Linear and Curvilinear Correlations of Brain Gray Matter Volume and Density with Age Using Voxel-Based Morphometry with the Akaike Information Criterion in 291 Healthy Children

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Abstract: We examined linear and curvilinear correlations of gray matter volume and density in cortical and subcortical gray matter with age using magnetic resonance images (MRI) in a large number of healthy children. We applied voxel-based morphometry (VBM) and region-of-interest (ROI) analyses with the Akaike information criterion (AIC), which was used to determine the best-fit model by selecting which predictor terms should be included. We collected data on brain structural MRI in 291 healthy children aged 5–18 years. Structural MRI data were segmented and normalized using a custom template by applying the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) procedure. Next, we analyzed the correlations of gray matter volume and density with age in VBM with AIC by estimating linear, quadratic, and cubic polynomial functions. Several regions such as the prefrontal cortex, the precentral gyrus, and cerebellum showed significant linear or curvilinear correlations between gray matter volume and age on an increasing trajectory, and between gray matter density and age on a decreasing trajectory in VBM and ROI analyses with AIC. Because the trajectory of gray matter volume and density with age suggests the progress of brain maturation, our results may contribute to clarifying brain maturation in healthy children from the viewpoint of brain structure. *Hum Brain Mapp* 34:1857–1871, 2013. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Brain development continues throughout childhood and adolescence. It has been revealed that human brain development is structurally and functionally a non-linear process [Giedd et al., 1999; Gogtay et al., 2004; Johnson, 2001; Lenroot et al., 2007; Thatcher, 1992]. Gray matter volume shows an inverted-U-shaped curvilinear trajectory, with a pre-adolescent increase followed by a post-adolescent decrease in healthy children [Giedd et al., 1999; Gogtay et al., 2004; Jernigan et al., 1990a,b, 1991; Lenroot et al., 2007; Pfefferbaum et al., 1994]. This phenomenon is thought to derive from a corresponding increase and decrease in the number of synapses per neuron and intracortical myelination in brain maturation [Huttenlocher, 1979; Huttenlocher et al., 1982, 1997; Paus, 2005]. Therefore, revealing the trajectory of gray matter volume with age may help to improve understanding of the progress of brain maturation in each gray matter region. Additionally, it is important to reveal the normal trajectory of brain gray matter volume with age in cortical and subcortical gray matter in healthy children, because several disorders, such as autistic spectrum disorder, show significant differences in gray matter volume both in the cortex [Boddaert et al., 2004; Bonilha et al., 2008; Jiao et al., 2010] and in subcortical regions, such as the putamen [Bonilha et al., 2008], compared with age-matched healthy children. Moreover, the trajectory of subcortical gray matter volume with age in subjects with autism is significantly different from that in healthy children [Langen et al., 2009].

Several studies have shown correlations between gray matter measures such as gray matter volume or cortical thickness and age. A recent study analyzing the linear and curvilinear trajectories of gray matter density with age in cortical regions showed that higher order association cortices mature only after lower order somatosensory and visual cortices [Gogtay et al., 2004]. Other studies have shown a significant positive linear correlation between gray matter volume and age in several regions, such as the bilateral anterior temporal cortex and insulae, and a significant negative linear correlation between gray matter volume and age in other regions, such as the basal aspect of the frontal lobe and posterior parietal cortices [Guo et al., 2007; Wilke et al., 2007] using voxel-based morphometry (VBM) [Ashburner et al., 2000]. VBM is an established automated neuroimaging technique that enables analysis of cortical and subcortical gray matter without a priori identification of a region of interest and is not biased towards any specific brain region. Using VBM, it is possible to focus on both gray matter density and gray

matter volume. Gray matter density represents the relative concentration of gray matter structures in spatially warped images (i.e., the proportion of gray matter relative to all tissue types within a region) [Mechelli et al., 2005], whereas gray matter volume represents the absolute amount of gray matter [Good et al., 2001; Mechelli et al., 2005]. Because brain volume and gray matter volume change significantly throughout childhood development [Giedd et al., 1999; Lenroot et al., 2007], focusing on both absolute gray matter volume and gray matter density may help our understanding of the mechanism of brain maturation. Recently, linear and curvilinear correlations between cortical thickness and age were estimated in cortical gray matter regions using data from a large number of healthy subjects [Shaw et al., 2008]. Another study also showed curvilinear regional cortical thinning with age in adolescence and young adulthood [Tamnes et al., 2010]. Moreover, a recent study analyzed the linear and curvilinear correlations between age and subcortical gray matter regions such as the caudate head, putamen, and thalamus, demonstrating the heterogeneity of the correlations [Ostby et al., 2009a]. Thus, although several studies have revealed the trajectory of gray matter volume or density with age in healthy children, the trajectory has been estimated in cortical and subcortical gray matter by linear correlation only [Wilke et al., 2007] or by curvilinear correlation, but not by examining both cortical and subcortical gray matter [Gogtay et al., 2004; Ostby et al., 2009a; Shaw et al., 2008; Tamnes et al., 2010], or by focusing only on gray matter density [Sowell et al., 2003]. A surface-based analysis, such as cortical thickness, evaluates cortical gray matter but not subcortical gray matter, whereas VBM evaluate both cortical and subcortical gray matter. To date, no reported study has analyzed the linear and curvilinear correlations between gray matter volume and age and between gray matter density and age in cortical and subcortical gray matter. Additionally, although the Akaike information criterion (AIC) is one of the widely used methods to determine the best-fit model for any correlations by selecting the function that shows the lowest AIC value [Akaike, 1974], no previous studies have applied AIC with VBM to determine a best-fit model to explain these correlations in healthy children.

Thus, the purpose of the present study was to examine the linear and curvilinear correlations of gray matter volume and density with age in a large number of healthy children by applying VBM and region-of-interest (ROI) analyses with AIC in whole gray matter regions using brain magnetic resonance (MR) imaging. We applied voxel-based analysis, because we focused on subcortical

Figure 1.

