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RESEARCH ARTICLE

Human Connectome Project: heritability of brain volumes in young healthy adults

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Abstract

Here we report on the heritability and Intraclass Correlation Coefficients (ICCs) of brain volumes in 1,103 young healthy adults with mean age 29.2 years. Among them are: 153 monozygotic (MZ) twin pairs and 86 dizygotic (DZ) twin pairs, 133 non-twin siblings of MZ twins, 76 non-twin siblings of DZ twins, 335 siblings, and 81 unrelated individuals. ICCs were calculated between pairs of the following genetic groups: (1) MZ twins; (2) DZ twins; (3) MZ twins—their singleton siblings; (4) DZ twins—their singleton siblings; (5) siblings (SB); and (6) unrelated individuals (NR). We studied 4 brain groups: global, lobar, subcortical, and cortical brain regions. For each of 4 brain groups we found the same order of ICCs ranging from the highest values for MZ twins, statistically significantly smaller for the DZ twins and 3 sibling groups, and practically zero for NR. The DZ twins and 3 sibling groups were not different. No hemispheric difference was found in any genetic group. Among brain groups, the highest heritability was for the global regions, followed by lobar and subcortical groups. Only the cortical brain group heritability was statistically lower than other brain groups. We found less genetic control on the left hemisphere than on the right but no significant difference between hemispheres, and no hemispheric lateralization of heritability for any of the brain groups. These findings document substantial and systematic heritability of global and regional brain volumes.

Keywords Monozygotic · Dizygotic twins · Global · Cortical · Subcortical brain volumes

Introduction

Twins are an excellent model for estimating the heritability of a particular phenotypic measure by separating the variance of individual differences into genetic and non-genetic components. For this purpose, both monozygotic (MZ) and dizygotic (DZ) twin data are required. The assumption that MZ twins share 100%, and that DZ twins and full siblings share on average 50%, of their segregating genes is widely accepted (Visscher et al. 2008).

Developmental and lifespan changes during childhood, adulthood, and later in life, are the result of a very complex interplay of genetic and environmental factors (Hedman et al. 2012). It has been shown that the brain undergoes many structural and functional changes during development and young adulthood (Wallace et al. 2006; Schmitt et al. 2010). Age-related changes such as volume decrease and heritability decline are common findings, and considered normal during the aging process (Batouli et al. 2014; Lukies et al. 2017). An age effect on heritability has been

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shown for brain volume rates of change of heritability that is higher in adults than in children (Brouwer et al. 2017).

Brain and heritability change over the lifespan are outlined above (Lukies et al. 2017; Strike et al. 2015). We found only a few studies on heritability in young healthy adult twins, with mean twin age between 20 and 30 years (Baaré et al. 2001; Bartley et al. 1997; Chou et al. 2009; Hulshoff Pol et al. 2006; Rentería et al. 2014; Scamvougeras et al. 2003; Wright et al. 2002). However, these studies have limitations, namely (a) small sample sizes in the studies by Bartley et al. (1997) and Wright et al. (2002), and (b) a small number of volumes measured. For example, Chou et al. (2009) reported only on the lateral ventricles; Baaré et al. (2001) reported only on whole brain, the gray and white matter of cerebrum, and lateral ventricles; Scamvougeras et al. (2003) studied only the corpus callosum; and Rentería et al. (2014) studied only subcortical structures.

Surprisingly, only a few studies have specifically examined families with singleton siblings of twins or just siblings. Brain structures in extended twin families were studied by Greenspan et al. (2016), Patel et al. (2017) and Posthuma et al. (2000). Hulshoff Pol et al. (2002) compared brain morphology between 112 pairs of adult twins with their 34 singleton siblings. White matter volume was smaller in twins compared with siblings, but the difference was no longer significant after correcting for twins' smaller intracranial volume (ICV). For total brain and lateral and third ventricular volumes, no twin-siblings difference was found. In addition, comparing twins to unrelated singletons (Ordaz et al. 2010) found no significant difference between twins and unrelated singletons' gray and white matter.

In this study, we analyzed data from the Human Connectome project (HCP, www.humanconnectome.org) a blueprint of NIH—funded project led by Washington University, University of Minnesota, and the University of Oxford provides state-of-the-art data. Their young adult project provides a rich dataset with MRI measures collected for a large family structure of 1200 subjects (Van Essen et al. 2013). Participants were scanned on a customized 3T scanner described in detail together with image acquisition methods by Uğurbil et al. (2013) and preprocessing pipelines by Glasser et al. (2013). We used this valuable free source of data as the others (Kochunov et al. 2019; Patel et al. 2018; Schmitt et al. 2019).

Our study is a broader exploration in a large number of young healthy twins and their singleton siblings, siblings, and unrelated individuals. Additionally, we focused on 4 genetic groups that share on average 50% of their genetic material: DZ twins, MZ twin—singleton siblings (MZsb), DZ twin—singleton sibling (DZsb), and only siblings (SB). We studied a considerable number of volumetric measures grouped as: (1) global-including, cerebrum, cerebellum, gray and white matter, (2) brain lobes, (3) subcortical, and (4) cortical regions of interest (ROIs).

Materials and methods

Participants

This study reports on data of a healthy population of 1206 participants (age range 22–36 years old) of the Human Connectome Project (HCP; www.humanconnectome.org) final data release. Out of 1206 HCP young adult participants, 1113 participants have MRI acquisitions. Genotyping analysis of genetic material from blood or saliva samples confirmed the biological family relationships, like zygosity of twin pair participants. Out of 1113 participants with imaging data, 1,053 participants had genetically confirmed family relations. Additionally, participants with self-assessment were included. Kochunov et al. (2019) found that heritability estimates from the self-reported relationship dataset and whole-genome empirical relationship dataset were highly correlated ($r > 0.9$) that allows us to combine those genetically confirmed and self-assessed participants. From a combined dataset of 1103 participants, we found that: 306 (153 pairs) are MZ twins, 172 (86 pairs) are DZ twins, 133 from 111 families are siblings of MZ twins, 76 from 61 families are siblings of DZ twins, 335 participants out of 142 families are siblings, and 81 are unpaired twins or unrelated individuals. The following 6 genetic groups of participants were studied by pairing the individuals of: (1) MZ twins (MZ); (2) DZ twins (DZ); (3) MZ twins and their singleton siblings (MZsb); (4) DZ twins and their singleton siblings (DZsb); (5) siblings (SB), and (6) unrelated individuals (NR).

