ORIGINAL ARTICLE

Hippocampus and Amygdala Morphology in Attention-Deficit/Hyperactivity Disorder

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Context: Limbic structures are implicated in the genesis of attention-deficit/hyperactivity disorder (ADHD) by the presence of mood and cognitive disturbances in affected individuals and by elevated rates of mood disorders in family members of probands with ADHD.

Objective: To study the morphology of the hippocampus and amygdala in children with ADHD.

Design: A cross-sectional case-control study of the hippocampus and amygdala using anatomical magnetic resonance imaging.

Settings: University research institute.

Patients: One hundred fourteen individuals aged 6 to 18 years, 51 with combined-type ADHD and 63 healthy controls.

Main Outcome Measures: Volumes and measures of surface morphology for the hippocampus and amygdala.

Results: The hippocampus was larger bilaterally in the ADHD group than in the control group ($t=3.35$; $P<.002$). Detailed surface analyses of the hippocampus further localized these differences to an enlarged head of the hippocampus in the ADHD group. Although conventional measures did not detect significant differences in amygdalar volumes, surface analyses indicated the presence of reduced size bilaterally over the area of the basolateral complex. Correlations with prefrontal measures suggested abnormal connectivity between the amygdala and prefrontal cortex in the ADHD group. Enlarged subregions of the hippocampus tended to accompany fewer symptoms.

Conclusions: The enlarged hippocampus in children and adolescents with ADHD may represent a compensatory response to the presence of disturbances in the perception of time, temporal processing (eg, delay aversion), and stimulus seeking associated with ADHD. Disrupted connections between the amygdala and orbitofrontal cortex may contribute to behavioral disinhibition. Our findings suggest involvement of the limbic system in the pathophysiology of ADHD.

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THE NEURAL BASIS OF ATTENTION-deficit/hyperactivity disorder (ADHD) is currently unknown. Affecting 3% to 7% of all children and adolescents,[1,2] ADHD is defined by distractibility, hyperactivity, and impulsivity.[3] Children with ADHD often also struggle with deficits in executive functioning,[4] working[5] and visuospatial memory,[6] temporal processing,[7] and difficulty tolerating delayed rewards.[8] The hippocampus likely subserves these functions in attention and cognition, disturbances of which are among the defining hallmarks of ADHD.[1,5,9-13] Involvement of the amygdala in the pathophysiology of ADHD[14,15] likely contributes to the increased risk for affective disorders in children with ADHD and their family members,[11,16-18] even in family members who themselves do not have ADHD.[19-21] Indeed, the association of affective and ADHD symptoms is sufficiently tight that affective symptoms previously were listed as associated features of ADHD in *DSM-III-R*.[22]

Replicated findings in anatomical magnetic resonance imaging studies of children with ADHD include reduced cerebral volumes[23-25] and more localized reductions in volume of the prefrontal cortex (PFC),[25-27] particularly its inferior aspect.[28] Connectivity of these prefrontal regions, especially the ventral medial PFC, with the hippocampus and amygdala regulates a variety of attentional, memory, and emotional processes[29-31] implicated in the pathophysiology of ADHD. Circuits connecting the amygdala and orbitofrontal cortex (OFC) support decision making[32] and reward reinforcement,[33] and disturbances of these circuits seem to cause behavioral disinhibition and impulsivity.[34-37]

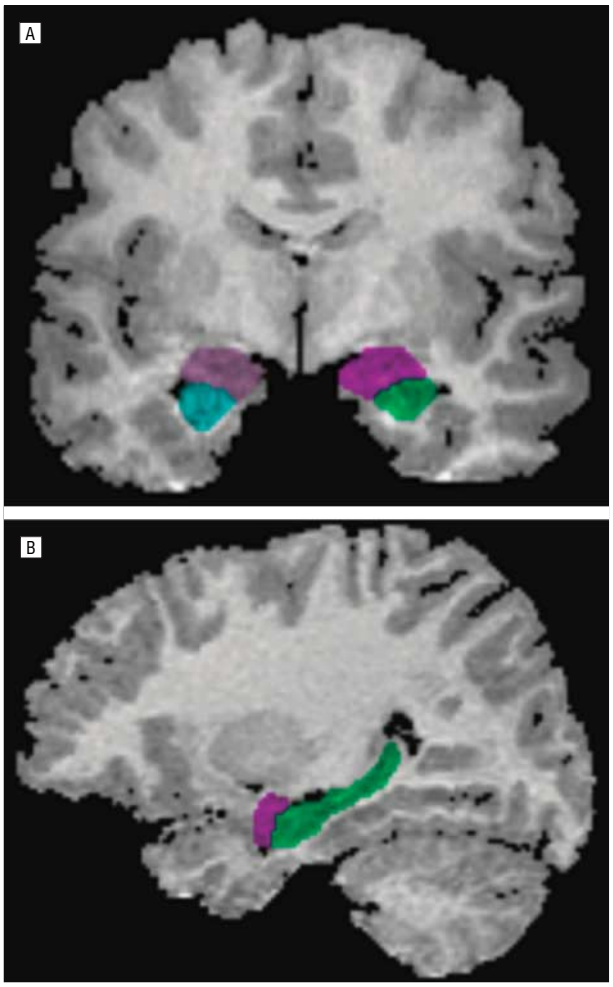

Figure 1. Location of hippocampus and amygdala in the context of the surrounding structures in the coronal (A) and sagittal (B) views.

We used magnetic resonance imaging to study hippocampus and amygdala morphologies in children with ADHD and age-matched healthy controls. Our a priori hypothesis was that volumes would differ across diagnostic groups.

METHODS

Subjects included 114 children and adolescents aged 7 to 18 years. We recruited children who met *DSM-IV* criteria[3] for the combined-type ADHD. Healthy controls were recruited randomly from a telemarketing list of 10 000 names, matched by zip code to subjects with ADHD. Exclusion criteria for controls included a lifetime history of ADHD, tic disorder, or obsessive-compulsive disorder or a current *DSM-IV* Axis I disorder. Exclusion criteria for children with ADHD included lifetime obsessive-compulsive disorder or tics or premature birth (gestation ≤36 weeks). Additional exclusion criteria for both groups included epilepsy, head trauma with loss of consciousness, lifetime substance abuse, psychotic disorder, developmental delay, or IQ less than 80, as measured by the Wechsler Intelligence Scale for Children–III,[38] the Wechsler Adult Intelligence Scale–III,[39] or the Kaufmann Brief Intelligence Test.[40] Written informed consent was obtained from all parents, and participants provided written assent.

