Heritability of Volumetric Brain Changes and Height in Children Entering Puberty

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Abstract: The human brain undergoes structural changes in children entering puberty, while simultaneously children increase in height. It is not known if brain changes are under genetic control, and whether they are related to genetic factors influencing the amount of overall increase in height. Twins underwent magnetic resonance imaging brain scans at age 9 ($N = 190$) and 12 ($N = 125$). High heritability estimates were found at both ages for height and brain volumes (49–96%), and high genetic correlation between ages were observed ($r_g > 0.89$). With increasing age, whole brain (+1.1%), cerebellum (+4.2%), cerebral white matter (+5.1%), and lateral ventricle (+9.4%) volumes increased, and third ventricle (−4.0%) and cerebral gray matter (−1.6%) volumes decreased. Children increased on average 13.8 cm in height (9.9%). Genetic influences on individual difference in volumetric brain and height changes were estimated, both within and across traits. The same genetic factors influenced both cerebral (20% heritable) and cerebellar volumetric changes (45%). Thus, the extent to which changes in cerebral and cerebellar volumes are heritable in children entering puberty are due to the same genes that influence change in both structures. The increase in height was heritable (73%), and not associated with cerebral volumetric change, but positively associated with cerebellar volume change ($r_p = 0.24$). This association was explained by a genetic correlation ($r_g = 0.48$) between height and cerebellar change. Brain and body each expand at their own pace and through separate genetic pathways. There are distinct genetic processes acting on structural brain development, which cannot be explained by genetic increase in height. *Hum Brain Mapp 34:713–725, 2013.* © 2011 Wiley Periodicals, Inc.

Key words: human brain; longitudinal twin study; heritability; MRI; development; height

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INTRODUCTION

The development of children entering puberty is characterized by considerable structural brain changes (Giedd et al., 1999), and a rapid increase in height (Tanner, 1962; Tanner and Whitehouse, 1976). From young childhood up to puberty and adulthood, complex, nonlinear, and region-specific structural changes occur in the human brain (Giedd et al., 1999). White matter tissue increases in volume, whereas gray matter tissue volume increases in young childhood and after peaking around puberty starts to decrease (Giedd et al., 1999; Lenroot et al., 2007; Paus, 2005; Sowell et al., 2002). These changes in structural brain development are of functional significance in healthy children (Shaw et al., 2006). Deviant brain developmental changes are associated with developmental brain disorders (Arango et al., 2008; Courchesne et al., 2011; Gogtay et al., 2002; Shaw et al., 2010; Wallace et al., 2010). The increase in the incidence of psychopathologies emerging during and right after puberty (Kessler et al., 2007; Paus et al., 2008) suggest a possible causal relationship with aberrant brain structure changes that occur in this period.

Genetic factors largely determine height in adulthood (Baare et al., 2001; Silventoinen et al., 2003), and in childhood (Silventoinen et al., 2007). This also holds for whole brain volumes which are to a high level heritable in adults (Baare et al., 2001; Kremen et al., 2010; Peper et al., 2007), as well as in children and adolescents (Peper et al., 2009; Schmitt et al., 2007a; Schmitt et al., 2007b; Wallace et al., 2006; Yoon et al., 2010). Moreover, we recently found that changes in brain structures were heritable in healthy adults (Brans et al., 2010) and in adults with schizophrenia (Brans et al., 2008). It is not known to what extent genetic factors influence brain changes during the period from childhood to adolescence, where probably different processes underlie structural brain changes compared to adulthood.

In this study, we address the question whether brain volume changes are a reflection of the strong increase in height, that occurs in children at the beginning of puberty (Tanner, 1962; Tanner and Whitehouse, 1976), or whether they reflect a different process, controlled by other genes. We studied the extent to which genes influence volumetric brain changes and increase in height in childhood and early adolescence. Furthermore, we explored whether the genetic influences acting on brain changes were overlapping with the genetic influences acting on increase in height in children entering puberty.

MATERIALS AND METHODS

Subjects

Twin families were recruited from the Netherlands Twin Register (Boomsma et al., 2006), and were an epidemiologically representative sample of the Dutch population. The children were invited to participate in a large longitudinal twin study to explore the genetic and environmental influences on brain maturation (see for more details of the study; van Leeuwen et al., 2008; Peper et al., 2009). Exclusion criteria for participation included having a pacemaker, any metal materials in the head (including dental braces), chronic use of medication, a known major medical or psychiatric history, and participation in special education.

At baseline, data on height were available for 218 twins, and 208 twins completed the structural scan procedure at the same day at the University Medical Center Utrecht (UMCU), The Netherlands. Response rate at follow-up was nearly 80%, resulting in 173 twins with available data on height. At follow-up, 136 twins completed the structural scan procedure at the UMCU. The major cause for missing scans at the follow-up was the higher prevalence of metal braces. Mean (SD) full scale IQ of the complete sample was 99.9 (13.5) at age 9, and 100.3 (14.1) at 12, illustrating that the sample was representative of the general population (van Soelen et al., 2011).

Secondary sexual characteristics of puberty, i.e., breast development in girls and penis development in boys, were determined by a trained researcher according Tanner criteria (Marshall and Tanner, 1969, 1970). At baseline, 6% of the boys and 18% of the girls showed first stages of puberty (i.e., Tanner stage ≥ 2). At follow-up, 56% of the boys and 68% of the girls showed development of secondary sexual characteristics, and within these groups the girls were more progressed in puberty stage than the boys [mean (SD) Tanner stage girls was 2.9 (1.1); boys was 2.1 (0.9)].

After exclusions based on scan quality, 190 scans at baseline and 125 scans at follow-up could be included for further image processing. Mean age at the moment of scan at baseline was 9.2 (SD = 0.1; range = 9.0–9.7) years, and at follow-up 12.1 (SD = 0.3; range = 11.7–13.1) years old. In total, 113 children had scans available at both measurements. Mean interval time between the two measurements was 2.9 (SD = 0.2; range = 2.5–3.5) years.

Zygosity of the same-sex twin pairs was determined based on DNA polymorphisms. At baseline the sample with available magnetic resonance imaging (MRI) and height data consisted of 82 (39 male/43 female) monozygotic (MZ) twins (38 complete twin pairs; 17 male/21 female), 75 (38 male/37 female) same-sex dizygotic (DZ) twins (32 complete twin pairs; 16 male/16 female), and 33 opposite-sex DZ twins (14 complete twin pairs). At follow-up, the sample consisted of 56 (30 male/26 female) MZ twins (23 complete twin pairs; 13 male/10 female), 45 (23 male/22 female) same-sex DZ twins (18 complete pairs; 8 male/10 female), and 24 opposite-sex twins (10 complete pairs). Handedness was determined based on Edinburgh Handedness Inventory (Oldfield, 1971). Parents and the children themselves gave written informed consent to participate in this study.

