

Conceptual and Data-based Investigation of Genetic Influences and Brain Asymmetry: A Twin Study of Multiple Structural Phenotypes

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Abstract

■ Right–left regional cerebral differences are a feature of the human brain linked to functional abilities, aging, and neurodevelopmental and mental disorders. The role of genetic factors in structural asymmetry has been incompletely studied. We analyzed data from 515 individuals (130 monozygotic twin pairs, 97 dizygotic pairs, and 61 unpaired twins) from the Vietnam Era Twin Study of Aging to answer three questions about genetic determinants of brain structural asymmetry: First, does the magnitude of heritability differ for homologous regions in each hemisphere? Despite adequate power to detect regional differences, heritability estimates were not significantly larger in one hemisphere versus the other, except left > right inferior lateral ventricle heritability. Second, do different genetic factors influence left and right hemisphere size in homologous regions? Inter-

hemispheric genetic correlations were high and significant; in only two subcortical regions (pallidum and accumbens) did the estimate statistically differ from 1.0. Thus, there was little evidence for different genetic influences on left and right hemisphere regions. Third, to what extent do genetic factors influence variability in left–right size differences? There was no evidence that variation in asymmetry (i.e., the size difference) of left and right homologous regions was genetically determined, except in pallidum and accumbens. Our findings suggest that genetic factors do not play a significant role in determining individual variation in the degree of regional cortical size asymmetries measured with MRI, although they may do so for volume of some subcortical structures. Despite varying interpretations of existing data, we view the present results as consistent with previous findings. ■

INTRODUCTION

Individual differences in the size of brain regions are under substantial genetic control, as revealed by human twin and family studies of MRI-based measures. This is true for the volume of subcortical structures as well as for measures of cortical size, such as thickness and surface area (Blokland, de Zubicaray, McMahon, & Wright, 2012; Eyler, Prom-Wormley, Panizzon, et al., 2011; Kremen et al., 2010; Schmitt, Eyler, et al., 2007). These findings help to pave the way for a more complete understanding of the origin of individual differences in local brain structure, which, in turn, facilitates the search for causes of brain disorders and age-related brain changes that may involve particular patterns of regional brain abnormalities.

A well-known feature of brain structure, observed in both subcortical and cortical regions, is a difference in size between homologous areas in the left and right hemisphere. Cerebral asymmetry, or laterality, was first appreciated through studies of the left hemisphere's functional dominance over the right hemisphere for language abilities in most people, as revealed by the effects of focal lesions (Geschwind & Levitsky, 1968). Corresponding structural asymmetries in the population as a whole were soon discovered in both the inferior frontal gyrus and the posterior temporal lobe, with the left hemisphere greatly exceeding the right hemisphere in size for these regions (Damasio & Geschwind, 1984; Geschwind & Levitsky, 1968). Other cortical and subcortical asymmetries in size have now been well characterized (Renteria, 2012). Atypical functional and structural brain asymmetries have been linked to neuropsychiatric illnesses such as schizophrenia and affective disorders (Crow, Chance, Priddle, Radua, & James, 2013), as well as to developmental disorders such as autism and dyslexia (Bishop, 2013; Preslar, Kushner, Marino, & Pearce, 2013; Eyler, Pierce, & Courchesne, 2012). Changes

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in the laterality of functional response may also be associated with cognitive aging (Eyler, Sherzai, Kaup, & Jeste, 2011; Cabeza, 2002).

Given the prominence of structural asymmetries and their likely relevance to understanding development of human features like language and disorders of cognition and emotion, it is of interest to understand the relative contributions of genetic and environmental factors to individual differences in structural brain asymmetry. There have been many different approaches taken to date, and there has been little conceptual clarity in this area.

There are three main questions that can be asked (see Table 1): (1) whether the magnitude of heritability is different in homologous left and right hemisphere regions; (2) whether different genetic factors influence left and right hemisphere size in homologous regions, that is, is the genetic correlation significantly different from 1.0; and (3) whether left–right size differences in homologous regions are heritable, that is, do genetic factors influence individual differences in the magnitude of structural asymmetry between homologous regions. Although each of these questions is relevant to the genetics of brain asymmetry, it is the third question that directly addresses what people most often have in mind when they speak of the genetics of brain asymmetry. To date, these important questions have been addressed incompletely or have not been examined at all for regional measures of subcortical volume, cortical surface area, and cortical thickness. A twin design with both monozygotic (MZ) and dizygotic (DZ) pairs has the power to address each of these questions and provide inferential statistics but has not previously been consistently employed to full benefit.

The first question, whether the heritability of left hemisphere regions differs in magnitude from the heritability of right hemisphere regions, has mainly been addressed in a qualitative manner in previous studies. Nine studies (see Table 1) presented heritabilities separately for the two hemispheres, and six drew various conclusions in the absence of any statistical test of the reliability of the differences. On the basis of the magnitude of the heritability estimates or confidence intervals (if presented), it appears to be highly unlikely any of the differences in heritability would be statistically significant. Yet four of the six concluded that regions in one hemisphere were more genetically determined than the homologous regions in the opposite hemisphere (Yoon, Perusse, & Evans, 2012; Yoon, Perusse, Lee, & Evans, 2011; Yoon, Fahim, Perusse, & Evans, 2010; Geschwind, Miller, DeCarli, & Carmelli, 2002). Winkler et al. (2010) presented heritabilities separately for left and right hemispheres for both surface area and thickness but did not comment on the magnitude of differences or test for significant differences.

Three studies statistically tested the question of whether heritabilities differ for homologous left–right brain regions. Wright, Sham, Murray, Weinberger, & Bullmore (2002) found no differences in left and right heritabilities when tested as part of a bivariate twin model. On the other

hand, using a surface-based analysis, Thompson et al. (2001) reported significantly lower right than left hemisphere heritabilities for gray matter density in Wernicke's area as determined by permutation testing. Both of these studies had very small samples (10 MZ and 10 DZ pairs), which may explain the discrepancy between their results (Rimol et al., 2010). In our previous study of 474 adult male twins (Eyler, Prom-Wormley, Panizzon, et al., 2011), we compared the magnitude of lobar heritabilities for cortical surface area using a bootstrapping procedure and found no evidence for pairwise differences between heritabilities of the same major lobe in one hemisphere versus the other (e.g., left frontal–right frontal), although some significant differences in the magnitude of heritability were observed between different lobes (e.g., frontal-medial temporal). Regional pairwise differences at a sublobar scale have not been examined for surface area, thickness, or the volume of subcortical structures, so it remains to be seen if there are differences in heritability in the left and right hemisphere for smaller regions of the brain.

