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Development and heritability of subcortical brain volumes at ages 9 and 12

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Subcortical brain structures are involved in a variety of cognitive and emotional functions and follow different trajectories of increase and decrease in volume from childhood to adulthood. The heritability of development of subcortical brain volumes during adolescence has not been studied comprehensively. In a longitudinal twin study, we estimated to what extent subcortical brain volumes are influenced by genetic factors at ages 9 and 12. In addition, we assessed whether new genes are expressed at age 12 and whether there is evidence for genotype by sex interaction. Brain scans were acquired for 112 and 89 twin pairs at 9 and 12 years of age. In both boys and girls, there was an increase in volumes of the thalamus, hippocampus, amygdala and pallidum, and a decrease in volumes of the caudate and nucleus accumbens. The putamen showed a decrease in boys bilaterally and an increase in girls in the left hemisphere. Heritability was high (>50%) for all structures – except for the left nucleus accumbens – with heritabilities ranging from 0.50 to 0.91 at age 9, and from 0.59 to 0.88 at age 12. There were no significant new genetic effects coming into play at age 12, and there was no evidence for genotype by sex interactions. These findings suggest that despite their sensitivity to environmental effects, the heritability of subcortical brain structures is high from childhood on, resembling estimates found in adult samples.

Keywords: Adolescence, bivariate model, brain structure, brain volume, development, heritability, longitudinal, MRI, subcortical, twin

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The heritability of global brain volumes is well established in adults, and also from a number of studies in adolescents and young children (Batouli *et al.* 2014; Blokland *et al.* 2012; Peper *et al.* 2007). Global brain volumes are moderately to highly heritable from birth onwards (Gilmore *et al.* 2010), increasing in heritability during childhood and adolescence, possibly followed by a decrease (Batouli *et al.* 2014; Giedd *et al.* 2010; Lenroot & Giedd 2008; Peper *et al.* 2009a; van Soelen *et al.* 2013; Wallace *et al.* 2006; Yoon *et al.* 2011).

Regional brain volumes, including the subcortical gray matter structures, may be more sensitive to environmental influences than global brain volumes (Draganski *et al.* 2004). In particular, plasticity of the hippocampus has been found to be associated with environmental influences in several studies: volume increase due to specific skills training was shown in studies of London taxi drivers (Woollett & Maguire 2011) and exercisers (Erickson *et al.* 2011; Schlaffke *et al.* 2014), whereas stressors like an earthquake have been associated with a decrease in hippocampus volume (Lui *et al.* 2013). Stress was also found to affect the amygdala, nucleus accumbens, caudate and putamen, all of which have a role in emotion processing, mood regulation, learning and cognitive functions (Davidson *et al.* 2002; Lucassen *et al.* 2014; Phelps 2004; Ring & Serra-Mestres 2002; Shohamy 2011).

Subcortical brain structures follow differential developmental patterns from child- to adulthood: decrease (e.g. caudate), increase (e.g. hippocampus) and inverted U-shaped trajectories (e.g. thalamus) have been reported (Dennison *et al.* 2013; Durston *et al.* 2001; Goddings *et al.* 2014; Ostby *et al.* 2009; Wierenga *et al.* 2014). Developmental changes in total brain volume and cortical thickness have been associated with genetic and environmental factors during the early adolescent years (van Soelen *et al.* 2012b, 2013). However, current knowledge about the extent to which genes and environment influence changes in subcortical brain volumes is much more limited. Recent twin studies in adults and children (for recent studies, see, for example, Bohlken *et al.* 2013; den Braber *et al.* 2013; Kremen *et al.* 2010; Yoon *et al.* 2011) and a comprehensive meta-analysis suggest that heritability for subcortical brain volumes is high. The wide confidence intervals around the point estimates stress the need for further studies (Blokland *et al.* 2012).

Here, the heritability of seven subcortical brain structures (thalamus, caudate, putamen, pallidum, amygdala, hippocampus and nucleus accumbens) is estimated at ages 9 and 12 in a population-based twin sample. The study is characterized by a longitudinal design, which allows to test for heritability changes over this age span and to test if new genetic factors are expressed at age 12. Differences in puberty status

between boys and girls will be small at age 9, but girls may be more advanced at age 12, so we will test for sex differences in heritability estimates. Because the study includes mono- and dizygotic male and female twin pairs, as well as opposite-sex pairs, we can assess both qualitative differences, i.e. test if the same genes are expressed in boys and girls, and quantitative differences, i.e. in the magnitude of genetic and environmental effects.

