical evaluations (mean follow-up, 5.7 years).

Main Outcome Measures: Cortical thickness across the cerebrum. Patients with ADHD were divided into better and worse outcome groups on the basis of a mean split in scores on the Children's Global Assessment Scale and persistence/remission of DSM-IV–defined ADHD.

Results: Children with ADHD had global thinning of the cortex (mean reduction, -0.09 mm; $P=.02$), most prominently in the medial and superior prefrontal and precentral regions. Children with worse clinical outcome had a thinner left medial prefrontal cortex at baseline than the better outcome group (-0.38 mm; $P=.003$) and controls (-0.25 mm; $P=.002$). Cortical thickness developmental trajectories did not differ significantly between the ADHD and control groups throughout except in the right parietal cortex, where trajectories converged. This normalization of cortical thickness occurred only in the better outcome group.

Conclusions: Children with ADHD show relative cortical thinning in regions important for attentional control. Children with a worse outcome have “fixed” thinning of the left medial prefrontal cortex, which may compromise the anterior attentional network and encumber clinical improvement. Right parietal cortex thickness normalization in patients with a better outcome may represent compensatory cortical change.

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ATENTION-DEFICIT/HYPER-activity disorder (ADHD) is a common neurobehavioral disorder that affects 3% to 5% of school-aged children in the United States.¹ It has been variously conceptualized as an inability to suppress inappropriate responses and thoughts,^{2,3} as a pathologic abnormality of executive “control” attentional networks,⁴ and as the result of an aversion to delay that stems from abnormal processing of rewards.⁵ These diverse models all implicate dysfunction of the prefrontal cortex (PFC) and the interconnected striatum. Structural change in the frontal lobe,^{6,7} particularly in the posterior cingulate, precentral gyrus, and superior and dorsolateral prefrontal gray matter, have all been found in ADHD.⁸⁻¹⁰ Functional imaging studies¹¹⁻¹⁴ report anomalous prefrontal activation in ADHD, most consistently in midline prefrontal regions during re-

sponse inhibition, decision making based on reward contingencies,¹⁵ and complex motor control.¹⁶ These deficits are also linked to hyperactivity and impulsivity, combined perhaps with pathologic abnormalities at the level of motor output in the motor cortices.¹⁷ The right parietal cortex is another major component of the distributed attention system involved in orienting attention to visual locations and in the maintenance of a vigilant state.^{18,19} Its compromise in ADHD is suggested by reports of structural⁶ and functional^{20,21} anomalies.

A striking feature of ADHD is its tendency to improve with age, with symptomatic improvement occurring in 31% to 43% of children as they move into late adolescence.²² A previous longitudinal study⁶ that did not consider clinical outcome demonstrated that the disorder is characterized by nonprogressive deficits in gray and white matter, except in the caudate, which nor-

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malizes in volume by late adolescence. It is possible that clinical improvement in a neurodevelopmental disorder such as ADHD may be associated with convergence to the normal trajectory of cortical development, with normalization prominent in regions that control attention.

Awareness that lobar volumetric studies may miss more regional cortical changes has prompted the examination of smaller regions of interest, frequently measured manually. Although informative, such studies are prone to operator error and are unsuited to large data sets, and it is possible that the boundaries of actual change in ADHD may not overlap with the limits of the a priori–defined regions of interest. We thus used a fully automated measure of cortical thickness across the entire cerebrum, unconstrained by predefined regions of interest. The technique has been validated through manual measurements²³ and a population simulation.²⁴ In addition, the method has been found to be sensitive to processes of normal aging and cognitive variation²⁵ and to cortical abnormalities,²⁶ making it an ideal tool for longitudinal mapping of cortical development. The technique has already been applied in a cross-sectional study²⁷ of 27 children with ADHD demonstrating highly localized cortical change.

Drawing inferences about developmental processes from cross-sectional data is fraught with methodological problems; thus, we used a longitudinal design, studying a large group of 163 children with ADHD and 166 controls. Most patients with ADHD (60%) had at least 2 magnetic resonance images (MRIs) and clinical evaluations acquired during mean follow-up of 5.7 years. We hypothesized that ADHD would be characterized by focal cortical anomalies in regions of the distributed neural system that mediate attention, specifically, the medial prefrontal and cingulate gyri and the right parietal cortex. On an exploratory basis, we speculated that different clinical functional outcomes in ADHD would be associated with differences in the pattern of cortical change at baseline and in trajectories of cortical development.

METHODS

PARTICIPANTS

One hundred sixty-six children and adolescents with DSM-IV–defined ADHD were recruited using the Diagnostic Interview for Children and Adolescents²⁸ and a Conners' Teacher Rating Scale hyperactivity rating greater than 2 SDs above age- and sex-specific mean ratings.²⁹ Parental history of probable ADHD was determined using the Wender Utah Rating Scale.³⁰ Exclusion criteria were a full-scale IQ score of less than 80 and evidence of medical or neurologic disorders. Neuroimaging data from 3 patients with ADHD could not be analyzed owing to motion artifact, and these patients were excluded from further analyses. Ninety-five percent of the patients had combined-type ADHD (n=157), 4 (2%) had inattentive ADHD, and 2 (1%) had the hyperactive subtype of ADHD. Unrelated controls (n=166) who had no personal or family history of psychiatric or neurologic disorders were also recruited from the community.

Approximately 60% of the individuals in each group underwent MRI at least twice. The institutional review board of the National Institute of Mental Health approved the research protocol, and written informed consent and assent to partici-

pate in the study were obtained from the parents and children, respectively.

CLINICAL OUTCOME MEASURES

The first outcome measure was the last available Children's Global Assessment Scale (CGAS) score,³¹ chosen because it provides a clinically relevant measure of outcome and was available at baseline and follow-up for most patients with ADHD (n=107). Patients with ADHD were divided into better (n=51) and worse (n=56) outcome groups based on mean final CGAS scores (mean CGAS score, 64; better outcome CGAS score, ≥ 64 ; and worse outcome CGAS score, < 64). The second outcome measure was whether patients continued to meet DSM-IV criteria for ADHD. Clinical assessments were performed independently of neuroimaging analyses. The mean ages of the groups at each wave of assessment and MRI did not differ significantly (**Table 1**).

