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Heritability of brain volumes in older adults: the Older Australian Twins Study

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ABSTRACT

The relative contributions of genetic and environmental factors to brain structure change throughout the lifespan. Brain structures have been reported to be highly heritable in middle-aged individuals and younger; however, the influence of genes on brain structure is less studied in older adults. We performed a magnetic resonance imaging study of 236 older twins, with a mean age of 71.4 ± 5.7 years, to examine the heritability of 53 brain global and lobar volumetric measures. Total brain volume (63%) and other volumetric measures were moderately to highly heritable in late life, and these genetic influences tended to decrease with age, suggesting a greater influence of environmental factors as age advanced. Genetic influences were higher in men and on the left hemisphere compared with the right. In multivariate models, common genetic factors were observed for global and lobar total and gray matter volumes. This study examined the genetic contribution to 53 brain global and lobar volumetric measures in older twins for the first time, and the influence of age, sex, and laterality on these genetic contributions, which are useful information for a better understanding of the process of brain aging and helping individuals to have a healthy aging.

1. Introduction

The development of the human brain is under the influence of both genetic and environmental factors. The classical method to examine these influences is the twin design, as monozygotic (MZ) twins share all their genes, whereas dizygotic (DZ) twins share on average only 50% of their segregating DNA (Plomin et al., 1994). The twin design is used to estimate the "heritability" of a trait, which is the proportion of the observable differences between individuals that is because of genetic factors. Previous studies have reported heritability for a number of structural brain measures, which include brain volume (BV) (Kremen et al., 2010; Pfefferbaum et al., 2000; Thompson et al., 2001), brain surface complexity (Gatt et al., 2012; White et al., 2002), white matter fractional anisotropy, (Chiang et al., 2011; Kochunov et al., 2010) and cortical thickness (Gatt et al., 2012; Panizzon et al., 2009; Winkler et al., 2010). A recent meta-analysis of BV heritability (Blokland et al., 2012) reported that comparing the results of different studies was difficult because of the demographic or methodological differences. However, a collation of the published data showed the influence of genes on brain structures to be in the range of 73%–91% for intracranial volume (ICV), 46%–94% for BV, 64%–89% for cerebrum, 56%–82% for gray matter (GM), 80%–88% for white matter (WM), 26%–84% for the frontal lobe, 30%–86% for the parietal lobe, 55%–88% for the temporal lobe, and 32%–74% for the occipital lobe (Baare et al., 2001; DeStefano et al., 2009; Geschwind et al., 2002; Gilmore et al., 2010; Wallace et al., 2006; Yoon et al., 2010a). It should be noted however, that most of these studies were performed on individuals younger than 65 years.

We found only 7 studies that examined BV heritability in individuals aged older than 65 years (Carmelli et al., 2002;

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DeStefano et al., 2009; Geschwind et al., 2002; Pfefferbaum et al., 2000, 2001, 2004; Sullivan et al., 2001). These studies reported moderate heritability for key BVs, e.g. 64% heritability for cerebrum (Geschwind et al., 2002), 46% for total BV (DeStefano et al., 2009), 54% for total frontal, 47% for total parietal, 46% for total temporal, and 28% for total occipital lobes (Geschwind et al., 2002). However, these studies had a number of limitations: the study by DeStefano et al. (2009) was a family study which usually has a lower power compared with a twin design; the other 6 studies were twin designs but were all performed on male twins only; and the study by Pfefferbaum et al. (2001) had a small sample size (15 MZ and 18 DZ pairs). Moreover, these studies selected a rather narrow range of brain volumetric measures, and therefore they do not give a comprehensive picture of heritability across multiple brain regions. Pfefferbaum et al. (2000, 2001, 2004) studied the corpus callosum, lateral ventricles, and ICV; Geschwind et al. (2002) reported on right and left frontal, temporal, occipital and parietal lobes, and the hemispheres; Sullivan et al. (2001) reported on the hippocampus, corpus callosum, and ICV; and Carmelli et al. (2002) reported on the right and left frontal, temporal, occipital and parietal lobes, and 2 cerebrospinal fluid (CSF) measures. To address these limitations and gaps in the literature, the present study used the twin design, included a large number of male and female twins, and studied a considerable number of brain volumetric measures, including ICV, cerebrum, cerebellum, total GM, total WM, hemispheric volumes, right and left lobar, GM and WM volumes, and the frontal, temporal, occipital, parietal and cerebellar lobes. These structures show significant volume changes in late lifetime, and therefore studying the reason of their changes would shed light on a better understanding of the aging process.

Heritability of the brain measures might change over the lifespan. Although many brain phenotypes have been genetically studied, evidence for the changes of brain heritability with age comes mostly from the neuroimaging studies of brain volume. For example, increments of heritability of BVs during development and early adulthood have been illustrated (Lenroot et al., 2009; Wallace et al., 2006). On the other hand, although very few studies have examined the changes of BV heritability in late life, and as listed previously they might have some limitations, decrement of the heritability of BVs after reaching adulthood is suggested (Geschwind et al., 2002; Pedersen, 2000; Pfefferbaum et al., 2000). Changes in the genetics of brain cognition with age have also been observed in a review study (Lee et al., 2010). One possible reason for these changes is the interaction of genes and environment, which is able to alter the number and variety of active genes or change their level of activity (Chiang et al., 2011; Plomin et al., 1994; Sarah et al., 2007; Walsh, 1980). Aging is associated with a reduction of brain volume (Jernigan et al., 2001; Resnick et al., 2000; Scahill et al., 2003; Trollor and Valenzuela, 2001), impairments in brain diffusivity (Kochunov et al., 2011) and cortical thinning (Brans et al., 2010), and it is important to understand the relative influence of genetic and environmental factors on these changes (Kremen et al., 2012).

Many brain phenotypes have been observed to show different genetic influences in men and women, and examples include total BV (Everaerd et al., 2012; Faass et al., 2013; Posthuma et al., 2000), brain WM integrity (Chiang et al., 2011) and WM hyperintesity volume (Atwood et al., 2004), brain functional connectivity (Damoiseaux et al., 2012), and more phenotypes as reviewed previously (Vink et al., 2012). However, the studies that have investigated sex differences of genetic influences in specific brain regions are very rare. Such examples would include the observation of sex-specific messenger RNA expression levels in medial preoptic area and ventromedial hypothalamus (Faass et al., 2013), differential influences of the X chromosome on different brain regions (Lentini et al., 2012), and the sex-specific influences of brain-derived neurotrophic factor gene on hippocampus, frontal cortex, and hypothalamus in an animal study (Chourbaji et al., 2012). These preliminary reports suggest that brain regions might vary in the degree to which sex influences genetic expression.

In this study, we analyzed data from the Older Australian Twins Study (OATS) to investigate heritability of brain volume in late life. Fifty-three global and lobar brain volumetric measures were selected. Based on previous reports, we hypothesized that brain structures would be highly heritable in older adults (Geschwind et al., 2002; Pfefferbaum et al., 2004; Sullivan et al., 2001), that genetic influences would decrease with age (Pfefferbaum et al., 2000) and that heritability would be higher in men (Chiang et al., 2011) and in the left hemisphere (Eyler et al., 2012; Thompson et al., 2001). We also expected to find high genetic correlations between the volumetric measures (Glahn et al., 2007; Hulshoff Pol et al., 2006c; Schmitt et al., 2010). To the best of our knowledge, this study for the first time examined the genetic contribution to certain brain volumes in an older cohort of twins, and the influence of age, sex, and laterality on these contributions.

2. Methods

2.1. Participants

Participants were drawn from the OATS, a population-based study of twins aged 65 years or older (Sachdev et al., 2009a) living in the 3 eastern states of Australia (New South Wales, Victoria, and Queensland) and registered with the Australian Twin Registry (www.twins.org.au). Individuals who consented to participate were included if they had a consenting co-twin and were sufficiently competent in English to complete a neuropsychological assessment in that language. They were excluded if they were currently suffering from a life-threatening illness or a psychotic disorder. In addition, participants were excluded from the imaging component of the study if they had claustrophobia or a contraindication for magnetic resonance imaging (MRI) such as a cardiac pacemaker, a ferromagnetic foreign body, or an implanted device.