Methods

Participants

Twins were recruited from the Netherlands Twin Register (NTR, Boomsma *et al.* 2006; van Beijsterveldt *et al.* 2013; Willemsen *et al.* 2013). Twins, aged 9 years, who were born in 1995–1996 with an older brother or sister, aged 10–14 years, were invited to participate in the Brainscale study of brain and cognitive development. This is a longitudinal study in which the NTR, the Brain Center Rudolf Magnus, and the University Medical Center Utrecht collaborate. The sample was largely unselected for phenotype, but children were excluded from participation in case of a pacemaker, metal material in their head, chronic use of medication, a major medical or psychiatric history, participation in special education or physical or sensory disabilities. At the first assessment, 112 twin pairs participated (mean age 9.10, ±0.10), and at follow-up 89 pairs came back for the second assessment (12.15, ±0.26). At age 9, there were 48 monozygotic (MZ) pairs (23 male/25 female) and 64 dizygotic (DZ) twin pairs (23 male/21 female/20 opposite sex). For demographics, see Table 1, and for more details on the sample and study design also see Van Soelen *et al.* (2012a).

Procedure

The Central Committee on Research involving Human Subjects approved this study. After the test administrator explained the testing procedure and the goal of the research project, both parents and children gave written informed consent. At age 9, twins came to the laboratory at the VU University Amsterdam for cognitive testing and to the University Medical Center Utrecht on a separate occasion for magnetic resonance imaging (MRI) scanning (preceded by a visit to the dummy scanner). At age 12, the cognitive assessment and MRI scans were completed on the same day at the University Medical Center Utrecht. Data on physical development (height, weight and Tanner phase) were measured by a trained researcher. At age 12, children were offered the option to provide self-report data on Tanner phase (16 girls, 28 boys). Morning urine, saliva samples and cheek swabs were collected at home on two consecutive days at fixed times and were used for assessment of estrogens, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and genetic markers (for details, see Koenis *et al.* 2013). Self- and maternal reports of health, lifestyle and behavioral and emotional problems of the children were collected by surveys. Magnetic resonance imaging scanning was performed on a 1.5-T Philips Achieva scanner on both occasions, using the same scan sequence parameters and image processing procedures (Peper *et al.* 2009a; van Soelen *et al.* 2013). At both baseline and follow-up image sequences for 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 = 4.6 millisecond, repetition time = 30 millisecond, flip angle = 30°, 160–180 contiguous slices; $1 \times 1 \times 1.2\ mm^3$ voxels, fiel d of view = 256/70%) was acquired for volumetric analysis.

Subcortical structures were segmented automatically by the publicly available Freeserver software package (version 5.1; Fischl *et al.* 2002, 2004). Our previously manually edited intracranial masks were inserted in this pipeline to compute subcortical structures with a high-quality brain mask. Quality control was performed to check segmentation accuracy in outlying volume measurements by visual inspection of the scans for movement effects. Insufficient detail of the subcortical volumes led to excluding participants or specific structures from the analyses (see Table S1, Supporting Information).

Analyses

To estimate heritability, the classical twin model focuses on the difference in resemblance (correlation or covariance) for a particular trait between dizygotic (DZ) twin pairs who share on average half of their segregating genes and monozygotic (MZ) twins who are (nearly) genetically identical. Comparing the cross-twin-within-trait correlations of MZ with DZ twins gives an indication of the sources of variation. Because MZ and DZ twins differ in their genetic similarity, genetic effects are suggested for a trait if the MZ cross-twin-within-trait correlation is higher than the DZ correlation. In addition, common environmental effects are also suggested to contribute to twin resemblance when the DZ correlation is larger than half the MZ correlation. In longitudinal data, comparing the cross-twin-cross-trait correlations (i.e. brain volume at age 9 in one twin with brain volume at age 12 in the cotwin) gives an indication of the sources causing covariance between traits: the phenotypic

Table 1: Sample characteristics

	Age 9	Age 12
Total number of twins (girls/boys)	112/112	89/89
Number of participants with complete MRI scan	210	136
Twin pair zygosity (MZ/DZ same sex/DZ opposite sex)	48/44/20	40/34/15
Mean age of twins in years (SD)	9.2 (0.1)	12.1 (0.3)
Height (cm)		
Girls (MZ/DZ/DOS)	136.6/138.8/140.6	151.1/153.3/155.1
Boys (MZ/DZ/DOS)	139.5/138.6/140.1	153.5/150.4/151.9
Weight (kg)		
Girls (MZ/DZ/DOS)	30.4/31.8/32.0	43.4/44.6/41.4
Boys (MZ/DZ/DOS)	31.8/31.2/31.9	44.5/41.9/39.4
Tanner stage 1/2/3/4/5 (missing values)		
Girls: Breast development	89/20/-/-/- (3)	10/16/36/17/7 (3)
Pubic hair	91/17/-/-/- (4)	17/17/18/23/5 (9)
Boys: Penis development	100/5/1/1/- (5)	20/37/21/5/- (5)
Pubic hair	96/10/0/0/- (6)	24/31/22/6/- (6)