MRI ACQUISITION AND ANALYSIS

T1-weighted images with contiguous 1.5-mm sections in the axial plane and 2.0-mm sections in the coronal plane were obtained using 3-dimensional spoiled gradient recalled echo in the steady state on a 1.5-T scanner (Signa; General Electric Medical Systems, Milwaukee, Wis) (echo time, 5 milliseconds; repetition time, 24 milliseconds; flip angle, 45°; acquisition matrix, 256 × 192; number of signals acquired, 1; and field of view, 24 cm). The native MRIs were registered into standardized stereotaxic space using a linear transformation and corrected for nonuniformity artifacts.³² The registered and corrected volumes were segmented into white matter, gray matter, cerebrospinal fluid, and background using an advanced neural net classifier.³³ A surface deformation algorithm was applied that first fits the white matter surface and then expands outward to find the gray matter–cerebrospinal fluid intersection defining a known relationship between each vertex of the white matter surface and its gray matter surface counterpart; cortical thickness can thus be defined as the distance between these linked vertices (40 962 such vertices are calculated).³⁴ The white and gray matter surfaces were resampled into native space by inverting the initial stereotaxic transformation. Cortical thickness was then computed in native space. To improve the ability to detect population changes, each patient's cortical thickness map was blurred using a 30-mm surface-based blurring kernel.²⁴

STATISTICAL ANALYSIS

Differences between groups at baseline were examined using 2-sample *t* tests for continuous variables and χ^2 tests of independence for categorical variables. Linear regression was used to examine the effects of outcome group and medication status on cortical thickness in baseline MRIs. Variables that significantly correlated with cortical thickness and that differed between groups were entered as covariates in regression analyses. For the longitudinal analyses, mixed-model regression was chosen because it permits the inclusion of multiple measurements per person, missing data, and irregular intervals between measurements, thereby increasing statistical power.³⁵ In unadjusted analyses, the resulting statistical maps were thresholded to control for multiple comparisons using the false discovery rate procedure, with $q=0.05$.^{36,37} For each regression model, all *P* values for all effects were pooled across all vertices, and a false discovery rate threshold was determined. Initial longitudinal analyses estimated the full quadratic model at each vertex, but because the squared age term did not contribute significantly to the model across the cortex, a linear model was used to fit the trajectories of the ADHD and control groups.

Table 1. Demographic and Clinical Details of Patients With ADHD With Better vs Worse Outcome

| Characteristic | Worse Outcome (n = 56) | Better Outcome (n = 51) | Test of Significance |
|---|---------------------------|----------------------------|-----------------------------|
| Age at initial assessment, mean (SD), y | 8.7 (1.9) | 9.2 (2.3) | $t_{105}=-1.4, P=.15$ |
| Age at final assessment, mean (SD), y | 14.1 (3.2) | 15.3 (3.7) | $t_{105}=-1.8, P=.70$ |
| Length of follow-up, mean (SD), y | 5.4 (2.1) | 6.1 (3.2) | $t_{105}=-1.3, P=.21$ |
| Outcome measures | | | |
| CGAS score at final follow-up, mean (SD) | 56 (7.2) | 72 (7) | $t_{105}=-11.5, P<.001$ |
| Initial CGAS score, mean (SD) | 46.6 (8.2) | 48.5 (7) | $t_{98}=-1.2, P=.25$ |
| DSM-IV criteria: diagnostic data available, No. | 48 | 35 | |
| In full remission at follow-up, No. (%)* | 3 (6) | 16 (46) | Fisher exact test, $P<.001$ |
| Still meeting DSM-IV criteria at follow-up, No. (%) | | | |
| All types of ADHD | 45 (94) | 19 (54) | |
| Combined type | 29 (61) | 4 (11) | |
| Inattentive subtype | 14 (29) | 11 (32) | |
| Hyperactive subtype | 2 (4) | 4 (11) | |
| Baseline characteristics | | | |
| Initial CBCL attention problem T score, mean (SD) | 74.8 (9) | 72.2 (9.6) | $t_{94}=1.34, P=.18$ |
| Initial Conners' Teacher Rating Scale hyperactivity factor score, mean (SD) | 1.72 (0.61) | 1.51 (0.66) | $t_{96}=1.6, P=.11$ |
| Initial TRF attention problems T score, mean (SD) | 70 (8.9) | 67.4 (9.4) | $t_{95}=1.3, P=.20$ |
| Sex, M:F, No. | 31:25 | 29:22 | $\chi^2=0.88, P=.87$ |
| IQ score, mean (SD) | 104 (13.8) | 114 (15.3) | $t_{105}=-3.4, P=.001$ |
| Strongly right-handed, No. (%) | 51 (91) | 41 (80) | $\chi^2=2.5, P=.28$ |
| Socioeconomic status, mean (SD) | 45 (22) | 45 (22) | $t_{105}=-0.04, P=.95$ |
| Medicated at time of first MRI, No. (%) | 41 (71) | 36 (73) | $\chi^2=0.09, P=.76$ |
| Age at first exposure to stimulants, mean (SD), y | 6.9 (1.2) | 7.4 (1.8) | $t_{72}=-1.7, P=.09$ |
| Parental history of ADHD, No. (%)† | 26 (59) | 24 (55) | $\chi^2=1.85, P=.67$ |
| Comorbidity, No. (%) | | | |
| Oppositional defiant disorder | 25 (45) | 22 (43) | |
| Conduct disorder | 6 (11) | 4 (8) | |
| Mood | 3 (5) | 3 (6) | |
| Anxiety | 8 (14) | 2 (4) | |
| Tic NOS | 4 (7) | 4 (6) | |
| Regular stimulant use at follow-up, No. (%) | 43 (77) | 36 (71) | $\chi^2=0.53, P=.47$ |
| No. of scans | | | |
| Time 1:2:3+ | 56:47:25 | 51:43:32 | |
| Age at MRIs, mean (SD), y | | | |
| Time 1 | 9.8 (3.0) | 10.6 (3.0) | $t_{105}=1.3, P=.19$ |
| Time 2 | 12.7 (3.2) | 13.3 (3.3) | $t_{98}=-0.86, P=.39$ |
| Time 3+ | 15.4 (2.9) | 16.7 (3.7) | $t_{55}=-1.3, P=.19$ |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist (rated by parents); CGAS, Children's Global Assessment Scale; MRI, magnetic resonance image; NOS, not otherwise specified; TRF, Teacher Report Form.