At the time of this analysis, a total of 285 individuals had been scanned in OATS. The exclusion of single twins (n = 17), siblings (n = 14), and opposite-sex DZ twins (n = 18), because of their confounding effects (Brun et al., 2009; Chou et al., 2009; Hulshoff Pol et al., 2006b; Yoon et al., 2011), resulted in 236 participants comprising 154 MZ and 82 DZ individuals (54 male MZ, 100 female MZ, 20 male DZ, and 62 female DZ). This sample had a mean age of 71.4 (±5.7) years (range 65–88 years, 1st quartile = 67, 3rd quartile = 73), Mini-Mental State Examination (Folstein et al., 1975) score of 28.71 (±1.40), Global Deterioration Scale (Sheikh and Yesavage, 1986; Yesavage et al., 1983) score of 1.60 (±2.90), handedness (Sachdev et al., 2009a) (right = 195, left = 25, mixed = 16), and 10.89 (±3.01) years of education. Notably, the MZ and DZ groups did not differ significantly (using "ttest2" function in MATLAB) in age (p-value = 0.38), Mini-Mental State Examination (p-value = 0.40), years of education (p-value = 0.33), handedness (p-value = 0.61) or Global Deterioration Scale (p-value = 0.52). There were more women (n = 164) than men (n = 72), and the men were slightly older (men mean age = 72.18 ± 4.9 (65–82 years; 1st quartile = 67; 3rd quartile = 76); women mean age = 70.19 ± 4.8 (65–88 years; 1st quartile = 66; 3rd quartile = 73); p = 0.0057). About 5% of the participants were classified as having mild cognitive impairment (MCI), but the

distribution of these participants had no particular pattern based on sex or zygosity.

Zygosity was initially determined using a self-report questionnaire (Sachdev et al., 2009a), and later confirmed using single-nucleotide polymorphism genotyping with the Illumina Omni Express array (Delano et al., 2011; Sachdev et al., 2009a).

2.2. MRI scanning

MRI data were obtained on 1.5 tesla scanners at 3 imaging centers: a Philips Gyroscan scanner (Philips Medical Systems, Best, Netherlands) in center 1, and Siemens Magnetom Avanto and Sonata scanners (Siemens Medical Solutions, Malvern PA, USA) with similar year of manufacture and upgrade in centers 2 and 3, respectively. Acquisition protocols were matched between the centers through standardization of the resolution and slice thickness, using a 3D phantom to correct geometric distortions, and using 5 volunteers who were scanned at the 3 centers (Sachdev et al., 2009a). Twin pairs were always scanned on the same scanner and were scanned either on the same day or temporally very close to each other (less than a few weeks).

Three-dimensional T1-weighted volumetric sequence was performed using a similar protocol in the 3 centers with in-plane resolution = 1×1 mm, slice thickness = 1.5 mm, slice number = 144, Repetition time =1530 ms, Echo time = 3.24 ms, Inversion time = 780 ms, flip angle = 8, and Number of Excitations = 1. Two T1-3D scans were acquired for each participant for an increased signal-to-noise ratio.

2.3. Image processing

The scans were de-identified to ensure anonymity and blinding to zygosity status. The scans were segmented into GM, WM, and CSF using the "New Segment" toolbox (Ashburner and Friston, 2005) of the Structural Parametric Mapping, version 8 (SMP8) program (Friston, 2003), through MATLAB (V 7.6.0.324, R2008a). This step created the Native Space plus Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) imported outputs (Ashburner, 2010), which were imported to the "Run DARTEL: create template" toolbox of the same package, using its default settings, to improve the accuracy of intersubject alignment by modeling the shapes of the brains through simultaneously aligning both gray and white matter images (Ashburner, 2010). After the templates were generated, the "Normalize to MNI space" toolbox was used to normalize all the GM and WM images to the Montreal Neurological Institute standard space. Because each participant had 2 T1 scans, 2 normalized images for each of the GM and WM were created per person. The 2 images were then averaged to a single normalized GM and WM image per person to improve the signal-to-noise ratio (Ashburner, 2010).

Fifty-three volumetric measures of the brain were selected, comprising ICV, cerebrum, cerebellum, total GM, total WM, hemispheric volumes, right and left lobar, GM and WM volumes, and the frontal, temporal, occipital, parietal and cerebellar lobes, as listed in Table 1. These measures included brain volumetric measures that were previously studied, but most of them (36 out of 53) were for the first time genetically studied in older twins. The parcellation templates of these regions were created, using the "WFU Pickatlas" tool of the SPM8 and the "TD-ICBM Human Atlas" (Talairach Daemon), which is one of the most widely used atlases in brain imaging researches (Lancaster et al., 2007). Then, using the "Coregister (Reslice)" toolbox of the SPM8, the parcellation images were coregistered and resliced with the normalized GM and WM images so that they had the same dimensions and slice thickness. Visual inspection of a few of the randomly selected scans showed accuracy of the alignment of the scans with the parcellation images.

Finally, the regions of interest (ROI) masks were multiplied to the normalized GM and WM images, and the values of all the voxels inside each mask were added together. Multiplying the added values into 3.375 mm^3 (the volume of 1 voxel) estimated the volume of that particular brain region. To calculate the total ICV, the cerebral and cerebellar volumes were added to the total CSF, which was estimated by the process discussed previously. All the volumetric measures were then corrected for the ICV ($V_2 = V_1 \times$ mean value/ICV [V_2: corrected measure; V_1: original measure]), because this correction improves the accuracy of the DARTEL results (Ashburner, 2010).

2.4. Statistical analysis

Normality of the volumetric measures was tested in MATLAB ($-2<$ skewness and/or sd of skewness <2) and all were normally distributed. Any volumetric measure greater than $\pm 3\sigma$ was excluded as an outlier (<1%). The mean and standard deviation of the volumetric measures, and their correlation with age, were estimated using the whole sample. In addition, the measures were divided into male and/or female and MZ and/or DZ to ascertain if the volumetric measures were significantly different based on sex or zygosity. Finally, any volumetric difference between the right and left brain hemispheres was tested.

A preliminary analysis of the relative genetic and environmental influences on brain volume was performed by calculating the intraclass correlations (ICC) for the MZ and DZ twin pairs. A higher ICC for MZ compared with DZ twin pairs indicated a genetic influence. The ICCs were calculated for the ROIs initially (Table 1), and then a voxel-wise calculation of ICC was performed to extract a 3D-map of the correlations for MZ and DZ twin pairs (Fig. 3), to obtain a better understanding of the spatial pattern of brain heritability. A p-value map (false discovery rate-corrected in MATLAB with alpha = 0.05) was also estimated for each ICC map to show the significant voxels. We used structural equation modeling in Mx GUI (Mx Graphical User Interface) program (Neale, 1994, 2011) to estimate heritability. The initial model tested was the ACE model (Fig. 1A), and then the reduced models of AE, CE, and E were tested to find the model with the best fit to the data (Swan and Carmelli, 2002). The fit of the models were assessed by: (1) the maximum likelihood-ratio χ^2 divided by degree-of-freedom (d.f); (2) Akaikes information criteria (AIC) (Akaike, 1987); (3) Root Mean Square Error of Approximation (RMSEA); and (4) the p-value. The most restrictive model was accepted to have the best fit, using the following criteria: χ^2/d.f<2, RMSEA <0.05, p-value >0.05 and the lowest Akaike information criteria. Because of the previous reports on the small contribution of the common environment factor to human phenotypes in late life (Carmelli et al., 2002; Kremen et al., 2010; Pfefferbaum et al., 2000; Sullivan et al., 2001), we expected to find the AE model as the best-fit model in our analyses. All our measures were corrected for ICV, scanner, age, and sex before ICC (using residuals) and structural equation modeling (including covariates) estimations (in both univariate and multivariate models).

To calculate the influence of age, sex, and laterality on the latent A and E factors (in the best-fit model), we included the uncorrected (except for ICV and scanner) volumetric measures in a second AE model including the covariates (Fig. 1B) (Neale and Schmitt, 2005; Purcell, 2002). The paths between one covariate and the A and E factors were estimated as the influences of that covariate on the A and E factors, whereas the measures were corrected for the rest of the covariates. Fig. 1B shows these estimations for the influence of age on the A and E factors. However, to test the influence of