Image Acquisition

All structural MRI was performed on a 1.5-T Philips Achieva scanner on both measurements. To limit possible effects of scanner instability over time, the same scan

parameters as well as image processing procedures were used at both baseline and follow-up. All children underwent a practice session in a dummy scanner to get familiarized with the scan procedure, small space and the sounds of the MRI machine (Durston et al., 2009). At both baseline and follow-up image-sequences of the whole head were acquired, including a short scout scan for immediate verification of optimal head positioning, and a clinical scan that was used for neurodiagnostic evaluation. A three-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256 × 256 matrix, Echo Time (TE) = 4.6 ms, Repetition Time (TR) = 30 ms, flip angle = 30°, 160–180 contiguous slices; 1 × 1 × 1.2 mm^3 voxels, field-of-view (FOV) = 256 mm/70%) was acquired for volumetric analysis. Additionally, a Diffusion Tensor Imaging (DTI)-B0 (transverse; 15–64 directions; Sensitivity Encoding (SENSE) factor 2.5, *b*-factor 1,000; flip angle 90°; 60 slices of 2.5 mm; slice gap 0; 128 × 96 acquisition matrix; FOV = 240 mm; TE = 78 ms) and a Magnetic Transfer Imaging (MTI) (transverse; Magnetization Transfer Contrast (MTC) frequency offset 1,100 Hz; 60 slices of 2.5 mm; slice gap 0; 128 × 96 acquisition matrix; FOV 240 mm; flip angle 8°; TE = 4.5 ms; TR = 37.5 ms) were acquired at both baseline and follow-up (as previously described in Peper et al., 2008). At follow-up, a T2-weighted image was added to the scan protocol for optimization of image processing as described below (transverse, parallel imaging, SENSE factor 2, TE1 = 15 ms, TE2 = 80 ms, TR = 6,000 ms, flip angle = 90°, 120 slices of 1.6 mm, slice gap 0.0 mm, FOV = 250 mm/80%).

Image Processing

All image processing steps were conducted at the UMCU. Scans were put into Talairach frame (no scaling), and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Quantitative assessment of intracranial volume (IC) of the first measurement was based on the DTI-BT0 and MTI images as described earlier (Peper et al., 2008). The IC segments for follow-up were created from the baseline IC segments using nonlinearly transformations. The T1-weighted images of the baseline measurements were nonlinearly warped onto the follow-up measurement up to a scale of 1.2-mm full-width-at-half-maximum by a combination of nonlinear warpings with increasing precision (Collins et al., 1995). This transformation was subsequently applied to the baseline intracranial mask. When no IC segment was available from baseline, the T2-weighted image at follow-up was used to create an IC segment ($N = 10$). For one participant, no scan data at baseline and no T2-weighted scan at follow-up were available, and therefore, the same method as described for the baseline measurement was used (DTI-BT0 and MTR) to create an IC segment for the follow-up measurement. All IC segments at baseline and follow-up were checked and edited where necessary. Total brain, and gray and white matter were segmented using a partial volume segmentation method incorporating a nonuniform partial volume distribution (Brouwer et al., 2010). Cerebellar, lateral ventricles, and third ventricle volumes were assessed (Schnack et al., 2001), and these segments were visually checked and edited where necessary. For one individual, lateral ventricles and third ventricle volumes could not be segmented reliably at baseline.

Genetic Analyses

MZ twin pairs are genetically identical and share (nearly) 100% of their genetic material, while DZ twin pairs and full siblings share on average 50% of their segregating genes. By comparing the MZ and DZ covariance structures on a specific phenotype, one can estimate the relative influences of genes and environment on variation of that phenotype (Boomsma et al., 2002). Additive genetic influences (A) represent the influences on the phenotype of multiple alleles at different loci on the genome that act additively. The proportion of the observed variance in a trait that can be attributed to genetic factors is termed heritability. Common environmental influences (C) include all environmental sources of variance that make twins who grow up within the same family resemble each other. Environmental influences that are unique to an individual and not shared with other family members are referred to as unique environmental influences (E), and also included measurement error (Falconer and Mackay, 1996).

If phenotypic variance is influenced by genetic factors, MZ twins will resemble each other more than the DZ twins. If MZ twin resemblance is twice as high as DZ twin resemblance, additive genetic influences are of importance. However, when DZ resemblance is higher than half MZ resemblance, both genetic and common environmental influences are contributing to the phenotypic variance. Finally, when DZ and MZ resemblance is equal, then only common environment can explain twin resemblance (Boomsma et al., 2002; Plomin et al., 2001).

Longitudinal Genetic Modeling

With longitudinal data it is possible to determine to what extent the covariance of a specific trait across time is due to correlated genetic and environmental effects. Differences in the cross-twin/cross-time correlation between MZ and DZ twin pairs contain information about the etiology of this association over time. Larger MZ cross-correlations between time points (twin 1 at baseline with twin 2 at follow-up and vice versa) compared to the DZ cross-correlations indicate that there is overlap between genetic factors at baseline and follow-up.

A longitudinal ACE model was fitted to the data (see Fig. 1). For detailed description of the path diagram see also van Soelen et al., (2011). The covariance between a phenotype (i.e., brain volume) at baseline and at follow-up is derived from multiplying the path coefficients that define the association between baseline and follow-up on