Our group and others have presented indirect evidence regarding the second question of whether different genetic factors affect the size of homologous left and right hemisphere regions. By examining the genetic correlation between homologous regions on either side of the brain, one can determine the degree to which the same genetic factors that influence size variation in one hemisphere also influence the other. Genetic correlations examine the genetic contribution to the covariation between traits, in this case, left and right hemisphere brain measures. Three features are important to note regarding genetic correlations. First, genetic variation may arise from multiple sources including polymorphisms in coding regions, promoters, and other gene expression control regions. Second, a genetic correlation between two traits may occur because these variants directly affect both traits or because variants that cause the trait are close to each other on the genome (known as linkage disequilibrium). Third, genetic covariance may be high between traits, but if the heritability is low for either one, this genetic covariance will contribute little to overall covariance.

On the basis of several previously published studies (Chen et al., 2011, 2012; Eyler, Prom-Wormley, Fennema-Notestine, et al., 2011; Rimol et al., 2010; Schmitt, Wallace, et al., 2007) that measured genetic correlations between regions or between points on the brain's surface, we have found high genetic correlations between homologous regions on either side of the interhemispheric fissure and very little evidence for lateralized genetic influences. For example, we observed very high interhemispheric genetic correlations (most above 0.90) for volumes of subcortical structures and found, using genetic factor analysis, that left and right structures always loaded together no matter the number of factors selected (Eyler, Prom-Wormley, Fennema-Notestine, et al., 2011). Similarly, when a matrix of genetic correlations of areal expansion measures between points on the brain's cortical surface was

Table 1. Laterality and Genetic Influences

<i>Question</i>	<i>Null Hypothesis</i>	<i>Test of Hypothesis</i>	<i>What It Means if H_0 Is Rejected</i>	<i>What It Does NOT Mean</i>	<i>Previous Human Studies</i>
1. Does the magnitude of heritability differ for homologous left and right hemisphere regions?	$b^2_L - b^2_R = 0$	Loss of fit of a bivariate twin model in which additive genetic effects are constrained to be equal in left and right hemispheres compared with an unconstrained model	Region size is more heritable (i.e., more strongly influenced by genetic factors) in one hemisphere than the other	Asymmetry of region size is heritable; there are different genes that influence each hemisphere	Some studies (Yoon et al., 2010, 2011, 2012; Hulshoff Pol et al., 2006; Geschwind et al., 2002; Pennington et al., 2000) presented b^2_L and b^2_R , but no statistical comparison. Thompson et al.'s (2001) voxel-based comparison with 40 twin pairs found one region (Wernicke's) where $b^2_L - b^2_R > 0$. Wright et al. (2002) and Eyster, Prom-Wormley, Panizzon, et al. (2011) did not reject $b^2_L - b^2_R = 0$ for lobar surface areas.
2. Do different genetic factors influence the size of homologous left and right hemisphere regions?	$r_{g(L,R)} = 1$	Loss of fit of a bivariate twin model when the genetic correlation (r_g) between hemispheres is constrained to be 1 compared with an unconstrained model	Different genetic factors influence region size on left compared with region size on right	Asymmetry of region size is heritable	Several studies (Chen et al., 2011, 2012; Eyster, Prom-Wormley, Fennema-Notestine, et al., 2011; Rimol et al., 2010; Schmitt, Wallace, et al., 2007) showed high, significant $r_{g(L,R)}$, but did not test if $r_{g(L,R)} = 1$
3. Is the left–right size difference between homologous regions heritable?	$b^2_{L-R} = 0$	Significant additive genetic component of variance in a univariate twin model with L-R size or (L – R)/(L + R) laterality score as dependent variable	Asymmetry of region size is heritable (This is what is typically thought of as genetic influences on brain asymmetry)	Region size is more heritable in one hemisphere than the other; there are different genes that influence each hemisphere	Jahanshad et al. (2010) presented b^2_{L-R} for regional DTI measures (reported heritabilities ranged from .00 to .42); only the anterior thalamic radiation laterality score was significantly heritable ($a^2 = 0.38, p = .05$).

subjected to fuzzy clustering, the resulting “genetic parcelations” always included both the left and right hemisphere homologous regions (Chen et al., 2011, 2012). The only hint of lateralized effects was that the exact positioning of the genetically based clusters on the brain’s surface differed slightly between hemispheres, particularly in the peri-sylvian region. In none of these studies, however, did we directly test whether there was any evidence for nonidentical genetic factors influencing each hemisphere by examining if any of the interhemispheric genetic correlations were significantly less than 1.0. Prior studies of this issue also did not examine multiple brain phenotypes with and without adjustment for global values in a large number of functionally relevant cortical and subcortical regions.

Interestingly, the answer to the third question of whether homologous left–right size differences are heritable depends on the answer to the second question. By definition, if the genetic correlation between the left and right side of a given region is nearly perfect, then the genetic contributions to the left–right difference score will tend to be low and nonsignificant (see Figure 1). This is because the genetic variance (V) of the difference score (D) is equal to the sum of the genetic variances of the left (V_L) and right (V_R) measures considered separately minus the part of the genetic variance of each that is shared between left and right, that is, their genetic covariance, C_{LR} . Therefore, $V_D = V_L + V_R - 2C_{LR}$. If the genetic variance is completely shared between left and right, then $2C_{LR} \approx V_L + V_R$, so after accounting for the shared variance, there is no genetic variance remaining and hence no heritability of the difference

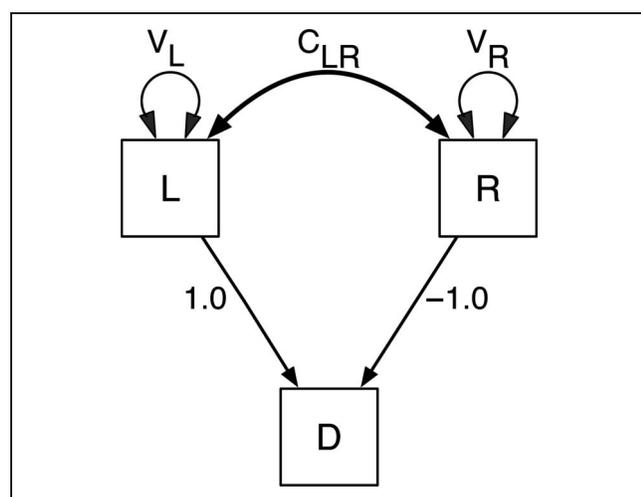


Figure 1. In the illustrative path diagram, L is a genetic factor for left hemisphere size, R is a genetic factor for right hemisphere size, and D is the computed difference between the phenotypes. If the genetic correlation between the hemispheres (r_g) is high, heritability of D will perforce be low. This is because the genetic variance (V) of the difference D , which is simply a linear combination of L and R with weights +1 and -1, is given by $V_D = V_L + V_R - 2C_{LR}$, where C_{LR} is the genetic covariance between left and right. If C_{LR} is close to V_L and $V_L = V_R$, the genetic variance of D approaches zero. That is, when the correlation is 1, $2C_{LR} = V_L + V_R$.

score. In the current study, we directly examined the question of the heritability of homologous left–right differences only for measures for which there is evidence of unique genetic influences on each hemisphere.