*Percentages indicate proportion of those with DSM-IV diagnostic data at follow-up.

†Data were available on 88 patients in the better and worse outcome groups (41 in each group).

Sex and the interaction of sex and diagnosis did not significantly affect the shape of growth curves across cortical regions and were excluded. Thus, in the final model for the ADHD vs control comparisons, the i th individual's j th cortical thickness at a given vertex was modeled as follows:

$$\text{Thickness}_{ij} = \text{Intercept} + d_i + \beta_{\text{control}} (\text{Diagnosis} = \text{Control}) + \beta_1 (\text{Age} - \text{Mean Age}) + \beta_2 (\text{Diagnosis} = \text{Control} \times [\text{Age} - \text{Mean Age}]) + e_{ij}$$

where d_i is a random-effects modeling within-person dependence; the intercept and β terms are fixed effects, and e_{ij} represents the residual error. Group differences in slope were determined by the significance of the interaction term (ie, β_2). Group differences in height, representing difference in cortical thickness, were determined by the significance of the β_{control} term. The t statistics at every cortical point were visualized through projection onto a standard brain template. Such visualization showed clusters of cortical points that differed significantly between the ADHD outcome groups and controls in the baseline MRIs or in the trajectory of cortical development. Analyses selected and averaged all cortical points within each of these clusters. Graphs illustrat-

ing the developmental trajectories of clusters were generated using fixed-effects parameter estimates.

We explored which baseline variables were significantly associated with CGAS scores at final follow-up, treating the CGAS score as a continuous variable (and thus included only the patients with ADHD). In addition, a linear discriminant analysis with leave-one-out cross-validation^{38,39} was used to assess the ability of the measures of cortical thickness to separate accurately the outcome groups, treated as categories, from each other and from controls.

RESULTS

COMPARISON OF THE ADHD AND CONTROL GROUPS

The groups were well matched on demographic and diagnostic characteristics, except for a significantly lower

IQ score in the ADHD group (**Table 2**). Comorbid diagnoses were relatively mild and in no case were the focus of treatment. The ADHD group had a significantly smaller estimated mean overall cortical thickness, most prominently in the prefrontal and anterior temporal cortices (**Table 3**) (see Supplementary Table 1a for additional details of cortical thickness in 56 subregions across the entire cerebrum, available at: <http://intramural.nimh.nih.gov/chp/cos/shaw2006archivessupplementarytables.htm>). When adjustment was made for differences in mean overall cortical thickness and IQ, diagnostic differences survived at *t* values greater than 2.0 in areas in the superior and medial frontal gyri and cingulate region bilaterally, left precentral gyrus, and right anterior/mesial temporal cortex (**Figure 1** and Table 3). There was no region of significant increase in cortical thickness for the ADHD group in the unadjusted data.

Children with ADHD who were medication naïve at the time of the first MRI were younger (mean±SD age, 8.2±2.5 years) than those who were medicated (mean±SD age, 10.7±2.7 years) ($F_{1,153}=31.8; P<.001$) but had a similar IQ, socioeconomic status, and sex mix. The *t* statistical maps showed no significant regional cortical differences between the medicated and nonmedicated groups after adjustment for age, except in a small region in the left anterior temporal cortex.

BETTER VS WORSE OUTCOME GROUPS: ANALYSES OF INITIAL MRIs

The better (*n*=51) and worse (*n*=56) outcome groups, defined on the basis of CGAS scores, had no significant baseline differences in any clinical measures, but the worse outcome group had a significantly lower mean IQ score, which was thus entered as a covariate in adjusted analyses. Follow-up DSM-IV diagnoses were available on 83 patients with ADHD. Mean duration of follow-up was approximately 5.7 years for both groups.

Patients who still met DSM-IV criteria for ADHD (any subtype) at follow-up had, on baseline MRIs, a significantly thinner medial prefrontal and cingulate cortex bilaterally relative to the control group. Patients with a worse clinical outcome, defined using CGAS scores, had a thinner cortex in similar medial and superior prefrontal regions, which was significant after adjustment for IQ and mean cortical thickness. In contrast, remitted patients, similar to those with CGAS-defined better outcome, showed a minimal significant difference in cortical thickness from controls. The better outcome group had a small region of cortical thinning in the left dorsolateral PFC relative to controls (**Figure 2, Table 4**, and Supplementary Table 1b, which gives the cortical thickness for outcome groups across 56 cortical region, available at: <http://intramural.nimh.nih.gov/chp/cos/shaw2006archivessupplementarytables.htm>).