Table 1
Volumetric analyses along with the ICC estimations

Measure	Mean (±SD)	Age corr.	M Vs F	MZ-ICC	DZ-ICC	R/L
ICV	1.632e+6 (±0.036e+5)	0.141	M>F**	0.85 (0.77, 0.90)	0.31 (0.00, 0.56)	
Total BV	1.381e+6 (±1.313e+4)	−0.33**	N.S	0.79 (0.70, 0.87)	0.40 (0.11, 0.63)	
Total cerebral volume	1.230e+6 (±1.340e+4)	−0.34**	N.S	0.78 (0.67, 0.86)	0.44 (0.15, 0.66)	
R. B.V	6.950e+5 (±6.447e+3)	−0.33**	N.S	0.79 (0.69, 0.86)	0.39 (0.09, 0.62)	R>L**
L. B.V	6.862e+5 (±6.810e+3)	−0.32**	N.S	0.78 (0.67, 0.85)	0.36 (0.05, 0.60)	
R. Cerebrum	6.196e+5 (±6.517e+3)	−0.34**	N.S	0.79 (0.69, 0.86)	0.41 (0.12, 0.64)	R>L**
L. Cerebrum	6.107e+5 (±6.970e+3)	−0.33**	N.S	0.78 (0.67, 0.86)	0.40 (0.11, 0.63)	
Total cerebral GM	6.622e+5 (±1.009e+4)	−0.17*	N.S	0.73 (0.61, 0.82)	0.40 (0.11, 0.63)	
Total cerebral WM	5.681e+5 (±1.474e+4)	−0.34**	N.S	0.87 (0.80, 0.91)	0.52 (0.25, 0.71)	
R. Cerebral GM	3.349e+5 (±5.253e+3)	−0.16*	N.S	0.71 (0.57, 0.80)	0.34 (0.04, 0.59)	R>L**
L. Cerebral GM	3.273e+5 (±5.198e+3)	−0.18*	N.S	0.69 (0.55, 0.79)	0.43 (0.14, 0.65)	
R. Cerebral WM	2.847e+5 (±7.431e+3)	−0.34**	N.S	0.83 (0.74, 0.89)	0.51 (0.25, 0.71)	N.S
L. Cerebral WM	2.834e+5 (±7.664e+3)	−0.32**	N.S	0.87 (0.80, 0.92)	0.49 (0.23, 0.69)	
Total cerebellum	1.509e+5 (±2.397e+3)	−0.09	M>F*	0.87 (0.81, 0.92)	0.40 (0.11, 0.63)	
R. Cerebellum	5.901e+4 (±1.001e+3)	−0.02	M>F**	0.81 (0.72, 0.88)	0.38 (0.08, 0.61)	N.S
L. Cerebellum	6.112e+4 (±1.106e+3)	−0.06	M>F**	0.85 (0.77, 0.90)	0.52 (0.25, 0.71)	
Total CSF volume	3.007e+5 (±3.241e+4)	0.33**	M>F**	0.78 (0.68, 0.86)	0.40 (0.11, 0.63)	
Total frontal volume	4.287e+5 (±6.366e+3)	−0.21**	M>F*	0.81 (0.71, 0.87)	0.62 (0.38, 0.78)	
Frontal GM	2.227e+5 (±4.663e+3)	−0.09	M>F*	0.75 (0.63, 0.83)	0.55 (0.30, 0.74)	
Frontal WM	2.060e+5 (±5.878e+3)	−0.21**	N.S	0.87 (0.79, 0.91)	0.63 (0.40, 0.78)	
R. Frontal	2.178e+5 (±3.058e+3)	−0.22**	M>F*	0.81 (0.71, 0.87)	0.57 (0.32, 0.75)	R>L**
L. Frontal	2.107e+5 (±3.420e+3)	−0.21*	M>F*	0.80 (0.71, 0.87)	0.61 (0.38, 0.77)	
R. Frontal GM	1.132e+5 (±2.455e+3)	−0.08	M>F*	0.68 (0.54, 0.78)	0.51 (0.23, 0.70)	R>L**
L. Frontal GM	1.093e+5 (±2.342e+3)	−0.08	M>F*	0.76 (0.64, 0.84)	0.59 (0.35, 0.76)	
R. Frontal WM	1.045e+5 (±3.077e+3)	−0.22*	N.S	0.82 (0.73, 0.88)	0.67 (0.46, 0.81)	R>L**
L. Frontal WM	1.014e+5 (±2.964e+3)	−0.21*	N.S	0.87 (0.81, 0.92)	0.58 (0.33, 0.75)	
Total temporal volume	2.212e+5 (±2.457e+3)	−0.32**	N.S	0.81 (0.72, 0.88)	0.44 (0.15, 0.66)	
Temporal GM	1.333e+5 (±2.632e+3)	−0.08	M>F*	0.67 (0.53, 0.78)	0.28 (0.00, 0.54)	
Temporal WM	8.785e+4 (±2.688e+3)	−0.34**	N.S	0.86 (0.78, 0.91)	0.57 (0.33, 0.75)	
R. Temporal	1.111e+5 (±1.288e+3)	−0.30**	N.S	0.82 (0.73, 0.88)	0.37 (0.07, 0.61)	R>L**
L. Temporal	1.099e+5 (±1.408e+3)	−0.33**	M>F*	0.73 (0.59, 0.82)	0.49 (0.22, 0.69)	
R. Temporal GM	6.701e+4 (±1.339e+3)	−0.05	M>F*	0.65 (0.49, 0.76)	0.09 (-0.22, 0.39)	R>L**
L. Temporal GM	6.628e+4 (±1.458e+3)	−0.12	N.S	0.63 (0.47, 0.75)	0.42 (0.13, 0.65)	
R. Temporal WM	4.419e+4 (±1.356e+3)	−0.36**	N.S	0.75 (0.64, 0.84)	0.43 (0.14, 0.65)	R>L**
L. Temporal WM	4.365e+4 (±1.507e+3)	−0.30**	N.S	0.86 (0.79, 0.91)	0.65 (0.43, 0.80)	
Total occipital volume	1.362e+5 (±2.150e+3)	−0.17*	M>F*	0.78 (0.68, 0.86)	0.21 (-0.10, 0.49)	
Occipital GM	7.879e+4 (±2.840e+3)	−0.05	M>F**	0.86 (0.78, 0.91)	0.56 (0.31, 0.74)	
Occipital WM	5.746e+4 (±2.917e+3)	−0.07	N.S	0.92 (0.88, 0.95)	0.70 (0.50, 0.83)	
R. Occipital	6.654e+4 (±1.185e+3)	−0.16*	M>F*	0.75 (0.63, 0.83)	0.23 (-0.09, 0.49)	L>R**
L. Occipital	6.944e+4 (±1.022e+3)	−0.14*	M>F*	0.77 (0.67, 0.85)	0.28 (-0.03, 0.54)	
R. Occipital GM	3.891e+4 (±1.466e+3)	−0.05	M>F**	0.82 (0.72, 0.88)	0.55 (0.29, 0.73)	L>R**
L. Occipital GM	3.967e+4 (±1.422e+3)	−0.05	M>F**	0.81 (0.71, 0.88)	0.53 (0.27, 0.72)	
R. Occipital WM	2.762e+4 (±1.570e+3)	−0.07	N.S	0.87 (0.80, 0.92)	0.74 (0.56, 0.85)	L>R**
L. Occipital WM	2.977e+4 (±1.403e+3)	−0.06	N.S	0.93 (0.88, 0.95)	0.63 (0.39, 0.78)	
Total parietal volume	1.708e+5 (±2.586e+3)	−0.26**	N.S	0.81 (0.71, 0.87)	0.38 (0.08, 0.61)	
Parietal GM	9.575e+4 (±2.641e+3)	−0.17*	N.S	0.76 (0.64, 0.84)	0.63 (0.40, 0.78)	
Parietal WM	7.501e+4 (±2.244e+3)	−0.19*	M>F*	0.85 (0.78, 0.91)	0.54 (0.28, 0.73)	
R. Parietal	8.493e+4 (±1.325e+3)	−0.26**	N.S	0.79 (0.68, 0.86)	0.39 (0.10, 0.63)	L>R**
L. Parietal	8.581e+4 (±1.362e+3)	−0.25**	N.S	0.81 (0.72, 0.88)	0.43 (0.15, 0.65)	
R. Parietal GM	4.849e+4 (±1.419e+3)	−0.15*	N.S	0.70 (0.56, 0.80)	0.62 (0.39, 0.78)	R>L**
L. Parietal GM	4.724e+4 (±1.340e+3)	−0.19*	N.S	0.73 (0.60, 0.82)	0.63 (0.41, 0.78)	
R. Parietal WM	3.643e+4 (±1.129e+3)	−0.21*	M>F*	0.76 (0.65, 0.85)	0.53 (0.26, 0.72)	L>R**
L. Parietal WM	3.857e+4 (±1.203e+3)	−0.17*	N.S	0.85 (0.77, 0.90)	0.53 (0.27, 0.72)	

Mean and standard deviation of brain volumetric measures (in cubic millimeter, un-corrected); The correlation of the volumetric measures with age (corrected for ICV, scanner and sex); The regional brain volumes of the male and female groups are compared (corrected for ICV, scanner and age) (* = $p < 0.05$, ** = $p < 0.001$); Estimation of Intra-Class Correlations (ICC) for the MZ and DZ groups plus their 95% confidence intervals (corrected for ICV, age, sex and scanner): A higher ICC in the MZ group indicates a genetic influence; comparing the volumetric measures in the right and left hemispheres. M>F: male larger than female; N.S: non-significant; R>L: right larger than left.
Key: BV, brain volume; CSF, cerebrospinal fluid; GM, gray matter; ICV, intracranial volume; L, left; R, right; WM, white matter.

laterality on the A and E factors of an ROI, both the right and left volumetric measures of that ROI were added to the models.