correlation between brain volume at two ages is explained by common genetic factors when the MZ cross-twin-cross-trait correlation is larger than the DZ correlation. Longitudinal modeling of all twin data was performed in OpenMx (Boker *et al.* 2011) by raw-data maximum likelihood, allowing for (any pattern of) missingness in the data. Therefore, we did not remove the cotwin if data of the other twin had to be excluded. Excluded participants were evenly spread between zygosity and sex groups. Bivariate analyses were run between the volume data collected at ages 9 and 12, separately for the left and right volume of each subcortical brain structure. First, in a saturated model, means, variances and twin correlations, within-age and across-age, were estimated for the five sex-by-zygosity groups (MZM, DZM, MZF, DZF and DZMF), and differences in mean volumes between boys and girls and between 9 and 12 years were tested for significance. Next, heritability was estimated in a series of genetic models. In the full longitudinal model, parameters representing the influence of additive genetic factors (A), common environment shared by twins (C) and unique environment (E) were estimated separately for boys and girls. The genetic correlation between opposite-sex twin pairs was estimated freely and changes in the fit of the model were compared to a model in which the correlation was equal (0.5) to the genetic correlation in same-sex DZ pairs. Quantitative sex differences were tested by constraining the influences of A, C and E to be equal for boys and girls. Then, the significance of common and genetic environmental factors was assessed by constraining their influence at zero. Finally, the significance of new genetic effects coming into play at age 12 was tested. Figure 1 presents the longitudinal model for two twins whose brain volumes were assessed at ages 9 and 12, and specifies which parameters were estimated. Parameter estimation was by raw-data maximum likelihood as implemented in OpenMx and the fit of nested submodels was compared by likelihood-ratio tests, based on the difference in minus twice the log likelihood (−2LL) between two models. The difference has a χ^2 distribution with the degrees of freedom (df) equaling the difference in df between the two models. If constraining parameters in a nested model did not result in a significantly worse fit, this more parsimonious model was deemed the best fitting model. All analyses were performed with and without adjustment for intracranial volume (ICV), which yielded similar results. Here, we report the results of the analyses without adjustment for ICV. Because tests were carried out for 14 related traits (left and right volume of seven brain structures), the Matrix Spectral Decomposition program (matSPd, Li & Ji 2005) was used to obtain the number of independent dimensions in the data. This was 10, leading to a *P*-value of 0.005. Correlations between changes in brain volumes and height and weight were calculated in the Statistical Package for the Social Sciences 21.0 statistical package for Windows (SPSS 21, IBM Corp. 2011).

Results

Brain volumes at ages 9 and 12

Table 1 presents sample characteristics at ages 9 and 12. Comparing height, weight and Tanner data between the two ages, we see the expected biological maturation. Figure 2 and Table S1 summarize the volumes of subcortical structure. The (left and right) thalamus, amygdala, putamen and pallidum were significantly larger in boys than in girls at ages 9 and 12; the volume of the nucleus accumbens was significantly larger in boys than in girls at age 9 but not at age 12. Volume of the thalamus, hippocampus, amygdala and pallidum increases between ages 9 and 12 in boys and in girls. In contrast, volume of the caudate and nucleus accumbens decreases in boys and girls, and findings for the putamen are mixed. However, at $\alpha = 0.005$ these differences do not always reach statistical significance (Table S1). We also tested whether these changes in brain volume coincide with increasing height and weight, but we found no evidence for this (see Table S3).

Volumes of the subcortical brain structures between 9- and 12-year-old correlate highly for the thalamus, hippocampus, amygdala, putamen and caudate (>0.70), and moderate (between 0.30 and 0.90) for the pallidum and nucleus accumbens (Fig. 2; Table S2).