In this study, we systematically addressed each of the above questions using a large sample of male twins from the Vietnam Era Twin Study of Aging (VETSA) who had undergone MRI scanning in middle age. Within each hemisphere as a whole and within regions from a standard sulcal-based parcellation system (Desikan et al., 2006), we examined both cortical surface area and thickness measures because these two features of cortical size appear to have distinct genetic influences and reflect different underlying biological processes (Panizzon et al., 2009; Rakic, 2009). We also examined volume of subcortical structures and the lateral ventricles. For every measure, we addressed our questions both with and without correcting for global measures of brain size. We used the twin design to determine whether there is evidence for (1) different genes influencing the size of homologous regions in each hemisphere, (2) genetic influences on left–right size differences in homologous regions, and (3) higher heritability of homologous regions in one hemisphere versus the other. On the basis of the findings in the literature, we expected to find few regions for which the heritability in the left hemisphere would be significantly different from the heritability of that region in the right hemisphere. We also expected that there would be very high interhemispheric genetic correlations (i.e., little evidence of different genetic influences on the size of left and right homologous regions) and that therefore there would be little heritability of left–right size differences.

METHODS

Participants

The VETSA project has been described previously (Kremen, Franz, & Lyons, 2013; Kremen et al., 2006). The VETSA sample was drawn from the Vietnam Era Twin (VET) Registry (Goldberg, Curran, Vitek, Henderson, & Boyko, 2002), a sample of male–male twin pairs born between 1939 and 1957 who had both served in the U.S. military between 1965 and 1975. The study sample is not a VA or patient group; the majority of individuals were not exposed to combat. MRI data were available on 534 VETSA participants, all of whom understood the study and gave written consent to participate. Zygosity for 92% of the sample was determined by analysis of 25 microsatellite markers that were obtained from blood samples. For the remainder of the sample, zygosity was determined through a combination of questionnaire and blood group methods (Eisen, Neuman, Goldberg, Rice, & True, 1989).

Mean age of the MRI participants was 55.7 (2.6) years (range = 51–60), and mean years of education was 13.8 ($SD = 2.11$). Within this sample, 460 participants were

right-handed, 70 were left-handed, and 4 were ambidextrous as determined by self-reported writing handedness. There were 83% non-Hispanic White, 5% Black, 4% Hispanic, and 2% “other” participants and 6% did not answer the question concerning their ethnicity. Self-reported overall health status was as follows: excellent (14%), very good (36%), good (38%), fair (10%), and poor (1%). Demographic characteristics of the VETSA MRI sample did not differ from the entire sample and are comparable to U.S. census data for similarly aged men (Kremen et al., 2006). There were no significant demographic differences between MZ and DZ twins.

Analyses reported below were only carried out on those participants for whom there was adequate image quality. For cortical thickness and surface area, there were 515 analyzable scans, which included 130 MZ pairs, 97 DZ pairs, 38 unpaired MZ twins, and 23 unpaired DZ twins. For most subcortical volume measures and lateral ventricle volume, the sample contained 511 individuals, including 128 MZ pairs, 96 DZ pairs, 39 unpaired MZ twins, and 24 unpaired DZ twins. For hippocampal volume, the sample contained 502 individuals, including 126 MZ pairs, 91 DZ pairs, 40 unpaired MZ twins, and 28 unpaired DZ twins. The use of unpaired twins in the analyses allows one to estimate and control for effects of volunteer bias and increases precision in estimating means and variances of the phenotypes of interest (Neale & Eaves, 1993).

All participants gave informed consent to participate in the research, and the study was approved by the institutional review boards of the University of California, San Diego, Boston University, and the Massachusetts General Hospital.

Image Acquisition

Sagittal T1-weighted MP-RAGE images (two per case) were acquired on Siemens 1.5 T scanners (289 at the University of California-San Diego; 245 at the Massachusetts General Hospital). Scan parameters were as follows: inversion time = 1000 msec, echo time = 3.31 msec, repetition time = 2730 msec, flip angle = 7 degrees, slice thickness = 1.33 mm, voxel size $1.3 \times 1.0 \times 1.3$ mm. Data were reviewed for quality, registered, and averaged to improve signal-to-noise ratio.

Image Processing

Using volumetric segmentation methods based on the publicly available FreeSurfer 3.0.1b software package (Fischl et al., 2002, 2004), volumetric measures were created for left and right hemisphere hippocampus, amygdala, caudate, putamen, nucleus accumbens, thalamus, and lateral ventricles. The automated, fully 3-D whole-brain segmentation procedure uses a probabilistic atlas and applies a Bayesian classification rule to assign a neuro-

anatomical label to each voxel. The atlas consists of a manually derived training set created by the Center for Morphometric Analysis (www.cma.mgh.harvard.edu/) from 20 unrelated, randomly selected VETSA participants. Automated volumetric measurements based on this atlas were within the 99% confidence interval with respect to the “gold standard” manual measurements made at the Center for Morphometric Analysis. This process required only qualitative review to ensure no technical failure of the application.

For cortical measures, the cortical surface was reconstructed using well-established Free Surfer methods (Desikan et al., 2006; Fischl et al., 2004; Fischl & Dale, 2000; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Processing began with correction for variation in image intensity because of magnetic field inhomogeneities, creation of a normalized intensity image, and removal of the skull (nonbrain). Preliminary segmentation using a connected components algorithm was performed, and interior holes in the components representing white matter were filled, resulting in a single filled volume for each cortical hemisphere. The resulting surface was covered with a polygonal tessellation and smoothed to reduce metric distortions. To obtain a representation of the gray/white boundary, a refinement procedure was applied, and the resulting surface was deformed outwards to obtain an explicit representation of the cortical (pial) surface. Once generated, the cortical surface model was manually reviewed and edited for technical accuracy. Minimal manual editing was performed by applying standard, objective editing rules.

