Cognitive performance across the lifespan and domains

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Chapter 8

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

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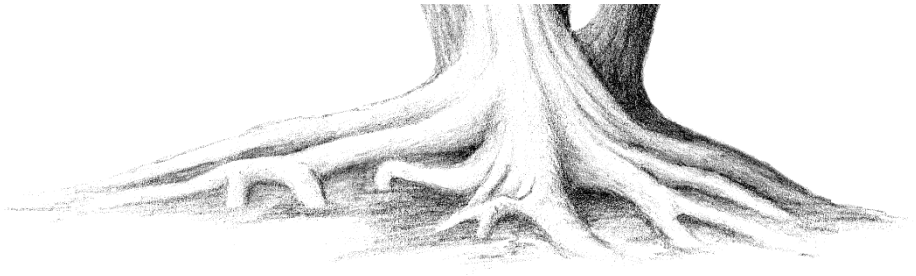


Introduction

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, Trollor, Wen, & Sachdev, 2014; Giedd et al., 2010; Lenroot & Giedd, 2008; Peper et al., 2009b; van Soelen et al., 2013; Wallace et al., 2006; Yoon, Perusse, Lee, & Evans, 2011).

Regional brain volumes, including the subcortical grey 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, Langen, Oranje, & Durston, 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; van Soelen et al., 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 (see for example Bohlken et al., 2013; den Braber et al., 2013a; 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 7 subcortical brain structures (thalamus, caudate, putamen, pallidum, amygdala, hippocampus, and nucleus accumbens) is estimated at ages 9 and 12 years 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, SD = 0.10), and at follow-up 89 pairs came back for the second assessment (M = 12.15, SD = 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 Vrije Universiteit Amsterdam for cognitive testing and to the University Medical Center Utrecht on a separate occasion for 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 (length, 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. MRI 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., 2008; 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 x 256 matrix, Echo Time = 4.6 ms, Repetition Time = 30 ms, flip angle = 30°, 160-180 contiguous slices; 1 x 1 x 1.2 mm3 voxels, field-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 Supplementary Table S1).

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 / DOS)	48/44/20	40/34/15
Mean age of twins in years (sd)	9.2 (0.1)	12.1 (0.3)
Height (centimeter)		
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 (kilogram)		
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)

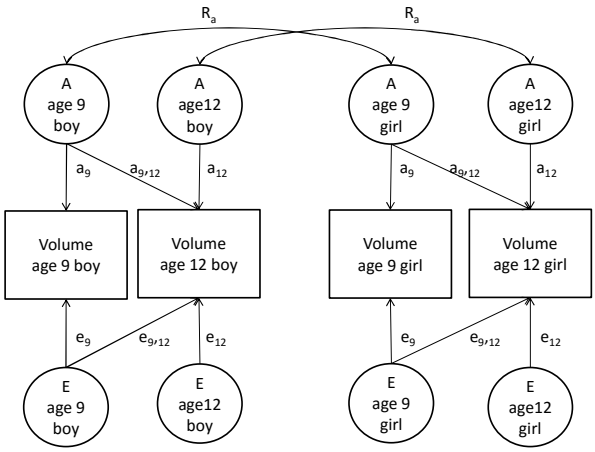
MZ = monozygotic, DZ = dizygotic same sex, DOS = dizygotic opposite sex

Analyses

To estimate heritability, the classical twin model focuses on the difference in resemblance (correlation or covariance) for a particular trait between dizygotic twin pairs (DZ) who share on average half of their segregating genes and monozygotic twins (MZ) 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. Additionally, common environmental effects are suggested to also 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 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 were 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 age 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. Next, significance of the common and genetic environmental factors was assessed by constraining their influence at zero. Last, the significance of new genetic effects coming into play at age 12 was tested. Figure 1 presents the longitudinal model for 2 twins whose brain volumes were assessed at ages 9 and 12 years, 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 chi-square ($\chi 2$) 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 done for 14 related traits (left and right volume of 7 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 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).

Figure 1. Longitudinal genetic path model for two twins with brain volume data at ages 9 and 12 years.