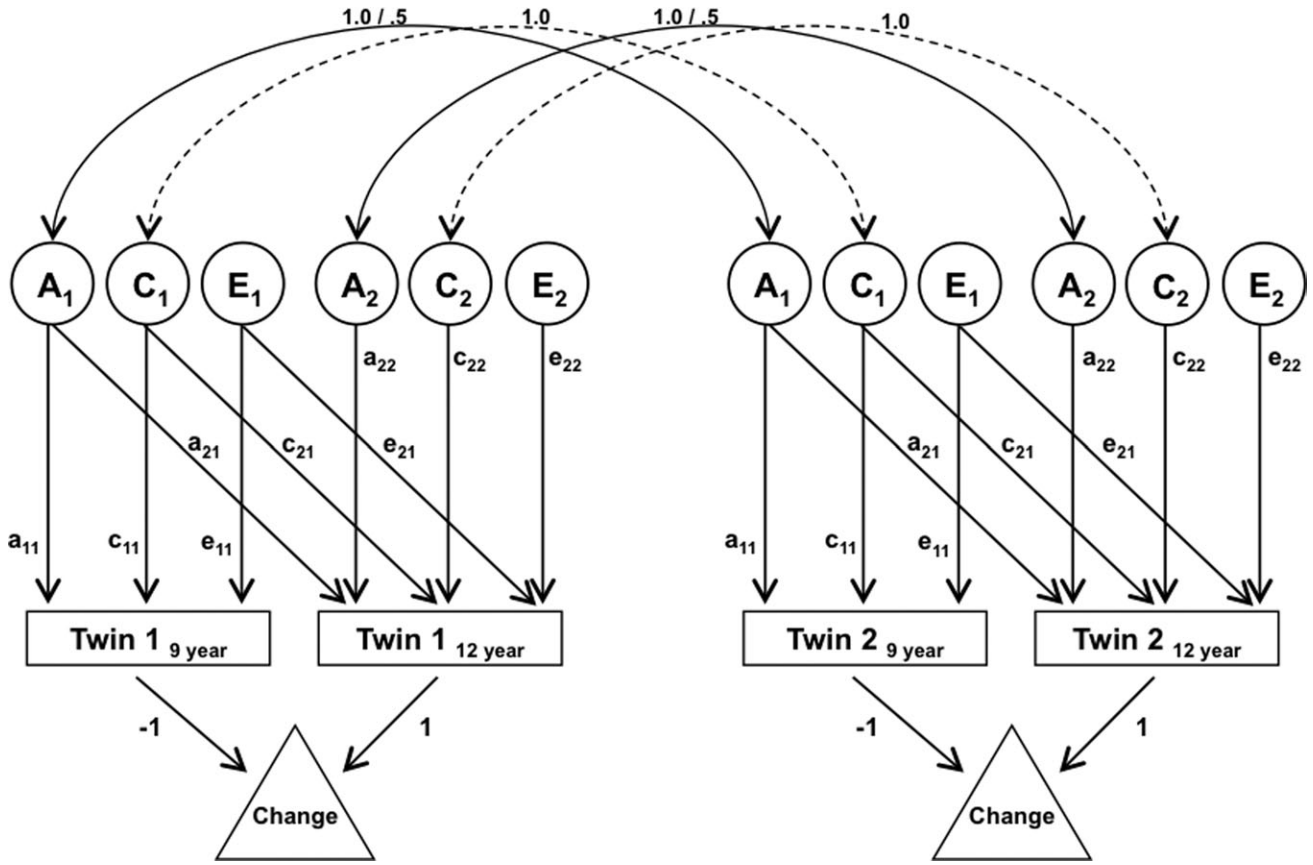

Figure 1.

Path diagram representing the longitudinal genetic model fitted to the data collected at age 9 and 12 years. Squares represent the observed phenotype of interest (e.g., height or brain volumes) in twin 1 and twin 2, and the circles represent latent, unobserved factors. A1, C1, and E1 influence the phenotype at age 9 and 12 years; A2, C2, and E2 influence the phenotype at age 12, but not at age of 9 years. Double headed arrows represent correlations between the genotypes of twins (1.0 for MZ and 0.5 for DZ pairs). The influence of the first set of latent factors on the phenotype at age 9 is represented by factor loadings (one headed arrows) a_{11}, c_{11}, e_{11} and at age 12 by a_{21}, c_{21}, and e_{21}. The second set of latent factors influence the phenotype at age 12 only, and is represented by the path coefficients a_{22}, c_{22}, and e_{22}. The triangle represents the developmental change for height or the different brain volumes.

that specific brain volume. The genetic covariance is given by $(a_{11} * a_{21})$, the common environmental covariance by $(c_{11} * c_{21})$, and the unique environmental covariance by $(e_{11} * e_{21})$. The total covariance is a summation of these three covariances, namely $(a_{11} * a_{21}) + (c_{11} * c_{21}) + (e_{11} * e_{21})$. The extent to which genetic factors influence brain volume at both baseline and follow-up can be calculated as the genetic correlation, $r_g = (a_{11} * a_{21})/\sqrt{[a_{11}^2 * (a_{21}^2 + a_{22}^2)]}$. In a similar way, the common environmental and unique environmental correlations can be obtained.

The longitudinal model included a calculation to gain insight into the contribution of genetic influences on individual differences in height or volumetric brain changes (see Fig. 1). The total variance on changes in height and brain volumes can be calculated by the following general formula; V change $= (a_{11}^2 + c_{11}^2 + e_{11}^2) + [(a_{21}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)] - 2 * [(a_{11} * a_{21}) + (c_{11} * c_{21}) + (e_{11} * e_{21})]$. The contribution of genetic influences on changes in height and brain volumes can be derived by $(a_{11}^2) + (a_{21}^2 + a_{22}^2) - [2 * (a_{11} * a_{21})]$. In a similar way, the contributions of common and unique environmental variance on changes in height and brain volumes can be calculated. Based on these formulas, genetic influences on change in height or brain volumes can only be present when there is either a change in effect size of the same genetic factors, the presence of different genetic factors that exert their influence at the different ages, or a combination of the above described genetic mechanisms (de Geus et al., 2007).

Genetic Influences on Changes in Height and Brain Volumes

For the brain volumes where significant heritability is found on volumetric change, it is of interest to explore to

TABLE I. Mean (SD) of age at moment of scan (years), height (cm), brain volumes (ml) at baseline (*N* = 190), follow-up (*N* = 125) and the differences between baseline and follow-up on height and brain volumes (*N* = 113) are given