The surface was then divided into cortical ROIs (Fischl et al., 2004). A label was given to each vertex based on (1) the prior probability of that label at that surface-based atlas location based on the manually parcellated training set, (2) local curvature information, and (3) contextual information, such as rules about spatial neighborhood relationships derived from the manual training set. Surface area and mean cortical thickness (average length of the lines from each vertex on the pial surface of the region to the white matter surface at an angle perpendicular to the local white matter surface plane) was then calculated for the 66 ROIs (33 per hemisphere) in the parcellation scheme (Desikan et al., 2006). Calculations were made in each subject’s native space. We renamed the posterior cingulate as rostral posterior cingulate and isthmus of the cingulate as retrosplenial cortex for clarity of presentation in the tables. Total hemispheric surface area was calculated as the sum of the areas of all ROIs in the hemisphere, and mean hemispheric cortical thickness was calculated as the average thickness across all the ROIs in the hemisphere, weighted by the area of the ROI. Previous examinations of the laterality of genetic influences on brain size have not generally corrected for head size or global measurements of thickness and surface area. We conducted analyses with and without correction for weighted mean thickness and total surface area for

cortical measures and correction for intracranial volume for the subcortical measures.

Statistical Analysis

We implemented univariate and bivariate applications of the classical twin design using the raw data application of the maximum likelihood-based structural equation modeling software OpenMx (Boker et al., 2011). In the univariate twin model, the variance of a phenotype is divided into the proportion attributed to additive genetic (A) influences, common or shared environmental (C) influences (i.e., environmental factors that make members of a twin pair similar to one another), and unique environmental (E) influences (i.e., environmental factors that make members of a twin pair different from one another, including measurement error; Neale & Cardon, 1992; Eaves, Last, Young, & Martin, 1978). Additive genetic influences are assumed to correlate perfectly (1.0) between monozygotic (MZ) twins because they are genetically identical. DZ twins share on average 50% of their segregating DNA, and are therefore assumed to correlate .50 for additive genetic influences. The shared environment is assumed to correlate 1.0 between both members of a twin pair, regardless of their zygosity. Unique environmental influences, by definition, are uncorrelated between the members of a twin pair. In bivariate twin analyses, the covariance between phenotypes is divided into genetic and environmental components; thus, the sum of the standardized genetic and environmental covariance estimates is equal to the phenotypic correlation. The genetic and environmental covariance estimates can also be used to calculate genetic and environment correlations. In statistical terms, the genetic correlation (r_g) between two phenotypes is equal to their genetic covariance, divided by the square root of the product of their separate genetic variances (Neale & Cardon, 1992). Put another way, the genetic correlation represents the degree to which the genetic influences of one phenotype are predictive of the genetic influences for another phenotype (Carey, 1988). In the present analyses, the two phenotypes of interest are (1) left and (2) right hemisphere measures of subcortical or ventricular volume, cortical thickness, or cortical surface area. On the basis of our previous findings of minimal C , or common environmental, influences on surface area (Eyler, Prom-Wormley, Panizzon, et al., 2011), cortical thickness (Kremen et al., 2010; Rimol et al., 2010), and volume (Kremen et al., 2010), we only examined the relative influences of A and E on each phenotype (i.e., only AE models were tested). AE models generally are also more powerful for detecting differences in the magnitude of genetic contributions than ACE models.

Before analysis, all phenotypes were statistically adjusted for the effects of age and scanner differences using multiple regression of these factors on each brain measure and retaining the residual scores for further analysis.

In a separate analysis, the effect of the relevant global measure (total surface area, global mean cortical thickness, or total estimated intracranial volume) was also regressed out before twin analyses. Results presented in the tables are for analyses of the regional measures unadjusted for global measures. To test the significance of specific parameters, model comparisons were performed using the likelihood ratio χ^2 test (LRT), which was calculated as the difference in the $-2 \log$ likelihood ($-2LL$) of a reduced model (one in which the parameter in question is fixed at either zero or unity) from that of the full model (one in which all parameters are freely estimated). Nonsignificant LRT values ($p > .05$) indicate that a reduced model does not result in a significant change in fit relative to the comparison model and thus provides a significance test for the parameter in question. Under certain regularity conditions, the LRT is distributed as a χ^2 with degrees of freedom (df) equal to the difference in the number of parameters between the two models (Steiger, Shapiro, & Browne, 1985). However, because there is an implicit lower bound of zero for variance components estimates and an implicit upper bound of 1.0 for genetic and environmental correlations, the distribution of the test statistics for the A and r_g parameters is distributed as a 50:50 mixture of zero and χ^2 with $df = 1$ (Dominicus, Skrandal, Gjessing, Pedersen, & Palmgren, 2006; Self & Liang, 1987). Failure to account for this mixed distribution produces p values that are too large; however, the issue is easily corrected by halving the p values obtained from the naive χ^2 with $df = 1$ distribution (Dominicus et al., 2006).

Test for Different Heritability Estimates in Homologous Left and Right Hemisphere Regions

To address this question, we fit a bivariate twin model (with left and right values in each region as the two variables of interest) and then tested whether the additive genetic parameters for each homologous hemispheric measure could be constrained to be equal. The fit of this model was compared against a model in which the additive genetic effects were allowed to differ between hemispheres. A significant worsening of fit indicates that the left and right hemisphere heritability estimates are not equal.

Test for Homologous Left and Right Hemisphere Regions Being Influenced by Different Genetic Factors

To test this question, bivariate twin models were again fit to the data. We then tested whether the genetic correlation between the two variables (left and right regional values) could be constrained to 1.0 without a significant reduction in model fit. A significant worsening of the model fit would indicate that the genetic correlation between left and right values is significantly different from unity, which means that there is evidence for somewhat

different or nonoverlapping genetic influences affecting right and left hemisphere region size.

Test for the Heritability of Left–Right Size Differences for Homologous Regions in Each Hemisphere

When genetic correlations between the hemispheres are high, the genetic contributions to the difference in size between the left and right hemispheres are, by definition, minimal. For those measures with some evidence for unique genetic effects in one hemisphere compared with the other, we used a standard univariate twin model to analyze within-subject left–right differences and laterality scores $[(L - R)/(L + R)]$ for each ROI. This yielded heritability estimates and confidence intervals around these estimates.