Examples of developmental trajectory for each function. N, negative correlation; P, positive correlation.

gray matter as well as cortical gray matter. To examine any correlation between gray matter volumes, we applied linear, quadratic, and cubic polynomial functions for explaining the correlation between gray matter volume and age and between gray matter density and age. This range of analyses was of interest because gray matter volume shows an inverted-U-shaped followed by a U-shaped curvilinear trajectory, which means that gray matter volume first increases, then slows, and then starts to decrease, followed by a slow rate of decrease in healthy children [Giedd et al., 1999; Gogtay et al., 2004; Lenroot et al., 2007]. Examples of the developmental trajectory for each function are shown in Figure 1. Specifically, a negative linear fit could describe the portion between the peak of the inverted-U- and the U-shaped curve. A positive linear fit could describe the portion before the peak of the inverted U-curve trajectory. Negative and positive quadratic fitting may describe the portions around the peaks of the inverted-U- and the U-shaped trajectories, respectively. Additionally, positive cubic fitting could describe the portion including the peaks of both the inverted-U- and the U-shaped trajectories. Moreover, by fitting the trajectory using polynomial functions, we may be able to estimate the progress of brain maturation. For example, the inverted-U-shaped trajectory and a positive cubic trajectory directly would demonstrate the age of the highest gray matter density and volume. Negative linear and positive quadratic trajectories would suggest that the age of highest gray matter density and volume is earlier than the age range included in this study. Additionally, the regions fitted by a positive quadratic trajectory would suggest earlier maturation than those fitted by a negative linear trajectory. Thus, we hypothesized that gray matter regions that mature earlier, such as the occipital lobe and the basal aspect of the frontal cortex, would have a negative linear or positive quadratic trajectory for the correlation between gray matter volume and age. In contrast, gray matter regions that mature later, such as the dorsolateral prefrontal cortex and temporoparietal region, have a negative

quadratic or positive cubic correlation between gray matter volume and age. Additionally, because white matter volume increases after gray matter volume increases [Giedd et al., 1999], gray matter density in most regions has a decreased trajectory with age.

MATERIALS AND METHODS

Subjects

All subjects were healthy Japanese children, recruited in the following manner. First, we distributed 29,740 advertisements summarizing the study to various kindergartens, elementary schools, junior high schools, and high schools in Miyagi Prefecture, Japan. A total of 1423 parents who had an interest in this study contacted us by mail. Next, a child version and a parent version of a detailed questionnaire seeking information relevant to the study were mailed to those parents. Then, 776 parents and subjects who were willing to participate contacted us again by mail. Subjects who had any history of malignant tumors, head trauma with a loss of consciousness lasting over 5 min, developmental disorders, epilepsy, psychiatric diseases, or claustrophobia were excluded by a preliminary telephone interview, a mail-in health questionnaire, and an oral interview. Of the subjects included, we failed to collect brain MR images from eight subjects due to claustrophobia (three subjects) and fatigue (five subjects). We collected brain MR images from 291 subjects in the order in which the notifications of their intention to participate in the project arrived by mail. To assess intelligence quotients (IQ), trained examiners administered the Japanese version of the Wechsler Adult Intelligence Scale (WAIS), third edition [Fujita et al., 2006], to subjects whose ages were at least 16 years; for subjects aged less than 16 years, we used the Japanese version of the Wechsler Intelligence Scale for Children (WISC), third edition [Azuma et al., 1998]. We calculated the full-scale IQ, verbal IQ, and performance IQ from the score on the WAIS/WISC for each subject. We also collected data regarding socioeconomic status from each subject's parent(s) by collecting family annual income information. Annual income data were collected using discrete variables as follows: annual income below 20,000 US dollars (currency exchange rate, 1 US dollar = 100 Yen), 1; 20,000–40,000 US dollars, 2; 40,000–60,000 US dollars, 3; 60,000–80,000 US dollars, 4; 80,000–100,000 US dollars, 5; 100,000–120,000 US dollars, 6; $\geq 120,000$ US dollars, 7. Thus, the final sample consisted of 291 participants (146 boys, aged 5.6–17.0 years, and 145 girls, aged 5.8–18.4 years). Subject characteristics are shown in Table I.

Written informed consent was obtained from each subject and his/her parent after receipt of a full explanation of the purpose and procedures of the study according to the Declaration of Helsinki [1991] before MR image scanning. Approval for these experiments was obtained from the institutional review board of Tohoku University.

TABLE I. Subject characteristics

	Boys (<i>n</i> = 146)	Girls (<i>n</i> = 145)	<i>P</i>
Age (years), (mean ± SD, range)	11.0 ± 2.90, 5.6–17.0	11.5 ± 3.35, 5.8–18.4	0.110 ^a
Socioeconomic status ^c (mean ± SD)	4.03 ± 1.50	3.84 ± 1.48	0.270 ^a
Full-scale IQ (mean ± SD, range)	104.3 ± 13.16, 77–137	100.8 ± 11.16, 71–128	0.017 ^b
Verbal IQ (mean ± SD, range)	105.5 ± 13.56, 67–152	101.7 ± 13.02, 67–134	0.015 ^a
Performance IQ (mean ± SD, range)	102.0 ± 14.15, 62–136	99.8 ± 11.10, 73–129	0.140 ^b

^aStudent's *t*-test.^bWelch's *t*-test.^cSocioeconomic status was divided as follows; annual income below 2 million yen (~20,000 US dollars), 1; 2–4 million yen, 2; 4–6 million yen, 3; 6–8 million yen, 4; 8–10 million yen, 5; 10–12 million yen, 6; ≥12 million yen, 7.

Image Acquisition

All images were collected using a 3-T Philips Intera Achieva scanner. Three-dimensional, high-resolution, T1-weighted structural images were collected using a magnetization prepared rapid gradient echo (MPRAGE) sequence. The parameters were as follows: 240×240 matrix, TR = 6.5 ms, TE = 3 ms, TI = 711 ms, FOV = 24 cm, 162 slices, 1.0-mm slice thickness, scan duration 8 min 3 s. We examined the collected images to determine whether there were any obvious artifacts in the images. If obvious artifacts, such as motion artifacts, were observed, we collected the MR images again.

Image Analysis

A schematic of the image analysis is shown in Figure 2. In image analysis, VBM with diffeomorphic anatomical

registration using exponentiated lie algebra (DARTEL) [Ashburner, 2007] was conducted. DARTEL has been shown to produce a more accurate registration than the standard VBM procedure [Klein et al., 2009] and enables improved sensitivity of findings such as the correlation between gray matter density and age. After image acquisition by MRI, all T1-weighted MR images were analyzed using statistical parametric mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, UK) in Matlab (Math Works, Natick, MA). First, the "New Segmentation" algorithm from SPM8 was applied to every T1-weighted MR image to extract tissue maps corresponding to gray matter, white matter, and cerebrospinal fluid (CSF). This algorithm, which is an improvement of the unified segmentation algorithm [Ashburner et al., 2005], uses a Bayesian framework to iteratively perform the probabilistic tissue classification and the spatial non-linear deformation to Montreal Neurological Institute (MNI)

Figure 2.
Schematic of the image analysis.