			Changes over time		
	Baseline Mean (SD)	Follow-up Mean (SD)	Mean (SD)	Percentage change compared to baseline (%)	*P* value
Age at scan	9.2 (*0.1*)	12.1 (*0.3*)	2.9 (*0.2*)		
Height[a]	138.8 (*5.3*)	152.3 (*7.1*)	13.8 (*3.6*)	9.9	<0.01
Total brain	1,332.8 (*114.3*)	1,352.0 (*120.3*)	14.6 (*16.8*)	1.1	<0.01
Cerebrum	1,164.7 (*103.7*)	1,182.0 (*110.4*)	12.4 (*15.1*)	1.1	<0.01
Cerebrum GM	703.8 (*59.2*)	692.5 (*63.0*)	−11.4 (*18.4*)	−1.6	<0.01
Cerebrum WM	460.9 (*52.7*)	489.5 (*56.7*)	23.8 (*18.2*)	5.1	<0.01
Cerebellum	153.4 (*14.4*)	159.6 (*14.2*)	6.4 (*2.8*)	4.2	<0.01
Cerebellum GM	107.7 (*10.8*)	109.6 (*10.0*)	2.7 (*5.5*)	2.5	<0.01
Cerebellum WM	45.6 (*6.4*)	50.0 (*7.0*)	3.7 (*5.8*)	8.1	<0.01
Lateral ventricle	9.6 (*7.0*)[b]	10.8 (*7.8*)	0.9 (*0.9*)	9.4	<0.01
Third ventricle	0.65 (*0.30*)	0.65 (*0.30*)	−0.03 (*0.16*)	−4.0	<0.05

Height and volumetric brain changes were calculated as percentage change compared to baseline. Height and all brain volumes showed a significant within-subject volumetric change between baseline and follow-up (paired *t*-test), where *P* values are corrected for familial dependence by adjusting the degrees of freedom.
GM = gray matter, WM = white matter.
[a]Data on height were available from more children, total *N* baseline = 218, *N* follow-up = 173, *N* with two measurements = 173.
[b]For lateral ventricle volume at baseline is total number of scans is 189.

what extent the genetic and environmental influences are shared between different structures. In addition, it is of interest whether these genetic factors in turn show an overlap between the genetic influences acting on changes in height. Therefore, we performed additional genetic modeling on the change scores. Instead of studying cross-twin/cross-time correlations, as described above, we investigated cross-twin/cross-trait correlation, thereby modeling the covariance structure between two or more different phenotypes, i.e., change in height (cm), volumetric change in structure A, and in structure B (ml). The genetic correlations that can be derived by calculations as illustrated above now describe the overlap of genetic influences acting on change in height and brain volumes, or the overlap of genetic influences on volumetric changes between different brain volumes.

Statistical Analyses

Changes in height and brain volumes observed within subjects over time were tested for significance by using a paired *t*-test in Statistical Package for the Social Sciences (SPSS), where the degrees of freedom (df) were adjusted for familial dependency. Genetic analyses were carried out using structural equation modeling (SEM) using the software package Mx (Neale et al., 2006). All available data were analyzed, i.e., regardless whether subjects participated once or twice in the study. Parameters were estimated by maximum likelihood. This was done for each trait separately. For brain volumes, data were corrected for sex, age at scanning and handedness at baseline and follow-up. For height, data were corrected for sex and age only.

In the first series of analyses, differences by birth order or zygosity in means and variances where tested. Twin correlations for MZ and DZ twin pairs were estimated for height and all brain volumes at both baseline and follow-up. In the second series of analyses, a longitudinal genetic model was fitted to the data (see Fig. 1). Tests of significance of parameters were carried out by first estimating them and then constraining the estimates at zero (e.g., a_{11}, a_{21}, see Fig. 1). The goodness of fit of different models was evaluated by comparing the difference in log-likelihood. The difference between −2-log likelihood is chi-squared distributed with the df equal to the difference in the number of parameters estimated in two nested models.

RESULTS

In Table I, the means (SD) of age, height and the observed volumetric measures are given, as well as the means (SD) of changes in height and in brain volumes between baseline and follow-up. Height and all brain volumes were normally distributed at both assessments, with the exception of the lateral and third ventricle volumes. After log transformation, these volumes were normally distributed. Changes in height and brain volumes were all normally distributed.

Between baseline and follow-up, children showed differences in height and brain volumes (Table I). Height, total brain, cerebral, and total cerebellar volumes all showed a within subject increase. Children increased on average