A multivariate model was used to investigate common genetic or environmental factors between different brain volumetric measures, using the Mx GUI program (Neale, 2011). For this, 4 general volumetric measures of total BV, cerebral GM, cerebral WM, and cerebellar volume were included in a Cholesky model (Carey, 2005; Neale and Schmitt, 2005). Because the AE model was the best fit for the univariate models, it was selected for the Cholesky model (Fig. 2). This model partitions the genetic and environmental variances into general and specific, and the correlations between measures can be calculated using the path estimates (Purcell, 2002; Rimol et al., 2010). For example, the genetic correlation between GM and WM (Fig. 2) was estimated through the following formula:

$$\mathrm{GM-WM} = (A_{12} \times A_{13} + A_{22} \times A_{23}) / \mathrm{Sqrt}\left[\left(A_{12}^2 + A_{22}^2\right) \times \left(A_{13}^2 + A_{23}^2 + A_{33}^2\right)\right]$$

(Neale, 2011)

This Cholesky model was significantly fitted to the data (significant fit indices). A second Cholesky model was

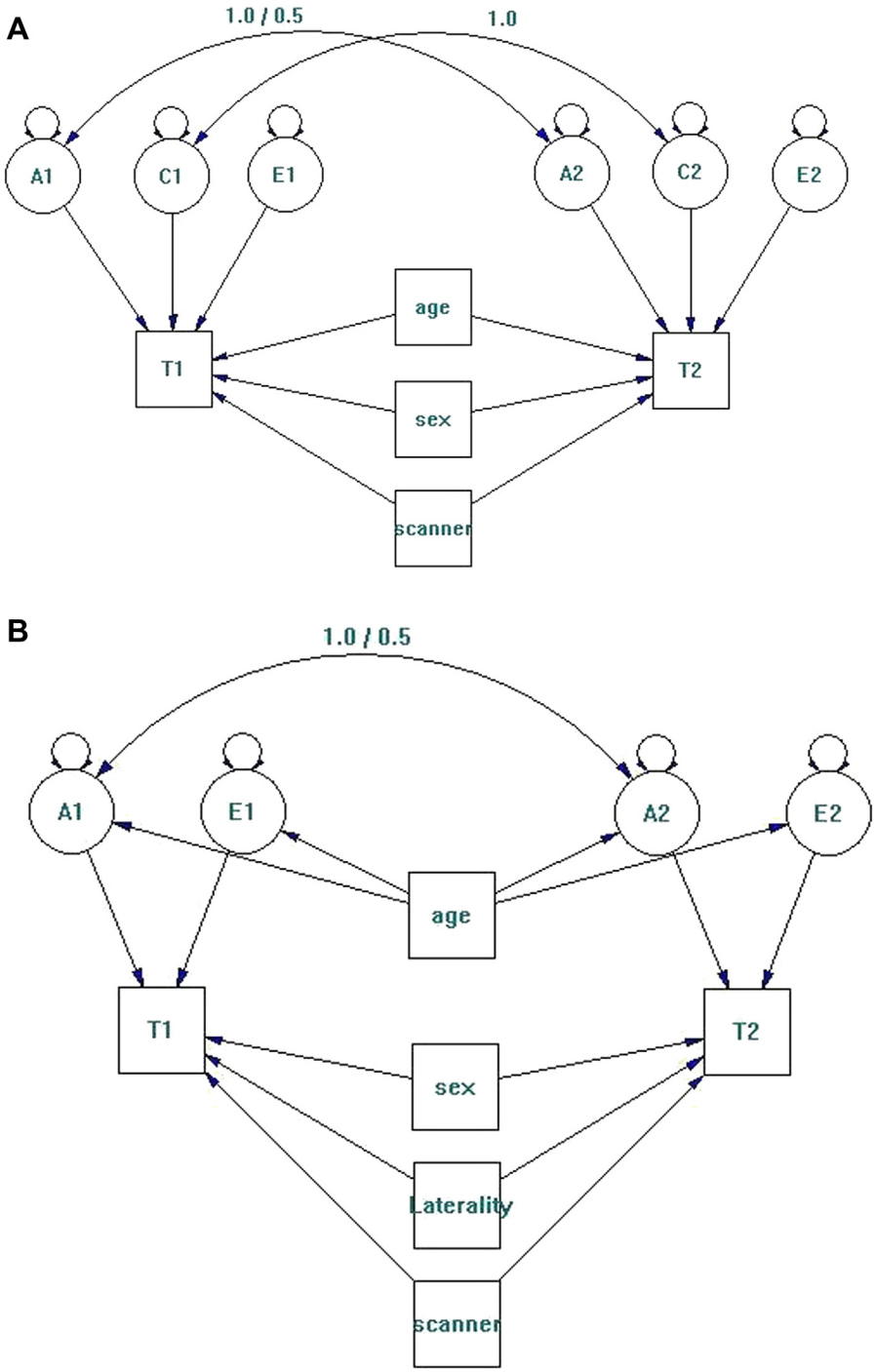

Fig. 1. (A, top) The path diagram for the genetic and environmental influences on a phenotypic variable in twins (Neale, 1994). Each twin's phenotypic measure (represented as a square) is assumed to be determined by an additive genetic component (denoted by A), an environmental component unique for each individual (denoted by E), and shared environmental component (C). Random noise, or experimental measurement error, is also included in the E component (ACE are unobserved or theoretical variables). One-headed arrows are used to represent fixed regression coefficients, and two-headed arrows to represent estimated variance, covariance, or correlation coefficients (A_1-A_2 correlation = 1.0 for MZ and 0.5 for DZ twins; C_1-C_2 correlation = 1.0 for both twins). The phenotypes are corrected in this model using the age, sex and scanner covariates. (B, bottom) The diagram to test how the genetic (denoted by A) and unique environmental (E) factors would change with age (Purcell, 2002; Neale and Schmitt, 2005), in the best fit model of AE. The phenotypes are corrected for sex, scanner and laterality. To test the influence of a moderator on the A and E factors, the measures were corrected for the rest of the covariates.

performed with the 5 measures of total cerebrum, and frontal, parietal, occipital, and temporal lobes to find common genetic factors between brain lobar volumes. This model was later repeated with the GM measures of these particular lobes. Both these models were also significantly fitted to the data.

3. Results

3.1. Volumetric measures

The mean volumes of the brain measures, their age correlations, test of volumetric differences between men and women and

