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Genetic Architecture of Subcortical Brain Regions: Common and Region-Specific Genetic Contributions

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Abstract

Understanding the etiology of patterns of variation within and covariation across brain regions is key to advancing our understanding of the functional, anatomical and developmental networks of the brain. Here we applied multivariate twin modeling and principal component analysis (PCA) to investigate the genetic architecture of the size of seven subcortical regions (caudate nucleus, thalamus, putamen, pallidum, hippocampus, amygdala and nucleus accumbens) in a genetically informative sample of adolescents and young adults ($N=1,038$; mean age= 21.6 ± 3.2 years; including 148 monozygotic and 202 dizygotic twin pairs) from the Queensland Twin IMaging (QTIM) Study. Our multivariate twin modeling identified a common genetic factor that accounts for all the heritability of intracranial volume (0.88) and a substantial proportion of the heritability of all subcortical structures, particularly those of the thalamus (0.71 out of 0.88), pallidum (0.52 out of 0.75) and putamen (0.43 out of 0.89). In addition, we also found substantial region-specific genetic contributions to the heritability of the hippocampus (0.39 out of 0.79), caudate nucleus (0.46 out of 0.78), amygdala (0.25 out of 0.45) and nucleus accumbens (0.28 out of 0.52). This provides further insight into the extent and organization of multiple genetic factors, which include developmental and general growth pathways, as well as functional specialization and maturation trajectories that influence each subcortical region.

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Keywords

Subcortical Volumes; Twin Study; Covariation; Structural MRI; Heritability; Multivariate

INTRODUCTION

Previous studies in both developing children (Supekar *et al.*, 2009) and healthy aging adults (Raz *et al.*, 2004, Raz *et al.*, 1997, Raz *et al.*, 2005) have shown covariation across different brain regions at the phenotypic level. For certain regions, these patterns of covariation remain significant even after accounting for the effects of factors such as age and overall brain size (Allen *et al.*, 2002, Colibazzi *et al.*, 2008, Kennedy *et al.*, 1998, Mechelli *et al.*, 2005). Thus, it is suggested that further research into the etiology of volumetric covariance may provide insights into the anatomical and functional networks of the brain in both health and disease (Colibazzi *et al.*, 2008).

Subcortical brain structures of the basal ganglia and limbic system co-vary in size and this covariation may reflect developmental and/or functional relationships amongst inter-connected regions (Eyler *et al.*, 2011). In addition, each subcortical region performs highly specialized functions. For instance, the hippocampus, amygdala and caudate nucleus are involved in memory formation, emotional processing and motor coordination, respectively (Bird & Burgess, 2008, Feinstein *et al.*, 2011, Grahm *et al.*, 2009). Also, each region follows a characteristic maturation trajectory across the lifespan according to its function (Eyler *et al.*, 2011, Raznahan *et al.*, 2014, Walhovd *et al.*, 2014). Therefore, correlation patterns among subcortical regions could result from both developmental similarities and/or functional associations.

Several studies have shown that genetic factors account for 50–80% of variance in subcortical structures (Den Braber *et al.*, 2013, Kremen *et al.*, 2010, Wallace *et al.*, 2006). A recent study of middle-age male twins (Eyler *et al.*, 2011) used hierarchical clustering and PCA to show that patterns of covariation among subcortical regions are partly due to common genes. Four correlated factors were identified. However, it is not known whether these genetic patterns are established earlier in life and/or are the product of regional losses due to mechanisms involved in aging (Eyler *et al.*, 2011), nor whether the patterns are similar in males and females. Similarly, the extent of common vs. region-specific genetic influences for each subcortical region has not been quantified, and may be useful for ongoing neuroimaging genetic efforts (Thompson *et al.*, 2014).

Here we explore the genetic architecture of subcortical brain volumes in a large sample of young adult twins, including both males and females. We used multivariate genetic modeling to investigate genetic and environmental sources of covariation across seven subcortical structures (thalamus, putamen, caudate nucleus, hippocampus, pallidum, amygdala and nucleus accumbens), and quantified the degree of region-specific vs. common genetic contributions across regions. We predicted that young adults would show a similar genetic architecture to that found in middle aged adults (Eyler *et al.*, 2011). This would in turn support the hypothesis of earlier developmental factors contributing to the association/relationship among subcortical regions.