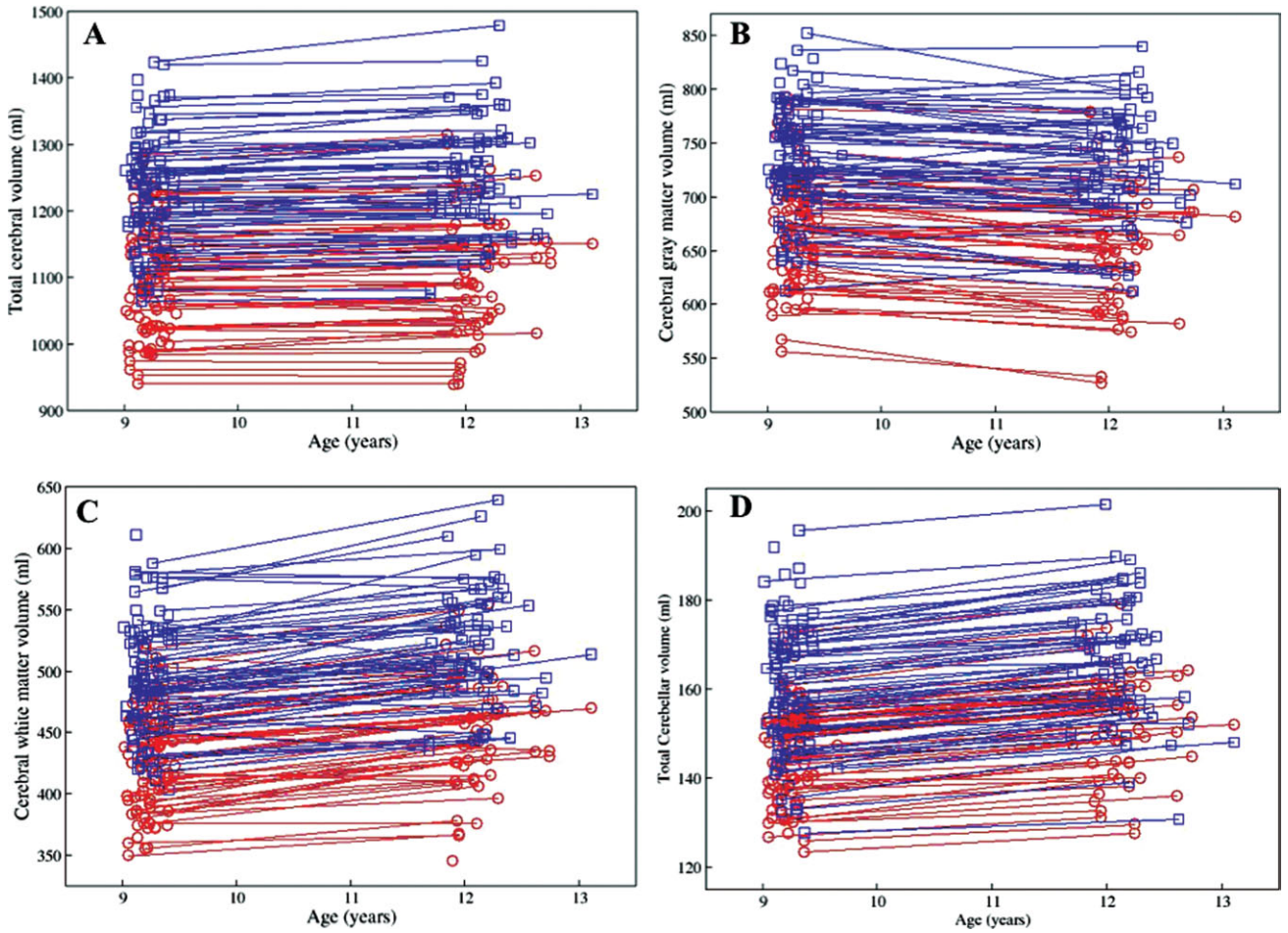

Figure 2.

Absolute brain volume of total cerebral volume (**A**), cerebral gray matter (**B**), cerebral white matter (**C**), and total cerebellar volume (**D**) are given on all included subjects at baseline and follow-up. Longitudinal data points are connected, and boys are depicted in blue, and girls in red.

9.9% in height. Total brain and cerebrum showed an increase of 1.1% in volume. Cerebellar volume showed a larger increase of 4.2% compared to baseline. After separation of gray and white matter tissue in the cerebrum and cerebellum, increased cerebral white matter (5.1%), cerebellar white (8.1%), and gray matter (2.5%) volumes were observed, whereas cerebral gray matter showed a decrease in volume (−1.6%). A relatively large increase was observed for lateral ventricles (9.4%) and the third ventricle decreased in volume (−4.0%). In Figure 2, individual volume changes can be observed between the two assessments for total cerebral, total cerebellar, and cerebral white and gray matter volumes.

Height was not different for boys or girls at baseline [mean (SD) was 139.5 (5.6) cm in boys and 138.2 (4.8) cm in girls; $P = 0.35$] or at follow-up [mean (SD) was 152.1 (7.1) cm in boys and 152.6 (7.1) cm in girls; $P = 0.22$]. The change in height was significantly different between boys and girls [mean change (SD) was 12.9 (3.1) cm in boys and 14.7 (3.9) cm in girls; $P < 0.01$]. Boys had significantly larger brain volumes than girls ($P < 0.01$). There were no significant differences between boys and girls on volumetric brain changes between baseline and follow-up ($P > 0.12$ for all brain volumes).

Genetic Modeling

Variances did not differ between birth-order and zygosity groups for height and all brain volumes. Total variances at follow-up were significantly larger than total variances at baseline for height and all brain volumes, with the exception of cerebellar gray matter and lateral ventricle volume, where the variances at both ages were similar.

Within pair correlations for MZ and DZ twins and the 95% confidence intervals (CI) for height and all brain

TABLE II. Monozygotic (MZ) and dizygotic (DZ) twin correlations with their 95% confidence intervals (CI) are displayed at baseline and follow-up separately for height and brain volumes

	Baseline		Follow-up	
	r MZ (*95% CI*)	*r* DZ (*95% CI*)	*r* MZ (*95% CI*)	*r* DZ (*95% CI*)
Height	0.94 (*0.90–0.96*)	0.56 (*0.37–0.70*)	0.93 (*0.89–0.96*)	0.46 (*0.32–0.71*)
Total brain	0.93 (*0.88–0.96*)	0.44 (*0.17–0.64*)	0.96 (*0.93–0.98*)	0.44 (*0.17–0.57*)
Cerebrum	0.93 (*0.89–0.96*)	0.43 (*0.17–0.64*)	0.96 (*0.93–0.98*)	0.45 (*0.19–0.65*)
Cerebral GM	0.88 (*0.80–0.92*)	0.46 (*0.20–0.64*)	0.91 (*0.83–0.95*)	0.43 (*0.16–0.62*)
Cerebral WM	0.89 (*0.81–0.93*)	0.43 (*0.15–0.63*)	0.88 (*0.78–0.93*)	0.46 (*0.13–0.67*)
Cerebellum	0.95 (*0.90–0.97*)	0.52 (*0.28–0.69*)	0.96 (*0.93–0.98*)	0.49 (*0.22–0.67*)
Cerebellar GM	0.92 (*0.86–0.95*)	0.38 (*0.10–0.58*)	0.75 (*0.61–0.85*)	0.37 (*0.03–0.61*)
Cerebellar WM	0.62 (*0.41–0.75*)	0.49 (*0.21–0.68*)	0.50 (*0.14–0.72*)	0.37 (*−0.08–0.65*)
Lateral ventricles[a]	0.81 (*0.70–0.88*)	0.55 (*0.29–0.71*)	0.78 (*0.64–0.87*)	0.52 (*0.27–0.69*)
Third ventricle[a]	0.57 (*0.32–0.73*)	0.29 (*−0.12–0.53*)	0.55 (*0.31–0.72*)	0.27 (*−0.20–0.64*)

GM = gray matter, WM = white matter. Data on height and brain volumes were corrected for age at scanning, sex, and handedness (for brain volumes only).
[a]Twin correlation for lateral ventricles and third ventricle volumes were estimated based on log-transformed data.

volumes at baseline and follow-up can be found in Table II. MZ correlations were higher than DZ correlations at both ages, indicating genetic influences at baseline and follow-up. Twin correlations were of the same magnitude at both ages, with exception of cerebellar gray matter, where MZ correlations were lower at follow-up than at baseline.

A longitudinal genetic model was evaluated that included A, C, and E effects. For height, influence of common environment was not significant. Although lateral ventricles volume showed some suggestive influence of common environment at both baseline and follow-up, common environmental influences were found to be nonsignificant for all brain volumes. Therefore, we continued with a longitudinal AE model.

Tables III and IV present the unstandardized and standardized estimates of genetic (i.e., heritability) and environmental influences on height and the brain volumes. Overall, heritability estimates at baseline and follow-up were high for height and brain volumes (see Table III). Somewhat lower heritability estimations were observed for the cerebellar white matter volume (i.e., 64% at baseline and 49% at follow-up).