In the stepwise regression we assessed the variance in outcome CGAS scores attributable to the following variables: mean thickness of the 2 main cortical regions, which differed between outcome groups (the left medial prefrontal/medial cortex for the worse outcome group and the left dorsolateral prefrontal region for the better outcome group), and demographic (age, sex, and socioeconomic status), clinical (Conners' Teacher Rating Scale hy-

Table 2. Demographic and Diagnostic Characteristics of Patients With ADHD and Controls

| Characteristic | ADHD Group (n = 163) | Controls (n = 166) | Test of Significance* |
|--|-------------------------|-----------------------|--------------------------|
| Age at initial MRI, mean (SD), y | 10.1 (3.1) | 10.4 (2.8) | $t_{327}=-1.0, P=.31$ |
| Sex, M:F, No. | 68:95 | 69:97 | $\chi^2_1=0.97, P=.98$ |
| Estimated IQ score, mean (SD) | 108 (15) | 115 (14) | $t_{311}=-4.1, P<.001$ |
| Socioeconomic status, mean (SD) | 46 (23) | 39 (19) | $t_{320}=3.5, P<.001$ |
| Strongly right-handed, No. (%) | 135 (83) | 155 (93) | $\chi^2_1=6.7, P=.08$ |
| MRI details, No. (%) | | | |
| Time 1 | 163 (100) | 166 (100) | NA |
| Time 2 | 97 (60) | 93 (56) | NA |
| Time 3 | 48 (29) | 49 (30) | NA |
| Time 4 | 10 (6) | 10 (6) | NA |
| Age at each MRI, mean (SD), y | | | |
| Time 1 | 10.1 (3.1) | 10.4 (2.9) | $t_{327}=-1.0, P=.31$ |
| Time 2 | 12.9 (3.3) | 12.7 (3.6) | $t_{188}=0.33, P=.74$ |
| Time 3 | 15.5 (3.2) | 14.3 (3.2) | $t_{65}=1.8, P=.08$ |
| Time 4 | 18.5 (3.8) | 16.5 (2.9) | $t_{18}=1.32, P=.20$ |
| Clinical details, mean (SD) | | | |
| Clinical Global Assessment Scale score | 47.7 (7.4) | NA | NA |
| CBCL attention problems T score | 72.1 (9.0) | NA | NA |
| TRF attention problems T score | 68.2 (9.5) | NA | NA |
| Conners' Teacher Rating Scale hyperactivity factor score | 1.6 (0.64) | NA | NA |
| Previous stimulant treatment, No. (%) | 108 (66) | NA | NA |
| Family history of ADHD, No. (%) | 72 (58)† | NA | NA |
| Comorbid diagnoses, No. (%) | | | |
| Oppositional defiant disorder | 60 (37) | NA | NA |
| Conduct disorder | 11 (7) | NA | NA |
| Learning disorder | 17 (10) | NA | NA |
| Mood disorder | 8 (5) | NA | NA |
| Anxiety disorder | 14 (9) | NA | NA |
| Tic disorder, NOS | 10 (6) | NA | NA |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist (rated by parents); MRI, magnetic resonance image; NA, not applicable; NOS, not otherwise specified; TRF, Teacher Report Form.

*For the ADHD group vs controls.

†Data on parental history of ADHD were available for 123 patients with ADHD: missing data on IQ and socioeconomic status are reflected in the degrees of freedom.

peractivity factor scores, Teacher Report Form attention problems *t* scores, and baseline CGAS scores), and neuropsychologic (estimated IQ) variables. Three variables entered the final model: thickness of the left medial PFC

Table 3. Cortical Thickness in the Regions That Differed Significantly Between Groups*

| | Unadjusted | | | | Adjusted† | | | |
|--|---------------------------|-------------------------|---------------------------|----------------------|---------------------------|-------------------------|---------------------------|----------------------|
| | ADHD Group, Mean (SD), mm | Controls, Mean (SD), mm | Difference (95% CI) | Test of Significance | ADHD Group, Mean (SD), mm | Controls, Mean (SD), mm | Difference (95% CI) | Test of Significance |
| Mean cortical thickness | 4.06 (0.03) | 4.15 (0.03) | -0.09 (-0.02 to -0.16) | $t=-2.5$ $P=.01$ | 4.07 (0.02) | 4.15 (0.02) | -0.08 (-0.02 to -0.15) | $t=-2.0$ $P=.04$ |
| Right superior/medial PFC cluster | 4.51 (0.04) | 4.69 (0.04) | -0.18 (-0.28 to -0.07) | $t=-3.5$ $P<.001$ | 4.75 (0.09) | 4.84 (0.10) | -0.08 (-0.13 to -0.04) | $t=-3.5$ $P<.001$ |
| Left superior/medial PFC cluster | 4.34 (0.03) | 4.51 (0.03) | -0.17 (-0.26 to -0.08) | $t=-3.6$ $P<.001$ | 4.63 (0.1) | 4.71 (0.1) | -0.07 (-0.13 to -0.03) | $t=-3.0$ $P=.004$ |
| Right anterior/medial temporal cluster | 3.98 (0.04) | 4.2 (0.04) | -0.21 (-0.32 to -0.11) | $t=-4.2$ $P<.001$ | 4.34 (0.13) | 4.46 (0.14) | -0.13 (-0.19 to -0.06) | $t=-3.7$ $P<.001$ |
| Left precentral cluster | 3.73 (0.03) | 3.85 (0.03) | -0.12 (-0.20 to -0.05) | $t=-3.3$ $P=.001$ | 3.78 (0.08) | 3.84 (0.09) | -0.06 (-0.10 to -0.02) | $t=-2.7$ $P=.008$ |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; PFC, prefrontal cortex.

*Shown in Figure 1.

†Adjusted for group differences in mean cortical thickness and IQ.