Clinical diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version[41] and a "best-estimate consensus procedure" that considered all available clinical and diagnostic information.[42] The ADHD symptoms were further assessed by the Conners Parent and Teacher Rating scales[43,44] and the DuPaul-Barkley ADHD rating scale[45,46]; anxiety symptoms were assessed with the Revised Children's Manifest Anxiety Scale[47]; and depressive symptoms, with the Children's Depression Inventory.[48] Socioeconomic status was estimated using the Hollingshead Four-Factor Index of Social Status.[49]

Subjects were predominantly right-handed (90.2% of children with ADHD, 93.7% of controls).[50] Statistical analyses included 51 children with ADHD and 63 controls of comparable age (mean [SD] age, children with ADHD, 12.3 [3.01] years; controls, 11.5 [3.04] years; $t=1.4$; $P=.16$), socioeconomic status (mean [SD] Hollingshead index score, children with ADHD, 45.0 [13.0]; controls, 48.3 [9.9]; $t=1.5$; $P=.14$), and IQ (mean [SD] full-scale IQ, children with ADHD, 108.3 [19.3]; controls, 114.6 [17.1]; $t=-1.7$; $P=.08$). The ADHD group contained fewer females (ADHD, 9%; controls, 21%; χ^2 $P<.06$). Thirty-five (69%) of the subjects with ADHD were taking medication: all of them were taking stimulants, 3 were taking α-agonists, and 2 were taking selective serotonin reuptake inhibitors. No controls were taking psychotropic medication. In the ADHD group, 14 (27%) had a lifetime diagnosis of depression, 3 of whom were currently depressed; 14 subjects (27%) had oppositional defiant disorder in their lifetimes, 5 currently; 8 (16%) met lifetime criteria for specific developmental disorder (eg, reading, mathematics, written expression, or motor coordination); and 6 (11%) had a lifetime diagnosis of specific phobia, 2 had a current diagnosis of specific phobia.

MAGNETIC RESONANCE IMAGING AND IMAGE ANALYSIS

Pulse Sequence

Head position was standardized using canthomeatal landmarks. T1-weighted, sagittal, 3-dimensional volume images were acquired using a spoiled gradient echo pulse sequence with repetition time=24 milliseconds, echo time=5 milliseconds, 45° flip angle, 256×192 matrix, 30-cm field of view, 2 excitations, section thickness=1.2 mm, and 124 contiguous sections.

Preprocessing

Image processing was performed on Sun Ultra 10 workstations with ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn). Operators were blind to subject characteristics and hemisphere (images were randomly flipped left to right prior to analysis). Large-scale variations in image intensity were removed,[51] and images were reformatted to standardize head positioning prior to region definition.[52] Axial sections were oriented parallel to both the anterior and posterior commissures, and sagittal sections were oriented parallel to standard midline landmarks.[52]

Amygdala and Hippocampus

Methods for defining the hippocampus and the amygdala followed previously published algorithms (**Figure 1**).[53] The rostral extent of the amygdala coincided with the most anterior section in which the anterior commissure crossed the midline. The transition between the amygdala and hippocampus was determined with a line connecting the inferior horn of the lateral ventricle with the amygdaloid sulcus or, when the sulcus was not obvious, with a straight horizontal line connecting the inferior horn of the lateral ventricle with the surface

on the uncus.[54] The most posterior section was the last section in which the crus of the fornix and the fimbria of the hippocampal formation could be delineated. Intraclass correlation coefficients, calculated using 2-way random effects,[55] were 0.91 and 0.92 for the right and left hippocampus and 0.89 and 0.88 for the right and left amygdala, respectively.

Whole Brain Volume

An isointensity contour function was used in conjunction with manual editing to isolate the cerebrum. This whole brain volume (WBV) measure included gray and white matter, ventricular cerebrospinal fluid, cisterns, fissures, and cortical sulci. Cerebrospinal fluid was included using a connected components analysis. The WBV did not differ significantly between the diagnostic groups and was therefore used as a covariate in statistical analyses to control for scaling effects.[56]

Cerebral Subdivisions

Prefrontal regions were delineated by subdividing the cerebrum into dorsal prefrontal, inferior occipital, midtemporal, orbitofrontal, premotor, parieto-occipital, subgenual, and sensorimotor regions, as described previously.[52] Additionally, corresponding gray matter volumes were defined and calculated for the different cortical regions. Volumes of gray matter in the dorsal prefrontal cortex (DPFC) and OFC were used for further analyses. Intraclass correlation coefficients were >0.98 for WBV and all cortical subdivisions.

Surface Analyses

Surface morphologies of the hippocampus and amygdala were compared across diagnostic groups while covarying statistically for age and sex to localize the portions of each structure that contributed most to the observed differences in global volume between groups. We computed the distance from each point on the surfaces of the hippocampus and amygdala of each subject to the corresponding point on the hippocampus and amygdala of a reference subject (R.B., L. H. Staib, PhD, D. Xu, PhD, H.Z., B.S.P., unpublished data, October-November 2005):

1. A rigid-body similarity transformation was used to register the cerebrum of each subject with that of a reference subject. The parameters of this transformation (3 translations, 3 rotations, and global scaling) were estimated with the constraint that they maximized the mutual information in gray-scale values across the 2 brains.[57]
2. These estimated parameters were used to transform the manually defined hippocampus and amygdala from each subject into this common coordinate space. Here the global-scaling parameter in the rigid registration process for the entire cerebrum, described in step 1, was applied to each hippocampus and amygdala, thereby accounting for scaling differences in these structures. These analyses therefore did not require further correction for overall brain size.
3. The transformed hippocampus and amygdala of each subject were individually and rigidly coregistered to the corresponding structure of the reference brain to further refine and improve their rigid-body registrations.
4. The hippocampus and the amygdala of each subject were warped to the hippocampus and the amygdala of a reference brain, respectively, using a high-dimensional, nonrigid warping algorithm based on fluid-flow dynamics.[57,58] Structures were warped to be exactly the same size and shape as the reference structure, permitting precise identification of corresponding points on the surfaces of structures from the subject and reference brains.
5. The warped hippocampus and amygdala were then unwarped into the refined coordinate space identified in step 3 by simply reversing the high-dimensional, nonlinear warping used to identify point correspondences in step 4 while maintaining the labels identifying corresponding points on the surfaces of the subject and the reference structures.

Detecting, localizing, and interpreting the statistically significant differences between groups in these surface analyses could conceivably depend on the choice of the reference brain. Therefore, in the steps to determine point correspondences between structures of each brain, we first selected a reference subject who was demographically as representative as possible of the children studied. The brains for all remaining subjects were coregistered to this preliminary reference. The point correspondences on the surfaces of their hippocampus and amygdala were determined, and we computed distances between the corresponding points. We then selected as the final reference the brain for which all points across the surface of the hippocampus and amygdala were closest, in terms of least squares, to the average of the computed distances. The procedures for registration, determination of point correspondences, and calculation of distances from the final reference structure were repeated for all subjects. The distances were then compared across groups.