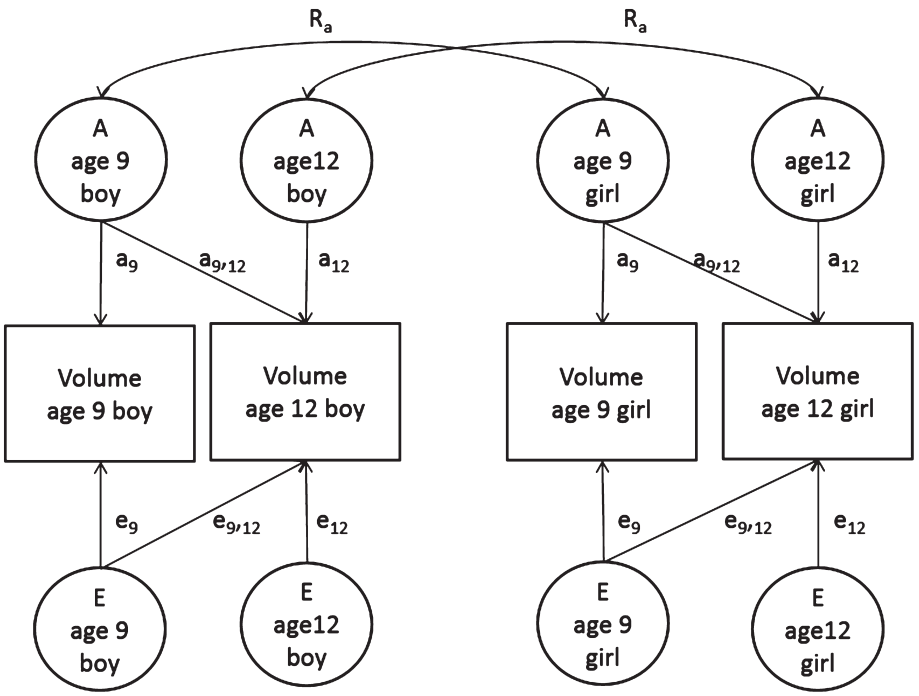

Figure 1: Longitudinal genetic path model for two twins with brain volume data at ages 9 and 12. Observed phenotype data for two twins at two ages are represented in boxes, latent (unobserved) traits are represented by circles: A, genetic factor score at ages 9 and 12; E, unique environment factor score at ages 9 and 12 ; R_a, correlation between factor scores of twins ($R_a = 1$ for MZ, 0.5 for DZ same sex, and was estimated in DZ opposite-sex pairs as is shown here); a_9 $a_{9,12}$ and a_{12} are factor loadings representing the influence of the latent factors on the phenotype. Based on this model, the stability of genetic and environmental influences [the genetic and environmental correlations r(g) and r(e)] can be calculated as: $r(g) = \frac{a_9 \times a_{9,12}}{\sqrt{a_9^2} \times \sqrt{a_{9,12}^2 + a_{12}^2}}$ $r(e) = \frac{e_9 \times e_{9,12}}{\sqrt{e_9^2} \times \sqrt{e_{9,12}^2 + e_{12}^2}}$.