MATERIALS & METHODS

Participants

Participants included 1038 twins and siblings from the Queensland Twin IMaging (QTIM) (De Zubicaray *et al.*, 2008) project. This is an ongoing study examining healthy young adult twins with structural and functional magnetic-resonance imaging (MRI) and high-resolution diffusion tensor imaging (DTI) (Blokland *et al.*, 2011, Braskie *et al.*, 2011, Chiang *et al.*, 2009, Jahanshad *et al.*, 2010). While the descriptive analyses were conducted on the entire sample (N=1,038), the genetic analyses focused only on available data from 350 complete twin pairs (n=700): 100 monozygotic (MZ) female, 48 MZ male, 81 dizygotic (DZ) female, 39 DZ male and 82 opposite-sex pairs (mean age=21.6 ± 3.19 years; range=16–29). All participants were screened (by self-report) for their suitability for imaging, as well as any significant medical, psychiatric, or neurological conditions (including head injuries), current or past diagnosis of substance abuse, and for current use of psychoactive medication. Twins were approached to participate in QTIM only if they were Caucasian and right-handed for throwing and writing as assessed by the Annett's Handedness Questionnaire (Annett, 1970), in order to achieve homogeneity in the imaging sample. Zygosity of same-sex twins was established by DNA typing of 9 markers (AmpF1STR Profiler Plus Amplification KIT, Applied Biosystems Inc.) and later confirmed for >80% of the sample who were genotyped on the Illumina 610K SNP array. 75 percent of twin pairs were scanned together on the same day, with the remainder, on average, within 12 days of each other. In addition, 80 participants (13 MZ and 14 DZ pairs, and 26 single twins) were rescanned (mean time between scans = 120 days ± 55 SD) after their initial scan to assess test-retest reliability of the protocol. Informed consent was obtained from each participant and parent or guardian for participants under 18 years of age. The study was approved by the Human Research Ethics Committees of the Queensland Institute of Medical Research, the University of Queensland, and Uniting Health Care, Wesley Hospital.

MRI Acquisition and Processing

We acquired T1-weighted whole-brain scans with an inversion recovery rapid gradient echo sequence on a 4 Tesla MRI scanner (Bruker Medspec; with acquisition parameters: TI/TR/TE=700/1500/3.35 ms; flip angle=8°; slice thickness=0.9 mm; matrix=256×256×256).

Images were analysed using FIRST (FSL v4.1.9), an automated processing pipeline which performs segmentation and registration of subcortical structures. Input images were registered to the Montreal Neuroscience Institute (MNI) space through two-stage affine transformation. Shape models were then used to segment subcortical structures, with a boundary correction program determining if neighboring voxels belong to the structure or not. Slight modifications as per the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) consortium's imaging protocol (http://enigma.loni.ucla.edu/wp-content/uploads/2012/03/ENIGMA_FSL_FIRST_Protocol.doc) were made to improve the MNI space transformation. 14 subcortical regions of interest (ROI) were extracted, including bi-lateral measures of the thalamus, caudate nucleus, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens. Quality of delineation was assessed following the ENIGMA protocol for subcortical structures (<http://enigma.loni.ucla.edu/protocols/imaging->

protocols/quality-checking-subcortical-structures), which resulted in the exclusion of 1.25% of volumes. Intracranial volume (ICV) was calculated as the inverse of the determinant of the affine transformation matrix, multiplied by the size of the MNI template.

In addition, we also used the software package FreeSurfer (FS) (v5.1, <http://surfer.nmr.mgh.harvard.edu/>) to extract the sub-cortical volumes in a subset of 80 participants that had been scanned twice. As discussed by Fischl et al. (Fischl *et al.*, 2002), images are skull stripped, transformed to Talairach space and a probabilistic atlas is used to assign each voxel a neuroanatomical label. FreeSurfer also provides a measure of ICV. Quality control following the ENIGMA consortium guidelines was conducted and resulted in the exclusion of 1.83% of FreeSurfer observations.

Subcortical Volumes—Using the 80 participants that were scanned twice, we first compared the sub-cortical volumes extracted using both software packages – FSL-FIRST and FS – and assessed their test-retest reliability through *Pearson* correlations. Our choice of test-retest correlation over other methods such as intra-class correlation was because, being a structural measure, we did not expect any considerable change in true scores, as it is common in, for example, functional MRI or cognitive test/tasks, due to learning or carry-over effects. Mean volume estimates tended to be higher when extracted with FS compared with FSL-FIRST. However this trend was only significant for the amygdalae (FS: left=1863, right=1954 mm³; vs. FSL: left=856, right=806 mm³) and right nucleus accumbens (FS: 834, FSL: 429 mm³). Because the amygdala and nucleus accumbens are the smallest of the subcortical structures, variability as a proportion of size is expected to be higher and likely to be exacerbated through different processing methods. In addition, the borders defining both structures are difficult to delineate, and likely to differ between automated pipelines due to the use of different reference atlases. Increased variability between automated measures has been previously reported for the nucleus accumbens (Hanson *et al.*, 2012) and amygdala (Dewey *et al.*, 2010, Hanson *et al.*, 2012, Morey *et al.*, 2009). As the test-retest reliabilities in the current sample were overall higher for FSL volumes compared with FS, including the nucleus accumbens and amygdala, a decision was made to process the entire sample ($N=1,038$) with FSL. No significant differences in the skewness of the distributions were observed, regardless of segmentation method used.