STATISTICAL ANALYSES

A Priori Hypothesis Testing

We tested our hypothesis that volumes would differ across diagnostic groups by assessing the main effect of group and the group × region interaction in a mixed-model analysis with repeated measures over a spatial domain (amygdalar and hippocampal volumes in each hemisphere). The model included the within-subjects factors "hemisphere" with 2 levels (left and right) and "region" with 2 levels (amygdala and hippocampus). Diagnosis (ADHD and control) was a between-subjects factor. Covariates included age, sex, and WBV. Beyond these independent variables, we considered all 2- and 3-way interactions of diagnosis (ADHD), sex, hemisphere, region, and age, as well as the 2-way interactions of WBV with hemisphere or region. Other variables considered in the model were handedness, socioeconomic status, medication, IQ, lifetime diagnoses of depression, oppositional defiant disorder, or specific developmental disorder (and their 2-way interaction with region); these were treated as potential confounding variables. Statistically nonsignificant terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated (ie, all possible lower-order terms were included in the model, regardless of statistical significance).[59] To control for a trend toward a sex imbalance across diagnostic groups, the procedure was repeated for boys only (n=42 in both groups). We considered P values <.025 statistically significant, given our testing of 2 a priori hypotheses. All P values were 2-sided. Statistical procedures were performed in SAS version 9.0 (SAS Institute Inc, Cary, NC) or Statistical Product and Service Solutions (SPSS Inc, Chicago, Ill).[60]

Correlations With Symptom Severity

Associations of hippocampal and amygdalar volumes with the severity of current ADHD symptoms were assessed in the ADHD group (n=47) while controlling for WBV, age, and sex using multiple linear regression. The correlations were restricted to the ADHD group only because of the presence of insufficient symptom variance in the control group. Correlations of the amygdala and hippocampus with anxiety and

depression symptoms were assessed similarly but in both diagnostic groups.

Group Comparisons of Prefrontal Volumes

Prefrontal gray matter volumes (OFC and DPFC volumes bilaterally) were compared between children with ADHD and controls using a 2-sided *t* test. This comparison was not part of our a priori hypothesis testing. We report the results of this comparison merely to document the presence of anatomical abnormalities in the frontal cortices of this sample that are similar to abnormalities reported previously in other samples of individuals with ADHD.

Correlations With Gray Matter Volumes of the PFC

We explored the presumed connectivity between the hippocampal, amygdalar, and PFC subregions (DPFC and OFC gray matter volumes). Correlations were controlled for WBV, age, and sex. Differences in correlation coefficients between diagnostic groups were tested using the test statistic *D* for comparing 2 Pearson correlations while correcting for df_i:

$$D = \frac{Z_1 - Z_2}{\sqrt{\frac{1}{df_1 - 1} + \frac{1}{df_2 - 1}}} \qquad Z_i = \frac{1}{2} \ln \frac{1 + q_i}{1 - q_i},$$

where Z_i is the Fisher transformation of the correlation coefficients for samples of size n_i, and $df_i = n - p - 1$, for partial correlations with $P = 3$ covariates (WBV, age, and sex).

Surface Analyses

The signed Euclidean distances between points on the surfaces of the amygdala and hippocampus for each subject and corresponding points on the respective reference structures were compared statistically between groups using linear regression at each voxel on the surface while covarying for age and sex. *P* values were color coded at each voxel and displayed across the surface of the reference structures. To minimize type I errors, a threshold of $P < .0001$ was set. Similar maps were constructed for *P* values associated with partial correlations *r* of surface measures with symptom severity in the ADHD group, while covarying with sex and age.

Correction for Multiple Comparisons in Surface Morphologies

Testing the null hypothesis at each point on a surface generally requires many statistical comparisons. Correction of *P* values for these comparisons is complicated by intercorrelations among the signed distances at neighboring points. We therefore used the theory of gaussian random fields (GRFs)[61] to correct *P* values appropriately for these multiple comparisons in the presence of intercorrelated measures across voxels. The signed distances determine a *t* statistic at each corresponding point, which together across the surface compose a random field *f*. The expected value of the Euler characteristic of the random field *f* was used to approximate the critical point for determining locations on the surface where the *t* statistics differ between groups at a prespecified significance level or statistical threshold (R.B., L. H. Staib, PhD, D. Xu, PhD, H.Z., B.S.P., unpublished data, October-November 2005).[62] Because the expected Euler characteristic was evaluated for a GRF, *t* statistics at each location of the brain were first converted into values from a gaussian random variable.[63] Thus, surface locations where the converted statistics were larger than the estimated critical point were considered statistically significant.

RESULTS

HYPOTHESIS TESTING

The test for fixed effects in a mixed model revealed a highly significant group × region interaction ($F_{1,12} = 7.96$; $P < .006$), demonstrating a regional specificity in group differences of amygdalar and hippocampal volumes.

POST HOC ANALYSES

Post hoc assessment of the origin of this regionally specific difference between groups in volume, using a test of differences in least-square means, indicated that the hippocampus was larger bilaterally in the children with ADHD than in the controls (3384.2 mm^3 vs 3164.1 mm^3; $t_{112} = 3.35$; $P < .002$). Amygdalar volumes did not differ significantly across diagnostic groups (ADHD, 2062.6 mm^3 vs 2106.0 mm^3; $t_{112} = -0.64$; $P = .53$). Other significant covariates in the model were WBV ($F_{1,11} = 39.8$; $P < .0001$), indicating the presence of significant scaling effects, and hemisphere ($F_{1,13} = 6.1$; $P < .02$), reflecting significantly larger volumes in the right hemisphere. A group × region × hemisphere interaction was not significant (at the point of elimination, $F_{1,11} = 0.3$; $P = .62$), indicating the absence of significant lateralizing effects across groups. The group × region × age interaction also was not significant ($F_{3,22} = 0.2$; $P = .70$), indicating the stability of findings across the age range of children studied. The variables sex ($F_{1,09} = 0.5$; $P = .48$) and age ($F_{1,09} = 0.7$; $P = .42$) were conservatively retained in the final model because of the biological plausibility that these variables could influence the overall findings.

BOYS ONLY

The group × region interaction remained significant ($F_{8,2} = 4.37$; $P < .04$), with a larger hippocampus in boys with ADHD compared with controls (3398.8 mm^3 vs 3222.6 mm^3; $t_{82} = 2.23$; $P < .03$).

SURFACE ANALYSES

Statistical maps revealed that global differences in hippocampal volume between groups arose mainly from enlargement of the anterior hippocampus in children with ADHD (**Figure 2**A), particularly over the anatomical subfields cornu ammonis (CA) and dentate gyrus (DG) (**Figure 3**). In posterior portions of the hippocampus, in contrast, smaller indented regions bilaterally suggested the presence of reduced volumes locally in underlying tissue in the ADHD group.