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 age 9 and 12 ; E = unique environment factor score at age 9 and 12 ; Ra = correlation between factor scores of twins (Ra = 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:

$$r(g) = \frac{a_9 \text{ x } a_{9,12}}{\sqrt{{a_9}^2} \text{ x } \sqrt{{a_{9,12}}^2 + {a_{12}}^2}} \qquad r(e) = \frac{e_9 \text{ x } e_{9,12}}{\sqrt{{e_9}^2} \text{ x } \sqrt{{e_{9,12}}^2 + {e_{12}}^2}}$$

Results

Brain volumes at age 9 and 12 years

Table 1 presents sample characteristics at ages 9 and 12 years. Comparing height, weight and Tanner data between the 2 ages, we see the expected biological maturation. Figure 2 and supplementary Table 1 summarize the volumes of the subcortical structures. The (left and right) thalamus, amygdala, putamen and pallidum were significantly larger in boys than in girls at age 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 α=0.005 these differences do not always reach statistical significance (Supplementary 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 Supplementary Table S2).

Volumes of the subcortical brain structures between 9 and 12 years 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 (Figure 2, and Supplementary Table S3).

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 (Supplementary 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 (Supplementary Tables S4-10). Table 2 summarizes for all subcortical brain volumes at age 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 0.43-0.76 at age 9, and from 0.42-0.72 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 Supplementary Tables S4-10). 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 Figure 1), from the model did not change the fit of nearly all brain volumes (S4-10). This indicates that the same genetic factors are influencing subcortical brain volumes at age 9 and at age 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 Supplementary Table S11).

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

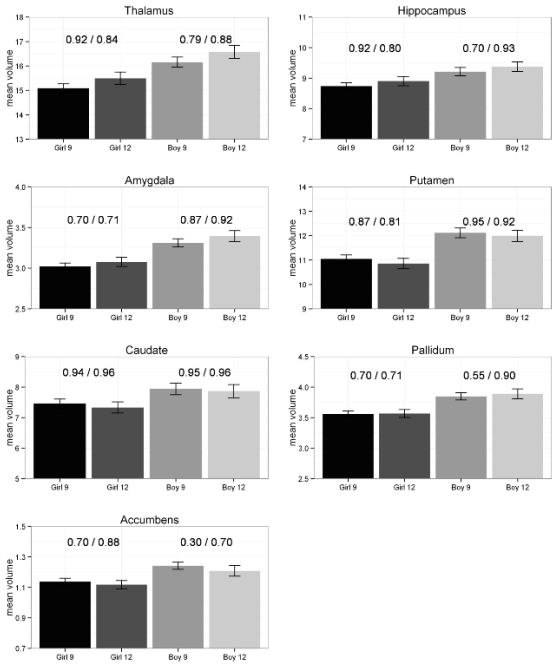


Table 2. ACE and AE model estimates (with 95% confidence intervals) and genetic correlations at age 9 and age 12, covariance explained by shared genetic factors, and fit in the AE model.