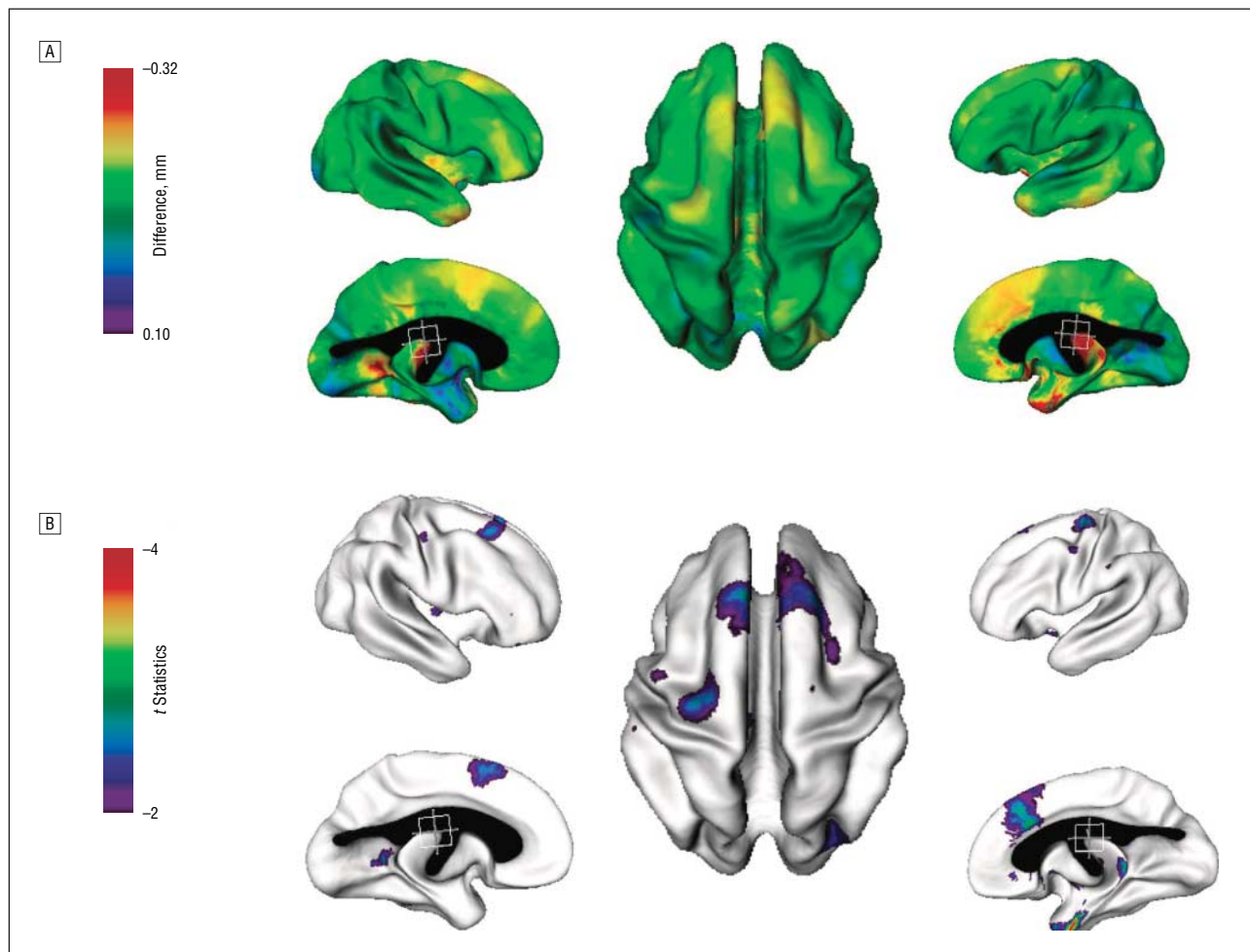


Figure 1. Cortical thickness in attention-deficit/hyperactivity disorder (ADHD) compared with controls. A, Estimated difference in cortical thickness in millimeters between patients with ADHD and controls. Significantly thinner regions in the ADHD group, applying a false discovery rate of 0.05, are shown in yellow. B, Group differences ($t > 2$) after adjustment for IQ and mean overall cortical thickness.

(standardized $\beta = .46$; adjusted $R^2 = 0.08$; $P < .001$), thickness of the left dorsolateral prefrontal cluster ($\beta = -.33$; $R^2 = 0.07$; $P = .005$), and hyperactivity factor scores at base-

line ($\beta = -.23$; $R^2 = 0.04$; $P = .03$). Thickness of the left medial and dorsolateral prefrontal regions thus accounts for approximately 15% of the variance in outcome scores.