space. Although we were only interested in the probabilistic tissue segmentation at this point, this new Bayesian segmentation and warping algorithm, which includes an improved set of tissue priors [Ashburner et al., 2009] for regularization, increased the robustness and accuracy of the segmentation compared with previous standard VBM algorithms. This step allowed obtaining probability maps of the three aforementioned tissues for each subject and to have them all rigidly registered by ignoring the non-rigid part of the warping to a temporary common space (which happened to be as close to the MNI space as can be reached by a rigid transform), because the following DARTEL step focused on estimating the “pure non-linear” component of the transformation and used rigidly registered tissues as input. Next, these 291 segmented tissue maps were used to create a customized, more population-specific template using the DARTEL template-creation tool [Ashburner, 2007]. DARTEL estimates a best set of smooth deformations from every subject’s tissues to their common average, applies the deformations to create a new average, then reiterates the process until convergence. Smoothness and reversibility of the deformation are obtained from the diffeomorphic properties of DARTEL’s transformations. The template space was matched to the MNI space using an affine-only registration, which enabled us to match our images’ custom coordinate space to the more standard MNI space [Bergouignan et al., 2009]. We used a set of standard MNI tissues maps and a multivariate tissue affinity registration algorithm provided by SPM and DARTEL for that process. At the end of the process, each subject’s gray matter map was warped using its corresponding smooth, reversible deformation parameters to the custom template space, and then to the MNI standard space. We also computed the group-wide mean and group-wide variance of all these images to visually confirm that the process had run correctly, by looking for a low variance near major landmarks. The major advantage of creating a population-specific template on which to register the tissues is that it limits the amount of stretching that each image has to undergo during the necessary step of spatial normalization. For the gray matter volume, the warped gray matter images were then modulated by calculating the Jacobian determinants derived from the special normalization step and multiplying each voxel by the relative change in volume as described in the method of Good et al. [2001]. This modulation step was performed to correct for volume changes in nonlinear normalization. Finally, the warped gray matter images and the warped modulated gray matter images were smoothed by convolving an 8-mm full-width at half-maximum isotropic Gaussian kernel. For the gray matter density, the warped gray matter images were not modulated. After completing these image analyses, we had obtained smoothed warped and smoothed modulated and warped gray matter images to be used for the statistical analysis. We examined all collected MR images and segmented images and confirmed that there were no obvious artifacts in the images and no

obvious mis-segmentation due to any artifact in visual inspection.

Statistical Analysis

For the VBM analysis, to analyze the linear and curvilinear trajectory of gray matter density and volume with age, the relationships of gray matter density and volume with age were estimated by fitting three polynomial functions of age (linear, quadratic, and cubic) to the whole gray matter density and volume images. We set three separate linear models: Age, Age² + Age, and Age³ + Age² + Age. For each model, an intercept term was added, and higher order polynomial regressors were orthogonalized to lower order polynomial regressors using the `spm_orth.m` function of SPM8, which enabled us to test each polynomial component individually if needed. We determined the best-fit linear model at each voxel by selecting the voxel with the smallest AIC value [Akaike, 1974]; thus, we used AIC to penalize the added parameters. Next, we obtained an inclusive mask image in which the gray matter regions that showed significant correlations with age, age², or age³ were included using an *F*-test of the cubic model. In the analysis, we applied a statistical threshold of $P < 0.05$, corrected for multiple comparisons, using the family-wise error rate based on random field theory. Then, we applied the inclusive mask to the results of voxel-based AIC analysis to restrict the information to statistically significant areas only. This two-step approach allowed us to initially define the global mask of statistically significant correlations between age and any of the models while keeping the degrees of freedom and threshold strictly the same in all instances. We then performed a fine-grained analysis to characterize the shape based solely on the information criterion. Separating the fit-significance assessment from the curve-shape characterization allowed us to achieve results that were easy to interpret.

For the ROI analysis, we set 34 ROIs that covered the entire gray matter structural region of the cerebrum and of the deep gray matter structures and each lobe of the cerebellum in each hemisphere to smoothed warped and to smoothed modulated and warped gray matter images using “WFU_PickAtlas” [Lancaster et al., 2000; Maldjian et al., 2003] and obtained the regional gray matter density and volume in each ROI. Then, we analyzed the relationship between matter density and volume, and age was estimated by fitting three polynomial functions of age (i.e., linear, quadratic, and cubic) to the whole gray matter density and volume images. We determined the best-fit linear model at each voxel by selecting the one that showed the smallest AIC value [Akaike, 1974]. We determined the significance level using the Bonferroni correction. The total number of ROIs was 34 in each hemisphere; thus, the significance level was set at $P < 0.05/34 = 0.0015$ in all statistical analyses of ROI analysis.

We performed the above statistical analyses on boys and girls separately, as several studies have shown that the trajectory of gray matter volume with age differs between boys and girls [Giedd et al., 1999; Lenroot et al., 2007].

RESULTS

VBM Analysis of the Correlations of Gray Matter Volume and Density with Age

The results for the correlation between gray matter volume and age in boys fitted by linear, quadratic, or cubic polynomial functions determined by AIC are shown in Figure 3, and those for girls are shown in Figure 4. As shown in the first upper line of Figures 3 and 4, several gray matter regions, such as the bilateral temporoparietal regions, the lateral aspect of the temporal lobe, the precentral gyrus, and cerebellum, showed quadratic or cubic trajectory with age. Other regions were mainly fitted by a linear function. In boys, significant correlations were found between age and the left cerebellum (quadratic, $Z = 7.84$, $P < 0.001$), the left middle frontal gyrus (linear, $Z = 6.23$, $P < 0.001$), and the right precentral gyrus (linear, $Z = 5.87$, $P < 0.001$). In girls, significant correlations were observed between age and the right lobe of the cerebellum (quadratic, $Z = 7.63$, $P < 0.001$), the left precentral gyrus (linear, $Z = 6.91$, $P < 0.001$), and the left orbitofrontal gyrus (linear, $Z = 6.80$, $P < 0.001$).

Additionally, the results for the correlations between gray matter density and age in boys fitted by linear, quadratic, or cubic polynomial functions determined by AIC are shown in Figure 5, and those for girls are shown in Figure 6. As shown in the first upper lines of Figures 5 and 6, several gray matter regions, such as the bilateral temporoparietal regions, the lateral aspect of the temporal lobe, the inferior frontal gyrus, and the cerebellum, showed quadratic or cubic trajectories with age. Other regions were mainly fitted by linear functions. In boys, significant correlations were identified between age and the right precentral gyrus (quadratic, $Z = 7.67$, $P < 0.001$), the right inferior frontal gyrus (linear, $Z = 7.54$, $P < 0.001$), and the right insula (linear, $Z = 7.67$, $P < 0.001$). In girls, significant correlations were noted between age and the right lingual gyrus (quadratic, $Z = \text{inf.}$, $P < 0.001$), the left precentral gyrus (linear, $Z = \text{inf.}$, $P < 0.001$), and the right lobe of the cerebellum (linear, $Z = 7.30$, $P < 0.001$).

ROI Analysis of the Correlations of Gray Matter Volume and Density with Age

The results of the correlation between gray matter volume and age in the ROI analysis are shown in Table II, and those between gray matter density and age in the ROI analysis are shown in Table III. In the tables, peak age is the estimated age of peak gray matter volume and density using the correlation function between gray matter volume

or density and age in each ROI. Overall, the correlation between gray matter volume and age showed a positive trajectory, especially a linear trajectory, in most ROIs in both boys and girls. On the other hand, the correlation between gray matter density and age showed negative linear, negative quadratic, or positive cubic trajectories in most ROIs in both boys and girls. In most regions that showed negative quadratic or positive cubic trajectories with age, gray matter density showed a decrease with age. In most regions, the areas that showed significant correlations between gray matter volume and age and those that showed correlations between gray matter density and age did not overlap.