Data Analysis

Quality Control—Following segmentation of the full sample ($N=1,038 \times 14$ subcortical regions and ICV), we excluded 0.61% of volumes (2 L-pallidum, 5 R-pallidum, 7 L-thalamus, 3 R-thalamus, 5 L-putamen, 6 R-putamen, 3 L-caudate, 9 R-caudate, 11 L-hippocampus, 6 R-hippocampus, 7 L-accumbens, 6 R-accumbens, 10 L-amygdala, 8 R-amygdala) due to poor structure delineation. All variables were normally distributed. 10 individual observations (2 L-thalamus, 1 R-thalamus, 2 R-caudate, 1 R-putamen and 4 R-pallidum) were deemed as outliers (>3.8 SD from the mean) and winsorized.

Twin analyses—We performed standard quantitative analyses to estimate common and region-specific genetic and environmental influences on individual differences in overall and regional subcortical brain volumes (Plomin *et al.*, 2013). The classical twin design

compares similarity in a given trait among pairs of identical (MZ) and fraternal (DZ) twins. While MZ twins share 100% of their genes, DZ twins share an average of 50% of their genes. In a standard ACE model, phenotypic variance in a trait can be disaggregated into three components: additive genetic (A), common environment (C) and unique environment (E). Multiple correlated variables can be analysed and the covariance partitioned into its genetic and environmental components through multivariate twin modeling. A usual starting point in multivariate twin analysis is the Cholesky decomposition, which is a method of triangular decomposition where the first variable (y_1) is assumed to be caused by a latent factor that can explain the variance in the remaining variables ($y_2, \dots, y_n$). The second variable (y_2) is assumed to be caused by a second latent factor (n_2) that can explain variance in the second as well as remaining variables ($y_2, \dots, y_n$). This pattern continues until the final observed variable (y_n) is explained by a latent variable (n_n). For further information, see (Gillespie & Martin, 2005). However, the Cholesky does not distinguish between common factor and specific factor variance and does not estimate a specific factor effect for any variable except the last. Alternate methods such as the common and independent pathway models can be used to estimate common and specific factor variance (Gillespie & Martin, 2005). Finally, two models can be compared using a likelihood ratio chi-squared statistic.

Covariates and Homotopic correlations—We examined covariate effects (sex, age, age², sex*age, sex*age² and ICV) in the whole dataset (N=1,038) using Mx (Neale *et al.*, 2003), which allows adjustment for relatedness among individuals. Out of all the covariates, only sex showed a significant effect. Thus, we carefully controlled for sex effects in all our subsequent analyses. Age effects were non-significant after adjustments for sex.

Phenotypic and genetic correlations across pairs of homotopic regions (mirror structures located in opposite hemispheres; e.g., left- and right- thalamus) were estimated. Moderate to high phenotypic correlations (0.38–0.89), and even higher genetic correlations (0.60–0.93) were observed, suggesting that volumetric variation of mirror structures located in both hemispheres is explained largely by the same genetic factors (Table 1). Therefore, and to avoid redundancy, we performed our genetic analyses on mean bilateral subcortical volumes, all of which showed good reliability (0.66 to 0.90), as shown in Table 1.

Phenotypic and genetic correlations and twin correlations across subcortical regions—We first assessed homogeneity of sampling for all variables by testing whether a reduction in fit of the model resulted by equating means and variances across birth order and zygosity groups. Mean homotopic volumes and ICV were adjusted for sex effects and residualised before estimation of pair-wise correlations. Maximum-likelihood genetic correlations and twin correlations for both five (MZ females, MZ males, DZ females, DZ males, DZ opposite sex) and two (MZ and DZ) zygosity groups were calculated using Mx (Neale *et al.*, 2003).

Multivariate twin modeling—We examined covariation across ICV and the seven subcortical volumes in the subset comprising full twin pairs (n=700) using multivariate twin modelling with Mx (Neale *et al.*, 2003), under a two zygosity (MZ/DZ) model. All variables were adjusted for sex effects. We started with a full Cholesky decomposition model, and then tested the fit of independent and common pathway models (Neale & Cardon, 1992a).

Then, the fit of different submodels with a constrained number of genetic and environmental factors were compared against the fit of the full Cholesky model to determine the minimum number of factors that can explain the genetic relationships between intracranial and subcortical volumes. A standard indicator of better fit is the Akaike information criterion (AIC), with the best fitting model having the lowest AIC.

Principal Component Analysis—Similar to the approach used by (Eyler *et al.*, 2011), we conducted a PCA on both phenotypic and genetic correlation matrices using the promax (oblique) rotation option in the psych package (Revelle, 2013) for R, in which factors are allowed to correlate. Based on a scree plot, the number of factors chosen was four. Altogether, a cumulative variance of over eighty percent was explained by four components, and no considerable gain in explained variance was observed when adding more components.