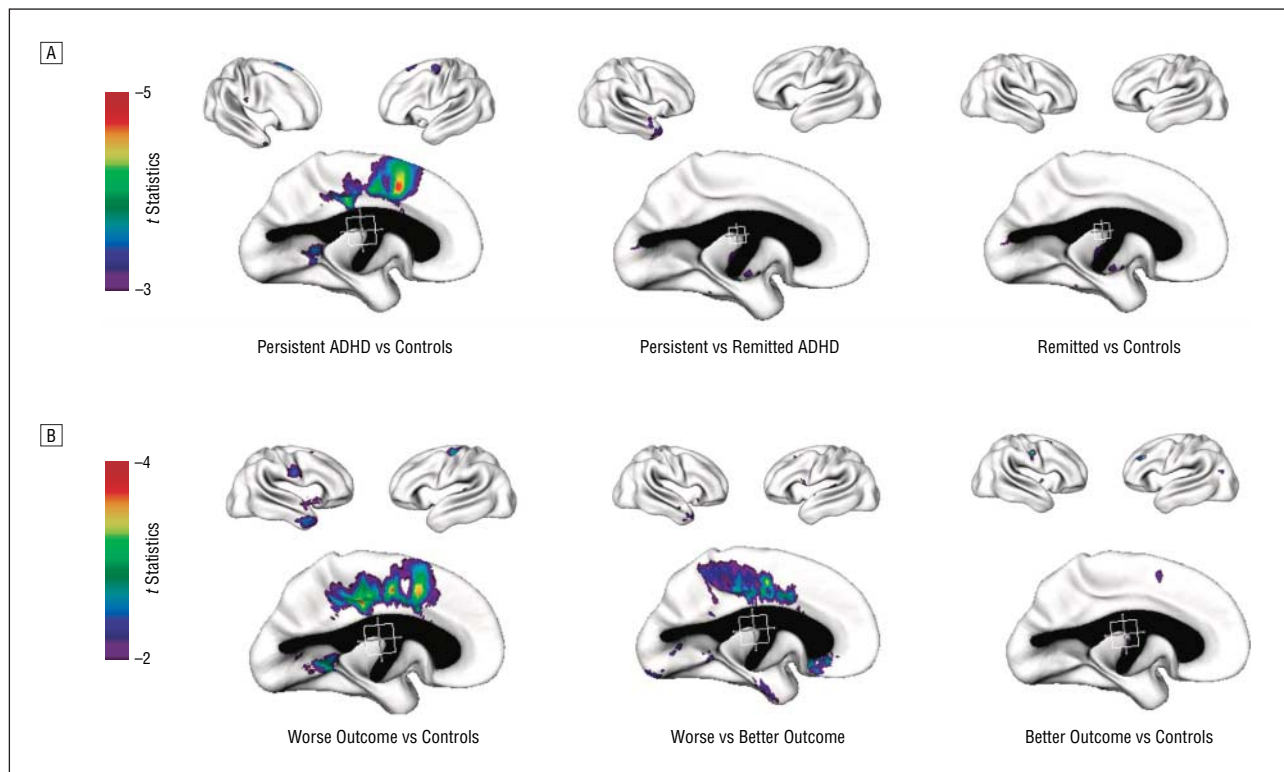


Figure 2. Contrasts between patients with attention-deficit/hyperactivity disorder (ADHD) with differing outcomes and controls. A, The t statistical maps of pairwise contrasts using persistence/remission of ADHD as the outcome measure. B, The t maps using Children's Global Assessment Scale scores as the outcome measure. Adjustment is made for IQ and mean cortical thickness.

Table 4. Cortical Thickness in Regions That Show a Significant Difference in Baseline MRIs in the Different ADHD Outcome Groups

| | Unadjusted | | | | | Adjusted* | | | | |
|---|-----------------------------------|------------------------------------|-------------------------|------------------------------|---|-----------------------------------|------------------------------------|-------------------------|------------------------------|---|
| | ADHD Worse Outcome, Mean (SD), mm | ADHD Better Outcome, Mean (SD), mm | Controls, Mean (SD), mm | Test of Significance | Group Difference d (Effect Size) | ADHD Worse Outcome, Mean (SD), mm | ADHD Better Outcome, Mean (SD), mm | Controls, Mean (SD), mm | Test of Significance | Group Difference d (Effect Size) |
| Overall mean cortical thickness | 4.11 (0.38) | 4.06 (0.42) | 4.15 (0.39) | $F_{2,270}=1.06$ $P=.35$ | NA | 4.13 (0.06) | 4.06 (0.05) | 4.15 (0.03) | $F_{2,260}=1.18$ $P=.28$ | NA |
| Left medial PFC/cingulate cluster (Figure 2B) | 4.15 (0.44) | 4.29 (0.49) | 4.4 (0.52) | $F_{2,270}=5.3$ $P=.005$ | Worse < control, † $d = 0.5$ | 4.17 (0.04) | 4.37 (0.04) | 4.38 (0.02) | $F_{2,260}=10.0$ $P<.001$ | Worse < control, † $d = 0.78$ Worse < better, † $d = 0.68$ |
| Left cingulate/medial PFC cluster (Figure 2B) | 3.7 (0.55) | 4.08 (0.72) | 3.95 (0.66) | $F_{2,270}=4.85$ $P=.009$ | Worse < better, † $d = 0.6$ Worse < control, ‡ $d = 0.4$ | 3.68 (0.07) | 4.15 (0.07) | 4.0 (0.04) | $F_{2,260}=9.7$ $P<.001$ | Worse < control, † $d = 0.62$ Worse < better, § $d = 0.92$ |
| Left DLPFC cluster (Figure 2B) | 4.27 (0.60) | 4.12 (0.57) | 4.35 (0.50) | $F_{2,270}=3.4$ $P=.03$ | Better < control, ‡ $d = 0.4$ | 4.29 (0.04) | 4.21 (0.04) | 4.33 (0.02) | $F_{2,260}=3.6$ $P=.03$ | Better < control, ‡ $d = 0.33$ |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DLPFC, dorsolateral prefrontal cortex; MRI, magnetic resonance image; NA, not applicable; PFC, prefrontal cortex.

*Adjusted for significant group differences in IQ and for mean overall cortical thickness.

† $P<.001$.

‡ $P<.05$.

§ $P<.01$.

Using the more stringent linear discriminant analysis with leave-one-out cross-validation, the mean thickness of the cluster of points in the left medial PFC (Figure 2A) as a single variable did not separate accurately the worse and better outcome groups from each other and from controls. This is not surprising given the modest amount of variance in final clinical outcome scores accounted for by each variable in the linear regression.

TRAJECTORY OF CORTICAL DEVELOPMENT

Parallel trajectories of cortical thickness for the ADHD and control groups were found for the overall cortical thickness and at individual vertices across the entire cortex except in the right parietal cortex (Figure 3). In this region, the entire ADHD group started at a significantly lower point, but the thickness of the right parietal cor-