In the frontal lobe, significant positive correlations between gray matter volume and age, but not between gray matter density and age, were found mainly in the lateral aspects, such as the bilateral superior frontal, middle frontal, and precentral gyri. These results suggest that, in these regions, actual gray matter volume increases with age, but relative gray matter volume does not significantly change. The ages of the peak volumes in those regions were estimated to be older than the upper limit of age range in this study (boys, 17.0 years; girls, 18.4 years). However, gray matter density showed significant negative correlations with age, but not with gray matter volume and age, mainly in the medial and basal aspects of the frontal lobe, such as the bilateral medial superior frontal, inferior frontal gyri, anterior cingulate cortices, cingulate, and rectal gyri. These results suggest that relative gray matter volume in these regions decreases with age, but that actual gray matter volume does not significantly change. The age for the peak volume in most of the regions was estimated to be younger than the lower limit of the age range in this study (boys, 5.6 years; girls, 5.8 years). In the parietal lobe, most regions showed no significant correlation between gray matter volume and age, but the medial aspect of the parietal lobe, such as the precuneus and posterior cingulate cortex, showed significant correlations between gray matter density and age. The trajectory of the gray matter density in these regions decreased with age. The ages of the peak densities in those regions were estimated to be younger than the lower limit of the age range in this study, except the bilateral posterior cingulate cortex in boys (left, 7.5 years; right, 6.9 years). In the mainly lateral inferior and medial aspects of the temporal lobe such as the inferior temporal gyrus, the hippocampus, and the uncus, significant positive correlations between gray matter volume and age were found. The age for the peak volume in those regions was estimated to be older than the upper limit of the age range in this study. In the basal aspect of the temporal lobe, such as the fusiform gyrus and lingual gyrus, there were significant negative linear or positive cubic correlations between gray matter density and age. The age for the peak density in those regions was estimated to be younger than the lower limit of the age range in this study, or younger than 10 years. Most regions in the occipital lobe were not significantly correlated between gray matter volume and age or between gray matter density and age. In the subcortical

Figure 3.

Correlations between gray matter volume and age in gray matter regions in boys fitted by linear, quadratic, or cubic polynomial functions, determined by Akaike information criterion (AIC). Above, upper row: the results are superimposed onto the surface of the brain; lower row: the results are masked by the results of the AIC computation by the results of an *F*-test of the cubic model's three age regressors, thresholded at a significance level of $P < 0.05$ for the family-wise error rate. Center: scatter plots of the correlations between gray matter volume and age in several regions that showed strong significant correla-

tions. Horizontal axis refers to age (years old), and vertical axis refers to regional gray matter volume (no units). Below: the masked results are superimposed onto the axial view. The left part of the figure is the left part of the brain. The blue color indicates the voxel regressed by linear function, green indicates the voxel regressed by quadratic function, and red indicates the voxel regressed by cubic function. In the surface rendering images (the upper part of this figure), yellow (a mix of red and green), and light blue (a mix of green and blue) colors are also shown, representing the mixing of neighboring voxels.

gray matter structures, significant negative correlations between gray matter density and age were observed in the caudate nucleus and the thalamus in girls. The age of peak

density in those regions was estimated to be younger than the lower limit of the age range in this study. In the insula, significant correlations between gray matter density and

Figure 4.

Correlations between gray matter volume and age in gray matter regions in girls fitted by linear, quadratic, or cubic polynomial functions, determined by AIC. Detail as for Figure 3.

age were observed, and these were negatively correlated with age. With the exception of data obtained from the right insula of boys (7.7 years), the age for the peak density in the insula was estimated to be equal to or younger than the lower limit of the age range in this study. The posterior lobe of the cerebellum showed a significant negative quadratic correlation between gray matter volume and age. The age for the peak volume in the region was estimated to be near or older than the upper limit of the age range in this study. The anterior lobe of the cerebellum showed a significant correlation between gray matter density and age, with

a trajectory that decreased with age. The age for the peak density in the region was estimated to be younger than the lower limit of the age range in this study in girls and ~8 years in boys.

DISCUSSION

To our knowledge, this is the first reported study revealing a correlation both between gray matter volume and age and between gray matter density and age in whole

Figure 5.

Correlations between gray matter density and age in gray matter regions in boys fitted by linear, quadratic, or cubic polynomial functions, determined by AIC. Detail as for Figure 3.

gray matter regions over a wide age range of healthy children by applying VBM and ROI analyses with AIC. We found that several regions, such as the lateral frontal cortex, precentral gyrus, and cerebellum, showed significant linear or curvilinear correlations between gray matter volume and age with an increasing trajectory. We also found several regions, such as the medial aspect of the frontal cortex, which showed significant linear or curvilinear correlations between gray matter density and age with a decreasing trajectory. We also estimated peak age of the gray matter volume or density in each region.

In this study, we were able to demonstrate correlations both between gray matter volume and age and between gray matter density and age, as gray matter volume and gray matter density derived from the VBM analysis are separate [Good et al., 2001; Mechelli et al., 2005]. As described in the Introduction, gray matter density represents the relative concentration of gray matter structures in spatially warped images (i.e., the proportion of gray matter relative to all tissue types within a region) [Mechelli et al., 2005], whereas gray matter volume represents the absolute amount of gray matter [Good et al.,

Figure 6.

Correlations between gray matter density and age in gray matter regions in girls fitted by linear, quadratic, or cubic polynomial functions, determined by the AIC. Detail as for Figure 3.

2001; Mechelli et al., 2005]. Because total gray matter volume and total white matter volume change with age [Giedd et al., 1999], gray matter density, in addition to gray matter volume, is thought to be important for understanding the trajectory of brain maturation from the viewpoint of gray matter. From the ROI analysis, we found that the regions that showed significant correlations between gray matter volume and age and those that showed correlations between gray matter density and age did not overlap. For example, several regions, such as the lateral aspect of the frontal lobe, showed significant posi-

tive correlations between gray matter volume and age, but not between gray matter density and age. These results suggest that actual gray matter volume in the region increases with age, but that relative gray matter volume in the region does not significantly change. As for the mechanisms of the gray matter volume change in children, several studies have shown a pre-adolescent increase due to synaptogenesis followed by a post-adolescent decrease in the number of synapses per neuron due to synapse elimination and intracortical myelination during brain maturation [Huttenlocher, 1979; Huttenlocher et al., 1982, 1997;