		ACE model estimates (95% CI)						AE model estimates (95% CI) 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	.70	.02	.28	.63	.01	.36	.72	.28	.64	.36	1	93	.17	1
		(.29-.81)	(0-.40)	(.19-.41)	(.27-.78)	(0-.32)	(.22-.54)	(.59-.81)	(.19-.41)	(.46-.77)	(.22-.54)				
	R	.76	0	.24	.72	0	.28	.76	.24	.72	.28	1	90	.32	1
		(.37-.85)	(0-.36)	(.15-.36)	(.31-.82)	(0-.38)	(.18-.44)	(.64-.85)	(.15-.36)	(.56-.82)	(.18-.44)				
Hippocampus	L	.63	.06	.31	.58	.14	.28	.68	.32	.72	.28	1	83	.48	.97
		(.21-.79)	(0-.40)	(.20-.49)	(.15-.82)	(0-.52)	(.17-.45)	(.52-.79)	(.21-.48)	(.55-.83)	(.17-.45)				
	R	.72	0	.27	.69	.01	.30	.71	.29	.70	.30	1	80	.58	1
		(.39-.84)	(0-.26)	(.16-.45)	(.17-.82)	(0-.46)	(.18-.50)	(.51-.83)	(.17-.49)	(.48-.82)	(.18-.52)				
Amygdala	L	.61	0	.39	.72	0	.28	.61	.39	.72	.28	1	83	.40	1
		(.25-.73)	(0-.32)	(.27-.56)	(.35-.84)	(0-.29)	(.16-.48)	(.44-.73)	(.27-.56)	(.52-.84)	(.16-.48)				
	R	.65	.05	.30	.53	.04	.44	.70	.30	.56	.44	1	87	.25	1
		(.19-.80)	(0-.46)	(.20-.45)	(.12-.71)	(0-.42)	(.28-.62)	(.56-.80)	(.20-.44)	(.38-.71)	(.29-.62)				
Putamen	L	.73	.18	.09	.71	.17	.12	.91	.09	.88	.12	1	100	-.04	.84
		(.44-.94)	(0-.47)	(.06-.15)	(.39-.92)	(0-.49)	(.07-.20)	(.85-.94)	(.06-.15)	(.79-.93)	(.07-.21)				
	R	.61	.27	.12	.63	.19	.18	.87	.13	.82	.18	1	97	.14	.57
		(.34-.90)	(0-.53)	(.08-.19)	(.34-.87)	(0-.47)	(.11-.28)	(.81-.91)	(.09-.19)	(.72-.88)	(.12-.28)				
Caudate	L	.50	.24	.26	.58	.21	.21	.74	.26	.79	.21	1	83	.66	.68
		(.14-.82)	(0-.55)	(.17-.40)	(.17-.86)	(0-.57)	(.13-.36)	(.62-.83)	(.17-.38)	(.66-.87)	(.13-.34)				
	R	.43	.32	.26	.42	.33	.26	.75	.25	.75	.25	1	82	.67	.47
		(.06-.81)	(0-.62)	(.16-.41)	(.04-.81)	(0-.64)	(.15-.42)	(.62-.84)	(.13-.38)	(.60-.85)	(.15-.40)				
Pallidum	L	.63	0	.37	.67	.01	.32	.63	.37	.68	.32	1	1	-.01	1
		(.34-.77)	(0-.22)	(.23-.56)	(.25-.80)	(0-.44)	(.20-.51)	(.44-.76)	(.24-.56)	(.49-.80)	(.20-.51)				
	R	.46	.03	.50	.49	.10	.41	.50	.50	.59	.41	1	91	-.11	.99
		(.05-.67)	(0-.32)	(.32-.74)	(.03-.75)	(0-.53)	(.25-.64)	(.28-.67)	(.33-.72)	(.36-.75)	(.25-.64)				
Accumbens	L	.09	.22	.70	.22	.05	.73	.32	.68	.25	.75	1	69	.16	.77
		(0-.51)	(0-.44)	(.49-.89)	(0-.57)	(0-.35)	(.41-.99)	(.09-.53)	(.47-.91)	(.01-.55)	(.45-.99)				
	R	.53	0	.46	.62	0	.38	.53	.47	.61	.39	1	85	.24	1
		(.12-.68)	(0-.37)	(.32-.65)	(.16-.77)	(0-.39)	(.23-.60)	(.35-.68)	(.32-.65)	(.40-.77)	(.23-.60)				

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 age 9 and 12; r(e)= environmental correlation, p= likelihood-ratio test statistic comparing the AE submodel to the ACE model.

Table 3. Heritability estimates (left / right) from twin studies in healthy children and adults. For each study the number of twin pairs (MZ/DZ) and age range (and mean) of the sample is given.

Children	N pairs	Age	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., (2009b, 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	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)	54/58	19-69 (31)		80/55						

* 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, hippocampus 58.5/53.2

[1,2,3,4] indicate that analyses are based (partly) on overlapping cohorts.

Note: vmb = 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.

Discussion

In this longitudinal twin study we measured volumes of seven subcortical grey 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 age 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 the present 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 grey 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 the current 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., 2009a; Peper, Hulshoff Pol, Crone, & van Honk, 2011).

The heritability estimates from our 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., 2013a; Kremen et al., 2010). Similarly, from their analyses the lower heritability of the nucleus accumbens as compared to 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 measured 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., 2013a). 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. 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., 2013a; 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 (in e.g., 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 (for example 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 grey matter structures.