Several portions of the surface of the amygdala suggested the presence of locally reduced volumes in the ADHD group that were not evident in the more conventional mea-

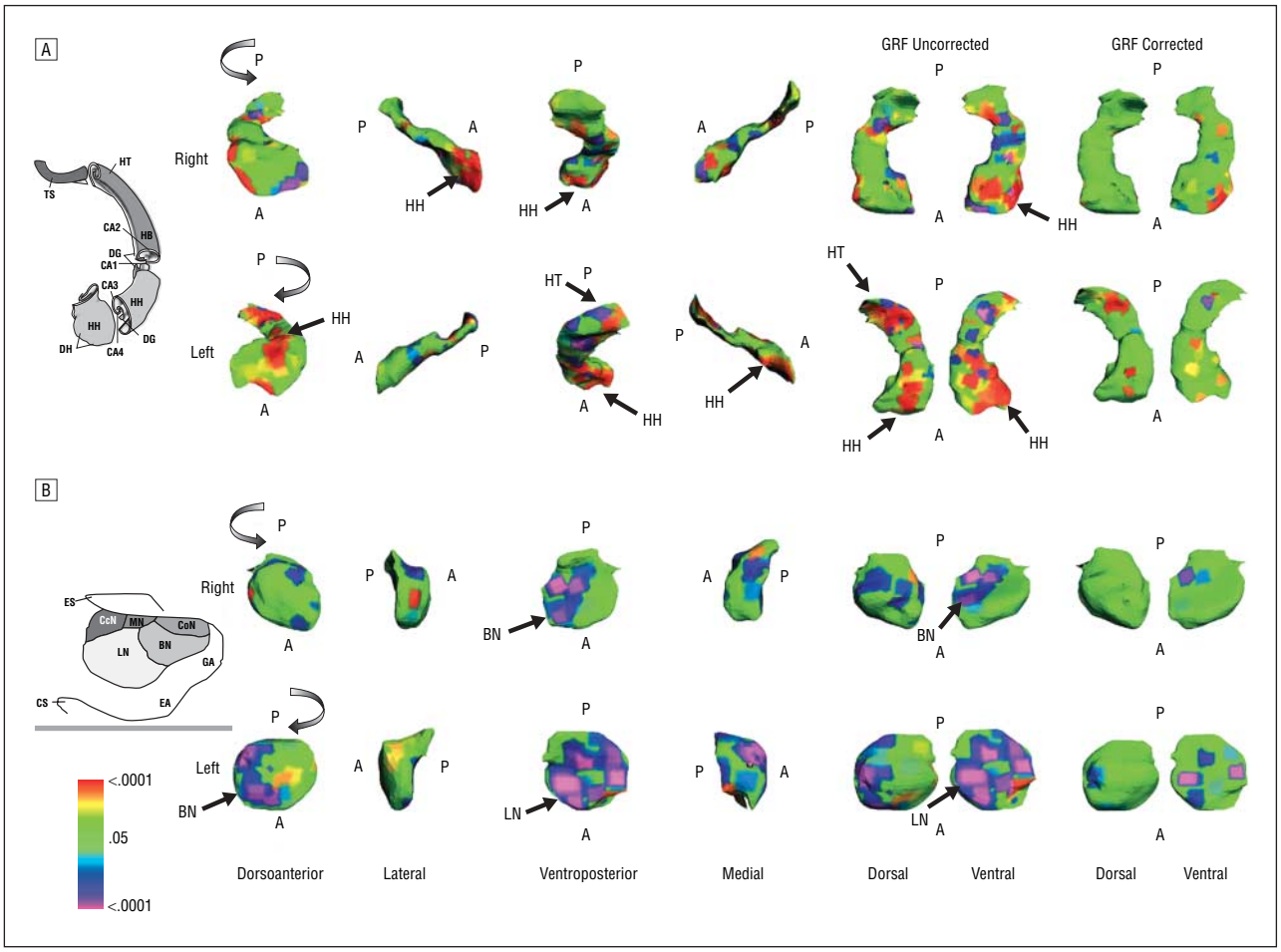

Figure 2. Group differences in surface measures of the hippocampus and amygdala. A, Views of the right (upper row) and left (lower row) hippocampus, anterior (A) and posterior (P) orientation. Arrows point to the main protrusion, most visible laterally in the right and dorsoanteriorly in the left head region of the hippocampus (HH), overlaying the dentate gyrus (DG) and the cornu ammonis (CA) subfields as well as the smaller, posteriorly located indentations and protrusions in the tail (HT). B, Views of the right (upper row) and left (lower row) amygdala, A and P orientation. Arrows point to the indentation located mainly over the ventroposterior aspect of the structure, corresponding to the basal nucleus (BN) in the right hemisphere and the lateral nucleus (LN) in the left hemisphere, thus corresponding to the basolateral complex bilaterally. The color bar depicts the statistical significance of group differences for *t* tests, ranging from $P<.0001$ in red (protrusions, or local volume enlargements, in the attention-deficit/hyperactivity group) to $P<.0001$ in purple (indentations, or local volume reductions, in the attention-deficit/hyperactivity group). The 2 outermost columns on the right side of the figure show the gaussian random field (GRF)–corrected dorsal and ventral views. TS indicates terminal segment of the HT; HB, hippocampal body; DH, digitationes hippocampi; ES, endorhinal sulcus; CoN, cortical nucleus; GA, gyrus ambiens; EA, entorhinal area; and CS, collateral sulcus.

sures of overall volume of this structure, with several clusters of voxels reaching *P* values <.0001 (Figure 2B). Differences in size were located primarily over the basal nucleus of the right amygdala and lateral nucleus of the left.

Gaussian random field–based corrections for multiple comparisons produced clusters of significant voxels that were similar in location to, but smaller in size than, clusters identified in uncorrected comparisons at a threshold of $P<.0001$ (**Figures 2**, **4**, and **5**).

CORRELATIONS WITH SYMPTOM SEVERITY

In children with ADHD only, while controlling for WBV, sex, and age, a statistical trend was detected for an inverse correlation of hippocampal volume with ratings of the severity of ADHD symptoms in the right ($r=-0.29$; $P=.06$) and left ($r=-0.27$; $P<.07$) hemispheres (**Figure 6**). Surface analyses also suggested that symptom severity correlated inversely with the local features of hippocampus morphology, particularly in portions that were enlarged relative to controls (Figure 4).

In children with ADHD only, volumes of the left ($r=0.3$; $P<.07$) and right ($r=0.3$; $P<.06$) amygdala showed strong trends toward positive correlations with hyperactivity scores (Figure 6B). Supporting the validity of these trends detected for overall volumes, analyses of symptom severity with surface features exhibited large clusters of positive correlations for hyperactivity scores bilaterally (Figure 5A). Inattention scores, in contrast, correlated inversely with surface morphology mainly in the left amygdala (Figure 5B). Symptoms of anxiety and depression did not correlate significantly with amygdalar or hippocampal volumes.

