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

Table 1. Developmental curves for different regions.

Structure	Male intercept	Female intercept	Age coefficient β_1	Age^2 coefficient β_2	*p* value for no change ($\beta_1 = 0, \beta_2 = 0$)	*p* value for only linear change ($\beta_2 = 0$)	*p* value for curves having same shape
Total cerebrum	1382 (12.3)	1260 (19.3)	5.6 (10.0)	–0.72 (0.15)	$p < 0.0001$	$p < 0.0001$	$p = 0.83$
Total gray	758 (7.3)	686 (11.3)	–0.50 (0.80)	–0.39 (0.12)	$p = 0.001$	$p = 0.001$	$p = 0.47$
Frontal gray	235 (2.3)	214 (3.8)	–0.38 (0.28)	–0.18 (0.04)	$p < 0.0001$	$p < 0.0001$	$p = 0.84$
Temporal gray	191 (1.7)	175 (2.6)	0.81 (0.22)	–0.10 (0.03)	$p < 0.0001$	$p = 0.002$	$p = 0.99$
Parietal gray	126 (1.3)	116 (20.0)	–0.31 (0.15)	–0.10 (0.02)	$p < 0.0001$	$p < 0.0001$	$p = 0.51$
Occipital gray	70.1 (1.2)	61.5 (1.7)	0.41 (0.14)	0.009 (0.02)	$p = 0.007$	$p = 0.69$	$p = 0.07$

The developmental curves are modeled by the equation: size = intercept + β_1 (age – mean age) + β_2 (age – mean age)^2 + ε where the intercept term is a random effect that varies by individual and intra-individual correlation of ε is taken into account. A Wald statistic assesses whether the curve changes with age (that is, whether β_1 and β_2 are both 0). A *z* statistic of β_2 assesses whether the curve is best fit by a linear ($\beta_2 = 0$) or quadratic curve ($\beta_2 \neq 0$). The curves were found to have similar shapes by sex (no significant differences for any structure), but because the height of the curves did vary, separate terms were used for boys and girls. Multivariate analysis showed that shapes for the four regions of gray matter significantly differed from one another ($p < 0.0001$), with parietal and frontal regions most similar and temporal the most distinct.

in volume; however, pre- and post-adolescent slopes were steeper for parietal than for frontal lobes. Temporal-lobe gray matter also followed a nonlinear developmental course, but maximum size was not reached until 16.5 years for males and 16.7 years for females, with a slight decline thereafter. Occipital-lobe gray matter increased linearly over the age range, without evidence of significant decline or leveling. Developmental curves for the different cortical regions significantly differed from each other; those for frontal and parietal lobes were the most similar. The absolute size of the cortical gray matter was approximately 10% larger in boys, and peaked slightly earlier in girls, but the shapes of the curves were not significantly different between boys and girls.

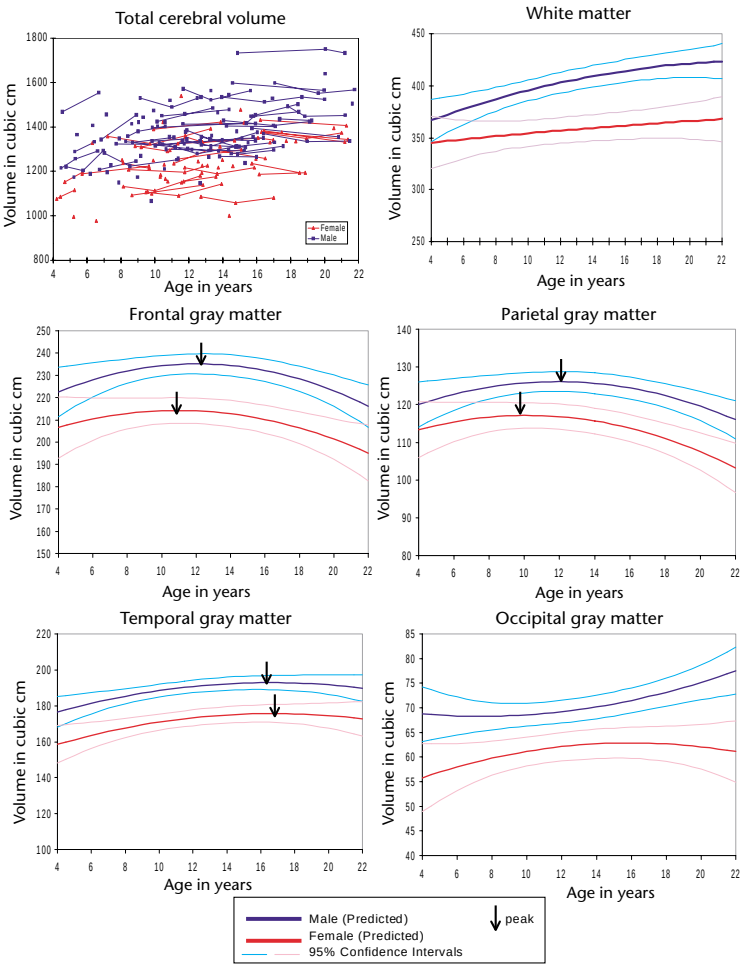

Fig. 1. Predicted size with 95% confidence intervals for cortical gray matter in frontal, parietal, temporal and occipital lobes for 243 scans from 89 males and 56 females, ages 4 to 22 years. The arrows indicate peaks of the curves.