TABLE II. Trajectory of regional gray matter volume with age in each ROI

Region	Boys						Girls					
	Left			Right			Left			Right		
	Function ^a	F	Peak age	Function ^a	F	Peak age	Function ^a	F	Peak age	Function ^a	F	Peak age
Medial superior frontal gyrus	Lin., P.	5.70*	>17.0	Lin., P.	5.12*	>17.0	Lin., P.	8.57*	>18.4	Lin., P.	6.21*	>18.4
Superior frontal gyrus	Lin., P.	15.10**	>17.0	Lin., P.	11.01**	>17.0	Lin., P.	33.08**	>18.4	Lin., P.	27.99**	>18.4
Middle frontal gyrus	Lin., P.	11.85**	>17.0	Qua., N.	4.63*	14.6	Lin., P.	21.00**	>18.4	Lin., P.	17.06**	>18.4
Inferior frontal gyrus	Cub., P.	2.64	>17.0	Lin., P.	9.08*	>17.0	Cub., P.	2.99*	>18.4	Cub., P.	3.45*	>18.4
Anterior cingulate cortex	Lin., P.	0.10	>17.0	Lin., N.	0.08	<5.6	Cub., P.	1.16	>18.4	Cub., P.	1.16	>18.4
Cingulate gyrus	Lin., N.	0.29	<5.6	Lin., N.	0.08	<5.6	Cub., P.	4.08*	8.9	Cub., N.	2.99*	8.8
Precentral gyrus	Lin., P.	29.23**	>17.0	Lin., P.	18.96**	>17.0	Lin., P.	41.05**	>18.4	Lin., P.	26.24**	>18.4
Orbital gyrus	Cub., P.	5.41*	>17.0	Cub., P.	5.36*	>17.0	Cub., P.	2.78*	>18.4	Lin., P.	3.95*	>18.4
Rectal gyrus	Cub., P.	1.20	>17.0	Cub., P.	1.02	>17.0	Cub., P.	0.71	9.2	Lin., N.	1.61	<5.8
Postcentral gyrus	Qua., P.	4.66*	>17.0	Lin., P.	0.21	>17.0	Lin., P.	12.88**	>18.4	Lin., P.	5.18*	>18.4
Paracentral lobule	Qua., P.	0.60	>17.0	Cub., P.	0.99	>17.0	Cub., P.	1.19	9.7	Lin., N.	6.53*	<5.8
Superior parietal lobule	Lin., P.	2.11	>17.0	Qua., P.	1.91	>17.0	Lin., P.	3.50	>18.4	Lin., P.	4.32*	>18.4
Inferior parietal lobule	Lin., P.	4.37*	>17.0	Lin., P.	2.96	>17.0	Lin., P.	2.20	>18.4	Qua., N.	2.77	13.5
Supramarginal gyrus	Lin., P.	3.10	>17.0	Qua., N.	1.97	13.6	Lin., P.	1.33	>18.4	Qua., N.	3.17*	12.5
Angular gyrus	Lin., P.	0.37	>17.0	Lin., P.	7.55*	>17.0	Lin., P.	3.77	>18.4	Lin., P.	4.63*	>18.4
Precuneus	Lin., N.	0.52	<5.6	Cub., P.	1.01	7.5	Lin., N.	2.66	<5.8	Lin., N.	4.01*	<5.8
Posterior cingulate cortex	Cub., P.	1.80	6.9	Qua., P.	0.74	<5.6	Lin., N.	14.15**	<5.8	Lin., N.	8.47*	<5.8
Superior temporal gyrus	Lin., P.	9.38*	>17.0	Qua., N.	2.97	13.3	Cub., P.	2.06	11.3	Cub., P.	4.00*	11.1
Middle temporal gyrus	Cub., P.	5.41*	>17.0	Lin., P.	12.98*	>17.0	Cub., P.	8.11*	>18.4	Cub., P.	5.44**	>18.4
Inferior temporal gyrus	Lin., P.	16.22**	>17.0	Lin., P.	22.85**	>17.0	Lin., P.	19.81**	>18.4	Cub., P.	6.27**	>18.4
Fusiform gyrus	Lin., P.	6.51*	>17.0	Lin., P.	8.69*	>17.0	Lin., P.	7.68*	>18.4	Cub., P.	3.54*	>18.4
Lingual gyrus	Lin., P.	5.41*	>17.0	Lin., P.	6.07*	>17.0	Lin., P.	2.17	>18.4	Qua., N.	2.66	13.0
Parahippocampal gyrus	Lin., P.	9.26*	>17.0	Lin., P.	7.97*	>17.0	Cub., P.	6.55**	>18.4	Cub., P.	4.14*	>18.4
Hippocampus	Lin., P.	13.67**	>17.0	Lin., P.	19.24**	>17.0	Cub., P.	9.31**	>18.4	Lin., P.	21.46**	>18.4
Uncus	Lin., P.	20.81**	>17.0	Lin., P.	15.73**	>17.0	Lin., P.	30.21**	>18.4	Cub., P.	7.25**	>18.4
Superior occipital gyrus	Lin., P.	3.79	>17.0	Cub., P.	2.77*	>17.0	Lin., P.	8.48*	>18.4	Lin., P.	8.25*	>18.4
Middle occipital gyrus	Lin., P.	6.48*	>17.0	Qua., P.	4.51*	>17.0	Lin., P.	8.79*	>18.4	Lin., P.	7.12*	>18.4
Inferior occipital gyrus	Lin., P.	13.27**	>17.0	Lin., P.	18.50**	>17.0	Lin., P.	10.99**	>18.4	Qua., N.	5.51*	14.8
Cuneus	Cub., P.	2.20	>17.0	Qua., P.	3.82*	>17.0	Lin., P.	2.60	>18.4	Lin., P.	1.25	>18.4
Caudate nucleus	Cub., P.	1.68	10.7	Lin., P.	2.38	>17.0	Cub., P.	2.39	10.3	Cub., P.	1.58	>18.4
Thalamus	Qua., N.	4.79*	14.2	Lin., P.	6.88*	>17.0	Cub., P.	1.55	>18.4	Cub., P.	1.47	>18.4
Insula	Lin., P.	0.00	<5.6	Cub., P.	0.86	9.0	Cub., P.	1.79	10.2	Lin., P.	0.02	>18.4
Cerebellum (Anterior lobe)	Cub., P.	2.23	>17.0	Lin., P.	5.05*	>17.0	Qua., N.	4.61*	14.8	Qua., N.	6.61*	16.3
Cerebellum (Posterior lobe)	Qua., N.	22.50**	15.8	Qua., N.	20.71**	16.9	Qua., N.	28.07**	16.7	Qua., N.	29.62**	17.3

Lin, linear; Qua, means quadratic; Cub, cubic; P, positive correlation; N, negative correlation.

^aBest fit model of the correlation between age and gray matter volume determined using the Akaike information criterion.

* $P < 0.05$; ** $P < 0.0015$. Bonferroni critical $\alpha = 0.0015$.

