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In vivo evidence for post-adolescent brain maturation in frontal and striatal regions

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We spatially and temporally mapped brain maturation between adolescence and young adulthood using a whole-brain, voxel-by-voxel statistical analysis of high-resolution structural magnetic resonance images (MRI). The pattern of brain maturation during these years was distinct from earlier development, and was localized to large regions of dorsal, medial and orbital frontal cortex and lenticular nuclei, with relatively little change in any other location. This spatial and temporal pattern agrees with convergent findings from post-mortem studies of brain development and the continued development over this age range of cognitive functions attributed to frontal structures.

A thorough understanding of human brain development from birth through adolescence to adulthood is essential to our understanding cognitive development, yet relatively little is known about normal brain maturation. Post-mortem studies show that myelination, a cellular maturational event, begins near the end of the second trimester of fetal development and extends well into the third decade of life and beyond[1,2]. Such autopsy studies reveal a temporally and spatially systematic sequence of myelination, progressing from inferior to superior and from posterior to anterior; that is, brain stem and cerebellar regions myelinate before cerebral hemispheres, and frontal lobes myelinate last[1]. This process may reflect regional patterns of functional maturation. Unfortunately, post-mortem studies typically include low numbers of subjects in childhood, adolescence and young adulthood because few specimens are available, and their interpretations are complicated by concomitant disease.

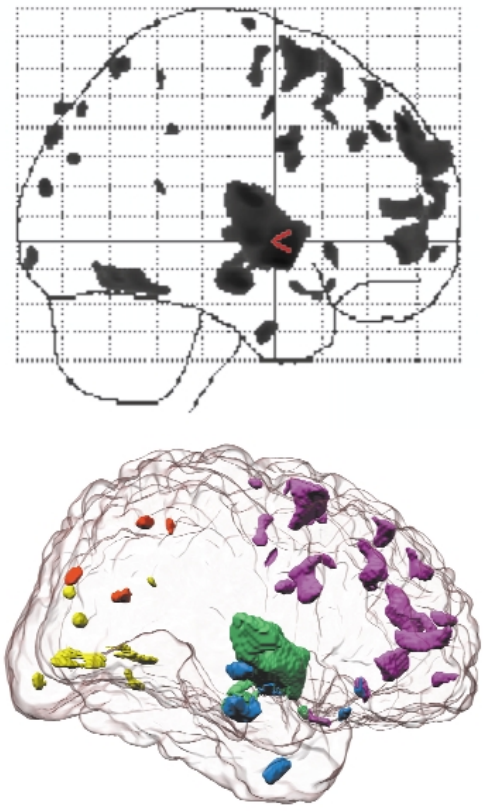

Fig. 1. Adolescent minus adult statistical parametric mapping. Traditionally presented *z-score map* (height threshold, 0.001; extent threshold, 50) for the gray-matter density reductions observed between adolescence and young adulthood (top). The same SPM is shown three-dimensionally inside a transparent rendering of one subject's cortex (bottom). Lobes and the subcortical region were defined anatomically on the same subject's brain (see Methods). Clusters were color coded based on location: clusters are shown in the subcortical region (green) and in frontal (purple), parietal (red), occipital (yellow) and temporal (blue) lobes.

In an earlier study using MRI and a voxel-by-voxel image analysis technique (voxel-based morphometry of whole-brain gray matter)[3], we found that cortical changes between childhood and adolescence were confined to dorsal brain regions and were most prominent in the parietal lobes. Findings from an earlier volumetric study prompted us to try these methods[4]. These results were complemented by another study assessing white matter change[5] and generally agreed with expectations based on post-mortem studies of cellular brain maturation. The relative prominence of changes in the parietal cortex as compared with frontal cortex, however, was surprising given the known posterior–anterior progression of maturational cellular events. We had expected brain image analysis to reflect considerable frontal maturation by age 16.

Here we assessed postadolescent brain maturation by studying a group of normal, young adults, 23–30 years of age, as well as 12–16-year-olds studied previously[3]. We anticipated that the pattern of brain maturation between adolescence and adulthood would differ from that observed between childhood and adolescence. Specifically, we anticipated more maturational changes in the frontal lobes than in other cortical regions because, in addition to the post-mortem findings of delayed frontal maturation, converging evidence from electrophysiological[6] and cerebral glucose-metabolism[7] studies reveals relatively late frontal maturation. Additionally, neuropsychological studies of normal development show that performance on tasks involving the frontal lobes continues to improve into adolescence[8]. Despite abundant empirical evidence for postadolescent frontal lobe development, the spatial and temporal progression of maturation into the frontal lobes has yet to be shown *in vivo*.

Adolescents (age range, 12–16; mean 13.8 ± 1.6 years; $n = 10$, 5 male), and young adults (23 to 30 years; mean age, 25.6 ± 2.0 years; $n = 10$, 5 male) were studied. Adolescents had been recruited as normal controls for a neurodevelopmental research center and the young adults as controls for neuropsychiatric studies of adult patients. Subjects were all right handed and were thoroughly screened for medical, neurological and psychiatric disorders. Informed consent was obtained from all subjects and/or their parents.