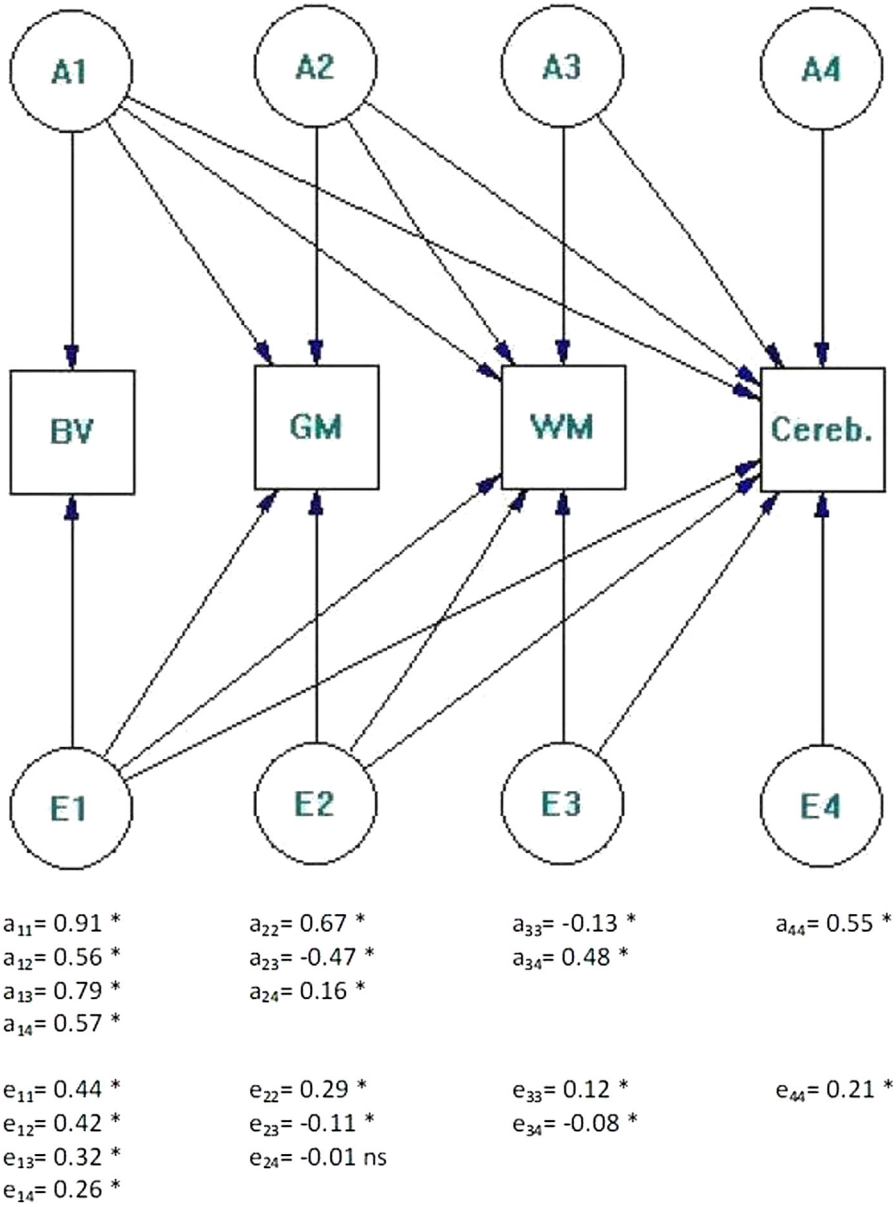

Fig. 2. The multivariate Cholesky model between the 4 volumetric measures of brain volume (BV), total gray matter (GM), total white matter (WM) and the cerebellum. The model only includes the additive genetic (A) and unique environmental factors (E), because the AE model was the best fit in the univariate analyses. The variances are divided into general and specific, and the genetic and environmental correlations between the measures were calculated using the path estimates. * = significant path estimates (95% confidence interval not crossing zero), ns = nonsignificant. The estimates of the paths are provided below the diagram. For example, the path from A1 to WM is a_{13} and from A2 to cerebellum is a_{24}. Abbreviations: BV, brain volume; GM, gray matter; WM, white matter.

between right and left hemispheres, in addition to the estimations of ICCs for the MZ and DZ twins are presented in Table 1 (measures were corrected for ICV, scanner, age and sex for ICC estimations and for ICV, scanner, and either of age or sex for sex/age correlations). Most of the volumetric measures showed negative correlations with age, including the total brain volume ($r = -0.33$; $p < 0.001$), total GM ($r = -0.17$; $p < 0.05$), and total WM ($r = -0.34$; $p < 0.001$). As expected, CSF volume showed significant increments with age ($r = 0.33$; $p < 0.001$).

3.1.1. Sex, zygosity, and laterality effects

In relation to sex, 22 volumetric measures were observed to be significantly larger in men, including: ICV, frontal, occipital, temporal, parietal, CSF, and cerebellar volumes (Table 1). When the MZ and DZ twins were compared, none of the volumetric measures were significantly different between the groups. When laterality was examined, the hemispheric, cerebral, frontal and temporal lobe volumes were significantly greater on the right whereas the occipital and parietal lobes were larger on the left.

3.2. Within-pair correlations

All within-pair correlations were significant for both the MZ and DZ twins, except for the right temporal GM. An examination of the results showed higher ICCs between the MZ than the DZ twins for all the volumetric measures, suggesting heritability (Table 1). The ICCs ranged from 0.63 to 0.92 in the MZ twins and from 0.21 to 0.74 in the DZ twins. Fig. 3 shows the 3D-maps of the MZ and DZ ICCs for the GM and WM volumes. A 3D-map of the significant voxels is also attached to each ICC map. The higher ICC of the MZ group than the

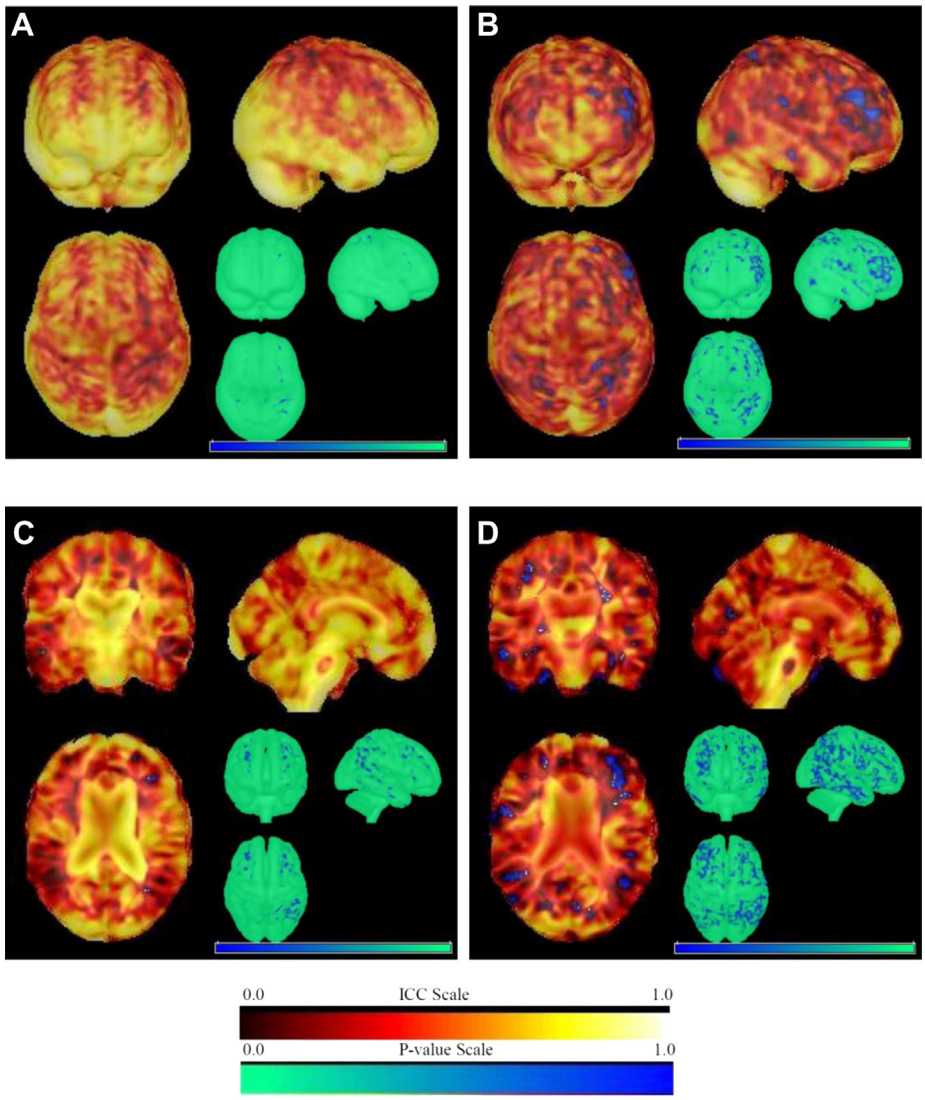

Fig. 3. Voxel-wise calculation of the intra-class correlations (ICC) for the (A) gray matter (GM) volume in the monozygotic (MZ) twins, (B) GM volume in the dizygotic (DZ) twins, (C) white matter (WM) volume in the MZ twins, (D) WM volume in the DZ twins. The value of each voxel is between 1.0 and −1.0, which is the intra-class correlation of that voxel within a pair (The color bar shows the scale of the ICCs). Also, an FDR-corrected *p*-value map (alpha = 0.05) is added to each larger ICC map showing all the significant voxels (bright blue voxels are significant and gray voxels are not). The maps show hotter ICCs in the MZ group in both the GM and WM than the DZ group, which is a sign of heritability. Abbreviations: DZ, dizygotic; FDR, false discovery rate; GM, gray matter; ICC, inta-class correlations; MZ, monozygotic; WM, white matter.

DZ group is visible in the maps with the hotter color of the MZ voxels.

3.3. Heritability estimations

Table 2 presents the results of structural equation modeling of the volumetric measures (corrected for ICV, scanner, age, and sex) in the AE model, which was the best-fit model for nearly all the measures. The results showed a significant influence of genetic factors on brain structure in older adults. The highest heritability estimates were 87% for occipital WM, 76% for left frontal WM, and 71% for cerebral WM and occipital GM. More moderate heritabilities were estimated for the general measures such as the ICV (64%), BV (63%), cerebrum (63%), cerebral GM and WM (68% and 71%, respectively), and cerebellum (67%), and the lobar measures such as the frontal (64%), occipital (67%), parietal (63%), and temporal (55%) lobes. The lowest genetic influences were observed for the right frontal GM (55%), left temporal (45%), and right parietal GM (53%).