TABLE III. Trajectory of regional gray matter density with age in each ROI

Region	Boys						Girls					
	Left			Right			Left			Right		
	Function ^a	F	Peak age	Function ^a	F	Peak age	Function ^a	F	Peak age	Function ^a	F	Peak age
Medial superior frontal gyrus	Lin., N.	15.55**	<5.6	Lin., N.	17.78**	<5.6	Lin., N.	7.33*	<5.8	Lin., N.	16.92**	<5.8
Superior frontal gyrus	Qua., P.	1.51	<5.6	Lin., N.	0.43	<5.6	Lin., P.	0.41	>18.4	Qua., N.	0.59	11.3
Middle frontal gyrus	Qua., P.	0.98	<5.6	Cub., P.	1.67	<5.6	Lin., N.	0.35	<5.8	Qua., N.	1.74	9.5
Inferior frontal gyrus	Cub., P.	6.80**	7.9	Qua., N.	6.05*	9.7	Lin., N.	13.28**	<5.8	Qua., N.	8.99**	9.3
Anterior cingulate cortex	Lin., N.	26.38**	<5.6	Lin., N.	21.50**	<5.6	Lin., N.	6.88*	<5.8	Lin., N.	5.30*	<5.8
Cingulate gyrus	Lin., N.	42.81**	<5.6	Lin., N.	46.28**	<5.6	Cub., P.	23.60**	7.1	Lin., N.	34.79**	<5.8
Precentral gyrus	Lin., P.	4.15*	>17.0	Qua., N.	1.38	12.9	Lin., P.	14.38**	>18.4	Cub., P.	1.81	14.4
Orbital gyrus	Cub., P.	4.15*	8.6	Cub., P.	2.43	8.5	Cub., P.	1.56	8.9	Lin., N.	6.20*	<5.8
Rectal gyrus	Cub., P.	11.68**	7.4	Cub., P.	9.13**	6.9	Qua., P.	27.28**	<5.8	Qua., P.	21.48**	<5.8
Postcentral gyrus	Qua., P.	2.90	<5.6	Lin., N.	11.35**	<5.6	Lin., N.	0.11	<5.8	Cub., N.	1.37	<5.8
Paracentral lobule	Qua., P.	3.51	<5.6	Qua., P.	4.14*	<5.6	Qua., P.	9.44**	<5.8	Qua., P.	12.67**	<5.8
Superior parietal lobule	Qua., P.	2.71	<5.6	Qua., P.	3.44*	<5.6	Qua., P.	2.77	<5.8	Lin., N.	0.60	<5.8
Inferior parietal lobule	Lin., N.	3.16	<5.6	Cub., P.	3.17*	<5.6	Lin., N.	5.05*	<5.8	Qua., N.	2.25	9.5
Supramarginal gyrus	Lin., N.	4.99*	<5.6	Qua., N.	3.78*	7.6	Lin., N.	0.54	<5.8	Qua., N.	4.60*	10.1
Angular gyrus	Qua., P.	4.01*	<5.6	Qua., N.	2.75	10.8	Lin., N.	1.70	<5.8	Qua., N.	1.73	10.8
Precuneus	Lin., N.	36.93**	<5.6	Qua., P.	23.48**	<5.6	Qua., P.	21.34**	<5.8	Lin., N.	50.64**	<5.8
Posterior cingulate cortex	Cub., P.	29.62**	7.5	Cub., P.	13.49**	6.9	Lin., N.	122.49**	<5.8	Lin., N.	117.86**	<5.8
Superior temporal gyrus	Cub., P.	7.75**	8.5	Cub., P.	16.34**	8.7	Qua., N.	21.09**	6.8	Cub., P.	22.25**	9.3
Middle temporal gyrus	Cub., P.	5.78**	9.1	Qua., N.	5.09*	10.7	Qua., N.	9.57**	8.8	Qua., N.	11.80**	11.1
Inferior temporal gyrus	Cub., P.	3.39*	>17.0	Cub., P.	3.26*	>17.0	Qua., N.	1.90	11.0	Qua., N.	6.57*	10.5
Fusiform gyrus	Cub., P.	2.23	8.6	Cub., P.	7.69**	8.6	Lin., N.	9.98*	<5.8	Cub., P.	6.68**	8.4
Lingual gyrus	Cub., P.	4.47*	9.0	Cub., P.	5.83**	7.9	Lin., N.	23.45**	<5.8	Lin., N.	22.73**	<5.8
Parahippocampal gyrus	Qua., N.	1.87	9.1	Lin., N.	5.77*	<5.6	Qua., N.	2.41	10.2	Qua., N.	7.62**	6.9
Hippocampus	Lin., P.	0.10	>17.0	Lin., P.	2.45	>17.0	Lin., P.	0.65	>18.4	Qua., N.	1.02	13.0
Uncus	Lin., N.	0.76	<5.6	Cub., P.	2.87*	7.6	Lin., N.	3.91*	<5.8	Cub., P.	7.61**	7.3
Superior occipital gyrus	Qua., N.	0.81	11.6	Lin., N.	1.37	<5.6	Lin., N.	2.25	<5.8	Cub., N.	2.16	<5.8
Middle occipital gyrus	Lin., N.	7.51*	<5.6	Lin., N.	1.62	<5.6	Lin., N.	1.96	<5.8	Qua., N.	0.81	11.2
Inferior occipital gyrus	Lin., P.	1.75	>17.0	Cub., P.	1.94	>17.0	Qua., N.	1.12	13.6	Qua., N.	3.54*	11.7
Cuneus	Lin., N.	7.02*	<5.6	Cub., P.	2.89*	7.8	Cub., P.	3.50*	<5.8	Lin., N.	13.94**	<5.8
Caudate nucleus	Lin., N.	0.20	<5.6	Cub., P.	1.41	<5.6	Lin., N.	10.79**	<5.8	Lin., N.	4.55*	<5.8
Thalamus	Qua., N.	0.59	10.6	Lin., P.	0.29	>17.0	Lin., N.	18.84**	<5.8	Lin., N.	15.23**	<5.8
Insula	Lin., N.	74.50**	<5.6	Cub., P.	18.59**	7.7	Lin., N.	24.40**	<5.8	Qua., N.	23.05**	5.8
Cerebellum (Anterior lobe)	Cub., P.	6.43**	8.8	Cub., P.	6.37**	8.6	Lin., N.	24.87**	<5.8	Lin., N.	19.72**	<5.8
Cerebellum (Posterior lobe)	Qua., N.	7.18**	10.6	Qua., N.	4.70*	10.6	Qua., N.	4.77*	8.9	Qua., N.	1.76	10.5

Lin, linear; Qua, quadratic; Cub, cubic; P, positive correlation; N, negative correlation.

^aBest fit model of the correlation between age and gray matter density determined using the Akaike information criterion.
* $P < 0.05$; ** $P < 0.0015$. Bonferroni critical $\alpha = 0.0015$.