The regional specificity of findings in cortical gray matter sheds light on the debate regarding synchronous versus heterochronous development of the cerebral cortex. Nonhuman primate studies generally reveal synchronous cortical development (that is, with similar timing in diverse cortical regions)[10]. However, in humans there are limited but compelling histological data to suggest that synapse elimination is heterochronous, with changes in primary visual and auditory cortex occurring before those in frontal cortex[11]. The present data support heterochronic development in human cerebral cortex. The pre-adolescent increase and post-adolescent decrease in cortical gray matter parallel developmental PET studies of cerebral glucose metabolism[12] and EEG studies of slow-wave sleep amplitude[13].

This MRI study demonstrates a pre-adolescent increase in cortical gray matter; this phenomenon was previously obscured, probably by the lack of longitudinal data, as even in an analysis of the 145 cross-sectional data points in our sample, the largest to date, we could not detect nonlinearity in these developmental curves. Whether this gray-matter increase is related to changes in neuropil, neuronal size or dendritic or axonal arborization will be best addressed by methods other

than MRI. If the increase is related to a second wave of overproduction of synapses, it may herald a critical stage of development when the environment or activities of the teenager may guide selective synapse elimination during adolescence. The relative prominence of the role of the environment in shaping late synaptogenesis is supported by rat studies[14,15]. That the frontal and parietal gray matter peaks approximately one year earlier in females, corresponding with the earlier age of onset of puberty, suggests a possible influence of gonadal hormones. Studies of healthy monozygotic and dizygotic twins, chromosomal aneuploidies (XXY, XXYY, XYY), congenital adrenal hyperplasia (producing high levels of testosterone *in utero*) and psychiatric illnesses are underway to address the effects of genes, hormones and environment on this process.

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A contingent aftereffect in the auditory system

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Pairs of stimulus attributes, such as color and orientation, that are normally uncorrelated in the real world are generally perceived independently; that is, the perception of color is usually uninfluenced by orientation and *vice versa*. Yet this independence can be altered by relatively brief exposure to artificially correlated stimuli, as has been shown for vision[1]. Here we report an analogous contingent aftereffect in the auditory system that can persist for four hours after the initial adaptation.

After a few minutes of alternately viewing an orange-black vertical grating and a blue-black horizontal grating, the white stripes in a vertical black-and-white grating appear blue-green, whereas the white stripes in a horizontal grating appear orange[1].

There are numerous demonstrations of other types of visual contingent aftereffect, such as color-contingent orientation[2] and motion[3,4] aftereffects and spatial frequency[5]- and motion[6,7]-contingent color aftereffects. These visual contingent aftereffects can be extremely persistent. For example, the motion-contingent color aftereffect and the color-contingent motion aftereffect can persist for at least 24 hours[3,6]. The motion-contingent color aftereffect can last as long as six weeks in some cases[7].

In contrast to the rich variety of reported visual contingent aftereffects, there are no reports of contingent aftereffects for

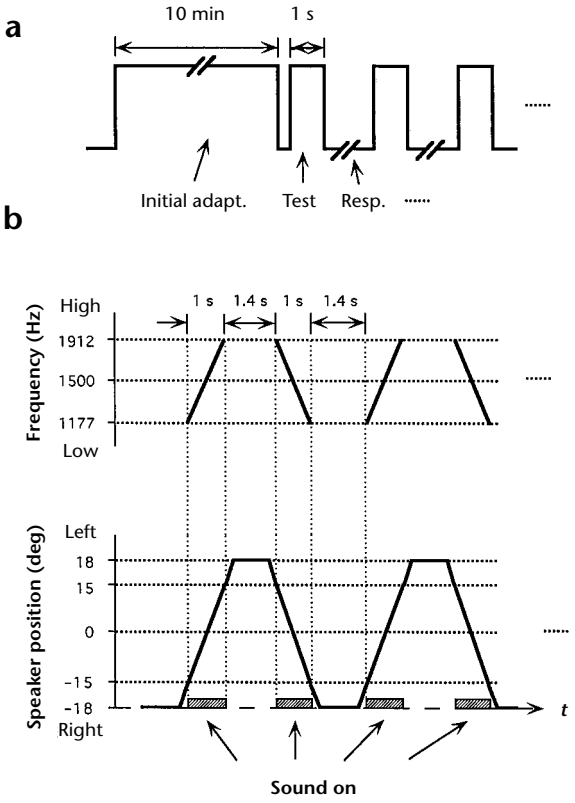

Fig. 1. Stimulus protocols. (**a**) Time sequence of stimuli. Each run began with 10 minutes of adaptation, followed by a series of brief test sounds (1 s), with either a rising (0.7 octaves per s) or a falling (–0.7 octaves per s) pitch presented by a loudspeaker moving at one of six different velocities (2°, 6° or 10° per s, either to the left or the right). For each test presentation, the subject was asked to press one of two buttons to indicate the direction (leftward or rightward) of spatial movement. (**b**) Detailed time sequence of adapting stimuli. While the central frequency of an adapting sound (1-octave band-pass noise) was moving upward (0.7 octave per s), the loudspeaker moved to the left (30° per s) for 1 second (from –15° to 15° in azimuth). Following a silent interval of 1.4 seconds, the loudspeaker moved to the right (–30° per s) for 1 second, while the central frequency of the sound moved downward (–0.7 octave per s). During adaptation, this sequence was repeated continuously. In the control condition, the loudspeaker moved over the same trajectory with the same time course, but the center frequency of the adapting sound was kept constant at 1.5 kHz. Note that the vertical axis in the top panel has a logarithmic scale.