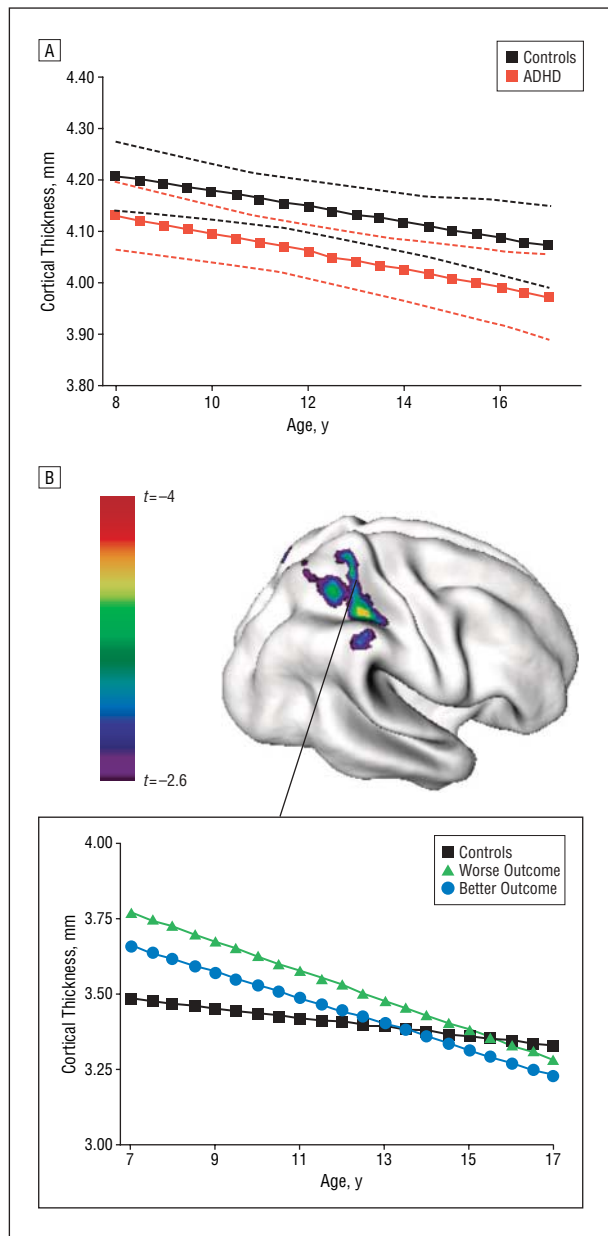


Figure 3. Trajectory of change in cortical thickness in patients with attention-deficit/hyperactivity disorder (ADHD) and controls. A, Estimated trajectories for mean overall cortical thickness. There was a significant difference in height ($P=.02$) but not in the gradient of the lines ($P=.78$). Dashed lines indicate 95% confidence intervals. B, The t map indicates vertices where there was a significant interaction in the contrast between the better outcome and control groups and age. The graph illustrates group trajectories in this region (difference in gradients: better outcome group vs controls, $P=.001$; better vs worse outcome groups, $P=.03$; and worse outcome group vs controls, $P=.60$).

tex converged with that of the control group by age 17 years. Normalization of cortical thickness in the right parietal cortex noted for the ADHD group as a whole was attributable to the morphologic changes in the better outcome group (Figure 3).

The cortical thickness gradients in the right parietal cortex differed significantly between the 2 outcome groups and between the better outcome group and controls. For the remaining cortex, the better outcome and control groups had parallel cortical thickness developmental tra-

jectories, without significant differences between the gradients of the fitted lines. The worse outcome group and those with persistent ADHD showed no significant deviation from a trajectory parallel to that of the control group in any region, including the right parietal cortex. Those who had full remission showed cortical normalization in the same region of the right parietal cortex as the better outcome group.

Given the wide range of duration of follow-up, the analyses were repeated using only the central 66% (follow-up, 3.5-8.4 years) and central 80% (follow-up, 2.7-9.3 years) of the outcome group data. The same pattern of results held with converging trajectories for the better outcome and control groups (with significant differences in the gradients of the trajectories, $P<.02$ for all) compared with parallel trajectories for the worse outcome and control groups (with no significant differences in the gradients of trajectories, $P>.10$ for all). The difference in outcome was not attributable to regular stimulant use during follow-up, which did not differ significantly between outcome groups (Table 1).

COMMENT

Using fully automated computational techniques, we examined the relationships among cortical thickness, baseline diagnosis, and clinical outcome in a large cohort of children and adolescents with ADHD. We replicate earlier findings of cortical anomalies in the disorder, prominent in prefrontal regions important for the control of attention and motor output. A thinner medial PFC in baseline MRIs discriminated poor from good outcome in patients with ADHD and controls, whether outcome was defined on the basis of overall functioning or persistence of *DSM-IV*-defined ADHD. A measure of cortical thickness in this region was significantly associated with future clinical outcome scores in a linear regression, although the amount of variance accounted for by cortical thickness was modest. The outcome groups also differed in the trajectory of development of cortical thickness: the good outcome group alone showed normalization of right parietal cortical thickness in a pivotal region in posterior attentional systems.

DIAGNOSTIC DIFFERENCES

The thinner PFC we report is congruent with previous volumetric studies demonstrating reduction in frontal lobe volume. The regions of cortical thinning overlap with reductions in gray matter density found in studies that obtained a high degree of spatial resolution, specifically, loss in the superior frontal gyrus, posterior cingulate, and dorsolateral PFC.^{27,40} However, unlike the present study, Sowell et al²⁷ also report an increase in cortical density in the posterior temporal and inferior parietal regions, a discrepancy that may reflect in part our native space analyses rather than the use of stereotaxic space.

Cortical change in the precentral gyrus is of interest because motor hyperactivity is a cardinal feature of the disorder. Unlike the findings for the prefrontal regions, previous volumetric studies with a smaller sample size

have not detected morphometric changes in the precentral gyrus.^{9,41} However, transcranial magnetic stimulation studies have demonstrated reduced intracortical inhibition in the motor cortex in ADHD, which may represent a neurophysiologic correlate of reduced behavioral inhibition.⁴² Stimulants have also been shown to correct abnormally high resting levels of cerebral blood flow in the precentral gyrus in patients with ADHD.¹⁷ Cortical thinning in the precentral gyrus may thus represent a substrate for impaired behavioral control at the level of motor output.

The thinner right mesial and left lateral temporal cortex is harder to interpret. Anomalous activation of the temporal lobes has been noted at rest and during functional MRI studies of response inhibition and working memory.⁴³⁻⁴⁵ As part of the lateral paralimbic motivational system the region may also contribute indirectly to delay aversion in ADHD.⁶ We did not find any significant effects of treatment with stimulants on cortical thickness at the time of the initial MRI or on the course of cortical development.