Paus, 2005]. Additionally, the post-adolescent decrease in the number of synapses per neuron and intracranial myelination is thought to be observable as a decrease in gray matter volume [Sowell et al., 2001]. Therefore, in regions where gray matter volume increases with age but where gray matter density does not significantly change, the increase in gray matter volume may be due to an increase in the number of synapses per neuron; a similar increase in the white matter volume due to myelination occurs simultaneously in these regions. On the other hand, several regions, such as the medial and basal aspects of the frontal lobe, showed a significant negative correlation with age, whereas no correlation was found between gray matter volume and age. These results suggest that relative gray matter volume in the region decreases with age due to the increase of white matter volume, but that actual gray matter volume in the region does not change significantly, even though a pre-adolescent increase or post-adolescent decrease in the number of synapses per neuron may occur in these regions. Thus, by focusing on both gray matter volume and gray matter density, we can estimate maturational changes in gray matter volume in each region more clearly than when focusing on just one of these factors.

We found several regions that showed significant correlations between gray matter volume and age and between gray matter density and age. For example, in the frontal lobe, the lateral aspect of the frontal lobe showed a significant positive correlation between gray matter volume and age, whereas the medial and basal aspects of the frontal lobe showed significant negative correlations between gray matter density and age. A positive correlation between gray matter volume and age indicates a progressive increase in the number and size of neurons and glia, the level of synaptic bulk, and the number of neurites [Draganski et al., 2004; May et al., 2007], whereas a negative correlation between gray matter density and age indicates an increase in white matter volume, compared with gray matter volume, in a given region. Because brain gray matter maturation progresses with an increase of volume followed by a decrease of volume [Courchesne et al., 2000; Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008], regions that show a negative correlation between gray matter density and age are thought to mature earlier than regions that show a positive correlation. Several studies have indicated that lateral aspects of the frontal lobe such as the middle frontal gyrus are involved in higher cognitive functions such as working memory [Baddeley, 2003; Klingberg, 2006] and executive function [Kramer et al., 2007; Zimmerman et al., 2006] and that brain regions involved in basic functions mature first, followed by regions involved in higher cognitive functions [Ardila, 2008]. Our results are consistent with these studies. In the parietal cortex, the posterior cingulate cortex and the precuneus showed significant correlations with age with a decreasing trend by linear negative, quadratic positive, or cubic positive functions. Several studies have shown that the limbic system, which includes the

posterior cingulate cortex, matures earlier than associated cortices such as the lateral parietal cortex [Sowell et al., 1999; Thompson et al., 2001; Whitford et al., 2007]. As described above, gray matter regions whose gray matter density show significant correlations with age in a decreasing trajectory are thought to mature earlier than other regions. Therefore, our results are consistent with these studies. In the hippocampus, a significant positive correlation was found between gray matter volume and age. This result is consistent with recent studies showing that hippocampal volume increases in adolescence and young adulthood [Guo et al., 2007; Ostby et al., 2009b]. In deep gray matter regions such as the caudate nucleus and thalamus, no significant correlation was observed between gray matter volume and age, again consistent with recent studies [Ostby et al., 2009b]. Thus, our results derived from VBM and ROI analysis with AIC are consistent with the aforementioned studies regarding brain maturation in children and suggest that focusing on correlations between both gray matter volume and age and between gray matter density and age is a valuable means of revealing gray matter maturation in children.

The age range of the subjects is thought to be an important factor for determining the best-fit function of the correlation of gray matter volume and density with age because gray matter volume has been found to show an inverted-U-shaped followed by a U-shaped curvilinear trajectory and then to stabilize in neuroimaging studies of children [Courchesne et al., 2000; Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008] and in post-mortem studies [Huttenlocher, 1979; Huttenlocher et al., 1982, 1997] due to a pre-adolescent increase followed by a post-adolescent decrease in the number of synapses per neuron and intracortical myelination occurring during brain maturation [Huttenlocher, 1979; Huttenlocher et al., 1982, 1997; Paus, 2005]. Therefore, if the age range of subjects is widened from early childhood to at least young adulthood, most gray matter regions show a cubic trajectory with age, as shown in a recent study [Shaw et al., 2008]. If we set a narrower age range, some gray matter regions show a linear trajectory, while others show quadratic or cubic functions according to the progress of maturational change. However, by restricting the age range to childhood, it is thought to be possible to highlight the progress of brain maturation by revealing the differences in the best-fit functions of the correlations between gray matter volume and age and between gray matter density and age [Colby et al., 2011]. In addition, using the VBM with AIC, as in this study, one can estimate which higher order polynomial function is the best-fit model and whether a significant correlation of age with gray matter volume or density exists independent of age range. Therefore, the VBM with AIC method used in this study is thought to be useful to estimate best-fit correlational models using higher order polynomial functions.

This study has some limitations. First, it was a cross-sectional study; that is, we showed the relationship

between gray matter volume and age and between gray matter density and age, but not the relationship over time. Thus, we are planning to perform a longitudinal analysis to examine the correlation between gray matter volume and age and between gray matter density and age. Second, we did not analyze the effect of gender or hemisphere on the maturational trajectory of gray matter volume or density because neither was a primary focus of this study. However, the effects of gender and hemisphere on the maturational trajectory of gray matter volume are also important in understanding gray matter maturation. Thus, we showed the correlation between gray matter volume, density, and age in each gender and in each hemisphere. Third, we collected MRIs for 1 year and 9 months. However, we did not measure scanner distortion or scanner drift. Thus, although the MR scanner we used has been regularly maintained, we cannot exclude the possibility that scanner drift or distortion may have affected the MRIs. Fourth, the correlations between gray matter volume and age in the common stereotactic space are believed to vary due to adjustments for the individual differences in intracranial volume or in total brain volume. Because we focused on the correlation between actual gray matter volume, the proportion of gray matter relative to all tissue types within a region (i.e., gray matter density), and age, we did not adjust for intracranial volume in our analyses. Therefore, the issue of adjustment should be taken into consideration when comparing the results of this study with those of similar studies.

In conclusion, we demonstrated linear and curvilinear correlations between gray matter volume and age in the cortical and subcortical gray matter using MRI in 291 healthy children aged 5–18 years, applying VBM and ROI analyses with AIC. We found that several regions, such as the lateral frontal cortex, precentral gyrus, and cerebellum, showed significant linear or curvilinear correlations between gray matter volume and age with an increasing trajectory. We also identified several regions, such as the medial aspect of the frontal cortex, that showed significant linear or curvilinear correlations between gray matter density and age with a decreasing trajectory in VBM and ROI analyses with AIC. We also estimated peak age of the gray matter volume or density in each region. Because the shapes of gray matter volume and density trajectories with age suggest brain maturation, our study may help in clarifying the mechanisms of normal brain maturation from the viewpoint of brain gray matter volume and enable a distinction between normal trajectories of gray matter volume and abnormal trajectories indicative of developmental disorders.