3.4. Influence of moderators on the A and E factors

The aim of this section was to test if the influence of genetic factors on the volumetric measures would change with age, and if they were different between men and women and between the right and left hemispheres. These were tested by entering the age, sex, and laterality covariates in the second AE model (Fig. 1B).

3.4.1. Age effects on the A and E factors

Table 2 shows negative path estimates between age and the A factor for most of the measures, including the significant estimates of −0.46 (BV), −0.45 (cerebrum), −0.36 (cerebral WM), −0.38 (total temporal), −0.39 (temporal WM), −0.19 (total parietal), and −0.21 (right parietal WM). In contrast, the influence of age on the E factors was mostly positive, with significant estimates of 1.21 (BV), 1.19 (cerebrum), 1.09 (cerebral WM), 0.89 (total temporal), and 0.37 (right parietal WM). These findings suggest a reduction of genetic and a corresponding increase of environmental influences on the brain

Table 2
Estimation of genetic and environmental influences on brain volumes along with the effects of moderators

Parameter	A	E	χ^2	d.f	AIC	Effect of the moderators on the A factor			Effect of the moderators on the E factor		
						Age	Sex	Laterality factors	Age	Sex	Laterality factors
ICV	64	36	17.08	18	−18.91	0.07 ns	−0.48*		−0.15 ns	1.01*	
Total B.V	63	37	15.80	18	−20.19	−0.46*	−0.09 ns		1.21*	0.24 ns	
Total cerebral volume	63	37	15.98	18	−20.01	−0.45*	−0.04 ns		1.19*	0.11 ns	
R. B.V	61	39	17.46	18	−18.53	−0.49*	−0.11 ns	−0.74*	0.98*	0.21 ns	−1.57*
L. B.V	63	37	16.25	18	−19.74	−0.43*	−0.08 ns		1.07*	0.21 ns	
R. Cerebrum	59	41	18.38	18	−17.61	−0.49*	−0.05 ns	−0.75*	0.98*	0.10 ns	−1.57*
L. Cerebrum	64	36	16.73	18	−19.27	−0.41*	−0.04 ns		1.06*	0.09 ns	
Cerebral GM	68	32	10.54	18	−25.46	−0.04 ns	−0.11ns		−0.11 ns	−0.22 ns	
Cerebral WM	71	29	11.91	18	−24.08	−0.36*	0.02 ns		1.09*	−0.07 ns	
R. Cerebral GM	62	38	11.3	18	−24.66	−0.03 ns	−0.12 ns	−0.82*	−0.05 ns	−0.20 ns	−1.49*
L. Cerebral GM	65	35	9.37	18	−26.63	−0.05 ns	−0.10 ns		−0.13 ns	−0.24 ns	
R. Cerebral WM	59	41	15.32	18	−20.68	−0.39*	0.04 ns	−0.10 ns	−0.81*	0.07 ns	−0.25 ns
L. Cerebral WM	72	28	12.06	18	−23.93	−0.32*	0.01 ns		1.01*	−0.04 ns	
Total cerebellum volume	67	33	10.61	18	−25.39	−0.02 ns	−0.26*		−0.04 ns	−0.59*	
R. Cerebellum	63	37	8.90	18	−27.09	0.11 ns	−0.28*	1.16*	−0.18 ns	0.44*	1.71*
L. Cerebellum	61	39	12.18	18	−23.82	0.06 ns	−0.27*		−0.10 ns	0.46*	
Total CSF volume	57	43	12.38	18	−23.62	0.29*	−0.54*		−0.47*	0.86*	
Total frontal volume	64	36	22.11	18	−13.88	−0.15 ns	−0.21*		0.45 ns	0.62*	
Frontal GM	66	34	9.57	18	−26.43	0.01 ns	−0.21*		0.02 ns	−0.41*	
Frontal WM	75	25	21.23	18	−14.76	−0.18 ns	−0.08 ns		0.58 ns	0.26 ns	
R. Frontal	70	30	20.19	18	−15.80	−0.16 ns	−0.19*	−1.24*	-0.41 ns	−0.51*	2.62*
L. Frontal	65	35	21.89	18	−14.11	−0.14 ns	−0.21*		−0.42 ns	−0.63*	
R. Frontal GM	55	45	13.86	18	−22.14	0.02 ns	−0.19*	−0.96*	−0.03 ns	0.29 ns	−1.46*
L. Frontal GM	66	34	8.66	18	−27.34	0.00 ns	−0.21*		0.01 ns	−0.44*	
R. Frontal WM	62	38	23.41	18	−12.58	−0.18 ns	−0.06 ns	−0.56 ns	0.39 ns	0.15 ns	−0.10 ns
L. Frontal WM	76	24	19.53	18	−16.47	−0.17 ns	−0.09 ns		0.58 ns	0.31 ns	
Total temporal volume	55	45	13.74	18	−22.26	−0.38*	−0.15 ns		0.89*	0.37 ns	
Temporal GM	59	41	9.74	18	−26.26	0.04 ns	−0.15 ns		0.06 ns	−0.28 ns	
Temporal WM	65	35	14.60	18	−21.39	−0.39*	0.00 ns		−0.86*	0.01 ns	
R. Temporal	54	46	14.34	18	−21.66	−0.36*	−0.14 ns	−0.88 ns	0.63*	0.24 ns	−0.52 ns
L. Temporal	45	55	18.21	18	−17.79	−0.38*	−0.17 ns		0.76*	0.34 ns	
R. Temporal GM	56	44	12.25	18	−23.75	0.08 ns	−0.16 ns	−0.31*	0.12 ns	−0.22 ns	−0.49*
L. Temporal GM	63	37	10.37	18	−25.62	−0.01 ns	−0.13 ns		−0.01 ns	−0.24 ns	
R. Temporal WM	46	54	14.03	18	−21.97	−0.49*	0.03 ns	−0.22*	−0.59*	0.04 ns	−0.38*
L. Temporal WM	62	38	18.97	18	−17.03	−0.32*	−0.02 ns		−0.83*	−0.07 ns	
Total occipital volume	67	33	12.65	18	−23.34	0.00 ns	−0.20*		0.01 ns	−0.51*	
Occipital GM	71	29	14.39	18	−21.61	−0.01 ns	−0.25*		−0.04 ns	−0.70*	
Occipital WM	87	13	19.00	18	−16.99	0.02 ns	0.08 ns		−0.09 ns	−0.30 ns	
R. Occipital	65	35	13.44	18	−22.56	−0.03 ns	−0.24*	1.15 ns	0.05 ns	0.52*	0.71 ns
L. Occipital	67	33	21.08	18	−14.92	0.03 ns	−0.16 ns		−0.06 ns	0.33 ns	
R. Occipital GM	67	33	14.01	18	−21.99	−0.02 ns	−0.30*	0.19 ns	0.06 ns	0.71*	0.23 ns
L. Occipital GM	71	29	14.45	18	−21.54	−0.01 ns	−0.20*		−0.01 ns	−0.49*	
R. Occipital WM	74	26	22.02	18	−13.97	0.01 ns	0.09 ns	0.65 ns	−0.04 ns	−0.24 ns	0.41 ns
L. Occipital WM	83	17	20.87	18	−15.13	0.03 ns	0.07 ns		−0.13 ns	−0.26 ns	
Total parietal volume	63	37	15.19	18	−20.80	−0.19*	−0.06 ns		−0.42*	−0.13 ns	
Parietal GM	63	37	20.03	18	−15.96	−0.07 ns	0.10 ns		−0.12 ns	0.18 ns	
Parietal WM	67	33	14.93	18	−21.07	−0.16 ns	−0.19*		−0.42 ns	−0.49*	
R. Parietal	59	41	16.44	18	−19.55	−0.21*	−0.08 ns	0.24 ns	0.34*	0.15 ns	0.26 ns
L. Parietal	65	35	16.96	18	−19.03	−0.18 ns	−0.05 ns		−0.41 ns	−0.08 ns	
R. Parietal GM	53	47	22.02	18	−13.97	−0.04 ns	0.12 ns	−0.57*	−0.05 ns	0.15 ns	−0.73*
L. Parietal GM	58	42	18.74	18	−17.25	−0.09 ns	0.09 ns		−0.15 ns	0.15 ns	
R. Parietal WM	56	44	12.65	18	−23.34	−0.21*	−0.24*	0.06 ns	0.37*	0.44*	−1.98 ns
L. Parietal WM	66	34	15.50	18	−20.47	−0.12 ns	−0.15 ns		−0.28 ns	−0.33 ns	

Additive genetic (A) and unshared environmental (E) estimates (shown as percentages of total variance) of the volumetric measures (Fig. 1A): the AE model was the best-fit model for the majority of the measures (the lowest AIC); Fit indices of the AE models to test models' significance under these criteria: $\times^{2/d.f} < 2$, p-value>0.05 and RMSEA<0.05 (all models had significant P-value and RMSEA); The path coefficients of age, sex and laterality factors on the latent A and E factors (Fig. 1B): * = significant path estimates (95% confidence intervals not crossing zero), ns = non-significant.
Key: BV, brain volume; CSF, cerebrospinal fluid; GM, gray matter; ICV, intracranial volume; L, left; R, right; WM, white matter.

with age. However, some measures did not show significant changes in the genetic and environmental influences with age, including cerebral GM, cerebellum and frontal and occipital lobes. As stated previously, the lowest heritability of all the measures was 46% in the right temporal WM, and interestingly this measure showed the highest negative influence of age (−0.49) on the A factor.