Brain volumes

Data were processed by three structural pipelines: PreFreeSurfer Pipeline, FreeSurfer Pipeline and PostFreeSurfer Pipeline with the aim to provide high-quality volume and surface data using the high-resolution T1w and T2w images. The pipeline is based on FreeSurfer 5.3.0-hpc version of the Freesurfer software and was modified to capitalize on HCP's high-resolution data (Glasser et al. 2013). Briefly, the surface-based FreeSurfer (FS; surfer.nmr.mgh.harvard.edu) analysis involves normalization of image intensities and removal of extracerebral tissues, followed by segmentation of the brain into gray and white matter, and estimation of the boundary between white matter and gray matter as well as pial surface and computing registration based on aligning the cortical folding patterns. The Desikan-Killiany atlas (Desikan et al. 2006) parcellation scheme labels cortical sulci and gyri into 68 and 2 hippocampi (35 for each hemisphere) ROIs. Volumes were calculated for four major lobes: frontal,

parietal, occipital, and temporal; as the sum of the relevant ROIs: 13 ROIs comprise frontal lobe, 4—occipital, 8—parietal (includes insula), and 10—temporal lobe per hemisphere. Additionally, volumes of global and per hemisphere gray and white matter of the cortex and cerebellum were obtained. In the volume-based stream, subcortical regions are automatically labeled in left and right hemispheres including thalamus, caudate, putamen, pallidum, amygdala, nucleus accumbens, and ventral diencephalon (DC). The list of ROIs is shown in the first column of Table 2.

Studies in the introduction above showed that the heritability depends on participant age. We also found a gender-based effect on heritability values. For example, the heritability of ICV is quite different values for male and female participants. We calculated intraclass correlation coefficient (ICC) and heritability values for male and female twins and found values of 0.807, 0.611, and 0.391 for male pairs, and 0.941, 0.611, and 0.660 for female pairs, respectively. Additionally, we compared regional volumes between participants, but the individual structures are larger in larger brains. To account for all above mentioned interindividual variabilities due to age, gender, and total brain size, we use the residuals of the linear regression of volumes against age, gender, and ICV. The estimated Total Intracranial Volume (eTIV) generated by FreeSurfer was used as an estimate for the ICV. A similar approach was used by Patel et al. (2018) who also studied the HCP data and found gender and age effect on the heritability of thickness and surface area of cortex. The left and right hemisphere brain volumes were analyzed separately.

Intraclass correlations and heritability

For each ROI, for each group of individuals, and for each set of pairs we calculated the ICC. For MZsb and DZsb groups we averaged ICC between twins and singleton siblings. In the SB, MZsb, and DZsb groups there are, within the same family, 2, 3, 4 or 5 siblings. For such families with more than 2 siblings, 2 out of the total number of siblings were randomly selected for pairing. That makes 142 pairs out of 284 selected siblings for the SB group. In the NR group, 81 individuals were randomly paired in 40 pairs. For each ROI, for SB and NR groups, we calculated ICC for randomly paired individuals. After repeating this process 1001 times, we found the median ICC of 1001 ICCs.

Negative ICC values are outside the theoretical range for an ICC, although such values are mathematically possible. When interpreting negative ICC values in the context of estimating inter-rater reliability, it is advised, "there is no other possible interpretation but poor agreement" across raters (Giraudeau 1996). Therefore, in these cases, the value was excluded.

Fisher's (Fisher 1958) r–z transformation was conducted to fit the ICC variable to a normal probability distribution. Then the means of the z-transformed ICC (zICC) for each genetic group for global, subcortical, lobar, and cortical ROI volumes were calculated.

Falconer's Formula (Falconer 1965; Falconer et al. 1996) is used in twin studies to determine the genetic heritability of a trait-based on the difference between intraclass correlations in MZ twins and DZ twins. Falconer's formula h^2 defines heritability as twice the difference in the intraclass correlation of a trait between MZ and DZ twins:

$$h^2 = 2\left(\mathrm{ICC}_{\mathrm{MZ}} - \mathrm{ICC}_{\mathrm{DZ}}\right) \quad (1)$$

In this study, Falconer's formula was used to calculate heritability in brain volumes.

Statistical analysis

For global, lobes, subcortical structure, and cortical ROIs analysis of variance (ANOVA) and general linear model were used to determine the differences among 6 genetic groups of participants: MZ twins, DZ twins, MZsb, DZsb, SB, and NR individuals. Additionally, the Bonferroni Post Hoc test was applied. Significance $P = 0.05$ was corrected for multiple comparisons.

Results

The descriptive statistics of age and gender of 6 genetic groups of participants are given in Table 1.

Intraclass correlations for 6 genetic groups of participants

Table 2 shows intraclass correlations with lower and upper bound of 95% confidence interval (CI) for MZ and DZ twins for 10 global areas, 8 brain lobes, 14 subcortical, and 70 cortical ROIs. The comparison shows that, overall, the intraclass correlations for DZ twins were lower than those observed for MZ twins, and included wider confidence intervals, with the lower bound sometimes approaching zero or even becoming negative. Higher MZ than DZ twin ICCs suggests the genetic influence.

Figure 1 presents the mean zICCs and standard error of the mean for 4 brain groups: global volumes, cortical lobar areas, subcortical structures, and cortical ROI volumes for the following 6 genetic groups: MZ, DZ, MZsb, DZsb, SB, and NR. However, comparison of brain groups showed that overall mean zICCs, specifically for MZ twins, were highest for global volumes (top left), followed by lobar volumes (top

Table 1 Demographics of the participants

	MZ	DZ	MZ sb	DZ sb	SB	NR
Total *N*	306	172	133	76	335	81
Male *N*	120	66	72	39	166	40
Female *N*	186	106	61	37	169	41
Age Mean (SD)	29.4 (3.4)	29.1 (3.6)	29.0 (4.0)	29.8 (3.7)	27.9 (3.7)	28.3 (3.7)
Male age Mean (SD)	27.7 (3.4)	26.8 (3.3)	28.9 (3.8)	29.9 (3.4)	27.8 (3.6)	27.4 (3.7)
Female age Mean (SD)	30.5 (2.9)	30.6 (3.0)	29.2 (4.2)	29.7 (3.9)	28.1 (3.8)	29.3 (3.6)

MZ monozygotic twins, *DZ* dizygotic twins, *MZsb* monozygotic twin singleton siblings, DZsb dizygotic twin singleton siblings, *SB* siblings, *NR* non-related participants, *N* number, *SD* standard deviation

right) and subcortical structures (bottom left), and lowest for the cortical ROIs (bottom right). (Same y-axis scale).

For each brain group, mean zICCs of 6 genetic groups followed the same pattern for genetic groups– the highest ICC for MZ twins, smaller ICCs for DZ, MZsb, DZsb, SB, and near-zero for NR (Fig. 1). zICC as a dependent variable, genetic groups, and brain groups as independent variables, the univariate general linear model showed high statistical significance for the brain groups ($F=59.147$, $P<0.001$) and for the genetic groups ($F=167.196$, $P<0.001$). Additionally, for global, lobar, subcortical, and cortical brain groups we found the following: (a) the MZ twins also had consistently and significantly higher ICC than that of DZ and also that of MZsb, DZsb, SB, and NR groups ($P<0.001$, Bonferroni Post Hoc, $P<0.05$ corrected for multiple comparisons); (b) the ICCs were not significantly different among following 4 genetic groups: DZ twins, MZsb, DZsb and SB; (c) mean zICCs were practically zero for the NR group and the lowest among 6 genetic groups ($P<0.006$, Bonferroni Post Hoc, $P<0.05$ corrected for multiple comparisons).