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

	Girls				**Boys**				
	N 9/12	**9**	**12**	**%**	**N 9/12**	**9**	**12**	**%**	
Thalamus L	106/63	7.56 (.58)	7.85 (.69)	3.8*	101/70	8.20 (.70)	8.44 (.73)	2.9	∩∟
Thalamus R	106/63	7.42 (.53)	7.56 (.66)	1.9	101/70	7.92 (.58)	8.12 (.64)	2.5*	∩∟
Hippocampus L	105/62	4.44 (.39)	4.53 (.42)	2.0*	100/69	4.67 (.42)	4.77 (.42)	2.1	
Hippocampus R	106/62	4.28 (.36)	4.35 (.40)	1.6	99/68	4.52 (.40)	4.60 (.40)	1.8	
Amygdala L	106/63	1.48 (.14)	1.52 (.14)	2.7*	101/69	1.64 (.17)	1.68 (.17)	2.4	∩∟
Amygdala R	106/63	1.53 (.14)	1.57 (.16)	2.6	101/70	1.70 (.17)	1.75 (.18)	2.9	∩∟
Putamen L	106/63	5.59 (.53)	5.62 (.59)	0.5	101/70	6.19 (.63)	6.16 (.57)	-0.5*	∩∟
Putamen R	106/63	5.44 (.53)	5.40 (.56)	-.07	101/70	5.97 (.57)	5.89 (.60)	-1.3	∩∟
Caudate L	106/62	3.67 (.45)	3.63 (.46)	-1.1	100/69	4.02 (.58)	3.94 (.52)	-2.0	
Caudate R	105/63	3.73 (.49)	3.69 (.49)	-1.1	100/68	3.99 (.57)	3.96 (.57)	-0.8	
Pallidum L	106/63	1.85 (.17)	1.88 (.18)	1.6*	101/70	2.02 (.18)	2.06 (.21)	2.0*	∩∟
Pallidum R	106/63	1.67 (.17)	1.71 (.15)	2.4	101/70	1.82 (.21)	1.85 (.23)	1.6	∩∟
Accumbens L	105/61	.54 (.08)	.54 (.08)	0	101/70	.60 (.09)	.58 (.10)	-3.3	∩
Accumbens R	106/62	.61 (.07)	.58 (.08)	-4.9*	101/70	.65 (.08)	.62 (.09)	-4.6*	∩

* indicates that the change in volume between age 9 and 12 is significant

∩ indicates significant difference in volume between boys and girls at age 9

∟ indicates significant difference in volume between boys and girls at age 12

Table S2. Correlations between change in brain volume (left / right) and change in height (centimeter) and weight (kilogram), separately for girls and boys.

		Change in height (Left / Right)	Change in weight (Left / Right)
Girls	Thalamus	-.03 / .07	.12 / -.03
	Hippocampus	.03 / .34*	.00 / .15
	Amygdala	-.09 / -.05	-.03 / -.02
	Putamen	-.03 / .10	.06 / -.13
	Caudate	.03 / -.08	.08 / -.17
	Pallidum	.15 / .02	.10 / -.16
	Accumbens	.09 / .01	.07 / .34*
Boys	Thalamus	-.17 / -.14	.00 / -.04
	Hippocampus	.01 / -.07	.01 / -.22
	Amygdala	.02 / .09	-.15 / .18
	Putamen	-.07 / -.06	-.13 / -.10
	Caudate	.03 / -.15	.10 / -.04
	Pallidum	.14 / .03	.20 / .08
	Accumbens	-.13 / -.05	.05 / -.13

* = significant at α=0.01.

Table S3. 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.