For height and all brain volumes high genetic correlations over time were observed, indicating that individual variation in height and brain volumes at the ages of 9 and 12 were completely explained by the same genetic factors. Indeed, no significant contributions of age specific genetic factors at baseline or follow-up were observed.

TABLE III. The standardized (heritability) estimates within the longitudinal AE model are given at baseline, follow-up and of the amount of height and volumetric brain changes with their 95% confidence intervals (CI) for each variable separately

	Baseline		Follow-up		Change score		
	A	*E*	*A*	*E*	*A*	*E*	r_g
Height	**0.93** (*0.89–0.96*)	0.07 (*0.04–11*)	**0.93** (*0.88–0.95*)	0.07 (*0.05–0.12*)	**0.73** (*0.58–0.83*)	0.27 (*0.17–0.42*)	**0.92** (*0.88–0.95*)
Total brain	**0.93** (*0.89–0.96*)	0.07 (*0.04–0.11*)	**0.96** (*0.93–0.98*)	0.04 (*0.02–0.07*)	**0.19** (*0.07–0.47*)	0.81 (*0.53–0.93*)	**1.00**[a]
Cerebrum	**0.93** (*0.89–0.96*)	0.07 (*0.04–0..11*)	**0.96** (*0.93–0.98*)	0.04 (*0.02–0.07*)	**0.20** (*0.08–0.45*)	0.80 (*0.55–0.92*)	**1.00**[a]
Cerebral GM	**0.88** (*0.81–0.93*)	0.12 (*0.08–0.19*)	**0.91** (*0.84–0.95*)	0.09 (*0.05–0.15*)	0.03 (*0.00–0.49*)	0.97 (*0.51–1.00*)	**1.00**[a]
Cerebral WM	**0.89** (*0.82–0.93*)	0.11 (*0.07–0.18*)	**0.89** (*0.81–0.94*)	0.11 (*0.06–0.19*)	0.18 (*0.00–0.45*)	0.82 (*0.55–1.00*)	**0.98** (*0.95–1.00*)
Cerebellum	**0.95** (*0.91–0.97*)	0.05 (*0.03–0.09*)	**0.95** (*0.92–0.97*)	0.05 (*0.03–0.08*)	**0.45** (*0.12–0.68*)	0.55 (*0.32–0.88*)	**0.99** (*0.98–1.00*)
Cerebellar GM	**0.93** (*0.88–0.95*)	0.07 (*0.05–0.12*)	**0.80** (*0.69–0.87*)	0.20 (*0.13–0.31*)	0.03 (*0.00–0.28*)	0.97 (*0.72–1.00*)	**1.00**[a]
Cerebellar WM	**0.64** (*0.46–0.76*)	0.36 (*0.24–0.54*)	**0.49** (*0.18–0.70*)	0.51 (*0.30–0.82*)	0.13 (*0.00–0.41*)	0.87 (*0.59–1.00*)	**0.89** (*0.61–1.00*)
Lateral ventricles[b]	**0.80** (*0.68–0.87*)	0.20 (*0.13–0.32*)	**0.75** (*0.60–0.84*)	0.25 (*0.16–0.40*)	0.29 (*0.00–0.68*)	0.71 (*0.32–1.00*)	**1.00**[a]
Third ventricle[a]	**0.61** (*0.42–0.76*)	0.39 (*0.24–0.58*)	**0.59** (*0.40–0.73*)	0.41 (*0.27–0.60*)	0.02 (*0.00–0.25*)	0.98 (*0.75–1.00*)	**1.00**[a]

Genetic correlation (r_g) is the extent of overlap between genetic influences at baseline and follow-up.
GM = gray matter; WM = white matter. Data on height and brain volumes were corrected for age at scanning, sex, and handedness (for brain volumes only).
Bold numbers differed significantly from zero ($P > 0.05$).
[a]Correlation estimated at its upper bound.
[b]Variance components for lateral ventricles and third ventricle volumes were estimated on log-transformed data;

TABLE IV. The unstandardized variance estimates within the longitudinal AE model are given at baseline, follow-up and of the amount of height and volumetric brain changes for each variable separately

	Baseline		Follow-up		Change score	
	A	*E*	*A*	*E*	*A*	*E*
Height	23.99	1.70	44.00	3.43	7.98	3.00
Total brain	7,060.92	525.79	8,273.09	345.05	47.99	207.06
Cerebrum	5,955.57	437.01	6,986.01	288.41	41.09	166.17
Cerebral GM	2,093.66	282.78	2,404.71	223.82	10.77	308.24
Cerebral WM	1,573.41	194.05	1,841.95	218.49	62.71	277.49
Cerebellum	138.17	8.17	165.36	7.50	5.09	4.34
Cerebellar GM	92.94	8.73	79.49	19.78	0.53	28.13
Cerebellar WM	19.56	10.20	17.92	18.78	4.69	29.67
Lateral ventricles[a]	3.86	0.98	3.60	1.22	0.04	0.09
Third ventricle[a]	2.44	1.53	3.06	2.13	0.04	1.43

GM = gray matter, WM = white matter. Data on height and brain volumes were corrected for age at scanning, sex and handedness (for brain volumes only).
[a]Variance components for lateral ventricles and third ventricle volumes were estimated on log-transformed data.

Significant heritability on change in height (73%) was found. Significant heritability on volumetric brain changes were found for total brain (19%), total cerebrum (20%), and total cerebellum (45%). For all these variables, this was a result of increases in genetic variances, which were found to be significant for height, total brain, total cerebral, and cerebellar volume ($P < 0.01$). Because no contribution of age-specific genetic factors at baseline or follow-up were found ($r_g > 0.90$), the heritability on changes in height, total brain, cerebral, and cerebellar volumes were caused by amplification of genetic factors already present at baseline (see Table IV).

To explore to what extent the genetic and environmental influences acting on developmental changes are shared between changes in height and brain volumes, we performed additional multivariate genetic analyses on these change scores. Longitudinal data were available for height in 173 children and for brain volumes in 113 children. Table V contains the phenotypic, genetic, and unique environmental correlations between changes in height, cerebral, and cerebellar volumes. The change in height was not associated with change in cerebral volume ($r_p = 0.09$, $P = 0.33$). Because of previous observed sex differences in change in height, correlations were explored in boys and girls separately, given a correlation of −0.07 in boys ($P = 0.59$) and 0.25 in girls ($P = 0.06$). Phenotypic correlation on the complete sample between change in height and cerebellar volume was 0.24 ($P = 0.01$), where a correlation of 0.06 was observed in boys ($P = 0.64$), and 0.37 in girls ($P < 0.01$). Correlation between change in cerebral and cerebellar volume was 0.49 ($P < 0.01$), where a correlation of 0.49 was observed in boys ($P < 0.01$), and 0.58 in girls ($P < 0.01$). Although both boys and girls show correlation in the same directions, girls seem to reflect higher phenotypic correlations compared to boys between changes in height and brain volumes but also on changes between cerebral and cerebellar volumes.