Asymmetry of intraclass correlations for 6 genetic groups of participants

Figure 2 shows the mean zICC separately for left and right hemisphere global (top left), lobar (top right), subcortical (bottom left), and cortical brain (bottom right) groups for all genetic groups. Mean values for the left and right hemispheres are very close with overlapping confidence intervals. For zICC was a dependent variable and brain groups, genetic groups, and hemispheres as factors, the univariate general linear model did not show the hemispheric difference (brain group $F=57.777$, $P<0.001$, genetic groups $F=163.302$, $P<0.001$ and hemisphere $F=0.021$, $P=0.885$).

Heritability of 4 brain groups

Table 2 shows heritability for 10 global areas, 8 brain lobes, 14 subcortical areas, and 70 cortical ROIs. Heritability varied between areas and covered the range from almost zero to 0.99. (Negative heritability and values > 1 were considered incorrect estimates and are marked as NaN).

Figure 3 shows the mean heritability per brain group. They are statistically different (ANOVA, $F=21.23$, $P<0.001$). The highest heritability was for the global regions, followed by lobar and subcortical regions but they were not statistically different. The lowest heritability was for the group of cortical ROIs. This group was statistically significantly lower than that for global and subcortical groups ($P<0.001$, Bonferroni Post Hoc comparisons, $P=0.05$ corrected), and lobar heritability but closer heritability value than other groups ($P=0.017$, Bonferroni Post Hoc comparisons, $P=0.05$ corrected).

The heritability values below 0.2 are considered low, those between 0.2 and 0.5 moderate, and estimates above 0.5 high. Specifically, the heritability was higher (> 0.5) for large volume measurements like global volumes: cortical gray and white matter, cerebellar gray and white matter, and some of the lobes (Table 2).

According to the above classification: (1) all global areas were highly heritable, (2) 5 of the lobes had the highest heritability and the rest 3 moderately heritable lobes, (3) 10 of the 14 subcortical areas were highly heritable and the remaining 4 moderately heritable, and (4) for cortical ROIs forty-five percent have moderate heritability, thirty-one percent were classified as having low heritability, and the remaining twenty-four percent-high heritability.

Zooming in on the details of each brain group (Table 2) the highest heritability in the global brain area was for the left white matter volume ($h^2=0.98$) and lowest for the left cortical gray matter ($h^2=0.55$). For the lobar areas, heritability ranged from 0.36 for the left occipital lobe to 0.72 for the left temporal lobe. The heritability calculated for the subcortical structure volumes ranged from 0.28 for the right accumbens area to 0.99 for the right thalamus proper and right putamen. Examining the heritability of the cortical Desikan ROIs, the results show that most areas have some degree of heritability. For the fusiform in the right hemisphere, the ICC for DZ twins was negative which is why heritability was not calculated. The ICC for the right caudal middle frontal cortex and left frontal pole were higher for

Table 2 Intraclass correlations and heritability

ROI name	MZ pairs $N=153$	95% Confidence interval		DZ pairs $N=86$	95% Confidence interval		Heritability
	ICC	Lower bound	Upper bound	ICC	Lower bound	Upper bound	
Global areas							
Cortical gray matter left	0.64	0.53	0.72	0.36	0.17	0.53	0.55
White matter left	0.80	0.73	0.85	0.31	0.10	0.48	0.98
Cerebellum white matter left	0.70	0.61	0.77	0.22	0.01	0.41	0.96
Cerebellum gray matter Left	0.85	0.79	0.89	0.49	0.31	0.64	0.71
Lateral ventrical left	0.73	0.65	0.80	0.25	0.05	0.44	0.95
Cortical gray matter right	0.67	0.58	0.75	0.35	0.15	0.52	0.65
White matter right	0.79	0.72	0.84	0.32	0.11	0.49	0.95
Cerebellum white matter right	0.68	0.58	0.76	0.31	0.10	0.48	0.75
Cerebellum gray matter right	0.84	0.78	0.88	0.46	0.28	0.61	0.75
Lateral ventrical right	0.59	0.47	0.68	0.16	– 0.06	0.36	0.86
Cortical lobar areas							
Frontal lobe left	0.74	0.66	0.81	0.41	0.22	0.57	0.66
Parietal lobe left	0.60	0.49	0.70	0.41	0.22	0.57	0.38
Temporal lobe left	0.64	0.54	0.73	0.29	0.08	0.47	0.72
Occipital lobe left	0.64	0.53	0.72	0.46	0.27	0.61	0.36
Frontal lobe right	0.78	0.70	0.83	0.43	0.24	0.59	0.69
Parietal lobe right	0.55	0.43	0.65	0.31	0.11	0.49	0.47
Temporal lobe right	0.63	0.53	0.72	0.29	0.08	0.47	0.70
Occipital lobe right	0.72	0.63	0.78	0.37	0.18	0.54	0.68
Subcortical structures							
Thalamus proper left	0.58	0.46	0.67	0.12	– 0.09	0.32	0.91
Caudate left	0.79	0.72	0.84	0.58	0.42	0.71	0.41
Putamen left	0.68	0.58	0.76	0.39	0.20	0.56	0.57
Pallidum left	0.53	0.40	0.63	0.31	0.11	0.49	0.43
Amygdala left	0.58	0.46	0.68	0.34	0.14	0.51	0.48
Accumbens area Left	0.51	0.38	0.62	0.17	– 0.05	0.36	0.69
VentralDC left	0.69	0.60	0.77	0.33	0.13	0.51	0.72
Thalamus proper right	0.65	0.55	0.73	0.15	– 0.06	0.35	0.99
Caudate right	0.80	0.74	0.85	0.48	0.30	0.63	0.65
Putamen right	0.85	0.80	0.89	0.36	0.16	0.53	0.99
Pallidum right	0.68	0.58	0.75	0.38	0.19	0.55	0.59
Amygdala right	0.69	0.60	0.77	0.22	0.01	0.41	0.94
Accumbens area right	0.51	0.38	0.61	0.37	0.17	0.54	0.28
VentralDC right	0.68	0.59	0.76	0.36	0.16	0.53	0.65
Cortical areas							
Banks superior temporal sulcus left	0.27	0.11	0.41	0.11	– 0.10	0.31	0.31
Caudal anterior cingulate cortex left	0.27	0.12	0.41	0.24	0.03	0.43	0.07
Caudal middle frontal gyrus left	0.35	0.21	0.49	0.29	0.08	0.47	0.13
Cuneus cortex left	0.56	0.44	0.66	0.40	0.21	0.56	0.32
Entorhinal cortex left	0.37	0.23	0.50	0.14	– 0.08	0.34	0.47
Fusiform gyrus left	0.27	0.11	0.41	0.16	– 0.05	0.36	0.22
Inferior parietal cortex left	0.45	0.31	0.57	0.27	0.07	0.46	0.35
Inferior temporal gyrus left	0.45	0.32	0.57	0.24	0.03	0.43	0.43
Isthmus cingulate cortex left	0.29	0.14	0.43	0.18	– 0.03	0.38	0.22
Lateral occipital cortex left	0.60	0.49	0.69	0.32	0.12	0.50	0.56
Lateral orbital frontal cortex left	0.53	0.41	0.64	0.35	0.15	0.52	0.37
Lingual gyrus left	0.52	0.40	0.63	0.38	0.18	0.54	0.29