	Thalamus		Hippocampus		Amygdala		Putamen		Caudate		Pallidum		Accumbens	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Fit:														
-2LL	7.5	1886.54	1617.93	1547.48	1003.33	1061.65	1732.62	1784.31	1677.14	1689.94	1191.24	1225.74	2302.45	2153.71
df	270	270	266	265	269	270	270	270	267	266	270	270	267	269
AIC	1476.28	1346.54	1085.93	1017.48	465.33	521.65	1192.62	1244.31	1143.14	1157.94	651.24	685.74	1768.45	1615.71
Phenotypic correlation volume age 9-12														
girls	.92	.84	.93	.80	.70	.71	.87	.81	.94	.96	.70	.71	.70	.88
boys	.79	.88	.70	.93	.87	.92	.95	.92	.95	.96	.55	.90	.30	.70
Twin correlations, age 9														
MZM	.79	.80	.75	.70	.67	.78	.94	.86	.65	.67	.66	.63	.12	.65
DZM	.60	.24	.48	.38	.32	.17	.29	.05	.56	.70	-.07	.12	.47	.34
MZF	.72	.80	.59	.82	.51	.85	.91	.87	.85	.85	.58	.46	.34	.71
DZF	.11	.43	.47	.25	.54	.24	.47	.70	.18	.09	.04	-.07	.22	.45
DZMF	.35	.51	.14	-.18	.07	.61	.73	.85	.60	.67	.42	.10	.24	-.11
Twin correlations, age 12														
MZM	.59	.70	.66	.73	.87	.65	.96	.86	.72	.64	.76	.79	.70	.53
DZM	-.03	.49	.27	.52	.08	.11	.27	.27	.59	.43	.68	.63	-.09	.16
MZF	.77	.79	.85	.66	.61	.71	.88	.70	.89	.75	.58	.26	.42	.79
DZF	.30	.32	.74	.80	.35	.22	.67	.72	.26	.52	.06	.02	-.16	.60
DZMF	-.11	-.13	.39	-.26	-.13	.41	.58	.64	.65	.64	.57	.47	-.34	.47
Twin correlations, cross age														
MZM	.80	.72	.49	.61	.85	.61	.91	.86	.68	.71	.66	.48	.52	.51
DZM	.31	.21	.33	.47	.20	.09	.62	.10	.52	.58	.15	.28	.28	.14
MZF	.88	.82	.88	.58	.77	.91	.91	.82	.90	.76	.58	.35	.08	.85
DZF	.26	.54	.57	.36	.30	.27	.67	.51	.17	.49	.28	.14	-.06	.69
DZ M_9F_{12}	.36	.31	.42	-.57	-.16	.37	.72	.77	.71	.55	.49	.54	.38	.19
DZ $M_{12}F_9$	-.08	.07	.18	.05	.08	.19	.68	.68	.47	.80	.52	.01	.12	-.32

2-LL = -2 log likelihood; df = degrees of freedom; MZM = monozygotic males; DZM= dizygotic males; MZF = monozygotic females; DZF = dizygotic females; DZMF = dizygotic opposite-sex twin pairs

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		1476.28	2016.28	270			
	1	Age 9, no sex difference	Sat	1490.92	2064.92	287	48.64	17	0
	2	Age 12, no sex difference	Sat	1487.41	2061.41	287	45.13	17	0
	3	Boys, no age difference	Sat	1471.12	2045.12	287	28.84	17	0.04
	4	Girls, no age difference	Sat	1487.37	2061.37	287	45.09	17	0
	ACE	Full ACE		1446.72	2080.72	317			
	1	Ra DZMF =0.5	ACE	1444.98	2080.98	318	.26	1	0.61
	2	No sex difference	1	1437.85	2091.85	327	10.87	9	0.28
	3	CE	2	1443.55	2103.55	330	11.7	3	0.01
	4	AE	2	1431.86	2091.86	330	.01	3	1
	5*	AE, drop a12	4	1429.86	2091.86	331	0	1	1
	6	AE, drop a9,12	4	1481.71	2143.71	331	51.85	1	0
Right	Sat	Saturated		1346.54	1886.54	270			
	1	Age 9, no sex difference	Sat	1358.49	1932.49	287	45.96	17	0
	2	Age 12, no sex difference	Sat	1355.16	1929.16	287	42.63	17	0
	3	Boys, no age difference	Sat	1361.56	1935.56	287	49.03	17	0
	4	Girls, no age difference	Sat	1347.86	1921.86	287	35.33	17	0.01
	ACE	Full ACE		1321.35	1955.35	317			
	1	Ra DZMF =0.5	ACE	1321.39	1957.39	318	2.04	1	0.15
	2	No sex difference	1	1307.83	1961.83	327	4.43	9	0.88
	3	CE	2	1316.85	1976.85	330	15.03	3	0.002
	4	AE	2	1301.83	1961.83	330	0	3	1
	5*	AE, drop a12	4	1299.83	1961.83	331	0	1	1
	6	AE, drop a9,12	4	1356.32	2018.32	331	56.5	1	0