The etiology of these associations were explore in more detail. The genetic influences acting on the amount of cerebral growth and the genetic influences acting on the amount of cerebellar growth showed an almost complete overlap ($r_g = 0.88$, $P < 0.05$). Interestingly, there was also

TABLE V. Results of the multivariate genetic model including the change in height (cm), and cerebral and cerebellar growth (ml)

	r_p[a]	r_g	r_e
Change in height and cerebral volume	0.09 (*−0.10–0.27*)	0.39 (*−0.18–1.00*)	−0.13 (*−0.45–0.22*)
Change in height and cerebellar volume	0.24 (*0.06–0.41*)	0.48 (*0.10–1.00*)	−0.05 (*−0.41–0.32*)
Change in cerebral and cerebellar volume	0.49 (*0.33–0.62*)	0.88 (*0.02–1.00*)	0.34 (*0.06–0.59*)

Phenotypic correlation (r_p) between height and cerebral and cerebellar volume changes are given, as well as the extent of overlap in genetic (r_g), and unique environmental influences (r_e) acting on height, cerebral and cerebellar growth with their 95% confidence intervals.
Total number of twins with available data on changes in height was 173 and cerebral and cerebellar volume changes were 113.
[a]Phenotypic correlations (95% CI) for male and female twins were between change in height and cerebral volume was −0.07 (−0.30 to 0.18) in boys and 0.25 (−0.01 to 0.48) in girls, change in height and cerebellar volume was 0.06 (−0.19 to 0.30) in boys and 0.37 (0.12–0.57) in girls, change in cerebellar and cerebral volume was 0.49 (0.28–0.66) in boys and 0.58 (0.38–0.73) in girls.

a significant unique environmental correlation ($r_e = 0.34$, $P < 0.05$). The correlation between cerebellar growth and increase in height was a result of significant genetic correlation ($r_g = 0.48$, $P < 0.05$) and nonsignificant environmental correlation ($r_e = -0.06$, $P = 0.76$).

DISCUSSION

This is the first longitudinal study investigating genetic and environmental contributions to volumetric brain changes in children. The main findings of this study are three-fold: First, height and brain volumes are highly heritable traits at both ages 9 and 12 years (up to > 90%). The stability that is seen for individual differences in these traits across age is explained by overlapping genetic factors ($r_g > 0.89$), i.e., the same genes influence individual differences in brain volumes at ages 9 and 12. Second, in children entering puberty, there is a 1.1% overall brain volume increase over this 3-year period that is most pronounced in the cerebellum which increased by 4.2%. Interestingly, while it encompasses only 12% of the total brain, the change in cerebellar volume was responsible for one-third of whole brain volume increase. Individual differences in volumetric brain changes were partly under genetic control (change in cerebral volume was 20% heritable and in cerebellar volume 45%). The association between changes in cerebellar and cerebral volumes ($r_p = 0.49$) was driven by shared genetic influences and, to a smaller extent, by shared unique environmental influences. Third, the change in height was highly heritable (73%) but was influenced by other genetic factors than the genetic factors implicated in changes in cerebral volume. What little was shared between height and cerebellar growth ($r_p = 0.24$), could be attributed partly to shared genetic influences ($r_g = 0.48$). We can conclude that we not only find developmental brain changes in this 3-year interval, as reported earlier over larger age spans in children and adolescents (Giedd et al., 1999), we also find these changes to be heritable. Furthermore, these changes in cerebral volume are not shared with the increase that seen in height, whereas the change in cerebellar volume is partly (genetically) correlated with changes in height.

We show that brain size is heritable in children. For example, total cerebral volume is highly heritable at age 9 (93%) and this heritability increases at age 12 (96%). We showed now for the first time that changes in height and brain volumes are heritable and that these genetic influences on the changes are caused by amplification of genetic factors already present at baseline. This genetic factor is also implicated in changes of both cerebral and cerebellar volumes and thus seems to represent a general structural brain developmental factor. This genetic factor appears to influence brain tissue specifically, because we found little overlap with other changes in children entering adolescence, as represented here by their increasing height. This increase in height was a poor predictor of changes in cerebral volume and was correlated to a smaller extent with changes in cerebral volume between 9 and 12. This suggests that cerebral brain development follows its own genetic pathway, which involves, at least during the age range of 9–12 years, the same genes as those implicated in overall head size. Change in cerebellar volume is partly correlated with change in height.

The finding of a general genetic factor acting on structural brain changes during childhood and early adolescence does not exclude that other genetic factors may be implicated in overall head size and volumetric changes over time later in life. In adult twins who were on average 30 years of age (ranging from 19 to 55 years), genetic influences on structural brain change differed from that implicated in brain structure (Brans et al., 2010). Possibly, the genetic mechanisms influencing volumetric changes differ in adolescence from those implicated in adulthood. For example, the genetic influences that occur during childhood brain development may be more intertwined with processes related to brain maturation compared to structural brain changes in adulthood, where they might represent a different process. Future longitudinal research, following the same individuals from childhood into adulthood, is the only way to provide the answers to these questions.

We also find that cerebral and cerebellum white matter increased in volume, while cerebral gray matter volume decreased between 9 and 12 years. Other studies exploring developing changes in children from young childhood up to adulthood reported that gray matter volume started to decrease around the age of 10–12 (Giedd et al., 1999; Giedd et al., 2006; Lenroot et al., 2007). This decrease in gray matter volume is not observed in the cerebellum, which can be explained by the fact that the cerebellum is a structure that shows a relatively late maturation process (Tiemeier et al., 2010). We found that changes in cerebellar volume were relatively large compared to changes in cerebral volume. Indeed, there is more suggestive evidence that the cerebellum volume increases considerably around this age period (Tiemeier et al., 2010). The biological processes underlying these volumetric changes in gray and white matter around puberty are only scarcely understood. One of the hypotheses of the biological mechanism underlying gray matter loss is the process of synaptic pruning (Huttenlocher and Dabholkar, 1997). Another interpretation involves increased myelination of axons, which causes white matter volume increase and gray matter volume decrease, i.e., white matter encroachment (Gogtay and Thompson, 2010; Paus et al., 2008).