Table 2 (continued)

ROI name	MZ pairs $N=153$	95% Confidence interval		DZ pairs $N=86$	95% Confidence interval		Heritability
	ICC	Lower bound	Upper bound	ICC	Lower bound	Upper bound	
Medial orbital frontal cortex left	0.33	0.18	0.46	0.25	0.05	0.44	0.15
Middle temporal gyrus left	0.50	0.37	0.61	0.13	– 0.09	0.33	0.75
Parahippocampal gyrus left	0.48	0.35	0.59	0.21	0.00	0.41	0.54
Paracentral lobule left	0.44	0.30	0.56	0.23	0.02	0.42	0.43
Pars opercularis left	0.41	0.27	0.54	0.07	– 0.14	0.27	0.69
Pars orbitalis left	0.36	0.22	0.49	0.06	– 0.15	0.27	0.61
Pars triangularis left	0.46	0.33	0.58	0.42	0.23	0.58	0.09
Pericalcarine cortex left	0.70	0.62	0.78	0.57	0.41	0.70	0.26
Postcentral gyrus left	0.32	0.17	0.46	0.21	0.00	0.40	0.23
Posterior cingulate cortex left	0.41	0.27	0.53	0.11	– 0.10	0.31	0.60
Precentral gyrus left	0.53	0.41	0.64	0.30	0.10	0.48	0.47
Precuneus cortex left	0.49	0.36	0.60	0.42	0.23	0.58	0.14
Rostral anterior cingulate cortex left	0.32	0.17	0.45	0.11	– 0.10	0.32	0.41
Rostral middle frontal gyrus left	0.50	0.37	0.61	0.36	0.17	0.53	0.27
Superior frontal gyrus left	0.50	0.37	0.61	0.35	0.16	0.52	0.29
Superior parietal cortex left	0.57	0.45	0.66	0.48	0.29	0.62	0.18
Superior temporal gyrus left	0.47	0.34	0.59	0.31	0.11	0.49	0.33
Supramarginal gyrus left	0.41	0.27	0.53	0.24	0.03	0.43	0.33
Frontal pole left	0.16	0.00	0.31	0.21	0.00	0.40	NaN
Temporal pole left	0.20	0.05	0.35	0.19	– 0.02	0.39	0.02
Transverse temporal cortex left	0.40	0.26	0.52	0.40	0.20	0.56	0.00
Insula left	0.43	0.29	0.55	0.37	0.17	0.54	0.12
Hippocampus left	0.56	0.45	0.66	0.24	0.03	0.43	0.66
Banks superior temporal sulcus right	0.29	0.14	0.43	0.17	– 0.04	0.37	0.24
Caudal anterior cingulate cortex right	0.31	0.16	0.44	0.01	– 0.20	0.22	0.60
Caudal middle frontal gyrus right	0.32	0.18	0.46	0.50	0.32	0.64	NaN
Cuneus cortex right	0.54	0.42	0.64	0.18	– 0.03	0.37	0.72
Entorhinal cortex right	0.41	0.27	0.54	0.08	– 0.13	0.28	0.67
Fusiform gyrus right	0.44	0.30	0.56	NaN	– 0.24	0.18	NaN
Inferior parietal cortex right	0.34	0.19	0.47	0.27	0.06	0.45	0.14
Inferior temporal gyrus right	0.31	0.16	0.45	0.22	0.01	0.42	0.17
Isthmus cingulate cortex right	0.22	0.06	0.36	0.18	– 0.03	0.38	0.08
Lateral occipital cortex right	0.51	0.39	0.62	0.34	0.14	0.51	0.35
Lateral orbital frontal cortex right	0.39	0.25	0.52	0.35	0.16	0.52	0.07
Lingual gyrus right	0.63	0.52	0.72	0.40	0.21	0.56	0.46
Medial orbital frontal cortex right	0.37	0.22	0.50	0.18	– 0.03	0.37	0.38
Middle temporal gyrus right	0.47	0.34	0.59	0.25	0.05	0.44	0.44
Parahippocampal gyrus right	0.46	0.32	0.57	0.39	0.19	0.55	0.14
Paracentral lobule right	0.46	0.32	0.58	0.38	0.19	0.55	0.15
Pars opercularis right	0.24	0.07	0.37	0.22	0.03	0.42	0.04
Pars orbitalis right	0.31	0.16	0.45	0.28	0.11	0.49	0.06
Pars triangularis right	0.36	0.21	0.49	0.26	0.01	0.41	0.20
Pericalcarine cortex right	0.72	0.64	0.79	0.48	0.30	0.63	0.48
Postcentral gyrus right	0.38	0.23	0.50	0.01	– 0.20	0.22	0.74
Posterior cingulate cortex right	0.44	0.30	0.56	0.07	– 0.14	0.28	0.73
Precentral gyrus right	0.56	0.44	0.66	0.21	0.00	0.40	0.70
Precuneus cortex right	0.48	0.35	0.59	0.35	0.15	0.52	0.25
Rostral anterior cingulate cortex right	0.35	0.21	0.49	0.10	– 0.11	0.31	0.51

Table 2 (continued)

ROI name	MZ pairs $N=153$	95% Confidence interval		DZ pairs $N=86$	95% Confidence interval		Heritability
	ICC	Lower bound	Upper bound	ICC	Lower bound	Upper bound	
Rostral middle frontal gyrus right	0.51	0.38	0.62	0.33	0.12	0.50	0.37
Superior frontal gyrus right	0.56	0.44	0.66	0.28	0.07	0.46	0.57
Superior parietal cortex right	0.53	0.40	0.63	0.34	0.14	0.51	0.38
Superior temporal gyrus right	0.51	0.38	0.62	0.44	0.25	0.60	0.14
Supramarginal gyrus right	0.35	0.20	0.48	0.29	0.08	0.47	0.12
Frontal pole right	0.10	– 0.06	0.25	0.03	– 0.18	0.24	0.14
Temporal pole right	0.25	0.10	0.39	0.23	0.03	0.42	0.03
Transverse temporal cortex right	0.46	0.33	0.58	0.36	0.16	0.53	0.21
Insula right	0.44	0.30	0.56	0.24	0.04	0.43	0.39
Hippocampus right	0.77	0.70	0.83	0.31	0.10	0.49	0.93