Power

Given that we expected not to find significant differences in the heritability of homologous left and right ROIs nor significant heritability of left–right differences, it is important to consider whether our sample size has sufficient power to detect small heritabilities and small differences in the magnitude of heritabilities. In previous work using the same sample, the difference between the upper and lower boundaries of the confidence intervals around heritabilities for cortical thickness and surface area ranged from .12 to .38, and heritabilities as low as 0.12 were significant (Eyler, Prom-Wormley, Panizzon, et al., 2011; Kremen et al., 2010). In addition, using permutation tests, we were able to demonstrate significantly different magnitudes of heritabilities of surface area between lobes (Eyler, Prom-Wormley, Panizzon, et al., 2011). For example, left medial temporal surface area heritability of 0.55 was significantly lower than left occipital surface area heritability of 0.79. Thus, we are generally powered to detect differences in heritability that are at least 0.25 between hemispheres.

RESULTS

Is the Magnitude of Heritability Different for Homologous Left versus Right Hemisphere Regions?

In this sample of over 500 VETSA participants, we again saw evidence for moderate to high heritability of most brain size measures (Tables 2a, 2b, and 2c). As can be seen, there was minimal numerical difference between the size of the heritability estimates on the left and right side of the brain for almost all structures. The largest numerical differences in heritability magnitudes were in the surface area of the paracentral lobule (right > left) and precuneus (left > right) and in the volume of the inferior lateral ventricle (left > right). When the significance of these apparent differences was tested by examining loss of fit for a model in which the *A* influences were constrained to be equal on the left and right, only the difference in the inferior lateral ventricle

survived correction for multiple comparisons. Analyses controlling for global surface area, mean thickness, and total intracranial volume yielded similar findings to the findings using uncorrected regional measures. Overall, we found little support for the magnitude of heritability differing between homologous left and right hemisphere regions. Furthermore, for regions with nonsignificant differences, heritability estimates were generally larger and had smaller confidence intervals when the two hemispheres' values were combined into a single bilateral measure. For example, for the pars opercularis region, heritability (95% confidence interval) for combined surface area was 0.57 (0.44, 0.66) compared with left alone – 0.42 (0.29, 0.54) or right alone – 0.42 (0.28, 0.54). The same effect was seen for hippocampal volume, with a larger and more reliable heritability estimate observed for the bilateral volume measure (0.83 [0.77, 0.87]) compared with either unilateral heritability (left: 0.75 [0.68, 0.80], right: 0.76 [0.69, 0.82]).

Are There Different Genetic Factors That Influence Homologous Left and Right Hemisphere Region Size? Genetic Correlations between Left and Right Hemisphere Size

Phenotypic and genetic correlations between left and right hemisphere size measures are given in Tables 3a, 3b, and 3c. As can be seen, the genetic correlations were very high, with the lower end of most confidence intervals hovering around 0.80 and the upper bounds generally at or close to 1.0. In some regions, low heritability in one or both hemispheres (regions that are starred in Tables 3a, 3b, and 3c indicate nonsignificant heritability; see Tables 2a, 2b, and 2c for heritability estimates) made it difficult to have adequate power to test a bivariate model, so confidence intervals on these genetic correlations ranged from –1 to 1. For 62 of the 75 regions tested (83%), there was no significant ($p < .05$) loss of fit of the bivariate model when the genetic correlation was set to 1.0. Subcortical volumes showed the most evidence for lateralized genetic influences; after Bonferroni correction for multiple comparisons, the pallidum and the accumbens still showed genetic correlations that were significantly lower than 1 (see Table 3c). The phenotypic correlation between left and right accumbens volumes was also relatively low. After adjustment for global measures, the results were very similar, and there was still evidence of unique genetic influences on relative pallidum and accumbens volumes on the left and right (adjusted pallidum $r_g = 0.80$ (0.70, 0.87), χ^2 test of model fit loss after setting r_g to 1: $p < .0005$; adjusted accumbens $r_g = 0.50$ (0.30, 0.65), $p < .0005$).

Are Left–Right Size Difference Scores Significantly Heritable?

Given the uniformly high genetic correlations between hemispheres, it would not be possible to detect significant heritability of laterality for most of the brain size

Table 2a. Heritabilities for Left and Right Surface Area Measures and Test of Equivalence of Hemispheric Heritabilities

	<i>Left Hemisphere Heritability (Confidence Interval)</i>	<i>Right Hemisphere Heritability (Confidence Interval)</i>	<i>Uncorrected p^a</i>
Total surface area	0.94 (0.92, 0.95)	0.94 (0.92, 0.96)	.42
<i>Frontal Lobe</i>			
Superior frontal gyrus	0.78 (0.72, 0.83)	0.74 (0.67, 0.80)	.26
<i>Middle Frontal Gyrus</i>			
Rostral middle frontal gyrus	0.59 (0.49, 0.68)	0.61 (0.52, 0.69)	.78
Caudal middle frontal gyrus	0.66 (0.57, 0.74)	0.56 (0.45, 0.66)	.10
<i>Inferior Frontal Gyrus</i>			
Pars opercularis	0.42 (0.29, 0.54)	0.42 (0.28, 0.54)	.97
Pars triangularis	0.31 (0.17, 0.44)	0.40 (0.24, 0.53)	.38
Pars orbitalis	0.24 (0.12, 0.36)	0.33 (0.20, 0.46)	.30
<i>Orbitofrontal Cortex</i>			
Lateral orbitofrontal cortex	0.51 (0.38, 0.62)	0.33 (0.21, 0.45)	.03
Medial orbitofrontal cortex	0.34 (0.20, 0.47)	0.45 (0.31, 0.57)	.25
Frontal pole	0.08 (0, 0.23)	0.03 (0, 0.15)	.51
Precentral gyrus	0.69 (0.60, 0.76)	0.63 (0.55, 0.71)	.34
Paracentral lobule	0.34 (0.23, 0.46)	0.56 (0.45, 0.66)	.005
<i>Parietal Lobe</i>			
Postcentral gyrus	0.59 (0.48, 0.69)	0.59 (0.49, 0.67)	.97
Supramarginal gyrus	0.62 (0.51, 0.71)	0.49 (0.36, 0.59)	.06
Superior parietal cortex	0.57 (0.47, 0.65)	0.62 (0.53, 0.70)	.38
Inferior parietal cortex	0.53 (0.42, 0.62)	0.63 (0.53, 0.71)	.06
Precuneus cortex	0.71 (0.63, 0.78)	0.56 (0.47, 0.64)	.005
<i>Occipital Lobe</i>			
Lingual gyrus	0.51 (0.38, 0.61)	0.41 (0.29, 0.52)	.21
Pericalcarine cortex	0.35 (0.21, 0.48)	0.43 (0.29, 0.54)	.40
Cuneus cortex	0.47 (0.34, 0.58)	0.34 (0.20, 0.46)	.11
Lateral occipital cortex	0.57 (0.46, 0.66)	0.45 (0.33, 0.55)	.09
<i>Temporal Lobe</i>			
Lateral aspect			
Superior temporal gyrus	0.56 (0.45, 0.66)	0.58 (0.47, 0.68)	.76
Middle temporal gyrus	0.43 (0.32, 0.54)	0.50 (0.38, 0.60)	.41
Inferior temporal gyrus	0.46 (0.31, 0.58)	0.47 (0.34, 0.58)	.92
Transverse temporal cortex	0.38 (0.25, 0.49)	0.22 (0.07, 0.36)	.09
Banks of the superior temporal sulcus	0.24 (0.09, 0.38)	0.23 (0.08, 0.37)	.92