RESULTS

Preliminary Analyses

To assess (FS vs. FSL-FIRST) cross-method reliability, we calculated both *Pearson* correlations and intra-class correlations (ICC) between the mean bilateral volume estimates obtained with FSL and Freesurfer (given in Table 1) in our test-retest subsample. We observed agreement between both methods in that correlations for both amygdala and nucleus accumbens were lower than those for other subcortical regions. The issue of low reliability for semi-automated segmentation of these structures has been raised previously (Nugent *et al.*, 2013).

Descriptive statistics (mean, standard deviation, range) and twin correlations for ICV and the seven mean subcortical volumes are provided in Table 1. On average, ICV was 14% larger for males than females, which is within the range reported by previous studies (Goldstein *et al.*, 2001, Lenroot *et al.*, 2007). Subcortical volumes were also larger in males compared to females (standardized regression β values ranging from 0.25 to 0.57, or 9–14%), but after controlling for ICV, sex differences were low and only significant for the putamen ($\beta=0.24$), pallidum ($\beta=0.20$) and thalamus ($\beta=0.11$). In addition, ICV accounted for a similar amount of the variance in subcortical volumes for both males and females, with standardized regression β values ranging from 0.32 to 0.72 in males and 0.29 to 0.78 in females (Table 1).

We also explored possible age effects. Although we initially observed a small but significant decrease of subcortical volume with age, this was no longer significant after adjusting for sex, that is, the age effect was due to sample composition, resulting from having slightly more older female than male participants. Further, to eliminate any potential bias due to the relatedness of the sample, covariate effects were explored in a subset comprising one individual per family, finding no significant differences.

Model-fitting analyses revealed homogeneity of sampling with no evidence of birth order [χ^2 ranged 0.88–3.46, $df=1$ (i.e. χ^2_1)] or zygosity effects ($\chi^2_1=0.18$ –3.17) in means nor variances (birth order $\chi^2_1=0.55$ –4.69, zygosity $\chi^2_1=0.12$ –3.45). Maximum-likelihood

twin correlations for both two (MZ/DZ) and five (MZf/MZm/DZf/DZm/DZos) zygosity groups are given in Table 1. MZ correlations ranged from 0.42 (amygdala) to 0.88 (putamen), whereas DZ correlations ranged from 0.22 (nucleus accumbens) to 0.44 (caudate nucleus).

Phenotypic and genetic correlations are given in Table 2 (variables were adjusted for sex effects). At the phenotypic level, ICV displayed the highest correlation with the thalamus (0.76) and the lowest with the nucleus accumbens (0.34) and amygdala (0.30). At the genetic level a similar pattern was observed, with the thalamus (0.86) and amygdala (0.41) displaying the highest and lowest correlations with ICV respectively. The strongest pair-wise correlations at the phenotypic level were those of pallidum with putamen and thalamus (0.60), with the amygdala displaying the lowest phenotypic correlations with other structures (0.10–0.37). Genetic correlations were slightly higher than at the phenotypic level, but overall a similar pattern was observed, with the basal ganglia structures being strongly correlated. Parallel analyses using both left- and right- volumes instead of mean volumes (data not shown) confirmed similar patterns of correlations.

Multivariate genetic modelling

Model fitting statistics are given in Table 3. We found that common environmental (C) factors could be dropped from the fully-saturated ACE Cholesky ($-2LL=188.44$; $df=36$), whereas additive genetic (A) factors could not be dropped without loss of fit ($-2LL=27.78$; $df=36$). The loadings on the genetic factor structure (shown in Table 4) suggested two common factors and six region-specific genetic factors. One common factor influenced overall brain size as well as subcortical volumes (i.e., Factor A1 in column 1), while another comprised only the subcortical regions (i.e., Factor A2 in column 2). Also, region-specific genetic influences were evident for most variables (indicated by the moderately large estimates on the diagonal). An independent pathway model (Neale & Cardon, 1992b) allowing for two common genetic factors (i.e., both an ICV- and a subcortical- genetic factors) and specific genetic influences to each variable also provided a good fit to the data. In fact, both AE Cholesky and AE 2-factor independent pathway models provided a better fit (lower AIC) than the ACE Cholesky (Table 3). While the AE Cholesky (Table 4) provided the best fit, we also present the independent pathway model in Figure 1, as it facilitates the distinction between common cross-region and region-specific genetic factors (Loehlin, 1996).

Heritability estimates of subcortical volumes (Figure 1) were high for ICV (0.88) and most subcortical structures (0.75–0.89), with the only exceptions being the amygdala (0.42) and nucleus accumbens (0.49). The common genetic factor, A_{C1} , explained 81% of the genetic variance in thalamic volume (i.e. 71 out of 88%), compared to only 29% for the amygdala and 31% for the nucleus accumbens. This factor also explained a large proportion of the genetic variance in volume of basal ganglia structures: pallidum 69%, putamen 48%, and caudate nucleus 44%. Common genetic factor A_{C2} showed moderate contributions to the heritability of the pallidum (29%), amygdala (24%), putamen (19%) and nucleus accumbens (12%), and only small contributions to hippocampus (3.84%), caudate (3.84%) and thalamus (1.13%) volumes. Notably, in this model, contributions of region-specific genetic factors

(A_S) were sizeable, accounting for 32–57% of the heritability of caudate nucleus (52%), nucleus accumbens (57%), amygdala (47%), hippocampus (47%) and putamen (32%). Only 1.3% of the heritability in pallidum volume was due to a region-specific genetic factor. Environmental contributions to variance were largely region-specific across structures, with the small overlap across structures in the Factor E1 (Table 4), possibly due to correlated measurement error.