Twin pairs intraclass correlations (ICC) with lower and upper bound of 95% confidence intervals for monozygotic twins (MZ: columns 2 to 4) and for dizygotic twins (DZ: columns 5 to 7). The last column shows heritability estimates. Each row presents the values for one region of interest (ROI) of global areas, subcortical structures, cortical lobar areas, and cortical areas. *MZ* monozygotic twins, *DZ* dizygotic twins**,** *DC* diencephalon

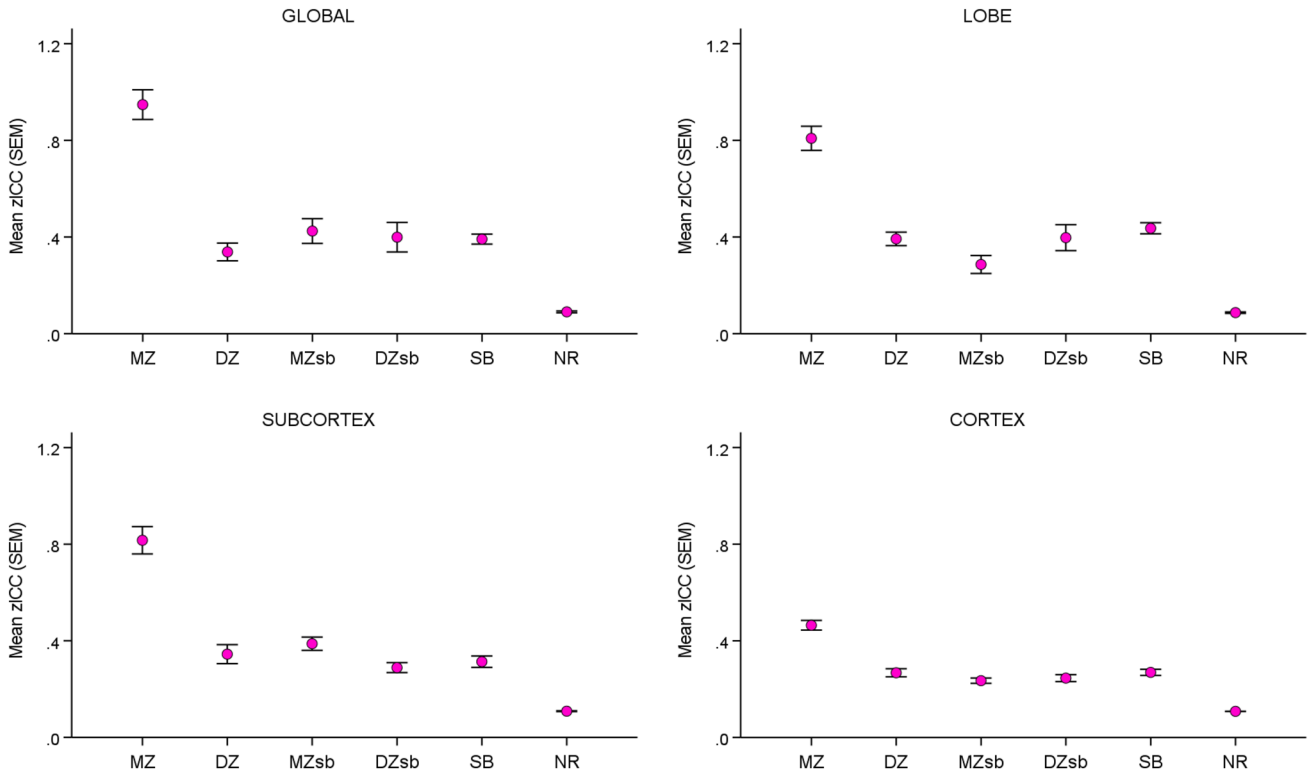

Fig. 1 Mean of z-transformed intraclass correlations (ICC) (Standard Error of Mean) of brain groups: global (top left) ($N=60$), lobar (top right) ($N=48$), subcortical (bottom left) ($N=84$), and cortical areas (bottom right) ($N=419$) volumes for genetic groups: monozygotic twins (MZ), dizygotic twins (DZ), MZ twins and their singleton siblings (MZsb), DZ twins and their singleton siblings (DZsb), siblings (SB), and unrelated (NR) individuals

DZ than MZ twins which is why heritability was not calculated. The heritability varied from the lowest value for the left hemisphere transverse temporal cortex (almost zero) to the highest value ($h^2=0.93$) for the right hippocampus.

Next, the pars opercularis ($h^2=0.69$) had the highest heritability while the caudal anterior cingulate ($h^2=0.07$) had the lowest heritability for the left frontal lobe. The precentral gyrus had the highest heritability ($h^2=0.7$), and pars