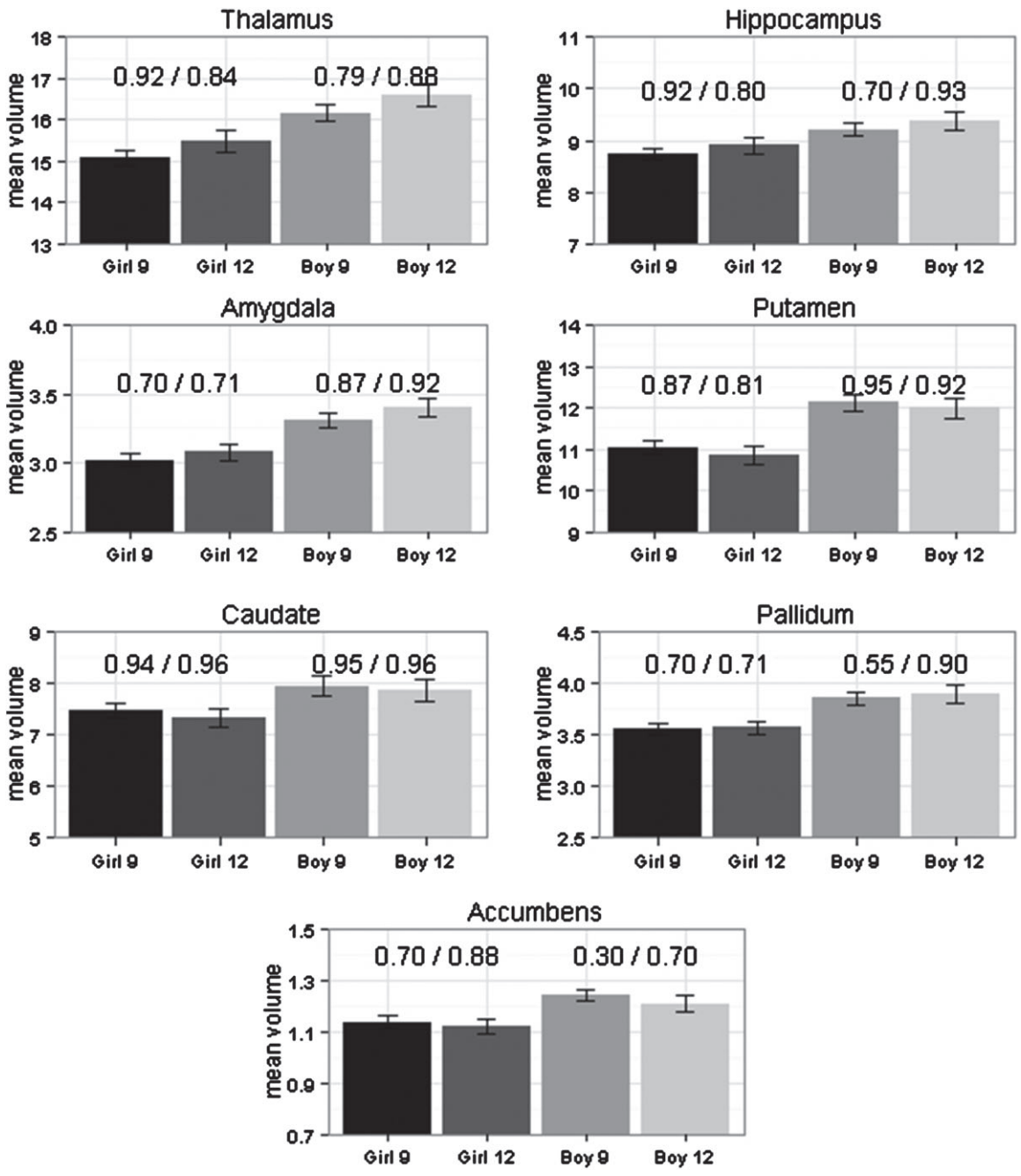

Figure 2: Mean volume in milliliter for the total (left + right) subcortical brain structure volume for girls and boys at ages 9 and 12 (including 95% error bars). The correlations between volumes at ages 9 and 12 are given (left/right).

Genetic analyses

Twin correlations were larger for the MZ twins than the DZ twin pairs, and were relatively similar for male and female twin pairs, suggesting that additive genetic factors explain most of the variance in subcortical brain volume and that there may not be sex differences in heritability (Table S2). Indeed, neither qualitative nor quantitative sex differences in heritability were significant, indicating that the same genetic factors, with the same effect, play a role in boys and girls (Tables S4–S10). Table 2 summarizes for all subcortical brain volumes at ages 9 and 12 the proportions of variance accounted for by A, C and E in the full ACE and the nested AE model. In the ACE model, genetic factors explain most of the variance for all brain volumes with exception of the left nucleus accumbens, ranging from 0.43 to 0.76 at age 9, and from 0.42 to 0.72 at age 12. For all volumes, an AE model did

not fit the data significantly worse than an ACE model, indicating that familial resemblance can be explained by genetic factors and that effects of the common environment are not significant (see Tables S4–S10). However, in the case of the left nucleus accumbens a CE model (familial resemblance is explained by shared environmental factors) fitted the data better.

Differences in heritability between ages 9 and 12 were small and the genetic correlations, r(g), over this 3-year interval were 1.0 (see Table 2). Dropping path a_{12}, which represent the influences of new genes as expressed at age 12 (see Fig. 1), from the model did not change the fit of nearly all brain volumes (Tables S4–S10). This indicates that the same genetic factors are influencing subcortical brain volumes at ages 9 and 12, and no significant new genetic effects come into play at age 12. In addition to the genotype, the non-shared environment also contributed to stability for most structures [r(e), Table 2].

As was described by de Geus *et al.* (2007) and van Soelen *et al.* (2013), a bivariate model allows for estimation of the heritability of change. To estimate heritability of change scores, the genetic variance is obtained as $(a_{9,12} - a_9)^2 + a_{12}{}^2$, where the first term reflects (de)amplification (the decrease or increase in shared genetic variance over the 3-year time interval) and the second term the emergence of novel genetic effects at age 12 years. Similar expressions can be derived for the environmental variance. As the results of the bivariate models indicated, estimates for $a_{9,12}$ and a_9 were of the same magnitude, and a_{12} tended to be estimated at zero. Thus, the heritability of change scores in brain volume tends to be around zero (see Table S11).

Discussion

In this longitudinal twin study, we measured volumes of seven subcortical gray matter structures, which play a major role in cognition and emotion. These structures each follow their own pattern of development between 9 and 12 years old. We find high heritabilities for subcortical brain volumes at these ages. No quantitative or qualitative sex differences are found for the heritability estimates, indicating that the same genes, and with the same effect, are expressed in both sexes for these brain volumes. The high correlations between the volumes at ages 9 and 12 are due to the stable effects of genetic and environmental influences.

During teenage development, total brain volume increases between the ages of 9 and 12 (van Soelen *et al.* 2013), but not all subcortical brain structures show the same volumetric increase. In this study, in both girls and boys we find trends of increasing left and right hemisphere volume of the thalamus, pallidum, hippocampus and amygdala between 9 and 12 years of age, while during the same age interval volumes of the caudate, nucleus accumbens, and putamen (bilaterally in boys; right-sided only in girls) decreased.