GROUP COMPARISONS OF PREFRONTAL VOLUMES

The ADHD group had significantly smaller volumes of the left OFC gray matter (ADHD, 10.535 cm^3 vs controls, 11.979 cm^3; $t=2.24$; $P<.03$) and a trend toward lower mean

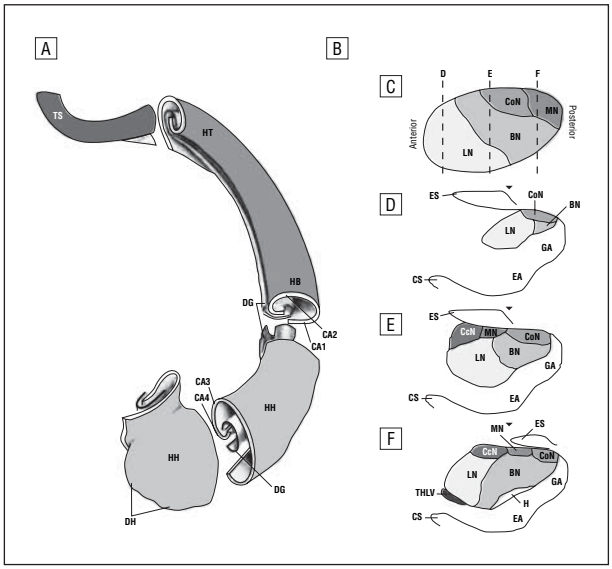

Figure 3. Subregions of the hippocampus and amygdala. A, Subregions of the hippocampus showing the head of the hippocampus (HH), the digitationes hippocampi (DH), the hippocampal body (HB), the hippocampal tail (HT), the terminal segment of the HT (TS), the dentate gyrus (DG), and the fields of the cornu ammonis (CA1-CA4). Adapted with permission from Springer Verlag, Heidelberg, Germany.[64] B, Subregions of the amygdala in the sagittal view (C), with the corresponding coronal views from anterior to posterior (D-F), showing the basal nucleus (BN), the lateral nucleus (LN), the medial nucleus (MN), the cortical nucleus (CoN), the central nucleus (CeN), the collateral sulcus (CS), the endorhinal sulcus (ES), the gyrus ambiens (GA), the entorhinal area (EA), the hippocampus (H), and the temporal horn of the lateral ventricle (THLV). The black arrowhead at the top of D, E, and F pointing downward through the amygdala indicates where the sagittal section depicted in C crosses the coronal plane.[65-68]

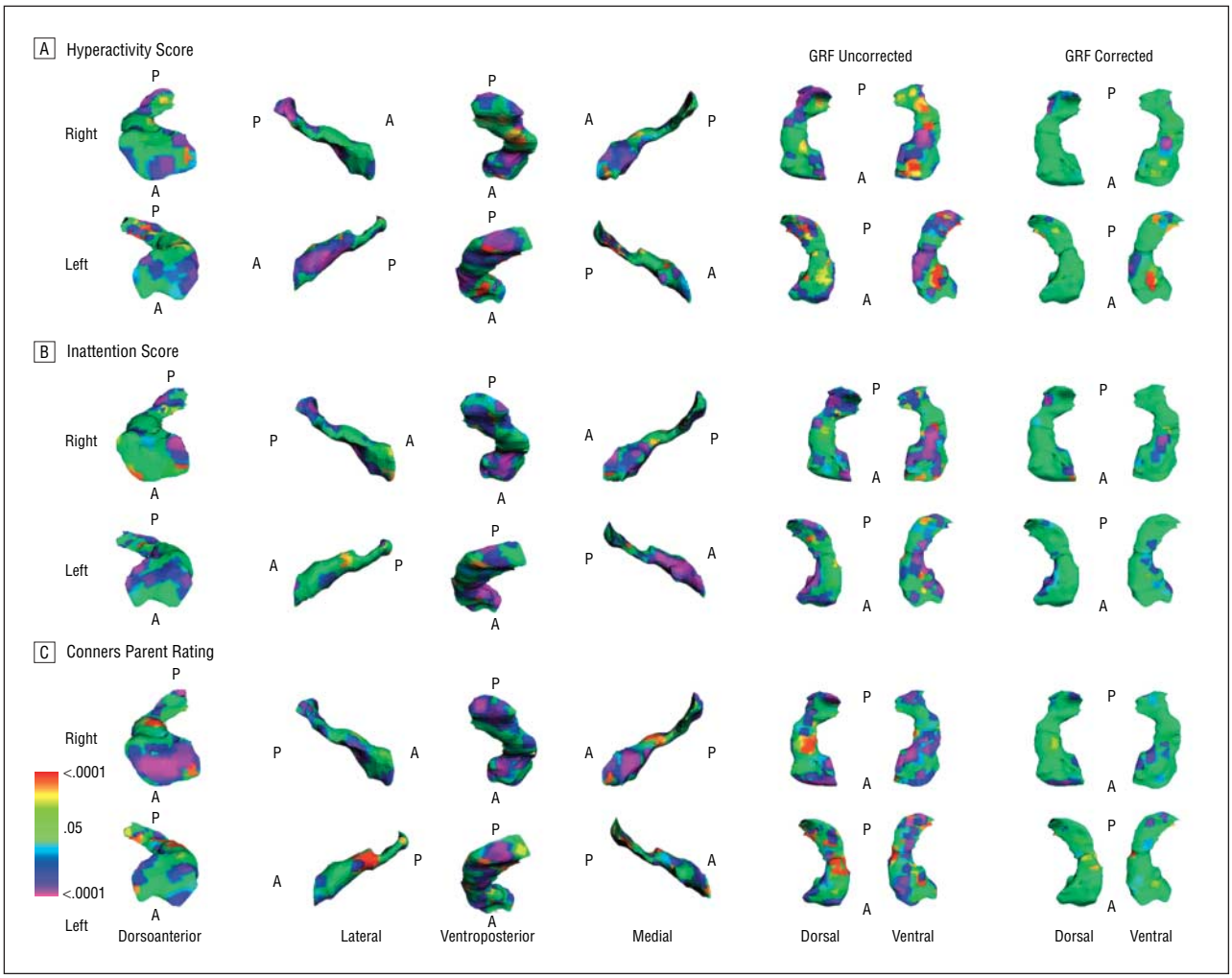

Figure 4. Symptom correlations with hippocampus surface morphology in children with attention-deficit/hyperactivity disorder. Correlation of surface measures, in signed Euclidean distances, with current hyperactivity scores (A), inattention scores (B), and total Conners Parent Rating Scale[43] scores (C) in the attention-deficit/hyperactivity disorder group, controlling for sex and age. The color bar depicts the *P* value for the partial Pearson correlation *r*, ranging from *P*<.0001 in red (highly significant positive correlations) to *P*<.0001 in purple (highly significant inverse correlations). The 2 outermost columns on the right side of the figure show the gaussian random field (GRF)–corrected dorsal and ventral views. A indicates anterior; P, posterior.