Subsequent modeling including only the volumes for the seven subcortical regions (after adjustment for ICV and sex effects) provided support for both a common subcortical genetic factor and considerable region-specific genetic factors for all structures but the pallidum (shown in Figure 2). The common factor (A_C) explained more than half of the genetic variance in volume for the pallidum, putamen and thalamus, whereas region-specific genetic contributions ($A_{S(1-7)}$) were larger for the caudate, nucleus accumbens and amygdala, and genetic contributions to hippocampal volume were equally split between common and specific factors.

Principal Component Analysis

PCA on the phenotypic correlation matrix identified 4 rotated factors, each with eigenvalues greater than one. Factors B and D resembled the previously reported factors (Eyler *et al.*, 2011), with factor B grouping together the “basal ganglia” structures: putamen, caudate nucleus and pallidum, and factor D clustering apart the nucleus accumbens. The amygdala also formed a factor on its own (factor C), whereas factor A comprised ICV, hippocampus and thalamus. Together, factors A and B explained 56% of the total variance and were correlated with one another (0.67). Factors C and D also showed significant correlations with factors A and B, ranging from 0.34 to 0.43. A similar component composition resulted from using the genetic correlation matrix (data not shown). In addition, excluding ICV from the analysis and including it as a covariate resulted in a similar component composition, except that the loadings for the thalamus were split, with around two thirds loading with hippocampus and the remaining third with the basal ganglia structures (shown in Tables 5 and 6). This is in line with results reported by Eyler *et al.* (2011), in which thalamus volume loaded moderately in both factors. Additionally, the amygdala and nucleus accumbens loaded each on separate factors and all four factors remained strongly correlated.

DISCUSSION

Here we sought to identify patterns of genetic covariation among seven subcortical brain volumes using both genetic modeling and PCA. We used one of the largest MRI-phenotyped twin cohorts to date, comprising both male and female adolescents and young adults. Total heritability estimates were similar to those reported previously for older samples (Den Braber *et al.*, 2013, Kremen *et al.*, 2010). We show that the strong phenotypic covariation across subcortical volumes is largely explained by a common genetic factor. This factor also accounted for all of the genetic variance ($h^2=0.88$) in global head size (ICV). In addition, region-specific genetic contributions explained ~50% or more of the heritability in four of the subcortical volumes. This provides the first quantification of common and region-

specific genetic contributions to variance in subcortical volumes and confirms the genetic architecture suggested in prior work in older male twins (Eyler *et al.*, 2011).

As shown in Figure 1, our multivariate independent pathway model suggests the existence of sets of genes with pleiotropic influences over the size of different brain regions. A_{C1} accounted for all of the genetic variance in overall head size, and explained between 29–81% of the heritability of individual regional volumes. This suggests the presence of an overall brain size genetic factor. Prior work shows that overall brain size and gray matter volume correlate with body height (Posthuma *et al.*, 2003, Taki *et al.*, 2012). This may be partially explained by the effects of general growth pathways such as those mediated by the insulin-like growth factor I and growth hormone, which are known to affect both height and the development of the nervous system (Rogers *et al.*, 2006, Taki *et al.*, 2012).

When ICV was included in the model as a covariate (Figure 2), a common subcortical genetic factor was evident across regions, which may reflect, at least in part, a brain specific developmental factor. During embryonic development, cortical and subcortical structures share a common origin in the prosencephalon (Gilbert, 2000, Volpe, 2008), which then divides into telencephalon and diencephalon. While the diencephalon is the precursor of the thalamus and hypothalamus, the telencephalon gives origin to the amygdala, hippocampus, basal ganglia and cortex (Gilbert, 2000, Volpe, 2008). The model shown in Figure 2 also highlights that, with the exception of the pallidum, subcortical volumes display large region-specific genetic contributions. Approximately half of the heritability of four regions was explained by region-specific genetic factors: hippocampus (49%), caudate nucleus (59%), nucleus accumbens (53%) and amygdala (56%). Increasing evidence from cross-sectional (Ostby *et al.*, 2009) and longitudinal (Raznahan *et al.*, 2014) studies suggest that maturation trajectories across subcortical regions are heterogeneous. The volumes of caudate, putamen, pallidum and nucleus accumbens tend to decrease linearly after reaching different peak volumes between ages 7.7 and 17.4 (Raznahan *et al.*, 2014). On the other hand, the maturation of the amygdala and hippocampus is generally slower and their volumes tend to increase nonlinearly until they reach a stable plateau (Ostby *et al.*, 2009). Brain structures that mature last are those that have undergone preferential expansion in primates and those involved in complex, integrative and late-maturing cognitive functions (Fjell *et al.*, 2013, Lenroot *et al.*, 2007, Shaw *et al.*, 2008). As noted by Eyler *et al.* (2011), other factors that may contribute to region-specific variance may include differences in neurotransmitter densities, individual variation in regional maturation, sensitivity to various environmental agents and plasticity-related connectivity differences.