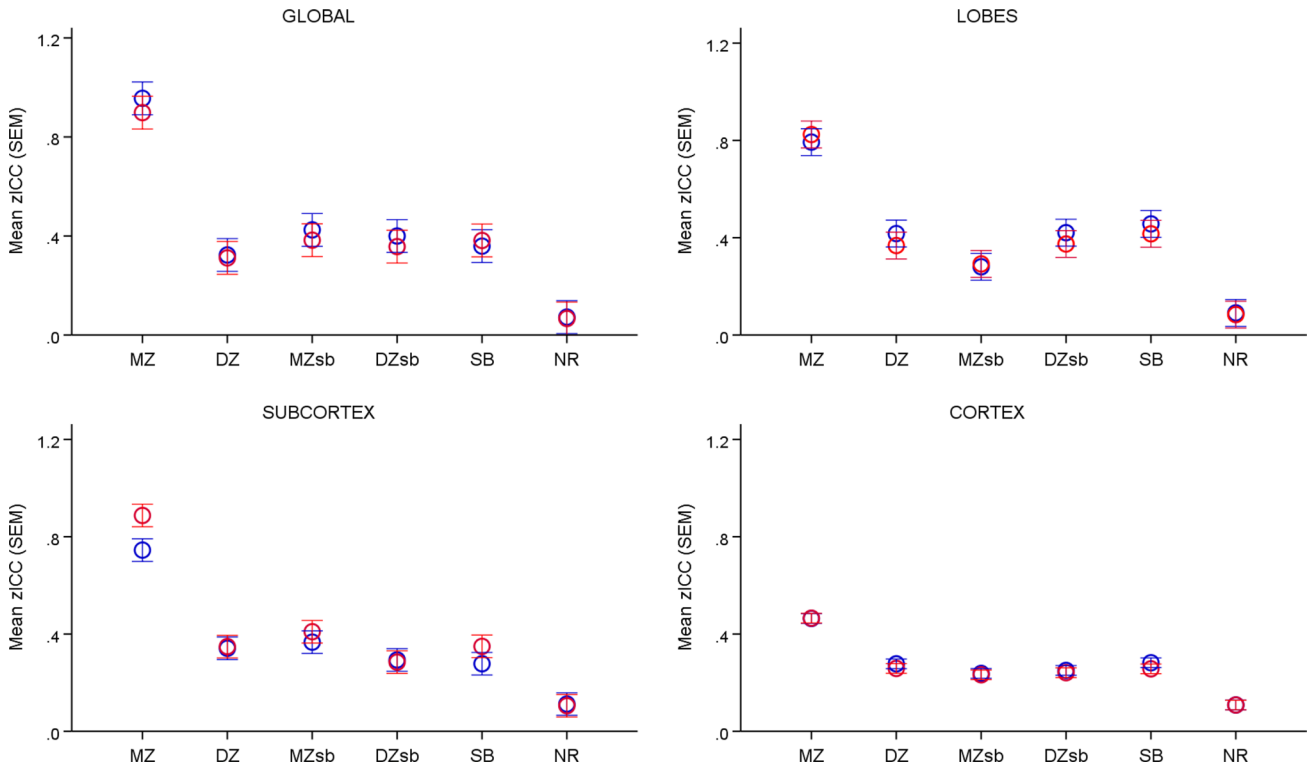

Fig. 2 Mean of z-transformed ICC (SEM) of brain groups: global (top left), lobar (top right), subcortical (bottom left), and cortical areas (bottom right) volumes for genetic groups: monozygotic twins (MZ), dizygotic twins (DZ), MZ twins and their singleton siblings (MZsb), DZ twins and their singleton siblings (DZsb), siblings (SB), and unrelated (NR) individuals for left (blue) hemisphere and right (red) hemisphere

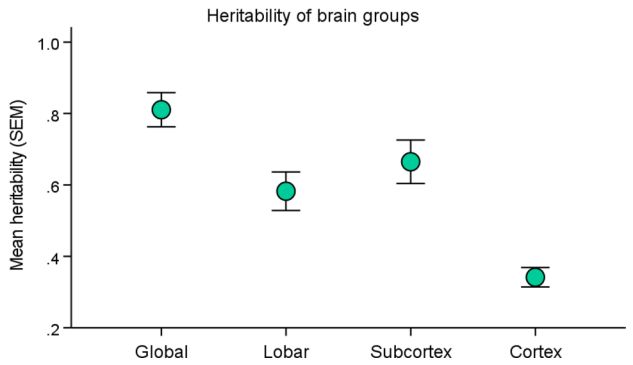

Fig. 3 Mean of heritability (Standard Error of Mean) of global ($N=10$), lobar ($N=8$), subcortical ($N=14$), and cortical ($N=67$), volumes

opercularis had the lowest heritability ($h^2=0.04$) in the right frontal lobe. The posterior cingulate had the highest heritability ($h^2=0.6$), while the insula had the lowest heritability ($h^2=0.12$) in the left parietal lobe. The postcentral had the highest heritability ($h^2=0.74$) and isthmus cingulate ($h^2=0.08$) had the lowest in the right parietal lobe. The middle temporal ($h^2=0.75$) had the highest heritability and the transverse temporal had the lowest heritability ($h^2=0.001$) in the left temporal lobe. The hippocampus ($h^2=0.93$) had the highest heritability and temporal pole ($h^2=0.03$) had the lowest in the right temporal lobe. The lateral occipital ($h^2=0.56$) had the highest heritability while pericalcarine cortex ($h^2=0.26$) had the lowest heritability for the left occipital lobe. The cuneus ($h^2=0.72$) had the highest heritability and lateral occipital ($h^2=0.35$) had the lowest in the right occipital lobe.

Asymmetry of heritability of 4 brain groups

Figure 4 shows the mean heritability for the left and right hemispheres. The mean heritability in the right hemisphere (0.473) was slightly higher than the left (0.435), with overlapping confidence intervals. We also studied the laterality in each brain group. Figure 5 shows the mean heritability for global, lobar, subcortical, and cortical brain groups separately for left and right hemispheres. For heritability as a dependent variable and genetic groups of participants and hemisphere as factors, general linear model ANOVA did not find hemispheric lateralization of heritability ($F=0.768$, $P=0.383$).

Looking in detail of subcortical structures, we found the highest laterality difference (left heritability > right) for the

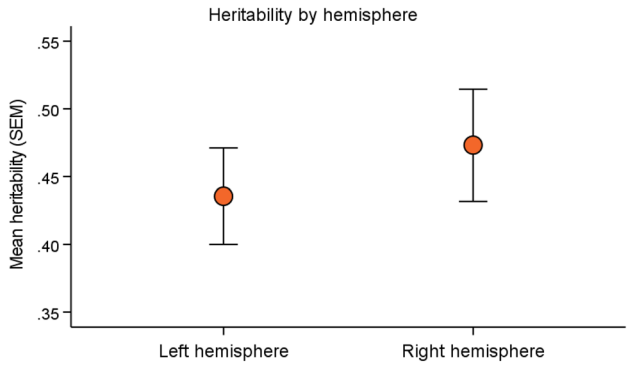

Fig. 4 Mean of heritability (Standard Error of Mean) of left ($N=50$) hemisphere and right ($N=49$) hemisphere

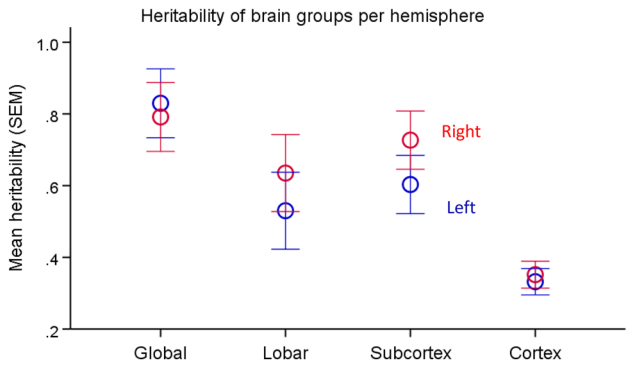

Fig. 5 Mean of heritability (Standard Error of Mean) of global, lobar, subcortical, and cortical volumes of left (blue) hemisphere and right (red) hemisphere. Global left ($N=5$), global right ($N=5$), lobar left ($N=4$), lobar right ($N=4$), subcortical left ($N=7$), subcortical right ($N=7$), cortical left ($N=34$), and cortical right ($N=33$)

nucleus accumbens, with the difference of left minus right heritability 0.41. Opposite, right-left hemisphere heritability difference was for the amygdala (0.46).