3.4.2. Sex effects on the A and E factors

Estimations showed all the significant paths between sex and the latent A factor to be negative, for example for the ICV (−0.48), cerebellum (−0.26), total frontal (−0.21), total occipital (−0.20), and parietal WM (−0.19). These findings suggest a lower influence of genes on the female brain. No volumetric measure significantly showed a higher heritability in women. However, no particular pattern was observed for the differences of environmental influences on the male and female brains. Accordingly, 16 paths were significant between sex and the latent E factor whereas 8 of them showed higher environmental influences in men and 8 showed higher in women.

3.4.3. Laterality of the A and E factors

Comparison of the heritability of the measures in the right and left hemispheres showed a higher genetic influence on left

Table 3
The genetic and environmental correlations of general brain volumes

	Environmental correlations				
Genetic correlation		BV	GM	WM	Cerebellum
	BV	–	0.825	0.889	0.725
	GM	0.643	–	0.563	0.587
	WM	0.854	0.165	–	0.578
	Cerebellum	0.606	0.521	0.362	–

The genetic (below the diameter) and environmental (above the diameter) correlations of brain volumetric measures in a Cholesky model, estimated using the path estimates of the model: moderate to high genetic correlations have been observed between the volumetric measures.
Key: BV, brain volume; GM, grey matter; WM, white matter.

hemispheric volumes for total brain, cerebrum, cerebral GM and WM, frontal and temporal lobes, GM and WM, and occipital and parietal lobes. To test the significance of these hemispheric differences, we included the laterality factor in the AE model (Fig. 1B). Most of the paths between the laterality and the A and E factors were significant and demonstrated higher heritability in the left hemisphere (Table 2).

3.5. Multivariate analyses

3.5.1. General measures

The multivariate Cholesky model for the general volumetric measures revealed considerable genetic correlations (Table 3), such as between BV and WM (0.85), GM (0.64), cerebellum (0.61), between GM and cerebellum (0.52), and a more moderate correlation of GM and WM (0.16). These findings illustrate that a common set of genetic factors are influencing different brain measures; however, the genetic determinants of GM and WM seem not to overlap much.

3.5.2. Lobar measures

High genetic correlations were also observed between the lobar volumetric measures (Table 4). Frontal and parietal (0.81), frontal and temporal (0.77), temporal and parietal (0.70), parietal and occipital (0.66), and temporal and occipital (0.63) lobes showed considerable genetic correlations. Similar findings were observed after repeating this lobar model with the GM measures of the lobes (Table 4). Accordingly, significant genetic correlations were observed between the frontal and parietal GM (0.62), temporal and frontal GM (0.42), and parietal and temporal GM (0.31). All the measures in the multivariate models were corrected for ICV, scanner, age, and sex.

4. Discussion

This study showed that the effect of genetic factors on total and regional brain volumes is relatively high in the late life. Reductions of genetic influences with age, as environmental influences increased, was observed in 18 total and regional volumetric measures, whereas CSF was the only measure with a significant heritability increment with age. Similarly, 18 total and regional measures significantly showed a higher genetic influence in men compared with women, whereas no finding for a higher heritability in women was observed. Also, 16 measures significantly showed a higher genetic influence in the left hemisphere of the brain, whereas cerebellum was the only measure with a higher heritability in the right hemisphere. Furthermore, moderate to high genetic correlations were observed between the total and lobar brain volumes suggesting the existence of shared genetic factors between the volumetric measures of interest. These findings show an age, sex, and laterality-related heritability change in brain volumes, although different brain regions did not show consistent behaviors. Our sample consisted of individuals older than 65 years, drawn from the community, with relatively well-preserved cognition and free from psychiatric disorders, and therefore our results are most likely applicable to a healthy aging population.

4.1. Brain heritability

The heritability of brain global and lobar measures was relatively high in our study. Although, few BVs have been genetically studied previously, our results are consistent with some of those findings, such as the reported 64% heritability for cerebrum, 64% and 67% for the right and left BV, 52% and 41% for right and left temporal, and 75% for right frontal, all at the age of 72 (Carmelli et al., 2002; Geschwind et al., 2002). However, other authors have published lower heritability estimates, e.g. 46% for BV at the age of 64 (DeStefano et al., 2009), 47% and 57% for total parietal, 28% and 37% for total occipital, and 54% for total frontal, at the age of 72 (Carmelli et al., 2002; Geschwind et al., 2002). Methodological differences might explain the discrepancies. The study by DeStefano et al. (2009) was a family study in contrast with a twin design used in the present investigation. Carmelli et al. (2002) and Geschwind et al. (2002) studied World war-II veterans with poor lifetime environmental conditions, and did not exclude participants with dementia. The quality of MRI scans was also different, with the earlier studies using larger slice thickness (4–5 mm), which can increase measurement error for volumes of structures.

4.2. Sex effects

We observed higher heritability in many of our volumetric measures in men, as suggested previously (Chiang et al., 2011; Posthuma et al., 2000). Higher heritability of brain function (van Beijsterveldt et al., 1996) and brain WM fiber integrity (Chiang et al., 2011) in men has also been observed previously. These findings suggest that women are more subjective to the influence of environmental factors, which might be a reason for their higher dementia risk (Azad et al., 2007; Brayne et al., 1995; Fratiglioni et al.,

Table 4
The genetic and environmental correlations of lobar brain volumes

	Environmental correlations					
		Cerebrum	Frontal	Parietal	Occipital	Temporal
Genetic correlations	Cerebrum	–	0.913 (0.870)	0.808 (0.647)	0.688 (0.482)	0.896 (0.783)
	Frontal	0.866 (0.749)	–	0.778 (0.515)	0.682 (0.371)	0.805 (0.596)
	Parietal	0.824 (0.716)	0.814 (0.623)	–	0.742 (0.375)	0.653 (0.317)
	Occipital	0.698 (0.363)	0.501 (0.105)	0.664 (0.159)	–	0.667 (0.364)
	Temporal	0.949 (0.770)	0.771 (0.417)	0.699 (0.312)	0.634 (0.288)	–

The genetic (below the diameter) and environmental (above the diameter) correlations of cerebrum and the four major lobes: frontal, parietal, occipital and temporal; The Cholesky model was initially run with the total volume of the lobes, but then a second model was run with the GM volumes of the lobes (the correlations of the GM measures are provided in parentheses); Both models of total volumes and grey matter volumes were significantly fitted to the data.

1997), higher brain atrophy rate (Courchesne et al., 2000; Ge et al., 2002), larger white matter lesions (Sachdev et al., 2009b) and more severe cognitive decline (Lee et al., 2010).