***** *indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		1085.93	1617.93	266			
	1	Age 9, no sex difference	Sat	1081.13	1647.13	283	29.2	17	0.03
	2	Age 12, no sex difference	Sat	1079.86	1645.86	283	27.93	17	0.05
	3	Boys, no age difference	Sat	1085.93	1651.93	283	34	17	0.01
	4	Girls, no age difference	Sat	1090.4	1656.4	283	38.47	17	0
	ACE	Full ACE		1054.36	1680.36	313			
	1	Ra DZMF =0.5	ACE	1052.73	1680.73	314	.37	1	0.54
	2	No sex difference	1	1047.51	1693.51	323	12.77	9	0.17
	3	CE	2	1049.95	1701.95	326	8.44	3	0.04
	4	AE	2	1041.78	1693.78	326	.27	3	0.97
	5*	AE, drop a_{12}	4	1039.82	1693.82	327	.01	1	0.83
	6	AE, drop $a_{9,12}$	4	1082.65	1736.65	327	42.87	1	0
Right	Sat	Saturated		1017.48	1547.48	265			
	1	Age 9, no sex difference	Sat	1015.03	1579.03	282	31.55	17	0.02
	2	Age 12, no sex difference	Sat	1013.14	1577.14	282	29.67	17	0.03
	3	Boys, no age difference	Sat	1016.82	1580.82	282	33.35	17	0.01
	4	Girls, no age difference	Sat	1014.01	1578.01	282	30.53	17	0.02
	ACE	Full ACE		1009.61	1633.61	312			
	1	Ra DZMF =0.5	ACE	1007.67	1633.67	313	.06	1	0.8
	2	No sex difference	1	1009.95	1653.95	322	20.28	9	0.02
	3	CE	2	1018.27	1668.27	325	14.33	3	0.002
	4	AE	2	1003.95	1653.95	325	0	3	1
	5*	AE, drop a_{12}	4	1005.73	1657.73	326	3.78	1	0.05
	6	AE, drop $a_{9,12}$	4	1034.66	1686.66	326	32.73	2	0

***** *indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		465.33	1003.33	269			
	1	Age 9, no sex difference	Sat	487.17	1059.17	286	55.84	17	0
	2	Age 12, no sex difference	Sat	484.77	1056.77	286	53.44	17	0
	3	Boys, no age difference	Sat	465.48	1037.48	286	34.15	17	0.01
	4	Girls, no age difference	Sat	471.49	1043.49	286	40.16	17	0
	ACE	Full ACE		435.82	1067.82	316			
	1	Ra DZMF =0.5	ACE	434.22	1068.22	317	.41	1	0.52
	2	No sex difference	1	425	1077	326	8.78	9	0.46
	3	CE	2	429.56	1087.56	329	10.56	3	0.01
	4	AE	2	419	1077	329	0	3	1
	5*	AE, drop a_{12}	4	417	1077	330	0	1	1
	6	AE, drop $a_{9,12}$	4	454.72	1114.72	330	37.73	1	0
Right	Sat	Saturated		521.65	1061.65	270			
	1	Age 9, no sex difference	Sat	554.29	1128.29	287	66.64	17	0
	2	Age 12, no sex difference	Sat	541.43	1115.43	287	53.78	17	0
	3	Boys, no age difference	Sat	516.79	1090.79	287	29.14	17	0.03
	4	Girls, no age difference	Sat	520.3	1094.3	287	32.65	17	0.01
	ACE	Full ACE		496.24	1130.24	317			
	1	Ra DZMF =0.5	ACE	496.28	1132.28	318	2.04	1	0.15
	2	No sex difference	1	484.25	1138.25	327	5.96	9	0.74
	3	CE	2	486.8	1146.8	330	8.55	3	0.04
	4	AE	2	478.29	1138.29	330	.04	3	1
	5*	AE, drop a_{12}	4	476.29	1138.29	331	0	1	1
	6	AE, drop $a_{9,12}$	4	521.97	1183.97	313	45.68	1	0