These results are in line with a growing body of literature that has assessed the volume development of all or most of these subcortical gray matter structures in cross-sectional, longitudinal or mixed-design studies (Dennison *et al.* 2013; Goddings *et al.* 2014; Ostby *et al.* 2009; Wierenga *et al.* 2014). All these studies show volume decrease of the caudate, nucleus accumbens and putamen, and increases in volumes of the amygdala and hippocampus with development. Results for the thalamus and pallidum are more varied: increases of thalamus volume are reported in this study and by Ostby *et al.* (2009), whereas a decrease was found by Dennison *et al.* (2013). Wierenga *et al.* (2014) reported a peak volume at 14 years of age followed by a decrease. Similarly, for the pallidum volume increase (our study and Dennison *et al.* 2013), decrease (Durston *et al.* 2001; Goddings *et al.* 2014; Ostby *et al.* 2009) and inverted U-shaped trajectories (Wierenga *et al.* 2014) are reported. Non-linear trajectories of development, with different peaks for boys and girls, may explain these diverse results. Future studies on brain development need to look beyond the effects of age, and instead take into account the associations of brain development with measurements of body size, hormone levels or pubertal status (Mills & Tamnes 2014). Such approaches help us further understand which biological pathways direct brain maturation, see, for example, longitudinal studies including measurements of body size like height (van Soelen *et al.* 2013) or studies exploring associations with hormone levels or pubertal status (Koenis *et al.* 2013; Peper *et al.* 2009b, 2011).

The heritability estimates from this study are summarized in Table 3, as well as those from all other twin studies that were performed for these seven brain structures. They include studies performed in adults ($n = 9$) and children ($n = 4$), based on nine independent samples (total number of subjects >1500). Overall, these studies report a wide range of heritabilities for all the subcortical brain structures: thalamus 0–88%; hippocampus 40–80%; amygdala 56–83%; putamen 9–91%; caudate 26–88%; pallidum 50–81%; nucleus accumbens 25–69%. In studies based on childhood samples between 4 and 19 years old, heritability estimates of the thalamus, caudate, putamen and pallidum were high (over 76%, Schmitt *et al.* 2007; Wallace *et al.* 2010; Yoon *et al.* 2011), similar to ours, although lower heritability estimates (26–59%) of the thalamus and caudate at age 8 have also been reported (Yoon *et al.* 2011). The only studies that have investigated the same seven structures were performed in adult samples, which report heritability estimates in the same range as were estimated in this paper (over 60%, Bohlken *et al.* 2013; den Braber *et al.* 2013; Kremen, *et al.* 2010). Similarly, from their analyses the lower heritability of the nucleus accumbens when compared with the other brain structures is also evident. Although we cannot rule out that accumbens volume is primarily determined by environmental factors, this is possibly a result of measurement error. It might be that the smallest of the subcortical volumes analyzed in this study is difficult to measure with high precision. This is reflected by the low correlations between volumes over the 3-year interval, as was also shown over a 5-year interval in adult twins (den Braber *et al.* 2013). In conclusion, even though heritability estimates may vary between studies, they all illustrate large and stable effects of genetic factors on individual differences in subcortical brain volumes, which does not seem to change substantially to adulthood. The absence of genetic influences on change measures should be interpreted with some care. Data processing was carried out using the cross-sectional Freesurfer

Table 2: ACE and AE model estimates (with 95% confidence intervals) and genetic correlations at ages 9 and 12, covariance explained by shared genetic factors, and fit of the AE model