Examining in detail the cortical ROIs, regionally specific differences between the two hemispheres were observed. Specifically, regions showing a strong leftward asymmetry of volume heritability (left heritability > right) were the opercular part of the inferior frontal gyrus (parsopercularis) and the orbital part of the inferior frontal gyrus (parsorbitalis). The opposite, rightward asymmetry (right heritability > left) was found for the caudal anterior cingulate cortex and the postcentral gyrus.

Discussion

In this study, we calculated the ICC and heritability of 6 genetic groups of participants for global, cortical, subcortical, and lobar volumes of the human brain. Our study has the following advantages compared to others. (1) The study design includes not only twins but also their singleton siblings, siblings, and unrelated individuals. (2) A wider range of brain areas was studied. (3) Data are from a relatively large cohort of healthy adults. (4) Participants are young adults in a relatively narrow age range (mean 29.2, between 22 and 36 years old). (5) A significant advantage was state-of-the-art data acquired with a modified 3 T scanner. High-resolution MRI T1-and T2-weighted scans had voxel dimensions of 0.7 mm × 0.7 mm × 0.7 mm while standard T1-weighted acquisition dimensions are 1 mm × 1 mm × 1 mm.

It is not easy to compare our results with the findings from other studies. In particular, there are methodological differences like sample size, different ages of participants, age trends toward the middle to advanced age, and solely twin participants. These papers also reported results on the narrow range of brain volumetric measures; therefore, they gave a limited picture of ICC and heritability across brain areas. Our findings, based on data set from healthy young adults (mean age 29 years), allows us to generalize the results for this age group and gives an excellent blueprint of heritability values for this particular age range. We reported the results on the wide range of brain volume measures—from global, lobar, cortical, and subcortical areas.

The assumption that MZ twins fully share genes is widely accepted (Visscher et al. 2008). Exceptions to this assumption are hard to find due to the complexity of genome sequencing. For example, whole-genome sequencing found no evidence of exception even in multiple sclerosis–discordant MZ twins (Baranzini et al. 2010). For DZ twins and full siblings, the assumption states that they share on average 50% of their segregating genes (Visscher et al. 2008). This was confirmed using genome-wide marker data from an identity-by-descent sharing (IBD sharing) method which estimates the proportion of alleles in two individuals that are derived identically from their ancestor. For example, in full siblings, the average proportion of the IBD of 4,401 sibling pairs was 0.498 (range of 0.374–0.617, Visscher et al. 2006) and the mean of 11,214 sibling pairs was 0.4994 (range 0.309–0.644, Visscher et al. 2007).

ICC

The ICCs for MZ twins were the highest, and also high overall, suggesting some environmental influence but

mainly genetic influence. Overall, the intraclass correlations for MZ twins were higher, and the confidence interval narrower, than those for DZ twins. Additionally, the ICCs for genetic groups: DZ, MZsb, DZsb, SB have been demonstrated (Fig. 1). Among these groups, ICCs were not significantly different than in other sibling groups. This revealed the expected pattern of genetic influence for a heritable trait, since MZ twins share all genetic effects, while DZ twins share on average 50% genetic effects. Siblings also share on average 50% of their genetics; however, it is expected that they would have lower zICC because their environmental variation is higher compared to twins. To our knowledge these 4 genetic groups of siblings have not been studied in detail. Mean zICCs were practically zero for the NR group and the lowest among 6 genetic groups as would be expected for unrelated individuals.

With the exception of the NR groups, other genetic groups in general showed a pattern of decreasing ICC with overall decreasing volume of brain regions from the larger global areas, through smaller lobe volumes, to the smallest subcortical and cortical ROIs (Fig. 1).

Asymmetry

We did not find significant laterality differences for any of the genetic or brain groups (Fig. 2).

Heritability

We studied heritability of 10 global, 8 lobar, 14 subcortical, and 70 cortical brain structures, and found that the volume of brain structures are heritable, ranging from low to high.

Age effect

The review of cross-sectional heritability of brain volume in different ages showed that from birth to early adulthood heritability increases, with the highest heritability in the second decade of life, followed by decline with age through mid and late-life (Batouli et al. 2014). Studies found strong effects of genetics on brain volume of different brain regions with changes of heritability with maturation. For example, increased cortical thickness heritability during the first 2 decades of life were reported by Schmitt et al. (2014). Another cortical thickness study of 11 years-old by Lenroot et al. (2009) found that regions that phylogenetically and ontologically develop earlier showed the genetic effect earlier in childhood. With the child's maturation, developed regions became more heritable. Additionally, the longitudinal pediatric study of Schmitt et al. (2018) found dynamic age-related changes of cortical lobar volume.

Above we outlined changes during development and maturation. Studies have shown heritability to be similar across young and older adults, for example, the heritability in subcortical structures in young (Rentería et al. 2014) and middle-age adults (Eyler et al. 2011). With advanced age brain volume decreases (Lukies et al. 2017) and heritability declines into old age (Batouli et al. 2014).

Above we outlined heritability changes accompanying inevitable brain changes early in life during brain development, throughout maturation and adulthood, and late in life with age-related changes. In summary, studies of age groups support the hypothesis that genetics contributes more to the brain structure at a young age with the highest heritability in the second decade of life and then linear decline with aging when environmental factors are more prominent (Batouli et al. 2014).

Our work focuses on the young adult population with a mean age of 29 years. Because of the above- mentioned age effect on heritability, we excluded age influence even though our dataset has a relatively narrow age range of 14 years. Indeed, we could not make a direct comparison of our study results with others because we excluded the age effect from our dataset by linearly regressing the age (and gender) from the volumes before analyzing the residuals.

Brain groups heritability

We found that the majority of volumes are heritable, with different brain tissue or brain regions possibly driven by distinct genetic patterns. We showed that in small regions such as cortical, only 24% of ROIs have high heritability. In contrast, all global regions, 63% of lobar regions, and 71% of subcortical regions have high heritability. But this is only a general trend because some small regions have high heritability while the large regions have small heritability. Regions of similar size can also have different heritability (Table 2). This is also concluded by Patel et al. (2018) and Eyler et al. (2012).

Global structures had the highest heritability among the 4 brain groups (Fig. 3). Using the same HCP dataset for cerebral and cortical gray matter and cerebral white matter volumes Kochunov et al. (2019) found heritability estimates even higher than ours. This discrepancy could be explained by the fact that they use the whole brain volumes while we studied the left and right hemispheres separately.