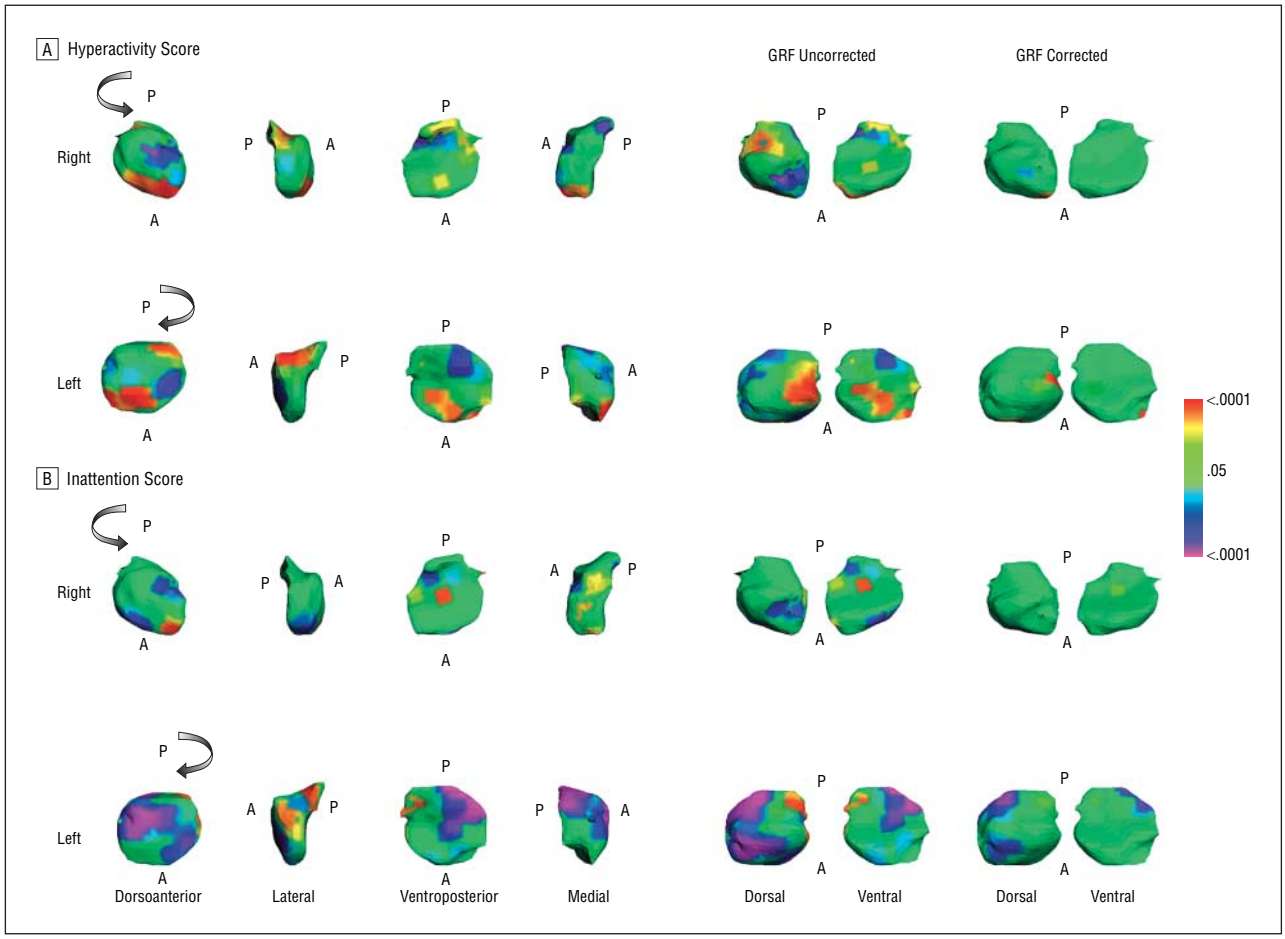

Figure 5. Symptom correlations with amygdala surface morphology in children with attention-deficit/hyperactivity disorder. A, Correlation of surface measures, in signed Euclidean distances, with current hyperactivity scores. B, Correlation of surface measures, in signed Euclidean distances, with inattention scores, controlling for sex and age, with the right amygdala (upper row) and left amygdala (lower row). The color bar depicts the *P* value for the partial Pearson correlation *r*, ranging from *P*<.0001 in red (highly significant positive correlation) to *P*<.0001 in purple (highly significant inverse correlations). The 2 outermost columns on the right side of the figure show the gaussian random field (GRF)–corrected dorsal and ventral views. A indicates anterior; P, posterior.

volumes of right OFC gray matter (ADHD, 10.973 cm^3 vs controls, 12.033 cm^3; $t=1.68$; $P<.09$) (**Table 1**). Groups did not differ in volumes of DPFC gray matter.

CORRELATIONS WITH VOLUMES OF PFC GRAY MATTER

Interregional correlation analyses revealed positive correlations in the control group (n=56) for the right and left amygdala with OFC gray matter (right, $r=0.66$; $P<.001$; left, $r=0.48$; $P<.001$) (**Table 2**). None of these correlations were significant in the ADHD group (n=47). The test statistic *D* for comparing 2 Pearson correlation coefficients confirmed significant group differences for these correlations for the left ($P<.02$) and right ($P<.001$) amygdala.

POTENTIAL CONFOUNDS

In separate assessments of the statistical model used for hypothesis testing, none of the possible confounds reached statistical significance: lifetime diagnosis of depression ($F_{111}=0.3$; $P=.61$), oppositional defiant disorder ($F_{111}=0.2$; $P=.67$), specific developmental disorder ($F_{111}=1.96$; $P=.17$), full-scale IQ ($F_{99}=0.3$; $P=.62$), handedness ($F_{109}=1.5$; $P=.22$), socioeconomic status ($F_{101}=1.0$; $P=.31$), medication status ($F_{110}=1.7$; $P=.20$), and stimulant medication ($F_{96}=2.2$; $P=.14$). In addition, verbal (right hippocampus, $r=-0.10$; $P=.32$; left hippocampus, $r=-0.10$; $P=.35$; right amygdala, $r=0.17$; $P=.11$; left amygdala, $r=0.15$; $P=.16$), performance (right hippocampus, $r=-0.10$; $P=.35$; left hippocampus, $r=-0.19$; $P=.07$; right amygdala, $r=0.15$; $P=.15$; left amygdala, $r=0.07$; $P=.47$), and full-scale IQs (right hippocampus, $r=-0.10$; $P=.33$; left hippocampus, $r=-0.14$; $P=.16$; right amygdala, $r=0.17$; $P=.09$; left amygdala, $r=0.12$; $P=.22$) did not correlate significantly with regional volumes of either the hippocampus or amygdala while controlling for WBV, sex, and age, further suggesting that IQ measures did not unduly influence findings of the primary analyses.