Table 2a. (continued)

	<i>Left Hemisphere Heritability (Confidence Interval)</i>	<i>Right Hemisphere Heritability (Confidence Interval)</i>	<i>Uncorrected p^a</i>
<i>Medial aspect</i>			
Entorhinal cortex	0.13 (0.02, 0.29)	0.27 (0.11, 0.42)	.23
Parahippocampal gyrus	0.36 (0.22, 0.49)	0.26 (0.11, 0.40)	.30
Temporal pole	0.15 (0, 0.30)	0.22 (0.05, 0.38)	.55
Fusiform gyrus	0.47 (0.36, 0.57)	0.47 (0.36, 0.57)	.99
<i>Cingulate Cortex</i>			
Rostral anterior cingulate cortex	0.17 (0.02, 0.32)	0.09 (0, 0.24)	.43
Caudal anterior cingulate cortex	0.30 (0.14, 0.45)	0.43 (0.25, 0.58)	.26
Rostral posterior division	0.52 (0.39, 0.62)	0.51 (0.39, 0.61)	.94
Retrosplenial cortex	0.49 (0.36, 0.60)	0.33 (0.18, 0.46)	.07

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that left and right genetic influences cannot be constrained to be equal and therefore suggest differences between hemispheres in the magnitude of genetic influences.

Table 2b. Heritabilities for Left and Right Cortical Thickness Measures and Test of Equivalence of Hemispheric Heritabilities

	<i>Left Hemisphere Heritability (Confidence Interval)</i>	<i>Right Hemisphere Heritability (Confidence Interval)</i>	<i>Uncorrected p^a</i>
Mean weighted cortical thickness	0.79 (0.72, 0.84)	0.78 (0.71; 0.83)	.82
<i>Frontal Lobe</i>			
Superior frontal gyrus	0.76 (0.68, 0.81)	0.72 (0.64, 0.78)	.24
<i>Middle Frontal Gyrus</i>			
Rostral middle frontal gyrus	0.49 (0.38, 0.59)	0.53 (0.41, 0.63)	.60
Caudal middle frontal gyrus	0.55 (0.43, 0.65)	0.57 (0.46, 0.66)	.77
<i>Inferior Frontal Gyrus</i>			
Pars opercularis	0.55 (0.44, 0.65)	0.36 (0.24, 0.48)	.01
Pars triangularis	0.42 (0.30, 0.54)	0.38 (0.23, 0.51)	.59
Pars orbitalis	0.36 (0.22, 0.49)	0.41 (0.28, 0.53)	.58
<i>Orbitofrontal Cortex</i>			
Lateral orbitofrontal cortex	0.48 (0.34, 0.59)	0.52 (0.39, 0.63)	.53
Medial orbitofrontal cortex	0.44 (0.31, 0.55)	0.46 (0.33, 0.57)	.81
Frontal pole	0.31 (0.14, 0.45)	0.12 (0, 0.28)	.11
Precentral gyrus	0.67 (0.57, 0.74)	0.67 (0.57, 0.74)	.99
Paracentral lobule	0.63 (0.54, 0.71)	0.62 (0.52, 0.70)	.80
<i>Parietal Lobe</i>			
Postcentral gyrus	0.64 (0.54, 0.72)	0.66 (0.57, 0.73)	.65
Supramarginal gyrus	0.56 (0.45, 0.66)	0.47 (0.35, 0.58)	.19

Table 2b. (continued)

	Left Hemisphere Heritability (Confidence Interval)	Right Hemisphere Heritability (Confidence Interval)	Uncorrected p^a
Superior parietal cortex	0.65 (0.56, 0.73)	0.67 (0.58, 0.75)	.73
Inferior parietal cortex	0.67 (0.58, 0.74)	0.53 (0.43, 0.62)	.02
Precuneus cortex	0.61 (0.50, 0.70)	0.56 (0.44, 0.65)	.42
<i>Occipital Lobe</i>			
Lingual gyrus	0.58 (0.47, 0.67)	0.61 (0.51, 0.70)	.60
Pericalcarine cortex	0.43 (0.31, 0.54)	0.41 (0.29, 0.51)	.78
Cuneus cortex	0.52 (0.40, 0.62)	0.54 (0.42, 0.64)	.74
Lateral occipital cortex	0.58 (0.48, 0.67)	0.55 (0.44, 0.64)	.54
<i>Temporal Lobe</i>			
Lateral aspect			
Superior temporal gyrus	0.56 (0.44, 0.65)	0.68 (0.58, 0.75)	.03
Middle temporal gyrus	0.42 (0.28, 0.54)	0.46 (0.33, 0.58)	.61
Inferior temporal gyrus	0.47 (0.36, 0.58)	0.54 (0.42, 0.63)	.40
Transverse temporal cortex	0.53 (0.41, 0.63)	0.50 (0.39, 0.60)	.75
Banks of the superior temporal sulcus	0.03 (0, 0.19)	0.25 (0.10, 0.39)	.04
Medial aspect			
Entorhinal cortex	0.33 (0.18, 0.46)	0.34 (0.18, 0.47)	.96
Parahippocampal gyrus	0.46 (0.32, 0.58)	0.54 (0.41, 0.65)	.31
Temporal pole	0.46 (0.34, 0.57)	0.27 (0.16, 0.40)	.04
Fusiform gyrus	0.47 (0.34, 0.58)	0.56 (0.44, 0.65)	.22
<i>Cingulate Cortex</i>			
Rostral anterior cingulate cortex	0.21 (0.08, 0.36)	0.26 (0.13, 0.39)	.57
Caudal anterior cingulate cortex	0.33 (0.19, 0.46)	0.39 (0.24, 0.52)	.55
Rostral posterior division	0.48 (0.34, 0.59)	0.46 (0.31, 0.58)	.80
Retrosplenial cortex	0.48 (0.35, 0.59)	0.43 (0.31, 0.54)	.54

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that left and right genetic influences cannot be constrained to be equal and therefore suggest differences between hemispheres in the magnitude of genetic influences.

measurements. For the pallidum and accumbens, however, we did test for heritability of the difference score between left and right volumes. Laterality scores were moderately heritable for the volume of both regions whether measured as the L minus R difference [b^2 (95% confidence interval) = 0.36 (0.21; 0.49) for pallidum and 0.40 (0.26; 0.52) for the accumbens] or as a standardized laterality score [(L - R)/(L + R); 0.32 (0.17; 0.46) for pallidum and 0.37 (0.23; 0.50) for the accumbens]. Thus, in these regions with some evidence for unique genetic contributions to the size of each hemisphere, there was also evidence that variation between

individuals in the magnitude of size differences between homologous regions in the left and right hemisphere is moderately genetically determined.