CORTICAL DIFFERENCES AND CLINICAL OUTCOME

It is striking that cortical thickness in the left medial prefrontal and cingulate cortex at baseline discriminated between children with ADHD who had differing clinical outcomes 5 years later. This does not reflect greater symptomatic severity at baseline, medication status, or comorbidities. A more plausible explanation of the findings invokes the increasing developmental importance of attentional processing modulated by the prefrontal regions.^{46,47} Performance on tasks measuring response inhibition and susceptibility to interference show a marked improvement stretching into adolescence.⁴⁸⁻⁵¹ Increased or more focused activation of the PFC (including the left middle and inferior prefrontal and cingulate gyri) may support this cognitive maturation.⁵²⁻⁵⁷ In ADHD, the development of this system is delayed, with reports of decreased and more diffuse activation of the medial prefrontal and cingulate regions during tasks that require response inhibition or higher-order motor control.^{12,13,16,58} In the present study, the medial and cingulate cortical thinning in patients with poor outcome persists into adolescence and, thus, could represent a compromised neural substrate that prevents age-appropriate attentional skills from coming "online" in early adolescence. In contrast, patients with ADHD with a better clinical outcome have a morphologically intact medial cortical wall, which might support the development of more refined cognitive control, leading to symptomatic relief and clinical improvement.

The thickness of the left medial PFC in baseline MRIs was more strongly associated with outcome scores than baseline clinical and demographic variables. However, in a discriminant analysis, this cortical measure, as a single variable, did not accurately predict outcome. Although this highlights the current limitations of anatomic imaging in predicting outcome, it is hoped that future multivariate discriminant analyses in a larger sample incorporating other neuroanatomic variables (such as white matter) may result in a more powerful predictive model.

TRAJECTORY OF CORTICAL DEVELOPMENT IN ADHD

The previous findings⁶ of fixed nonprogressive lobar cortical deficits in ADHD are partially modified by the demonstration of cortical normalization in portions of the right parietal cortex. Because we did not collect cognitive and behavioral data in tandem with neuroanatomic data, we cannot give a definitive answer to the functional significance of this structural change. However, recent studies⁵⁸ suggest that activation of the right parietal cortex during tasks of alerting and reorienting of attention is not fully mature until adulthood and that this posterior component of the attentional network may develop during adolescence. In ADHD, structural^{6,8,27} and functional anomalies at rest²⁰ and during tasks of selective attention¹² and response inhibition²¹ have been shown in the right parietal cortex. In addition, previous studies have established links between structure and function in ADHD; for example, reduction in prefrontal gray matter volume and metabolism additionally correlate with deficits in response inhibition^{59,60} and symptom severity.^{6,61} Thus, normalization of the right parietal cortex, noted only in children with better clinical outcome, may support the maturation of components of the attentional network through adolescence. The striking difference in cortical development in the better and worse outcome groups might alternately suggest 2 distinct entities in ADHD, in different underlying neural substrates.

The apparent lack of normalization in the motor cortex warrants comment given the prominence of improvement in hyperactivity and impulsivity in ADHD during adolescence. First, the inferior portion of the right motor cortex and the dorsolateral cortices bilaterally were the only regions that showed a trend to normalization in the better outcome group (revealed by relaxing the false discovery rate to 0.10). Second, structural change in the right parietal cortex may have distal effects on the richly interconnected cingulate/medial PFCs,⁶²⁻⁶⁴ regions important for response inhibition and interference suppression, which in turn may contribute to impulsivity and higher-order motor control.

Cortical thinning in adolescence, underpinned possibly by synaptic pruning,⁶⁵ and increased myelination^{66,67} may accompany cognitive maturation,²⁵ and, thus, the lack of thinning in the better outcome group may seem counterintuitive. However, the exact nature of the relationships among cellular events, cortical dimensions, and cognitive change in humans is largely speculative. It is possible that a relatively late persistence of synapses in the better outcome group is associated with normalization of cortical thickness and affords an extended period for the sculpting of complex neural circuits supporting attention.

The changing cortical thickness we report is likely to reflect alterations in the gray/white boundary related to myelination and changes in the cortical mantle itself. The T1-weighted MRIs used cannot disentangle the relative contribution of these factors to changes in gray and white matter at the cortical border. This will require an MRI protocol that includes measures of high-resolution relaxometry and diffusion tensor imaging that can quantify changes in

myelination. However, the link between clinical outcome and cortical change in a region pivotal for the control of attention suggests that the finding is biologically meaningful and deserves further exploration.

The present study is limited partly by the attrition rate in the study of 35% for the ADHD group, although those lost to follow-up were representative of the inception cohort. The similarity in results between the 2 different definitions of clinical outcome (CGAS scores and DSM-IV definition) is reassuring but reflects in part the large overlap in membership between the worse outcome and persistent ADHD groups. We did not collect clinical measures on the typically developing controls, and, thus, a similar, if much attenuated, pattern of cortical change may occur in typically developing children who show improvement in (subthreshold) attention and hyperactivity symptom scores. The sample was composed almost entirely of children who had combined-type ADHD, and, thus, we cannot address the possibility of different developmental trajectories of the different subtypes of ADHD.

In estimating cortical thickness we chose a 30-mm-bandwidth blurring kernel on the basis of population simulations that showed that this bandwidth maximized statistical power while minimizing false positives.²⁴ Although this bandwidth filter may seem large, 30-mm blurring along the surface using a diffusion smoothing operator represents considerably less cortex than the equivalent volumetric gaussian blurring kernel because it preserves cortical topologic features. Repeating the analyses with a 15-mm blurring kernel showed a similar pattern of results.

In conclusion, we demonstrate a pattern of cortical thinning in ADHD, predominantly in prefrontal regions, which comprise key regions associated with attentional mechanisms. A fixed nonprogressive deficit of the medial prefrontal and cingulate regions, which might compromise the anterior attentional network, was associated with relatively poor clinical outcome. In contrast, normalization of the right parietal cortex, which might support compensatory change in the posterior attentional network, was associated with relative clinical improvement.

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