		ACE model estimates (95% confidence interval)						AE model estimates (95% confidence interval) and nested fit statistic							
		Age 9			Age 12			Age 9		Age 12					
		A	C	E	A	C	E	A	E	A	E	*r*(g)	%^{g}	*r*(e)	*P*
Thalamus	L	0.70 (0.29–0.81)	0.02 (0–0.40)	0.28 (0.19–0.41)	0.63 (0.27–0.78)	0.01 (0–0.32)	0.36 (0.22–0.54)	0.72 (0.59–0.81)	0.28 (0.19–0.41)	0.64 (0.46–0.77)	0.36 (0.22–0.54)	1	93	0.17	1
	R	0.76 (0.37–0.85)	0 (0–0.36)	0.24 (0.15–0.36)	0.72 (0.31–0.82)	0 (0–0.38)	0.28 (0.18–0.44)	0.76 (0.64–0.85)	0.24 (0.15–0.36)	0.72 (0.56–0.82)	0.28 (0.18–0.44)	1	90	0.32	1
Hippocampus	L	0.63 (0.21–0.79)	0.06 (0–0.40)	0.31 (0.20–0.49)	0.58 (0.15–0.82)	0.14 (0–0.52)	0.28 (0.17–0.45)	0.68 (0.52–0.79)	0.32 (0.21–0.48)	0.72 (0.55–0.83)	0.28 (0.17–0.45)	1	83	0.48	0.97
	R	0.72 (0.39–0.84)	0 (0–0.26)	0.27 (0.16–0.45)	0.69 (0.17–0.82)	0.01 (0–0.46)	0.30 (0.18–0.50)	0.71 (0.51–0.83)	0.29 (0.17–0.49)	0.70 (0.48–0.82)	0.30 (0.18–0.52)	1	80	0.58	1
Amygdala	L	0.61 (0.25–0.73)	0 (0–0.32)	0.39 (0.27–0.56)	0.72 (0.35–0.84)	0 (0–0.29)	0.28 (0.16–0.48)	0.61 (0.44–0.73)	0.39 (0.27–0.56)	0.72 (0.52–0.84)	0.28 (0.16–0.48)	1	83	0.40	1
	R	0.65 (0.19–0.80)	0.05 (0–0.46)	0.30 (0.20–0.45)	0.53 (0.12–0.71)	0.04 (0–0.42)	0.44 (0.28–0.62)	0.70 (0.56–0.80)	0.30 (0.20–0.44)	0.56 (0.38–0.71)	0.44 (0.29–0.62)	1	87	0.25	1
Putamen	L	0.73 (0.44–0.94)	0.18 (0–0.47)	0.09 (0.06–0.15)	0.71 (0.39–0.92)	0.17 (0–0.49)	0.12 (0.07–0.20)	0.91 (0.85–0.94)	0.09 (0.06–0.15)	0.88 (0.79–0.93)	0.12 (0.07–0.21)	1	100	−0.04	0.84
	R	0.61 (0.34–0.90)	0.27 (0–0.53)	0.12 (0.08–0.19)	0.63 (0.34–0.87)	0.19 (0–0.47)	0.18 (0.11–0.28)	0.87 (0.81–0.91)	0.13 (0.09–0.19)	0.82 (0.72–0.88)	0.18 (0.12–0.28)	1	97	0.14	0.57
Caudate	L	0.50 (0.14–0.82)	0.24 (0–0.55)	0.26 (0.17–0.40)	0.58 (0.17–0.86)	0.21 (0–0.57)	0.21 (0.13–0.36)	0.74 (0.62–0.83)	0.26 (0.17–0.38)	0.79 (0.66–0.87)	0.21 (0.13–0.34)	1	83	0.66	0.68
	R	0.43 (0.06–0.81)	0.32 (0–0.62)	0.26 (0.16–0.41)	0.42 (0.04–0.81)	0.33 (0–0.64)	0.26 (0.15–0.42)	0.75 (0.62–0.84)	0.25 (0.13–0.38)	0.75 (0.60–0.85)	0.25 (0.15–0.40)	1	82	0.67	0.47
Pallidum	L	0.63 (0.34–0.77)	0 (0–0.22)	0.37 (0.23–0.56)	0.67 (0.25–0.80)	0.01 (0–0.44)	0.32 (0.20–0.51)	0.63 (0.44–0.76)	0.37 (0.24–0.56)	0.68 (0.49–0.80)	0.32 (0.20–0.51)	1	1	−0.01	1
	R	0.46 (0.05–0.67)	0.03 (0–0.32)	0.50 (0.32–0.74)	0.49 (0.03–0.75)	0.10 (0–0.53)	0.41 (0.25–0.64)	0.50 (0.28–0.67)	0.50 (0.33–0.72)	0.59 (0.36–0.75)	0.41 (0.25–0.64)	1	91	−0.11	00.99
N. accumbens	L	0.09 (0–0.51)	0.22 (0–0.44)	0.70 (0.49–0.89)	0.22 (0–0.57)	0.05 (0–0.35)	0.73 (0.41–0.99)	0.32 (0.09–0.53)	0.68 (0.47–0.91)	0.25 (0.01–0.55)	0.75 (0.45–0.99)	1	69	0.16	0.77
	R	0.53 (0.12–0.68)	0 (0–0.37)	0.46 (0.32–0.65)	0.62 (0.16–0.77)	0 (0–0.39)	0.38 (0.23–0.60)	0.53 (0.35–0.68)	0.47 (0.32–0.65)	0.61 (0.40–0.77)	0.39 (0.23–0.60)	1	85	0.24	1

A, additive genetic effects; C, common environment; E, unique environment; *r*(g), genetic correlation; %^{g}, the contribution of shared genetic factors to the covariance between ages 9 and 12; *r*(e), environmental correlation; *P*, likelihood-ratio test statistic comparing the AE submodel fit with the ACE model fit.

Table 3: Heritability estimates (left/right) from twin studies in healthy children and adults

Children	*N* pairs	Age range	Thalamus	Hippocampus	Amygdala	Putamen	Caudate	Pallidum	Accumbens	Other
Wallace *et al.* (2010)[4]	107/53	4–19 (12)					85			
Schmitt *et al.* (2007)*,[4]	127/36	5–18 (11)	88						Basal ganglia: 77	
Yoon *et al.* (2011)*	57/35	8	59/47			79/77	49/26	81/76		
Peper *et al.* (2009a, vbm)[1]	45/62	9			83					
This study[1]										
9 years old	48/64	9	72/76	69/73	61/70	91/87	74/75	63/50	33/53	
12 years old	40/49	12	64/72	72/70	72/56	88/82	79/75	68/59	27/61	
Adults	*N* pairs	Age range	Thalamus	Hippocampus	Amygdala	Putamen	Caudate	Pallidum	Accumbens	Other
Kremen *et al.* (2010)*,[2]	110/92	51–59 (56)	68/60	63/64	63/66	85/84	79/70	66/75	60/48	
den Braber *et al.* (2013)[3]	176/88	11–56 (29)	80/81	73/78	65/69	86/84	88/86	75/65	65/69	
Bohlken *et al.* (2013)[3]	50/56	19–55 (30)	81	75	76	80	79	71	49	
Sullivan *et al.* (2001)*	44/40	68–78 (72)		40						
van Erp *et al.* (2004)*	23/29	N/A (48)		71						
Panizzon *et al.* (2012)[2]	89/68	51–59 (56)		62/66						
Wright *et al.* (2002)*	10/10	18–54 (27)	0/0	66/71		9/79			Striatum: 33/60	
Brun *et al.* (2009, vbm)*	23/23	22–25 (24)	25						Basal ganglia: 40	
Hulshoff Pol *et al.* (2006, vbm)[3]	54/58	19–69 (31)		80/55						