In line with the genetic modeling, our PCA identified four principal components that were moderately to strongly correlated with one another. The factor structure was similar to that reported by Eyler *et al.* (2011) in middle aged male twins, including *basal ganglia* and *accumbens* factors. Overall, our results confirm our prior hypothesis and provide evidence for similar genetic architectures in young adults and middle aged individuals. Furthermore, we observed that this architecture is similar in both males and females. However, unlike in the previously reported PCA (Eyler *et al.*, 2011), our limbic factor did not include the amygdala. This may be due to the use of different segmentation strategies in the two studies. In our test-retest sample subset, a smaller association between hippocampus and amygdala

volumes was found with FSL ($r_p=0.23$; $r_g=0.43$) compared to Freesurfer ($r_p=0.40$; $r_g=0.61$), with the latter method being used in the study by Eyer *et al.* (2011).

In agreement with previous studies (Blokland *et al.*, 2012, Den Braber *et al.*, 2013, Kremen *et al.*, 2010, Wallace *et al.*, 2006), heritability estimates for the nucleus accumbens and amygdala were lower compared to those of other subcortical structures. This may be partly due to limitations in both current MRI technology resolution and accuracy of semi-automated segmentation of smaller brain structures. While test-retest correlations (shown in Table 1) inform about the repeatability of a measurement, they do not provide information about the accuracy of segmentation, which may result in measurement error. Visual inspection of all our images suggested that border delineation for hippocampus, pallidum, amygdala and nucleus accumbens, all of which showed comparable test-retest reliabilities, was difficult and subject to segmentation methodological limitations. We predict that, as future methodological and technological improvements become available, these limitations may be overcome, and more accurate heritability estimates for the amygdala and nucleus accumbens can be estimated. Furthermore, our twin modeling results suggest that environmental contributions are largely region-specific (Table 4), indicating that correlated measurement error may be small or subsumed by our correction for intracranial volume.

We note that the results of this paper are based on analyses carried out on data from adolescent and young adult right-handers, and the generalisability of these results to other populations warrants further attention. Furthermore, given that only subcortical volumes were considered in the present study, it is possible that the structure of the genetic architecture may vary when other brain regions (i.e. cortical) are taken into account. For instance, a recent study (Walhovd *et al.*, 2014) that investigated brain maturation between the ages of 8 and 22 found evidence for coordinated covariation in size between subcortical and cortical regions. Such covariation partly followed macrostructural circuits such as those between hippocampus and the Papez circuit and between the basal ganglia and prefrontal cortex. It remains to be established to what extent those cortical-subcortical covariation patterns are due to either common or region-specific genetic or environmental factors.

In summary, here we provide insights into how genetic factors contribute to volumetric variation and covariation of subcortical regions, and show that the degree and source (common or region-specific) of these genetic factors varies for each region. This is particularly relevant in the context of recent genome-wide association mapping efforts, which have identified genetic loci for intracranial and hippocampal volumes (Bis *et al.*, 2012, Ikram *et al.*, 2012, Stein *et al.*, 2012, Thompson *et al.*, 2014). As these GWAS efforts expand and identify more genetic loci, it is anticipated that novel genetic associations with either pleiotropic or region-specific effects will be uncovered, thus improving our understanding of the development, connectivity, function and pathology of the brain.

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Figure 1.

Parameter estimates for independent variable 2 factor model showing covariation between ICV and subcortical volumes. The model shows common (A_{C1} , A_{C2}) and region-specific (A_{S0} – A_{S7}) additive genetic sources. ICV-specific source (A_{S0}) was set to zero for the model to be identified. Estimates are standardized such that when squared they indicate the percentage of variance accounted for (95% CI indicated in parenthesis). Environmental influences (not shown here) were modelled as Cholesky and are similar to those shown in Table 4.

Figure 2.

Common (A_c) and region-specific (A_s) contributions to heritability estimates (h^2) of subcortical brain volumes (adjusted for ICV). The greater contributing genetic factor (either common or specific) is indicated in bold for each region.

Table 1

Homotopic correlations, test-retest correlations, descriptive statistics, covariate effects and twin correlations for subcortical volumes.