Heritability estimates for brain volumes were very high at both ages 9 and 12, reaching up to 96%. Furthermore, there was a large overlap between the genetic factors acting on brain volumes at ages 9 and 12. The extent to which the individual differences in volumetric changes are reliable they seem to be driven by genetic influences, as was observed for total brain, total cerebrum, and cerebellum. No significant genetic influences on changes for

white and gray matter volumes were found. Although we observed some increase in genetic variance on gray and white matter volumes from age 9 to 12, and high genetic correlations over time, this was not accompanied by significant heritability estimates for gray or white matter volumetric changes. This may be a function of statistical power and samples size. Although the sample is large for imaging standards, it could be that even larger samples are needed to detect a subtle heritability on volumetric changes of gray and white matter. To determine the sample size needed to detect these relatively low heritability estimates, a power analysis was conducted within the longitudinal twin model, as used in this article. A sample size of around 150 twin pairs (based on a sample of 45% MZ pairs) has a power of 80% to detect an 18% heritability on volumetric changes in cerebral white matter with alpha 0.05 (i.e., testing the assumption that genetic amplification between age 9 and 12, and genetic innovation at age 12 are both absent in the model, resulting in 0% heritability on the change score).

Findings of the variation in gray and white matter changes being mainly environmental need not to be entirely surprising. There are several studies that illustrate structural brain changes as a result of environmental factors (e.g., Draganski and May, 2008). For example, structural changes were observed after training on a complex visuomotor task (Draganski et al., 2004), whole body balancing task (Taubert et al., 2010), or after a period of extensive learning (Draganski et al., 2006). The effects of these specific training paradigms cannot directly be compared to the normal development in a sample of unselected children, who are exposed randomly to a wide variety of environmental factors of every day life but still serve to illustrate that environmental factors can be of importance in structural brain changes.

Heritability estimates for brain volumes were at least as high at age 12 as at age 9, as also reported earlier (Peper et al., 2009). The heritability estimates for total brain, cerebrum, and gray and white matter are comparable to those of other cross-sectional pediatric twin studies (Wallace et al., 2006). The only exception seem to be cerebellum volume, which was found to be highly heritable in the present study, whereas a lower heritability was reported in an earlier study. However, in this earlier study (Wallace et al., 2006), children between the ages 4 and 19 years were included which makes heritability interpretation per age group challenging. To date, only one other twin study explored a twin sample with a narrow age range. In 8-year-old twins, lower but significant heritabilities for brain volumes were reported (Yoon et al., 2010). For example, in this study, heritability estimates of 71% for total brain volumes, 65% for total gray matter, and 80% for total white matter volume were found (Yoon et al., 2010).

No significant influences of common environmental influences shared by family members were seen on global volumetric measures. This is similar to findings over the whole range of imaging studies, which all acknowledge that common environmental effects do not reach significance. Thus, it seems that familiar influences are of little or no importance on overall brain development in children entering puberty.

The heritability estimates for both height and brain volumes are likely to reflect the involvement of many different genes. There are many biological processes that all can have some effect on how tall a person will be or how large the brain volume will become. For example, specific polymorphisms of the brain-derived neurotrophic factor were found to be associated with prefrontal cortex and hippocampal volume in healthy individuals (Pezawas et al., 2004). Another example is the Epsilon 4 allele of the Apolipoprotein gene, which is associated with Alzheimer disease. This genetic variant was associated with an altered developmental brain trajectory in children (Shaw et al., 2007). Finding the actual genes or the specific alleles that are associated with variation in a trait of interest is a challenging job not only for height in adults (Allen et al., 2010) and brain measures in healthy individuals (Thompson et al., 2010) but also for psychiatric disorders (Manolio et al., 2009; van Haren et al., 2008).

When interpreting the results of this study several limitations have to be taken into consideration. When investigating a sample consisting of twins only can raise questions about the justification to generalize the results to the overall population, consisting of mostly singletons. Brain volumes of singletons and twins were previously found to be comparable in childhood (Ordaz et al., 2009), and in adulthood (Hulshoff Pol et al., 2002). Thus, we may assume that these results on brain volume changes in children can also be generalized to the singleton population.

In this study, data of boys and girls were pooled when exploring changes in height and the association with brain growth. It is known that girls enter puberty at an earlier age than boys (Mul et al., 2001), which is accompanied with a growth spurt at the average age of 11 in girls and 14 years in boys (Tanner et al., 1966; Tanner and Whitehouse, 1976). It is possible that because girls are earlier with the start of puberty, they find themselves in a slightly different phase of body or brain development than boys, as illustrated by the more advanced Tanner stage of puberty in the girls than the boys in the current sample. We did not observe sex differences in the amount of brain growth. However, we did observe a larger increase in height for the girls. In girls, there also was a slightly higher association between change in height and brain volumes, but CI around the phenotypic correlation are large and overlapping between boys and girls. Higher correlations between change in height and brain volumes in girls gives an interesting perspective of possible sex differences in developmental stages of body and brain, but these results should be interpreted with caution, considering the sample size. Mean height (and changes) were always corrected for sex to limit the possible confounding effects of sex to a minimum.

We report on global brain volume changes only. However, it may be expected that there are considerable focal changes in brain structure present in these children as based on earlier findings on age related changes on cortical thickness (Gogtay et al., 2004). Genes exert specific influences on cortical thickening and thinning in adults (Brans et al., 2010), and on white matter density at age 9 years (Peper et al., 2009).

Because of the birth cohort approach, we can only present longitudinal changes on a limited age-range, in this case between 9 and 12 years, and inferences regarding changes in more advanced stage of puberty and young adulthood await further longitudinal follow-up in this and other samples. However, the strong point of this study is the focus on children entering puberty, which represents a unique period in the transition from childhood into adulthood, for both body and brain.

We have shown that changes in brain volumes from childhood to early adolescents, particularly prominent in the cerebellum, are heritable. There are shared genes and shared unique environmental influences responsible for the association between changes in both cerebral and cerebellar volumes. Simultaneously, children grow considerable in height in the same period. The amount of increase in height was heritable, but these genetic influences did not show an overlap with the genetic influences implicated in cerebral, and to a smaller extent with cerebellar volumetric increases. Therefore, we can conclude that there are distinct genetic processes acting on brain development, which could not be explained by simply the increase in height during the same period.

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