For each study, the number of twin pairs (MZ/DZ) and (mean) age of the sample is given.
[1,2,3,4] indicate that analyses are based (partly) on overlapping cohorts. Vbm, heritability estimates from voxel-based morphometry, all estimates of other studies are based on volumetric measurements. Basal ganglia include the caudate, putamen, pallidum and nucleus accumbens; striatum includes the caudate and putamen. N/A, age range not available.
*Studies are part of the meta-analysis by Blokland *et al.* (2012). Estimates (left/right) from this meta-analysis were: thalamus 61/52.4, caudate 72.3/64, putamen 78.4/81.6, pallidum 70.7/75.3 and hippocampus 58.5/53.2.

pipeline. The longitudinal Freesurfer pipeline (Reuter *et al.* 2012) may increase the power to detect heritability of change as it increases segmentation accuracy. Between the sexes, subcortical volumes were on average larger in the males than in the females. Despite the gender differences in average volumes and despite differences in development of sexual characteristics during puberty, we find an absence of significant quantitative and qualitative sex differences in heritability. This finding is in accordance with other studies on heritability of subcortical brain structures and a variety of phenotypes on health and behavior (den Braber *et al.* 2013; Vink *et al.* 2012).

Our sample provides the unique opportunity to assess heritability without confounding effects of age: this study is the first to measure a cohort with only 9-year olds and a follow-up when they were all 12 years old. This thus leaves very little room for effects due to individual differences in age at the time of the scans. The heritability estimates in childhood resemble estimates found in adult samples, which suggests that children may considerably add power in quests trying to find genetic variants influencing brain volume, such as the ENIGMA consortium (Stein *et al.* 2012; Thompson *et al.* 2014).

Conclusion

The genome is the most important influence on individual differences in brain volume, both for total volume measures and for most subcortical volumes. Still, there are environmental influences as well. Both genetic and environmental factors need to be identified in follow-up studies aiming to detect genetic variants (e.g. in genome-wide association studies) and characterize environmental exposures (e.g. stressors, like life events). Many studies have focused on global brain development and factors determining individual differences thereof. Subcortical brain structures should be studied next. First of all, they are important for cognitive functions, or play a role in networks that underlie cognitive functions (Aggleton *et al.* 2010; Aron *et al.* 2007). During the teenage years, many of these cognitive skills improve (e.g. executive and social functions, Best & Miller 2010; Blakemore 2012; Gur *et al.* 2012), stressing the importance of healthy brain development during these years. Secondly, during the teenage years there is a high incidence of psychiatric disorders (Lenroot & Giedd 2006; Paus *et al.* 2008), many of which are accompanied by (subcortical) brain morphometric changes (Giedd & Rapoport 2010). The sensitivity of these areas to training, stress, and their involvement in cognitive skills and psychiatric disorders makes it particularly useful to characterize the genetic and environmental causes of (ab)normal brain development of the subcortical gray matter structures.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1: Mean volumes (in ml, with SD) of left (L) and right (R) subcortical brain structures at ages 9 and 12 of girls and boys, and the percentage in volume change (%).

Table S2: The fit of saturated models in −2 log likelihood (−2LL) and Akaike information criterion (AIC). Phenotypic-, twin- and cross-age correlations in the saturated model are given.

Table S3: Correlations between change in brain volume (left/right) and change in height (cm) and weight (kg), separately for girls and boys.

Table S4: Model fitting results of the bivariate model of thalamus volume at ages 9 and 12.

Table S5: Model fitting results of the bivariate model of hippocampus volume at ages 9 and 12.

Table S6: Model fitting results of the bivariate model of amygdala volume at ages 9 and 12.

Table S7: Model fitting results of the bivariate model of putamen volume at ages 9 and 12.

Table S8: Model fitting results of the bivariate model of caudate volume at ages 9 and 12.

Table S9: Model fitting results of the bivariate model of pallidum volume at ages 9 and 12.

Table S10: Model fitting results of the bivariate model of nucleus accumbens volume at ages 9 and 12.

Table S11: ACE model estimate of the heritability of change in brain volume between ages 9 and 12.