	ICV	Thalamus	Putamen	Caudate	Hippocampus	Pallidum	Amygdala	Accumbens
Descriptives (N=1024-1038)								
Mean (mm ³)	1298345	7520	5005	3688	3566	1656	807	452
SD (mm ³)	143176	723	544	427	363	177	196	114
Range (mm ³)	(908943, 1725507)	(5495, 9827)	(3368, 6586)	(2456, 4969)	(2615, 4730)	(1150, 2178)	(293, 1495)	(115, 800)
Covariate effects (N=1024-1038)								
% Males > Females	14%	11%	13%	9%	9%	13%	12%	14%
Std. β value (Sex)	0.57*	0.55*	0.56*	0.37*	0.40*	0.57*	0.26*	0.25*
Std. β value (Sex) - adjusted for ICV	-----	0.11*	0.24*	0.03	0.05	0.20*	0.03	0.03
Std. β value (ICV) - Males	-----	0.70*	0.50*	0.47*	0.49*	0.61*	0.33*	0.35*
Std. β value (ICV) - Females	-----	0.78*	0.48*	0.52*	0.59*	0.66*	0.29*	0.32*
Twin correlations								
MZ (n=137-145 pairs)	.88 (.84, .91)	.65 (.55, .73)	.83 (.77, .88)	.70 (.61, .77)	.73 (.65, .80)	.83 (.77, .87)	.42 (.28, .55)	.47 (.33, .59)
DZ (n=183-197 pairs)	.35 (.23, .47)	.35 (.22, .47)	.43 (.31, .53)	.44 (.32, .54)	.41 (.29, .52)	.42 (.29, .52)	.23 (.09, .36)	.22 (.08, .35)
MZ females (n=93-98 pairs)	.83 (.76, .88)	.67 (.55, .77)	.86 (.76, .92)	.77 (.68, .84)	.81 (.72, .87)	.83 (.75, .88)	.46 (.14, .69)	.56 (.41, .68)
MZ males (n=44-47 pairs)	.78 (.64, .86)	.61 (.40, .76)	.82 (.74, .87)	.56 (.33, .72)	.58 (.35, .74)	.84 (.74, .91)	.45 (.19, .65)	.39 (.09, .62)
DZ females (n=76-79 pairs)	.48 (.29, .63)	.23 (.02, .43)	.47 (.28, .62)	.57 (.40, .70)	.45 (.26, .61)	.41 (.21, .57)	.31 (.13, .46)	.28 (.01, .52)
DZ males (n=33-38 pairs)	.36 (.08, .59)	.47 (.18, .69)	.38 (.07, .62)	.33 (.02, .58)	.46 (.18, .67)	.30 (.01, .55)	.15 (-.07, .36)	.15 (-.07, .36)
DZ opposite sex (n=74-80 pairs)	.60 (.44, .71)	.39 (.19, .56)	.41 (.21, .58)	.41 (.21, .58)	.35 (.14, .52)	.43 (.25, .58)	.19 (-.03, .40)	.18 (-.06, .39)
Test-retest Pearson correlation (r) (FSL-FIRST and FS), cross-method correlations (r and intra-class) correlations								
Test-retest r (N=72-80)	FSL: 0.98 FS: 0.77	FSL: 0.90 FS: 0.70	FSL: 0.88 FS: 0.77	FSL: 0.87 FS: 0.87	FSL: 0.67 FS: 0.75	FSL: 0.77 FS: 0.72	FSL: 0.66 FS: 0.52	FSL: 0.77 FS: 0.51
Cross-method r (95% CI)	-----	.56 (.44, .67)	.76 (.67, .82)	.70 (.61, .78)	.44 (.29, .56)	.45 (.31, .57)	.28 (.13, .43)	.20 (.12, .42)
Cross-method ICC (95% CI)	-----	.72 (.60, .80)	.85 (.79, .89)	.82 (.75, .87)	.60 (.45, .72)	.61 (.46, .72)	.34 (.08, .53)	.34 (.08, .52)
L-R correlation (FSL) Phenotypic	-----	.89*	.83*	.82*	.58*	.75*	.38*	.50*
L-R correlation (FSL) Genetic	-----	.84*	.86*	.90*	.67*	.93*	.74*	.60*

*=Correlation is significant; All variables displayed normal distributions and means for all structures except for the two amygdalae were within the consensus volume estimates determined by manual segmentation in prior studies. Sample size (N) ranges reflect data missingness.

Table 2

Phenotypic (lower-triangle) and genetic (upper-triangle) correlations (95% CI) across intracranial and mean subcortical volumes.