High-resolution MRI brain images were acquired for each subject in the same magnet. We used an imaging protocol with a gradient-echo (SPGR) T_1-weighted series with $TR = 24$ ms, TE = 5 ms, NEX = 2, flip angle = 45°, a field of view of 24 cm and section thickness of 1.2 mm, with no gaps. Previously detailed image-analysis methods[3] are briefly summarized here. First-image volumes were resliced into a standard orientation, making it easier to define cerebral and non-cerebral

Table 1. Voxel coordinates in Talairach space and associated z scores for the most significant voxels in the five largest clusters in the adolescent-minus-adult SPM.

Cluster size (mm^3)	Talairach coordinates (mm)			z score
	x	y	z	
9271	40	–9	15	5.11
5774	–11	2	–7	5.82
2470	–19	50	40	4.65
1047	22	10	64	4.24
1325	–32	–52	–15	3.92

regions. Three-dimensional digital filtering was applied to each volume to reduce signal-value variability due to radio-frequency inhomogeneity artifacts. Each image set was subjected to semi-automated tissue segmentation to classify voxels as gray matter, white matter or cerebrospinal fluid (CSF) based on signal value. Nonbrain tissue and cerebellar structures were subtracted from each image. For statistical parametric mapping (SPM) analyses, each subject's brain volume was scaled into a standard space using an automated 12-parameter linear transformation[9].

For importation into SPM96 software[10], the skull-stripped, tissue-segmented supratentorial image sets were binarized to include only gray-matter voxels. Binary gray-matter volumes were then smoothed with an 8-mm FWHM isotropic Gaussian kernel to create a spectrum of intensities that represented gray-matter 'density'. However, note that here 'density' refers not to cell packing, but to the amount of gray matter labeled by the segmentation procedure per unit volume. Cell packing or specific laminar changes either could not be measured by MRI or were lost during tissue classification.

Statistical analyses were conducted with SPM96. We used a simple voxel-by-voxel contrast to compare the average gray-matter map for adolescents to that for young adults, focusing on the negative effects of age on gray-matter. We tested for regional differences in the location of voxels that segmented as gray matter in adolescents and either white matter or CSF in young adults (presumably representative of increasing myelination). Voxels that were different between groups ($p < 0.001$) and clustered in groups of 50 or more voxels were considered significant. To correct for multiple statistical comparisons, an initial significance level was assigned to the SPM by modeling the residuals as isotropic stationary Gaussian fields with homogeneous smoothness across the brain volume. We also applied a nonparametric statistical approach, in case theoretical assumptions were violated in our sample[11]. Here adolescents and adults were randomly assigned to groups for 20 additional SPM analyses. All results were significant at the $p < 0.05$ level under both nondistributional and stationary random-process statistical models.

To test the hypothesis that differences between adolescents and adults are greater in frontal regions, several brain regions (frontal, temporal, parietal and occipital lobes and a subcortical region) were manually defined on one image set, aided by a brain-surface rendering in which central and lateral sulci could be easily identified; where available, cortical gyri were used to separate lobar regions. Significance for each lobe and the subcortical region was assessed by counting the number of significant voxels per unit volume in each region of the SPM and comparing this distribution to the null hypothesis (that all regions would be uniform) using a chi-squared test.

The SPM of differences between adolescents and adults observed here (**Fig. 1**) contrasted with the SPM of differences between childhood and adolescence[3]. Specifically, parietal, temporal and occipital lobes showed little maturational change; as predicted, dorsal, medial and lateral regions of the frontal lobes showed large group differences. A large cluster was also seen in the subcortical region. Significant changes were observed in 0.014% of frontal lobes, 0.002% of parietal lobes, 0.007% of temporal lobes, 0.005% of occipital lobes and 0.076% of the subcortical region. A chi-squared test confirmed that these results were statistically significant ($\chi^2 = 180$, $p < 0.001$). Table 1 contains Talairach coordinates of the most significant voxels in the five largest clusters. Significant group differences were mapped onto an averaged brain (**Fig. 2**). In permutation tests used to assess the overall significance of the SPM, the mean number of significant clusters for the 20 randomized tests was 7.4 (range, 0–16), compared with 44 significant clusters in the omnibus group test ($p < 0.05$; permutation test).

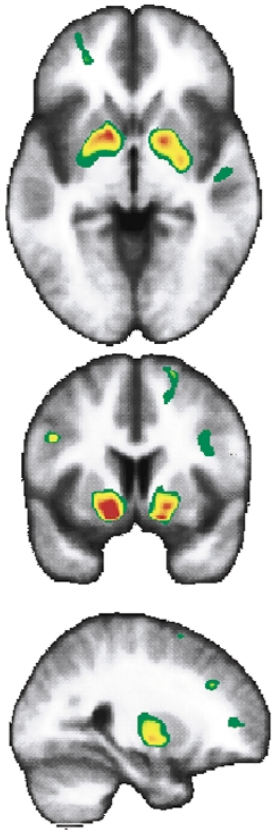

Fig. 2. Voxels showing significant changes in gray matter between adolescents and adults, mapped onto an averaged brain. Note the clear striatal and more prominent frontal reductions in gray-matter density. Red shades correspond to the highest z-statistic values and green to the lowest.