DISCUSSION

Our study is the first to examine three different questions related to laterality of brain size and the role that genetic influences play in determining individual differences in asymmetry. Interestingly, very few previous studies addressed the question that is generally thought of as the “true” test of the genetics of brain asymmetry. That

Table 2c. Heritabilities for Left and Right Ventricular and Subcortical Volume Measures and Test of Equivalence of Hemispheric Heritabilities

	<i>Left Hemisphere Heritability (Confidence Interval)</i>	<i>Right Hemisphere Heritability (Confidence Interval)</i>	<i>Uncorrected p^a</i>
Lateral ventricle	0.82 (0.76, 0.86)	0.79 (0.73, 0.84)	.37
Inferior lateral ventricle	0.72 (0.63, 0.79)	0.49 (0.37, 0.60)	.0002 ^b
Thalamus	0.81 (0.75, 0.86)	0.82 (0.76, 0.86)	.66
Caudate	0.91 (0.88, 0.93)	0.88 (0.84, 0.91)	.04
Putamen	0.88 (0.85, 0.91)	0.85 (0.80, 0.89)	.17
Pallidum	0.76 (0.69, 0.82)	0.81 (0.75, 0.85)	.21
Hippocampus	0.75 (0.68, 0.80)	0.76 (0.69, 0.82)	.71
Amygdala	0.68 (0.58, 0.75)	0.70 (0.62, 0.77)	.56
Accumbens	0.55 (0.42, 0.65)	0.47 (0.34, 0.58)	.34

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that left and right genetic influences cannot be constrained to be equal and therefore suggest differences between hemispheres in the magnitude of genetic influences.

^bSignificant after Bonferroni correction for multiple (75) regional comparisons.

Table 3a. Phenotypic and Genetic Correlations between Left and Right Surface Area Measures and Test of Whether Genetic Correlation Can Be Constrained to Unity

	<i>Phenotypic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Genetic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Uncorrected p^a</i>
Total surface area	0.99 (0.988, 0.992)	0.999 (0.996, 1.00)	.06
<i>Frontal Lobe</i>			
Superior frontal gyrus	0.78 (0.75, 0.82)	0.97 (0.92, 1.00)	.07
<i>Middle Frontal Gyrus</i>			
Rostral middle frontal gyrus	0.63 (0.57, 0.68)	1.00 (0.92, 1.00)	.50
Caudal middle frontal gyrus	0.57 (0.50, 0.63)	0.90 (0.79, 0.98)	.03
<i>Inferior Frontal Gyrus</i>			
Pars opercularis	0.41 (0.33, 0.48)	0.89 (0.68, 1.00)	.16
Pars triangularis	0.32 (0.24, 0.40)	0.66 (0.37, 0.91)	.02
Pars orbitalis	0.33 (0.25, 0.41)	1.00 (0.73, 1.00)	.50
<i>Orbitofrontal Cortex</i>			
Lateral orbitofrontal cortex	0.42 (0.34, 0.49)	0.96 (0.76, 1.00)	.37
Medial orbitofrontal cortex	0.37 (0.29, 0.45)	0.95 (0.71, 1.00)	.36
Frontal pole ^b	0.13 (0.05, 0.22)	1.00 (-1.00, 1.00)	.50
Precentral gyrus	0.68 (0.63, 0.73)	1.00 (0.95, 1.00)	.50
Paracentral lobule	0.48 (0.40, 0.54)	0.99 (0.81, 1.00)	.48

Table 3a. (continued)

	Phenotypic Correlation between Left and Right Hemisphere (95% Confidence Interval)	Genetic Correlation between Left and Right Hemisphere (95% Confidence Interval)	Uncorrected p^a
<i>Parietal Lobe</i>			
Postcentral gyrus	0.64 (0.58, 0.69)	1.00 (0.91, 1.00)	.50
Supramarginal gyrus	0.52 (0.45, 0.59)	0.87 (0.73, 0.98)	.04
Superior parietal cortex	0.61 (0.55, 0.67)	1.00 (0.90, 1.00)	.50
Inferior parietal cortex	0.69 (0.64, 0.73)	1.00 (0.96, 1.00)	.50
Precuneus cortex	0.66 (0.61, 0.71)	1.00 (0.93, 1.00)	.50
<i>Occipital Lobe</i>			
Lingual gyrus	0.48 (0.41, 0.55)	0.97 (0.81, 1.00)	.35
Pericalcarine cortex	0.46 (0.39, 0.53)	0.95 (0.75, 1.00)	.36
Cuneus cortex	0.38 (0.30, 0.45)	0.88 (0.65, 1.00)	.17
Lateral occipital cortex	0.57 (0.51, 0.63)	1.00 (0.89, 1.00)	.50
<i>Temporal Lobe</i>			
Lateral aspect			
Superior temporal gyrus	0.62 (0.56, 0.67)	1.00 (0.90, 1.00)	.50
Middle temporal gyrus	0.45 (0.38, 0.52)	1.00 (0.84, 1.00)	.50
Inferior temporal gyrus	0.44 (0.36, 0.51)	0.91 (0.71, 1.00)	.19
Transverse temporal cortex	0.29 (0.20, 0.37)	0.71 (0.38, 1.00)	.08
Banks of the superior temporal sulcus	0.08 (−0.01, 0.17)	0.67 (0.21, 1.00)	.14
Medial aspect			
Entorhinal cortex	0.27 (0.19, 0.35)	0.98 (0.40, 1.00)	.48
Parahippocampal gyrus	0.32 (0.24, 0.40)	0.93 (0.60, 1.00)	.36
Temporal pole ^b	0.16 (0.07, 0.24)	0.37 (−0.37, 1.00)	.06
Fusiform gyrus	0.48 (0.40, 0.54)	1.00 (0.88, 1.00)	.50
<i>Cingulate Cortex</i>			
Rostral anterior cingulate cortex ^b	0.11 (0.02, 0.20)	0.17 (−1.00, 1.00)	.15
Caudal anterior cingulate cortex	0.22 (0.13, 0.3)	0.46 (0.12, 0.76)	.01
Rostral posterior division	0.41 (0.33, 0.48)	0.82 (0.66, 0.96)	.02
Retrosplenial cortex	0.41 (0.34, 0.49)	0.92 (0.70, 1.00)	.27

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that r_g cannot be constrained to equal 1 and therefore suggest different genetic factors acting on each hemisphere (lateralized genetic influences).