The reasons for sex differences in the heritability of brain structures are not well understood. Although there are sex differences in the genetic blueprint (Bailey and Pillard, 1991; Hamer et al., 1993), the hormonal and other environmental differences that influence the two sexes differentially might be equally important. Hormones can directly influence brain structure and function, as shown by the increase in total brain volume in women treated with androgen (Hulshoff Pol et al., 2006a), and sex differences in behavior produced by neonatal exposure to gonadal steroids (McEwen, 1994; McEwen et al., 1987). Hormones might also modify genetic influences on the brain (Chiang et al., 2011), such as the effect of testosterone on gene expression in avian brains (Absil et al., 2003), or the epigenetic effects of steroid hormones on the nervous system (McCarthy et al., 2009). An increasing influence of genetic factors on hippocampal volume as a function of increasing testosterone level has also been observed previously (Panizzon et al., 2012). Although some studies have reported that same genes are influencing different human phenotypes in men and women (Vink et al., 2012), the sexual differences of genetic influences is suggested to be under the influence of a complex gene-by-hormone interaction (Menger et al., 2010; Panizzon et al., 2012). Menger et al. (2010) in a review study have shown that hormonal activations are controlled by the epigenetic mechanisms, whereas these mechanisms might themselves be under the control of hormones. Therefore, epigenetic changes offer a mechanism by which the hormonal effects in early life are enabled to be hardwired into the genome, which causes subsequent hormonal and behavioral responses in the adulthood time (McCarthy et al., 2009). In addition to the influence of hormones on human sexual differences, environmental factors, such as coping with the challenges of life which are different for men and women, might also lead to sex differences in the brain structure (Hart and Sussman, 2009; Silk, 2007).

These findings show that the influence of sex on brain heritability is deserving of further and more detailed study. Furthermore, as sex differences have been observed in the incidence of many diseases, the factors that cause sex differences in brain genetics as well as their magnitude and character of their impact should be investigated (Anderson, 2005).

4.3. Brain laterality

Our finding of higher heritability in the left hemisphere is consistent with previous reports in twins younger than our study (Eyler et al., 2012; Yoon et al., 2011). One possible reason is the dominance of the left hemisphere in language processing (Giedd et al., 2007; Tramo et al., 1995; Yoon et al., 2010b). However, more factors seem to be associated with brain asymmetry, including age (Jahanshad et al., 2010), sex (Luders et al., 2003; Witelson and Kigar, 1992), and handedness (Geschwind, 1970; Narr et al., 2007). Handedness seems to be the most prominent factor, because of its strong heritability (Hicks and Kinsbourne, 1976) and its influence on the degree of cerebral laterality inheritance (Klar, 1999; McManus, 1991). The heritability of the left hemisphere is reported to be lower in non right-handed individuals (Geschwind et al., 2002), and most of the participants in our study (88.6%) were right-handed.

4.4. Genetic factors

Determination of the genes, which influence brain structure has been challenging, as many genes are involved and there are likely gene-gene interactions. It is believed that nearly two-thirds of the approximately 30,000 genes in the human genome are related to the brain (Petrella et al., 2008). A few specific genes have been identified as influencing brain structures: examples of associations include Brain-derived neurotrophic factor-Met allele associated with hippocampal and prefrontal volumes (Nemoto et al., 2006; Pezawas et al., 2004); microcephalin 1 with cranial volume (Wang et al., 2008); ACE and nitrogen oxide synthase with subcortical WM (Henskens et al., 2005); disrupted in schizophrenia with prefrontal GM (Callicott et al., 2005; Hennah et al., 2006); kidney and brain expressed protein with memory-related brain structures (Petrella et al., 2008); apolipoprotien $\varepsilon 4$ with hippocampal and WM volumes (DeCarli et al., 1999; Plassman et al., 1997); plexin-haplotype-A with WM volume (Rujescu et al., 2006); and prion protein gene with parenchymal volume (Knight and Will, 2004).

Although a group of genes might influence one brain structure, one gene might itself influence more than 1 brain region (pleiotropy). This is the most likely explanation for the genetic correlations between the various brain measures in our study. We observed strong genetic correlations between the global brain measures and the lobar values, as it has been reported previously between few brain regions (Glahn et al., 2007; Pfefferbaum et al., 2000; Posthuma et al., 2003). In addition, high phenotypic correlations (data not provided in the manuscript) were observed between those measures that were genetically correlated, in agreement with the previous reports (Bartzokis et al., 2001). These show that not only do genes play a significant role in controlling the brain structure, but that most of these genetic variances are shared between the major neural subdivisions (Giedd et al., 2007).

It is noteworthy that the WM showed only a moderate genetic correlation with GM, as found by a previous study (van Leeuwen et al., 2009). It is possible that different tissue types in the brain have different genetic determination, with some overlap (Schmitt et al., 2010). In addition, age-related changes are different in the GM and WM (Benedetti et al., 2006; Giorgio et al., 2010; Good et al., 2001; Piguet et al., 2009; Ziegler et al., 2011). The interaction of environmental influences with the genetics is also reportedly stronger for WM than GM (Fields, 2008; Posthuma et al., 2002; Zatorre et al., 2012). These findings could explain the lower GM-WM genetic correlation.

The volume and heritability of ICV, which is calculated as the sum of BV and CSF, remains constant through the lifespan after the initial period of increase in childhood (Baare et al., 2001; Blatter et al., 1995; Sullivan et al., 2001; Walhovd et al., 2005). Therefore, any age-related decline in BV leads to a corresponding increase in CSF volume, which accounts for the different behavior of CSF compared with brain structures in our study.

We also observed moderate genetic correlations between cerebellum and other measures. Spatial proximity is suggested to have a prominent role in the high genetic or environmental correlations between brain structures (Schmitt et al., 2007, 2009, 2010), which could be a possible explanation for the lower genetic correlation of the cerebellum with other measures in our study.

4.5. Implications of the findings for aging

Our results showed decrement in the heritability of brain structures with age, which was observed previously for limited brain regions (Pedersen, 2000; Pfefferbaum et al., 2000). A review of the literature on the heritability of brain structures through the lifespan also supports this (Baare et al., 2001; Bartley et al., 1997; Carmelli et al., 2002; DeStefano et al., 2009; Geschwind et al., 2002; Hulshoff Pol et al., 2006c; Winkler et al., 2009; Wright et al., 2002). Decrement in heritability of cognitive function with age has also been demonstrated (Finkel et al., 1998; Lee et al., 2010).

Although estimation of the gradient of the heritability decline with age in different brain regions was not an interest of the present study, we observed that the anterior and posterior regions of the brain did not show a significant change in their genetic or environmental influences with age, such as the frontal and occipital lobes and the cerebellum, whereas temporal and parietal lobes did, suggesting that the medial regions of the brain might be more vulnerable to the aging influences. Decrement of BV heritability could occur because exposure to environmental factors accumulates throughout life and these factors finally outweigh the genetic influences (Chiang et al., 2011; Pfefferbaum et al., 2000; 2004). In a longitudinal study on the heritability of brain structure in older twins (Pfefferbaum et al., 2004), evidence for new environmental influences at time 2 not present at time 1 was observed, whereas genetic variance showed no change. In addition, we observed increment in the heritability of CSF volume, which is in agreement with the higher heritability of ventricles in older individuals (Kremen et al., 2012). Also, common environmental variance was not significant in our analyses, which could be because of the age of our sample, as studies have reported dissipation of this variance as twins live apart (Brun et al., 2009).

Despite the moderate to high heritability of our measures, environmental influences on brain structure should not be neglected, as they can have both positive and negative effects. Positive effects include changes in WM structure (Scholz et al., 2009) or myelination of unmyelinated axons (Zatorre et al., 2012) with experience, and alteration of myelin thickness and axon diameter with increased motor activity (Canu et al., 2009). Negative effects include reduction of impulse conduction velocity because of physical inactivity (Ruegg et al., 2003), and association of brain atrophy with environmental risk factors (Hulshoff Pol et al., 2004). In addition, environmental exposure can indirectly influence the brain through interaction with genes, such as epigenetic changes in the nervous system induced by life experiences, hormonal exposure, trauma, and injury (McCarthy et al., 2009). An animal study has also illustrated changes in the rate of genetic activity, or in the number and variety of active genes, because of environmental exposure (Walsh, 1980). These findings suggest that to age well, enriched environmental conditions should be provided once brain heritability has started to decline, to avoid both direct and indirect negative influences of the environment on the brain.

4.6. Strengths and limitations

Our study had a number of strengths. It was one of the largest MRI studies of older twins to have examined the major brain structures. Although we used 3 different scanners, twin pairs were always scanned on the same scanner and temporally very close to each other, and systematic scanner differences were taken into account by using scanner as a covariate in the analysis. However, our study was limited to a cross-sectional approach in the age range of 65–88 years, which did not give a complete picture of brain heritability changes over the lifespan. In addition, approximately 5% of our participants were diagnosed as having MCI. Although repeating the analyses after excluding those with MCI did not alter our findings, we cannot exclude the possibility that Alzheimer's disease pathology had a minor impact on the results. Also, we studied cortical volume, which is composed of cortical thickness and surface area, which are found not to have significant genetic correlations (Panizzon et al., 2009). The relative contribution of cortical thickness and surface area to the estimates cannot therefore be determined without further analyses. Finally, defining a standard measure to estimate the degree of alignment between the scans and the atlases could be used as an evidence of the accuracy of this step.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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