***** *indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		1192.62	1732.62	270			
	1	Age 9, no sex difference	Sat	1220.38	1794.38	287	61.76	17	0
	2	Age 12, no sex difference	Sat	1210.25	1784.25	287	51.63	17	0
	3	Boys, no age difference	Sat	1194.37	1768.37	287	35.75	17	0
	4	Girls, no age difference	Sat	1188.63	1762.63	287	30.01	17	0.03
	ACE	Full ACE		1190.56	1824.56	317			
	1	Ra DZMF =0.5	ACE	1190.57	1826.57	318	2	1	0.16
	2	No sex difference	1	1181.06	1835.06	327	8.5	9	0.48
	3	CE	2	1216.17	1876.17	330	41.1	3	0
	4	AE	2	1175.89	1835.89	330	.83	3	0.84
	5*	AE, drop a_{12}	4	1174	1836	331	.11	1	0.74
	6	AE, drop $a_{9,12}$	4	1294.47	1956.47	331	120.58	1	0
Right	Sat	Saturated		1244.31	1784.31	270			
	1	Age 9, no sex difference	Sat	1262.5	1836.5	287	52.18	17	0
	2	Age 12, no sex difference	Sat	1254.23	1828.23	287	43.91	17	0
	3	Boys, no age difference	Sat	1231.97	1805.97	287	21.66	17	0.2
	4	Girls, no age difference	Sat	1238.28	1812.28	287	27.97	17	0.05
	ACE	Full ACE		1206.09	1840.09	317			
	1	Ra DZMF =0.5	ACE	1209	1845	318	4.91	1	0.03
	2	No sex difference	1	1195.55	1849.55	327	4.55	9	0.87
	3	CE	2	1213.33	1873.33	330	23.78	3	0
	4	AE	2	1191.56	1851.56	330	2.02	3	0.57
	5*	AE, drop a_{12}	4	1189.56	1851.56	331	0	1	1
	6	AE, drop $a_{9,12}$	4	1286.13	1948.13	331	96.57	1	0

** indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		1143.14	1677.14	267			
	1	Age 9, no sex difference	Sat	1138.46	1706.46	284	29.32	17	0.03
	2	Age 12, no sex difference	Sat	1136.18	1704.18	284	27.05	17	0.06
	3	Boys, no age difference	Sat	1126.58	1694.58	284	17.44	17	0.42
	4	Girls, no age difference	Sat	1125.27	1693.27	284	16.13	17	0.51
	ACE	Full ACE		1104.23	1732.23	314			
	1	Ra DZMF =0.5	ACE	1104.85	1734.85	315	2.61	1	0.11
	2	No sex difference	1	1105.95	1753.95	324	19.11	9	0.02
	3	CE	2	1107.94	1761.94	327	7.99	3	0.05
	4	AE	2	1101.46	1755.46	327	1.5	3	0.68
	5*	AE, drop a_{12}	4	1099.46	1755.46	328	0	1	1
	6	AE, drop $a_{9,12}$	4	1156.32	1812.32	328	56.87	1	0
Right	Sat	Saturated		1157.94	1689.94	266			
	1	Age 9, no sex difference	Sat	1158.93	1724.93	283	34.99	17	0.01
	2	Age 12, no sex difference	Sat	1156.61	1722.61	283	32.66	17	0.01
	3	Boys, no age difference	Sat	1157.45	1723.45	283	33.5	17	0.01
	4	Girls, no age difference	Sat	1155.01	1721.01	283	31.06	17	0.02
	ACE	Full ACE		1134.59	1760.59	313			
	1	Ra DZMF =0.5	ACE	1134.94	1762.95	314	2.36	1	0.12
	2	No sex difference	1	1129	1775	323	12.06	9	0.21
	3	CE	2	1128.2	1780.2	326	5.19	3	0.16
	4	AE	2	1125.52	1777.52	215	2.52	3	0.47
	5*	AE, drop a_{12}	4	1123.52	1777.52	327	0	1	1
	6	AE, drop $a_{9,12}$	4	1179.56	1833.56	327	56.04	1	0