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REFERENCES

- Akaike H (1974): A new look at statistical model identification. *IEEE Trans Automatic Control* 19:716–723.
- Ardila A (2008): On the evolutionary origins of executive functions. *Brain Cogn* 68:92–99.
- Ashburner J (2007): A fast diffeomorphic image registration algorithm. *Neuroimage* 38:95–113.
- Ashburner J, Friston KJ (2000): Voxel-based morphometry—The methods. *Neuroimage* 11:805–821.
- Ashburner J, Friston KJ (2005): Unified segmentation. *Neuroimage* 26:839–851.
- Ashburner J, Friston KJ (2009): Computing average shaped tissue probability templates. *Neuroimage* 45:333–341.
- Azuma H, Ueno K, Fujita K, Maekawa H, Ishikuma T, Sano H (1998): Japanese Wechsler Intelligence Scale for Children, 3rd ed. Tokyo: Nihon Bunka Kagakusha.
- Baddeley A (2003): Working memory: Looking back and looking forward. *Nat Rev Neurosci* 4:829–839.
- Bergouignan L, Chupin M, Czechowska Y, Kinkingnehun S, Lemogne C, Le Bastard G, Lepage M, Garnero L, Colliot O, Fossati P (2009): Can voxel based morphometry, manual segmentation and automated segmentation equally detect hippocampal volume differences in acute depression? *Neuroimage* 45:29–37.
- Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, Barthelemy C, Mouren MC, Artiges E, Samson Y, Brunelle F, Frackowiak RS, Zilbovicius M (2004): Superior temporal sulcus anatomical abnormalities in childhood autism: A voxel-based morphometry MRI study. *Neuroimage* 23:364–369.
- Bonilha L, Cendes F, Rorden C, Eckert M, Dalgalarrondo P, Li LM, Steiner CE (2008): Gray and white matter imbalance—Typical structural abnormality underlying classic autism? *Brain Dev* 30:396–401.
- Colby JB, Van Horn JD, Sowell ER (2011): Quantitative in vivo evidence for broad regional gradients in the timing of white matter maturation during adolescence. *Neuroimage* 54:25–31.
- Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, Harwood M, Hinds S, Press GA (2000): Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology* 216:672–682.
- Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A (2004): Neuroplasticity: Changes in gray matter induced by training. *Nature* 427:311–312.
- Fujita K, Maekawa H, Dairoku H, Yamanaka K (2006): Japanese Wechsler Adult Intelligence Scale, 3rd ed. Tokyo: Nihon Bunka Kagakusha.
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL (1999): Brain development during childhood and adolescence: A longitudinal MRI study. *Nat Neurosci* 2:861–863.
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF III, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM (2004): Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA* 101:8174–8179.
- Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ (2001): A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21–36.
- Guo X, Chen C, Chen K, Jin Z, Peng D, Yao L (2007): Brain development in Chinese children and adolescents: A structural MRI study. *Neuroreport* 18:875–880.

- Huttenlocher PR (1979): Synaptic density in human frontal cortex—Developmental changes and effects of aging. *Brain Res* 163:195–205.
- Huttenlocher PR, Dabholkar AS (1997): Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol* 387:167–178.
- Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H (1982): Synaptogenesis in human visual cortex—Evidence for synapse elimination during normal development. *Neurosci Lett* 33:247–252.
- Jernigan TL, Press GA, Hesselink JR (1990a): Methods for measuring brain morphologic features on magnetic resonance images. Validation and normal aging. *Arch Neurol* 47:27–32.
- Jernigan TL, Tallal P (1990b): Late childhood changes in brain morphology observable with MRI. *Dev Med Child Neurol* 32:379–385.
- Jernigan TL, Trauner DA, Hesselink JR, Tallal PA (1991): Maturation of human cerebrum observed in vivo during adolescence. *Brain* 114:2037–2049.
- Jiao Y, Chen R, Ke X, Chu K, Lu Z, Herskovits EH (2010): Predictive models of autism spectrum disorder based on brain regional cortical thickness. *Neuroimage* 50:589–599.
- Johnson MH (2001): Functional brain development in humans. *Nat Rev Neurosci* 2:475–483.
- Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, Christensen GE, Collins DL, Gee J, Hellier P, Song JH, Jenkinson M, Lepage C, Rueckert D, Thompson P, Vercauteren T, Woods RP, Mann JJ, Parsey RV (2009): Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage* 46:786–802.
- Klingberg T (2006): Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsychologia* 44:2171–2177.
- Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, Weiner MW, Chui HC (2007): Longitudinal MRI and cognitive change in healthy elderly. *Neuropsychology* 21:412–418.
- Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000): Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 10:120–131.
- Langen M, Schnack HG, Nederveen H, Bos D, Lahuis BE, de Jonge MV, van Engeland H, Durston S (2009): Changes in the developmental trajectories of striatum in autism. *Biol Psychiatry* 66:327–333.
- Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zijdenbos AP, Evans AC, Thompson PM, Giedd JN (2007): Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage* 36:1065–1073.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19:1233–1239.
- May A, Hajak G, Ganssbauer S, Steffens T, Langguth B, Kleinjung T, Eichhammer P (2007): Structural brain alterations following 5 days of intervention: Dynamic aspects of neuroplasticity. *Cereb Cortex* 17:205–210.
- Mechelli A, Price CJ, Friston KJ, Ashburner J (2005): Voxel-based morphometry of the human brain: Methods and applications. *Curr Med Imaging Rev* 1:105–113.
- Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB (2009a): Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *J Neurosci* 29:11772–11782.
- Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB (2009b): Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *J Neurosci* 29:11772–11782.
- Paus T (2005): Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci* 9:60–68.
- Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994): A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol* 51:874–887.
- Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Greenstein D, Clasen L, Evans A, Rapoport JL, Giedd JN, Wise SP (2008): Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci* 28:3586–3594.
- Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999): Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587–597.
- Sowell ER, Thompson PM, Tessner KD, Toga AW (2001): Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *J Neurosci* 21:8819–8829.
- Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003): Mapping cortical change across the human life span. *Nat Neurosci* 6:309–315.
- Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB (2010): Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cereb Cortex* 20:534–548.
- Thatcher RW (1992): Cyclic cortical reorganization during early childhood. *Brain Cogn* 20:24–50.
- Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Toga AW, Rapoport JL (2001): Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci USA* 98:11650–11655.
- Whitford TJ, Rennie CJ, Grieve SM, Clark CR, Gordon E, Williams LM (2007): Brain maturation in adolescence: Concurrent changes in neuroanatomy and neurophysiology. *Hum Brain Mapp* 28:228–237.
- Wilke M, Krageloh-Mann I, Holland SK (2007): Global and local development of gray and white matter volume in normal children and adolescents. *Exp Brain Res* 178:296–307.
- Zimmerman ME, Brickman AM, Paul RH, Grieve SM, Tate DF, Gunstad J, Cohen RA, Aloia MS, Williams LM, Clark CR, Whitford TJ, Gordon E (2006): The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am J Geriatr Psychiatry* 14:823–833.