Our data are consistent with those reported previously for strong genetic factors in lobar volumes. Schmitt et al. (2010) found the genetic effect to be distinct across lobes while Batouli et al. (2014) found it more general than specific. The actual extent of genetic influence on brain structures and volumes is likely to vary spatially across the brain. A plausible developmental hypothesis could be that the earliest-maturing brain regions have structural volumes that are more genetically influenced. However, because human brain development is structurally and functionally a

nonlinear process, regions within a lobe have different maturation patterns. Therefore, another plausible developmental hypothesis is that the brain regions that are developing and maturing slowly are regions under constant genetic influence. For example, the temporal lobe has the highest heritability among the four lobes. It is also one of the last lobes to mature fully; however, certain areas of the temporal lobe, such as the medial aspects of the inferior temporal lobe, mature early and do not change much thereafter (Gogtay et al. 2004). A similar pattern is found for the frontal lobe, which had the second-highest heritability. The parietal and occipital lobes have lower heritability values. This result could be because parts of the brain associated with more basic functions matured early (Gogtay et al. 2004) and the heritability of brain volume changes over time (Pfefferbaum et al. 2000).

We show in Fig. 3 the mean heritability of brain groups and found that the mean cortical heritability was statistically lower than that of other brain groups including subcortical regions. One possible explanation for our finding was given by Strike et al. (2019) who compared results for cortical thickness and surface area with the results of Rentería et al. (2014) for the subcortical volumes for the same dataset. Strike et al. (2019) found for the subcortical structure smaller environmental variance and larger genetic variance compared to the cortex. Their explanation is that the cortex is under more environmental influence because it is involved in human abilities like learning and social interaction (language). In contrast, the evolutionarily older subcortical structure less subject to environmental influence (Strike et al. 2019).

Size of region

Our estimates of heritability range from near zero to 0.99. Higher heritability estimates were found for larger brain structures relative to smaller brain regions like cortical ROIs. Indeed, we found that all global regions and the majority of lobar and subcortical regions were classified as highly heritable and the rest were moderately heritable. This is not the case for cortical ROIs where the majority of regions have moderate heritability. Additionally, this is the only brain group that showed ROIs with low heritability values (<0.2). A substantial part of the cortex—almost one third of all ROIs -have low heritability. It has been suggested that the size of the region is related to its heritability (Strike et al. 2015) but subcortical regions are generally not larger than cortical regions. The plausible explanation is that cortical ROI, specifically the smaller ones, was less precisely measured (Strike et al. 2015). Small measurement error has a greater impact in small regions than in large regions. This hypothesis can explain the smaller values of ICC for the cortical brain group in comparison with the other brain groups (Fig. 1) because ICC reflects the similarities between compared values. For example, CI for ICC is larger for DZ twins, even negative for some cortical ROIs. However, it is not true for larger structures like global and lobar (Table 1). The measurement error contribution to unique environmental variance may cause a decrease of heritability value (Eyler et al. 2011).

Asymmetry

Asymmetry of cortical thickness and surface area heritability

Lateralization of human brain functions, like language and high order cognitive functions, is known (Toga and Thompson 2003). Functional lateralization and structural asymmetry are interrelated (Powell et al. 2006; Tzourio et al. 1998). Among the structural brain studies, the large study (>17 thousand participants) Kong et al. (2018) found that most of the genetic effects on cortical thickness and surface area were bilateral, but for some regions, there were different genetic effects on each hemisphere. Additionally, asymmetries in some regional thickness and surface area were heritable. The authors found similar results for the HCP dataset. Another study of cortical thickness found asymmetry with higher heritability in the right frontal lobe versus left (Schmitt et al. 2014).

The opposite was found by Eyler et al. (2014): no significantly larger heritability in one hemisphere than the other, no evidence of different genetic influence on left versus right hemisphere, and no genetic factor influencing regional cortical asymmetry.

Interestingly, asymmetry is not a unique human feature. Nonhuman primates also showed such asymmetry but it is more pronounced in humans than in chimpanzees (Gómez-Robles et al. 2016). In this comparison, the authors found a stronger environmental influence on human asymmetry.

Asymmetry of volume heritability

Regarding the laterality of volume heritability, studies show different results. For example, the lobar brain volumes study of twin veterans found less genetic control on the left hemisphere than on the right hemisphere with an environmental influence on frontal and temporal lobes about half as small as on the right hemisphere (Geschwind et al. 2002).

In contrast, for heritability of the lobar and subcortical volume Wen et al. (2016) found high genetic correlations between left and right hemisphere regions. Also, the genetic correlations between most of the homologous ROIs were highly significant. Mixed results were reported by Wright et al. (2002) that from bilateral regions, only the paralimbic

structures and lateral temporal cortex were under common genetic control.

Recently, there has been an alternative method to the twin/family heritability estimates. The single-nucleotide polymorphisms (SNP) heritability derives from the average across all common SNPs on phenotypes among unrelated samples (Toro et al. 2015). Zhao et al. (2019) applying SNP methodology on 9000 middle or aged participants found a symmetrical heritability pattern on the left and right hemispheres.

Our general finding is in agreement with theirs for less genetic control on the left hemisphere than on the right (Fig. 4) but no significant difference between hemispheres.

Similarly, we found, for lobar, subcortical, and cortical brain groups, less genetic control on the left hemisphere than on the right (Fig. 5). We found the opposite for global areas: slightly higher left hemisphere heritability than right.

The study of subcortical brain structures showed that a substantial proportion of the heritability was identified by a common genetic factor (Rentería et al. 2014; Eyler et al. 2014) which is in line with our general findings for subcortical structures (Table 2, Fig. 5). Our biggest subcortical right-left hemisphere heritability difference was for the amygdala, as in Rentería et al. (2014) and Wen et al. (2016). Additionally, we also found the highest laterality difference (left heritability > right heritability) for nucleus accumbens, similar to the results of Rentería et al. (2014) and Eyler et al. (2014).

Between homologous regions of both hemispheres, high and statistically significant genetic correlations were obtained by Wen et al. (2016) suggesting a common genetic factor for both hemispheres. This is in line with our general findings that genetics does not have statistically different lateralization effects.

Regionally specific differences between the two hemispheres were observed for some cortical ROIs. Specifically, the region showing the strongest leftward asymmetry of volume heritability was the opercular part of the inferior frontal gyrus (parsopercularis). This region represents the posterior part of Broca's area that is part of the language-related region. This is a common finding of our study and that of Thompson et al. (2001). They found significant asymmetry in the volume of the language-related cortex, specifically significant heritability for the Wernicke's and Broca's speech area of the left hemisphere.

In recent decades the widespread availability of non-invasive magnetic resonance imaging has facilitated the study of brain structures of healthy individuals and patients, including twin studies. Imaging recently was combined with genome mapping efforts in the new field called neuroimaging genetics that finds the variations of the human genome related to the brain. Results of studies like ours could be used as guidelines for further genome-wide associations to find the genetic loci for brain structures. For example, new genetic loci were discovered for human intracranial volume (Adams et al. 2016), hippocampal volume (Hibar et al. 2017), hippocampal subfield volume (van der Meer et al. 2020), cerebellar gray matter, and whole-brain (Bearden and Thompson 2017). Future discoveries will broaden our knowledge and understanding of human brain anatomy and function in health and disease.

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Compliance with ethical standards

Conflict of interest The authors declare no financial disclosures or conflicts of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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