	ICV	Pallidum	Putamen	Thalamus	Hippocampus	Caudate	Accumbens	Amygdala	GENET. CORR.
ICV	1	.80 (.77, .82)	.63 (.59, .67)	.86 (.84, .88)	.67 (.63, .70)	.60 (.56, .64)	.46 (.40, .51)	.41 (.35, .46)	ICV
Pallidum	.65 (.61, .69)	1	.76 (.73, .79)	.74 (.71, .77)	.65 (.61, .69)	.59 (.55, .63)	.58 (.53, .62)	.58 (.53, .62)	Pallidum
Putamen	.49 (.43, .53)	.60 (.55, .64)	1	.62 (.62, .89)	.49 (.44, .54)	.54 (.49, .58)	.48 (.43, .53)	.32 (.26, .37)	Putamen
Thalamus	.76 (.73, .78)	.60 (.55, .64)	.51 (.46, .55)	1	.63 (.59, .67)	.52 (.47, .57)	.48 (.43, .53)	.33 (.27, .39)	Thalamus
Hippocampus	.55 (.51, .59)	.46 (.47, .88)	.40 (.33, .45)	.52 (.46, .55)	1	.40 (.34, .45)	.46 (.40, .51)	.43 (.37, .48)	Hippocampus
Caudate	.48 (.45, .55)	.46 (.40, .51)	.44 (.39, .50)	.44 (.38, .49)	.34 (.28, .40)	1	.33 (.27, .39)	.13 (.06, .19)	Caudate
Accumbens	.34 (.28, .40)	.42 (.37, .48)	.34 (.28, .39)	.35 (.29, .40)	.30 (.25, .38)	.27 (.20, .33)	1	.27 (.20, .33)	Accumbens
Amygdala	.30 (.25, .37)	.37 (.31, .42)	.19 (.13, .25)	.23 (.16, .28)	.28 (.21, .33)	.10 (.03, .16)	.20 (.13, .25)	1	Amygdala
PHENO. CORR.	ICV	Pallidum	Putamen	Thalamus	Hippocampus	Caudate	Accumbens	Amygdala	

Table 3

Model fitting results.

Model	-2 log Likelihood	df	AIC
ACE Cholesky	11328.53	5410	508.53
AE Cholesky	11356.31	5446	464.31
CE Cholesky	11516.97	5446	624.97
AE 2-factor Independent pathway*	11387.12	5460	467.12

* =This model comprises two common and eight specific genetic factors and a full E cholesky matrix.
Best fitting model is shown in bold.

Table 4

Cholesky AE decomposition matrices

Standardized Additive Genetic (A) Path Estimates								
	Factor A1	Factor A2	Factor A3	Factor A4	Factor A5	Factor A6	Factor A7	Factor A8
ICV	0.94							
Pallidum	0.73	0.47						
Putamen	0.64	0.42	0.54					
Thalamus	0.83	0.09	0.05	0.41				
Hippocampus	0.65	0.14	-0.05	0.01	0.58			
Caudate	0.58	0.14	0.13	-0.12	-0.01	0.62		
Nucleus Accumbens	0.38	0.23	0.04	0.05	0.07	-0.03	0.53	
Amygdala	0.36	0.34	-0.12	-0.08	0.08	-0.12	-0.06	0.43

Standardized Unique Environmental (E) Path Estimates								
	Factor E1	Factor E2	Factor E3	Factor E4	Factor E5	Factor E6	Factor E7	Factor E8
ICV	0.35							
Pallidum	0.22	0.45						
Putamen	0.09	0.09	0.33					
Thalamus	0.15	0.09	0.10	0.30				
Hippocampus	0.13	0.04	0.11	0.07	0.42			
Caudate	0.15	0.09	0.09	0.12	0.04	0.42		
Nucleus Accumbens	0.20	0.14	0.10	0.07	0.09	0.07	0.65	
Amygdala	0.21	0.01	0.03	-0.02	0.00	0.02	0.05	0.68

Table 5

PCA results based upon genetic correlation matrix

	PC1	PC2	PC3	PC4
Pallidum	0.51	0.14	0.35	0.15
Putamen	0.77	−0.15	0.13	0.20
Thalamus	0.37	0.62	−0.08	0.04
Hippocampus	−0.13	1.02	0.03	−0.01
Caudate nucleus	1.11	−0.02	−0.21	−0.21
Amygdala	−0.12	0.01	−0.11	1.09
Nucleus accumbens	−0.13	0.01	1.07	−0.11
SS loadings	2.16	1.50	1.26	1.20
Cumulative Var	0.31	0.52	0.70	0.88

Factor loadings greater than 0.35 are indicated in bold.

Table 6

PCA results based upon phenotypic correlation matrix

	PC1	PC2	PC3	PC4
Pallidum	0.61	0.07	0.26	0.12
Putamen	0.79	−0.01	0.02	0.05
Thalamus	0.39	0.55	−0.05	0.02
Hippocampus	−0.15	1.05	−0.02	−0.04
Caudate nucleus	1.02	−0.16	−0.15	−0.12
Amygdala	−0.05	−0.03	−0.05	1.04
Nucleus accumbens	−0.07	−0.03	1.03	−0.05
SS loadings	2.12	1.37	1.10	1.07
Cumulative Var	0.30	0.50	0.65	0.81

Factor loadings greater than 0.35 are indicated in bold.