COMMENT

Children and adolescents with ADHD had larger hippocampal volumes than did healthy controls, primarily deriving from larger volumes of the head of the hippocampus. Larger volumes tended to accompany less severe ADHD symptoms. Although overall volumes of the amyg-

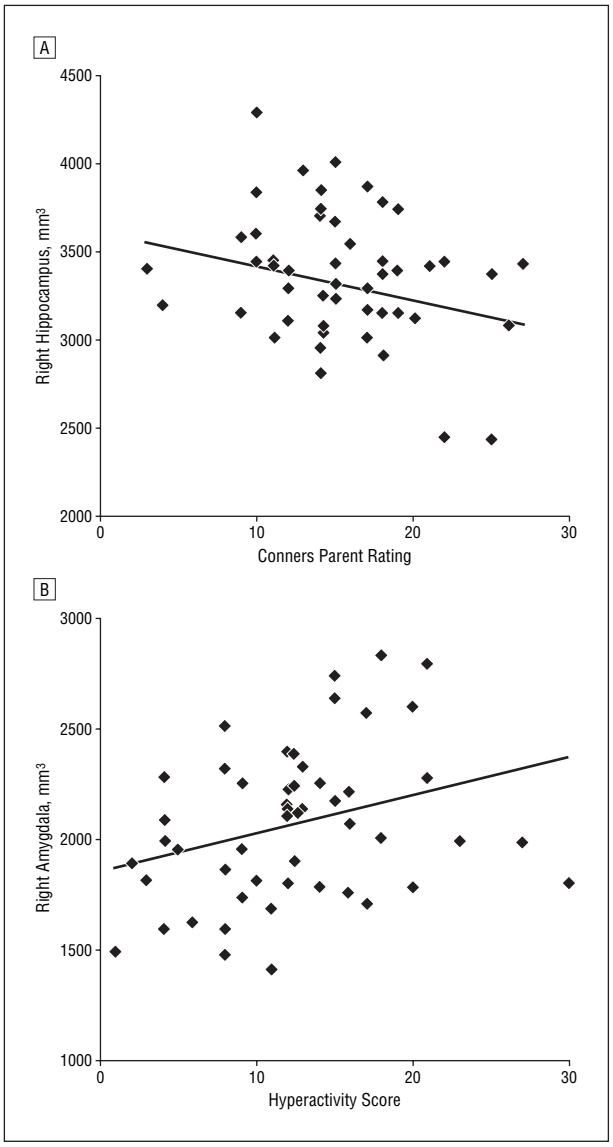

Figure 6. Scatterplots demonstrating correlations with symptom severity. A, Right hippocampal volumes (adjusted for age, sex, and whole brain volume) correlate inversely with Conners Parent Rating Scale[43] scores (n=47) (r=0.3; P<.06). B, Right amygdalar volumes (adjusted for age, sex, and whole brain volume) correlate positively with current hyperactivity scores (n=47) (r=0.3; P<.06).

dala did not differ between subjects with ADHD and controls, surface analyses showed that several amygdalar subregions were smaller in children with ADHD than in controls, and these same regions generally correlated significantly and positively with the severity of ADHD symptoms. Finally, interregional correlations suggested that connectivity between the amygdala and the OFC was disrupted in the ADHD group. Medication, comorbid illnesses of affective and anxiety disorders, symptoms of depression and anxiety, and group differences in IQ did not account for our findings.

HIPPOCAMPUS

Surface analyses revealed enlarged anterior-most portions of the hippocampus in the ADHD group, particularly in its dorsal and lateral aspects, corresponding respectively to the DG and CA1-CA2 subregions.[54,64] Significant inverse correlations with hyperactivity scores were localized laterally over the CA1 and CA2 subfields, and inverse correlations with inattentive symptoms were located medially, primarily over the CA3 and DG subfields. Although we cannot infer causation from these cross-sectional, correlational findings,[69,70] the most likely explanation for the association of more prominent enlargement with fewer ADHD symptoms, particularly in the presence of overall enlargement (ie, progressively fewer symptoms that accompany an increasingly more prominent morphological abnormality relative to controls), would seem to be that the hippocampal enlargement represents a compensatory plastic hypertrophic response to the presence of ADHD symptoms. This interpretation is consistent with abundant preclinical evidence for the presence of synaptic remodeling[71,72] and neurogenesis[73] within the hippocampus, which supports improved learning and memory functions in response to experiential demands.[74,75]

An enlarged anterior hippocampus could represent a localized compensatory response of neural processes to the presence of functional disturbances in these same neural systems within the anterior hippocampus, as is thought to occur in the presence of impaired neural processing.[76,77] Alternatively, given evidence herein and elsewhere[24,28,78,79] for the presence of impaired structure and function of the PFC in children with ADHD, the enlarged anterior portions of the hippocampus may represent a neural compensation for disturbances in prefrontal portions of a PFC-hippocampal network. The absence of a significant contribution of age to the correlations of hippocampus morphology with the severity of symptoms could evidence an initiation of a plastic response early in the course of disease, a possibility consistent with the shorter time frames (days to weeks) in which plasticity typically manifests.[80]

The anterior hippocampus encodes the spatial and temporal relationships between sensory experiences,[81-84] which the posterior hippocampus then consolidates for storage in long-term memory.[85,86] Working within a distributed network that includes the PFC, the encoding of temporal relationships within the hippocampus helps to define and encode the serial ordering of events,[82,87-90] the cognitive function probably most consistently disturbed in children with ADHD.[7,91-96] In humans, the anterior hippocampus plays a prominent role in indexing novelty, detecting change, and exploring new environments,[86,97-99] and thus, the stimulus-seeking behaviors of children with ADHD[100] may engage these anterior hippocampal functions. Given that stimulus-enriched environments[101,102] and physical activity[103-105] potently enhance DG neurogenesis, the anterior hippocampal hypertrophy that we detected conceivably could also be a neuronal consequence of exaggerated stimulus-seeking behaviors in the children with ADHD. Moreover, stimulus seeking and attention to nontemporal stimuli are hypothesized to serve as strategies that reduce the length of experienced time while children with ADHD are experiencing the delayed delivery of an anticipated reward,[94] an experience to which they have an intense aversion.[8] Thus, both stimulus seeking and its pre-

Table 1. Comparison of Brain Morphometric Measures*

	Raw Volumes, cm³			Adjusted Volumes, cm³		
	Children With ADHD	Controls	*P* Value	Children With ADHD	Controls	*P* Value
WBV	1351.772 (133.731)	1348.37 (128.753)	.89			
Right hippocampus	3.377 (0.386)	3.175 (0.395)	<.007	3.374 (0.366)	3.169 (0.348)	<.002
Left hippocampus	3.362 (0.378)	3.135 (0.425)	<.003	3.394 (0.362)	3.159 (0.378)	<.002
Right amygdala	2.066 (0.406)	2.101 (0.422)	.66	2.064 (0.348)	2.107 (0.420)	.53
Left amygdala	2.030 (0.382)	2.081 (0.413)	.50	2.061 (0.325)	2.104 (0.383)	.53
Right DPFC gray matter	38.535 (6.496)	37.191 (5.188)	.26	38.923 (5.443)	37.353 (4.174)	.11
Left DPFC gray matter	37.154 (7.131)	36.999 (4.859)	.89	37.238 (6.045)	36.960 (3.697)	.78
Right OFC gray matter	10.973 (3.548)	12.033 (2.685)	.09	11.483 (2.989)	12.379 (2.295)	.09
Left OFC gray matter	10.535 (3.660)	11.979 (2.775)	<.03	10.863 (3.316)	12.243 (2.298)	<.02

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DPFC, dorsal prefrontal cortex; OFC, orbitofrontal cortex; WBV, whole brain volume.
*Values are expressed as mean (SD). Differences were tested with a *t* test (*P* values). Adjusted values for the hippocampus and amygdala are predicted by using the final models used in the SAS PROC MIXED (SAS Institute Inc, Cary, NC) statement with WBV, age, sex, and hemisphere as covariates. Prefrontal measures were adjusted by using WBV, age, and sex as covariates.

sumed morphological consequence, plastic hypertrophy in the anterior hippocampus, could help to allay disturbances in the perception of time and difficulties with delay aversion in children with ADHD.