***** *indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		651.24	1191.24	270			
	1	Age 9, no sex difference	Sat	679.05	1253.05	287	61.8	17	0
	2	Age 12, no sex difference	Sat	665.87	1239.87	287	48.62	17	0
	3	Boys, no age difference	Sat	653.14	1227.14	287	35.9	17	0
	4	Girls, no age difference	Sat	787.34	1361.34	287	170.1	17	0
	ACE	Full ACE		644.48	1278.48	317			
	1	Ra DZMF =0.5	ACE	642.51	1278.51	318	.02	1	0.88
	2	No sex difference	1	630.6	1284.6	327	6.09	9	0.73
	3	CE	2	638.03	1298.03	330	13.43	3	0.004
	4	AE	2	624.6	1284.6	330	0	3	1
	5*	AE, drop a_{12}	4	622.6	1284.6	331	0	1	1
	6	AE, drop $a_{9,12}$	4	660.85	1322.85	331	38.25	1	0
Right	Sat	Saturated		685.74	1225.74	270			
	1	Age 9, no sex difference	Sat	712.49	1286.49	287	60.75	17	0
	2	Age 12, no sex difference	Sat	694.17	1268.17	287	42.43	17	0
	3	Boys, no age difference	Sat	684	1258	287	32.25	17	0.01
	4	Girls, no age difference	Sat	686.59	1260.59	287	34.85	17	0.01
	ACE	Full ACE		673.3	1306.55	317			
	1	Ra DZMF =0.5	ACE	670.83	1306.83	318	.28	1	0.6
	2	No sex difference	1	671.04	1325.04	327	18.21	9	0.03
	3	CE	2	669.83	1329.83	330	4.79	3	0.19
	4	AE	2	665.17	1325.17	330	.13	3	0.99
	5*	AE, drop a_{12}	4	663.17	1325.17	331	0	1	1
	6	AE, drop $a_{9,12}$	4	687.67	1349.67	313	24.5	1	0

** indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		Model fitted	Against	AIC	-2LL	df	Δ-2LL	Δdf	p
Left	Sat	Saturated		1768.45	2302.45	270			
	1	Age 9, no sex difference	Sat	1772.9	2340.9	284	38.45	17	0
	2	Age 12, no sex difference	Sat	1766.45	2334.45	284	32	17	0.02
	3	Boys, no age difference	Sat	1758.83	2326.83	284	24.37	17	0.11
	4	Girls, no age difference	Sat	1758.85	2326.85	284	24.4	17	0.11
	ACE	Full ACE		1732.7	2360.7	314			
	1	Ra DZMF =0.5	ACE	1731.42	2361.42	315	.72	1	0.4
	2	No sex difference	1	1725	2373	324	11.58	9	0.24
	3*	CE	2	1719.72	2373.72	327	.72	3	0.87
	4	AE	2	1720.16	2374.16	327	1.16	3	0.76
	5	AE, drop a_{12}	4	1718.2	2374.2	328	.01	1	0.84
	6	AE, drop $a_{9,12}$	4	1723.76	2379.76	328	5.6	1	0.02
Right	Sat	Saturated		1615.71	2153.71	269			
	1	Age 9, no sex difference	Sat	1619.23	2191.23	286	37.52	17	0
	2	Age 12, no sex difference	Sat	1615.57	2187.57	286	33.86	17	0.01
	3	Boys, no age difference	Sat	1624.4	2196.4	286	42.68	17	0
	4	Girls, no age difference	Sat	1625	2197	286	43.29	17	0
	ACE	Full ACE		1607.89	2239.89	316			
	1	Ra DZMF =0.5	ACE	1606.93	2240.93	317	1.04	1	0.31
	2	No sex difference	1	1596.32	2248.32	326	7.39	9	0.06
	3	CE	2	1597.95	2255.95	329	7.63	3	0.05
	4	AE	2	1590.32	2248.32	329	.01	3	1
	5*	AE, drop a_{12}	4	1588.32	2248.32	330	0	1	1
	6	AE, drop $a_{9,12}$	4	1621.52	2281.52	330	33.2	1	0

***** *indicates the best fitting model.*

AIC = Akaike Information Criterion; -2LL = -2 log likelihood; df= degrees of freedom; p = p-value.

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

		A	C	E
Thalamus	Left	0.0014	0.0012	0.9974
	Right	0.0199	0.0	0.9801
Hippocampus	Left	0.0003	0.0555	0.9442
	Right	0.3146	0.0101	0.6753
Amygdala	Left	0.0141	0.0	0.9859
	Right	0.0021	0.0016	0.9963
Putamen	Left	0.0515	0.0005	0.9480
	Right	0.0133	0.0081	0.9786
Caudate	Left	0.0077	0.0616	0.9307
	Right	0.0018	0.0059	0.9922
Pallidum	Left	0.0150	0.0060	0.9790
	Right	0.0013	0.0238	0.9749
Accumbens	Left	0.0378	0.0363	0.9259
	Right	0.0229	0.0078	0.9693

A= additive genetic effects; C= common environment; E= unique environment.