In regions of frontal cortex, we observed reduction in gray matter between adolescence and adulthood, probably reflecting increased myelination in peripheral regions of the cortex that may improve cognitive processing in adulthood. This was predicted by post-mortem[1,2], electrophysiological[6], positron-emission tomography[7] and neuropsychological[8] studies of normal cognitive and neurological development. Neuropsychological studies show that the frontal lobes are essential for such functions as response inhibition, emotional regulation, planning and organization[12]. Many of these aptitudes continue to develop between adolescence and young adulthood. On the other hand, the parietal association cortices are involved in spatial relations and sensory functions, and the lateral temporal lobes are involved in auditory and language processing, aspects of cognitive development that are largely mature by adolescence[13]. Thus, observed regional patterns of static versus plastic maturational changes between adolescence and adulthood are consistent with cognitive development.

The striatal changes observed, primarily in the putamen and globus pallidus, probably result from some combination of regressive events, myelination and iron deposition[14]. Their functional significance in the postadolescent brain may seem somewhat more difficult to assess than that of frontal lobe changes, given that striatal structures are involved in motor function that is likely fully developed by late adolescence. However, striatal motor functions are mediated by

the frontal cortex[15]. Striatal structures are involved in cognitive functions such as learning, which is linked to frontal system function[15] and improves throughout adolescence[8]. This suggests temporal and functional relationships between simultaneous postadolescent reductions in gray-matter density in frontal and striatal regions.

Thus, we describe *in-vivo* documentation for a temporal and spatial progression of postadolescent maturation into the frontal lobes, highlighting the potential importance of frontal/striatal maturation to adult cognition.

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Brain development during childhood and adolescence: a longitudinal MRI study

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Pediatric neuroimaging studies[1–5], up to now exclusively cross sectional, identify linear decreases in cortical gray matter and increases in white matter across ages 4 to 20. In this large-scale longitudinal pediatric neuroimaging study, we confirmed linear increases in white matter, but demonstrated nonlinear changes in cortical gray matter, with a preadolescent increase followed by a postadolescent decrease. These changes in cortical gray matter were regionally specific, with developmental curves for the frontal and parietal lobe peaking at about age 12 and for the temporal lobe at about age 16, whereas cortical gray matter continued to increase in the occipital lobe through age 20.

The subjects for this study were healthy boys and girls participating in an ongoing longitudinal pediatric brain-MRI project at the Child Psychiatry Branch at the National Institute of Mental Health. Subjects were recruited from the community as previously described, using phone screening, questionnaires mailed to parents and teachers and face-to-face physical and psychological testing; approximately one in six volunteers were accepted[5]. At least 1 scan was obtained from each of 145 healthy subjects (89 male). Of these, 65 had at least 2 scans, 30 had at least 3 scans, 2 had at least 4 scans and 1 had 5 scans, acquired at approximately two-year intervals. The age range was from 4.2 to 21.6 years. There were no significant sex differences for age, Tanner stage, ethnicity, socioeconomic status, height, weight or handedness.

All subjects were scanned on the same GE 1.5 Tesla Signa scanner using the same three-dimensional, spoiled-gradient, recalled echo in the steady state (3D SPGR) imaging protocol, with an axial-slice thickness of 1.5 mm, a time-to-echo of 5 ms, a repetition time of 24 ms, flip angle of 45°, a 192 (256 acquisition matrix, 1 excitation and a field of view of 24 cm. A clinical neuroradiologist evaluated all scans; no gross abnormalities were reported.

Volumes of white and cortical gray matter were quantitatively analyzed by combining a technique using an artificial neural network to classify tissues based on voxel intensity with non-linear registration to a template brain for which these tissue regions had been manually defined[7]. This technique supplemented MRI signal-intensity information with predetermined brain anatomy and provides lobar (frontal, parietal, temporal and occipital) parcellation of cortical gray- and white-matter volumes.

We used previously described statistical analysis techniques that combine cross-sectional and longitudinal data[8]. These longitudinal methods are more sensitive to detecting individual growth patterns, even in the presence of large interindividual variation[9]. We assessed if there was significant change with age, if developmental curves differed by sex and/or region and whether the developmental curves were linear or quadratic.

The volume of white matter increased linearly with age (**Fig. 1**; **Table 1**), increasing less in females than in males. The net increase across ages 4 to 22 was 12.4%. Curves for white-matter development did not significantly differ among various lobes. In contrast, changes in volume of cortical gray matter were nonlinear and regionally specific. Gray matter in the frontal lobe increased during pre-adolescence with a maximum size occurring at 12.1 years for males and 11.0 years for females, followed by a decline during post-adolescence that resulted in a net decrease in volume across this age span. Parietal-lobe gray matter followed a similar pattern, increasing during pre-adolescence to a maximum size at age 11.8 years for males and 10.2 years for females, followed by decline during postadolescence and a net decrease