The hippocampus is also the pacemaker for theta wave activity in the central nervous system,[106] and individuals with ADHD have unusually high relative theta activity (4-8 Hz) in their electroencephalograms.[107-109] Thus, an enlarged hippocampus could account for excess theta activity in this group, particularly given that theta activity underlies working memory processes and the retrieval and consolidation of long-term memories[110-112] and has been documented in animals during exploratory behaviors in unfamiliar surroundings.[113-115]

AMYGDALA

Although overall volume of the amygdala did not differ between subjects with ADHD and controls, surface analyses indicated the presence of significant reductions in volume overlying the lateral and basal nuclei, which together with the accessory basal nucleus have been designated the basolateral complex,[116] a portion of the amygdala that is particularly densely connected with the PFC.[33,117,118] Hyperactivity scores showed a trend toward positive correlation with overall volume of the amygdala and should as a statistical trend be interpreted cautiously. Nevertheless, surface analyses also detected positive correlations of hyperactivity symptoms with amygdala morphology at considerably greater levels of statistical significance, particularly in the region overlying the basolateral complex bilaterally, where volumes were reduced locally in the ADHD group. Inattention scores correlated inversely with surface measures most prominently over the basal and lateral nuclei of the left amygdala. Volume reductions and correlations with measures of symptom severity were localized primarily over the basolateral complex, the portion of the amygdala most consistently implicated in the attribution of affective valence to sensory stimuli,[119-121] and the nuclei most likely to subserve fear conditioning.[122-125] We postulate that morphological disturbances in the basolateral complex may interfere with both the attribution of valence to sensory stimuli and the development of normal fear responses in children with ADHD, which may in turn disrupt emotional learning and the affective drive to sustain attention to otherwise mundane sensory stimuli.

Table 2. Interregional Correlations*

	r (*P* Value)		
Interregional Correlation	Children With ADHD	Controls	*P* Value
Right hippocampus with DPFC gray matter	0.11 (.48)	–0.01 (.97)	.58
Left hippocampus with DPFC gray matter	0.07 (.64)	0.04 (.81)	.87
Right hippocampus with OFC gray matter	–0.09 (.57)	–0.02 (.91)	.72
Left hippocampus with OFC gray matter	0.02 (.88)	0.17 (.25)	.41
Right amygdala with DPFC gray matter	–0.15 (.33)	0.03 (.86)	.39
Left amygdala with DPFC gray matter	–0.06 (.68)	0.07 (.65)	.60
Right amygdala with OFC gray matter	–0.16 (.29)	0.66 (<.001)	<.01
Left amygdala with OFC gray matter	–0.03 (.87)	0.48 (<.001)	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DPFC, dorsal prefrontal cortex; OFC, orbitofrontal cortex.
*Partial Pearson correlation coefficients for prefrontal cortical subregions and the amygdala and hippocampus in the ADHD and the control groups. Whole brain volume, age, and sex are covariates. *P* values in the right column indicate the significance of the difference of correlation across the diagnostic groups.

INTERREGIONAL CONNECTIVITY

Interregional correlations suggested the presence of disturbed connectivity between the amygdala and OFC in the children with ADHD. The significant positive correlation of amygdalar volumes bilaterally with volumes of OFC gray matter in healthy controls was inverted significantly in the

ADHD group. Connections between these regions are rich,[126,127] and they support decision making by supplying information about positive and negative outcomes during choice behaviors.[36,37] Neurons in the amygdala are thought to signal the value of specific reinforcers, information that is used subsequently by OFC neurons firing in expectation of the behavioral outcome to guide and reinforce behavior.[128] Interaction of the OFC and amygdala is therefore needed to learn reinforcements and to suppress unwanted behaviors,[129] as well as to evaluate the emotional and reinforcing salience of sensory stimuli.[32,130-132] The poor performance of children with ADHD on delay-aversion tasks,[8] their preferences for smaller immediate rewards,[133] and their more frequent risk-taking behaviors[134] all suggest that they are impaired in decision-making capabilities.[135] More generally, learning and behavioral control depend on the integrity of limbic-prefrontal connections, and we suspect that disturbances in these connections contribute to the impulsive behaviors that are a defining hallmark of ADHD.[13,136]

The basolateral complex of the amygdala, in concert with the hippocampus and medial PFC, plays a central role in the consolidation of learning and memory functions, a role mediated through adrenergic, dopaminergic, and cholinergic neurotransmitter systems.[137,138] Disruption of connectivity in amygdala-PFC pathways in children with ADHD is therefore consistent with some of the cognitive deficits associated with the disorder and with the cognition-enhancing effects of stimulant medications, which potentiate noradrenergic and dopaminergic transmission.[139]

RELATION TO PREVIOUS STUDIES

Two previous studies have reported normal hippocampal volumes in children and adolescents with ADHD. In both studies, 1 comprising 57[26] and the other 15 boys with ADHD,[27] larger hippocampal volumes were detected in the ADHD group, though not at the level of statistical significance. The statistical significance of our hippocampal findings may be attributable to a large sample size and to the use of images with higher resolution and improved signal-to-noise characteristics. Moreover, neither of the prior studies conducted detailed surface analyses of the hippocampus, which in our analyses revealed larger anterior and smaller posterior regions, effects that tend to offset one another when comparing overall volumes across diagnostic groups. These opposing effects within the same structure may explain why morphological abnormalities were difficult to detect previously.

LIMITATIONS

The ultrastructural determinants of group differences in morphology of the hippocampus and amygdala are unknown, as is the extent to which disturbances in surface morphology relate to abnormalities in the underlying nuclei within these structures. Addressing these limitations will require detailed post-mortem studies. Additionally, the multiple statistical tests performed in our analyses increased the likelihood of type I error, which we minimized in our surface-based analyses through use of conservative statistical thresholds and GRF-based corrections for multiple comparisons.[62,140] Voxels that did not survive GRF correction of course should be interpreted with caution. Furthermore, correlations of surface morphology with clinical symptoms were exploratory and hypothesis generating and therefore also should be interpreted cautiously, as well as confirmed in future studies. Finally, we cannot entirely discount the possibility that medications or comorbid affective and anxiety disorders contributed to our findings, although we did not detect any evidence for these effects.

CONCLUSIONS

Our findings of hippocampal enlargement in children with ADHD and the association of progressively fewer symptoms with an increasing degree of this morphological abnormality suggest that hippocampal enlargement may represent neural responses within the hippocampus that compensate for problems in temporal processing and delay aversion. Disturbances in connectivity between the amygdala and OFC may contribute to problems of self-regulatory control and goal-directed behaviors. This study provides further evidence that the pathophysiology of ADHD involves limbic structures and limbic-prefrontal circuits.

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