^bOne or both hemispheres had nonsignificant heritability for this region, making genetic correlations difficult to interpret.

question is our third question: whether the size difference between homologous left and right hemisphere regions is heritable.

We did not find much evidence in support of the idea that genetic factors play a greater role in determining the

size of regions of one hemisphere compared with the other. Even in this large sample, the confidence intervals around the heritability estimates for left compared with right hemisphere measures overlapped considerably, and with the exception of the inferior lateral ventricles,

Table 3b. Phenotypic and Genetic Correlations between Left and Right Cortical Thickness and Test of Whether Genetic Correlation Can Be Constrained to Unity

	<i>Phenotypic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Genetic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Uncorrected p^a</i>
Mean weighted cortical thickness	0.93 (0.92, 0.95)	1.00 (0.995, 1.00)	.50
<i>Frontal Lobe</i>			
Superior frontal gyrus	0.88 (0.85, 0.90)	1.00 (0.98, 1.00)	.50
<i>Middle Frontal Gyrus</i>			
Rostral middle frontal gyrus	0.66 (0.60, 0.71)	1.00 (0.96, 1.00)	.50
Caudal middle frontal gyrus	0.68 (0.63, 0.73)	0.95 (0.86, 1.00)	.15
<i>Inferior Frontal Gyrus</i>			
Pars opercularis	0.56 (0.49, 0.62)	0.99 (0.84, 1.00)	.43
Pars triangularis	0.49 (0.42, 0.55)	0.91 (0.70, 1.00)	.22
Pars orbitalis	0.48 (0.40, 0.54)	0.98 (0.76, 1.00)	.42
<i>Orbitofrontal Cortex</i>			
Lateral orbitofrontal cortex	0.62 (0.56, 0.67)	0.97 (0.85, 1.00)	.30
Medial orbitofrontal cortex	0.53 (0.47, 0.60)	1.00 (0.89, 1.00)	.50
Frontal pole	0.27 (0.19, 0.35)	0.66 (0.01, 1.00)	.19
Precentral gyrus	0.83 (0.80, 0.85)	1.00 (0.98, 1.00)	.50
Paracentral lobule	0.70 (0.65, 0.75)	1.00 (0.95, 1.00)	.50
<i>Parietal Lobe</i>			
Postcentral gyrus	0.76 (0.71, 0.79)	1.00 (0.97, 1.00)	.50
Supramarginal gyrus	0.60 (0.54, 0.66)	1.00 (0.87, 1.00)	.50
Superior parietal cortex	0.79 (0.75, 0.82)	1.00 (0.96, 1.00)	.50
Inferior parietal cortex	0.70 (0.65, 0.74)	1.00 (0.95, 1.00)	.50
Precuneus cortex	0.68 (0.63, 0.73)	0.93 (0.85, 1.00)	.07
<i>Occipital Lobe</i>			
Lingual gyrus	0.65 (0.60, 0.70)	1.00 (0.92, 1.00)	.50
Pericalcarine cortex	0.54 (0.47, 0.60)	1.00 (0.86, 1.00)	.50
Cuneus cortex	0.61 (0.55, 0.66)	0.93 (0.81, 1.00)	.10
Lateral occipital cortex	0.73 (0.69, 0.77)	1.00 (0.94, 1.00)	.50
<i>Temporal Lobe</i>			
Lateral aspect			
Superior temporal gyrus	0.71 (0.66, 0.75)	0.95 (0.87, 1.00)	.08
Middle temporal gyrus	0.56 (0.49, 0.62)	0.89 (0.73, 1.00)	.09
Inferior temporal gyrus	0.56 (0.49, 0.62)	1.00 (0.88, 1.00)	.50

Table 3b. (continued)

	<i>Phenotypic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Genetic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Uncorrected p^a</i>
Transverse temporal cortex	0.57 (0.51, 0.63)	1.00 (0.88, 1.00)	.50
Banks of the superior temporal sulcus ^b	0.24 (0.16, 0.32)	1.00 (-1.00, 1.00)	.50
<i>Medial aspect</i>			
Entorhinal cortex	0.39 (0.31, 0.46)	0.85 (0.58, 1.00)	.17
Parahippocampal gyrus	0.54 (0.48, 0.60)	0.83 (0.67, 0.95)	.02
Temporal pole	0.36 (0.28, 0.43)	1.00 (0.74, 1.00)	.50
Fusiform gyrus	0.61 (0.55, 0.67)	0.93 (0.82, 1.00)	.11
<i>Cingulate Cortex</i>			
Rostral anterior cingulate cortex	0.27 (0.19, 0.35)	0.98 (0.53, 1.00)	.46
Caudal anterior cingulate cortex	0.28 (0.20, 0.36)	0.70 (0.43, 0.95)	.03
Rostral posterior division	0.54 (0.48, 0.61)	0.88 (0.73, 1.00)	.07
Retrosplenial cortex	0.49 (0.42, 0.56)	1.00 (0.84, 1.00)	.50

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that r_g cannot be constrained to equal 1 and therefore suggest different genetic factors acting on each hemisphere (lateralized genetic influences).

^bOne or both hemispheres had nonsignificant heritability for this region, making genetic correlations difficult to interpret.

bivariate model fit was not significantly compromised by constraining the left and right hemisphere heritabilities to be equal. Our conclusion is consistent with the conclusion of Hulshoff Pol et al. (2006) and Pennington et al. (2000), but it contrasts with the interpretation of results by Yoon et al. (2010, 2011, 2012) and Geschwind et al. (2002).

Geschwind et al. concluded that genetic influences were stronger in some right hemisphere cortical regions, whereas Yoon et al. concluded that genetic influences were stronger in the left hemisphere. Although our conclusions differ, it is our view that none of the data from any of these studies supports the conclusion that the magnitude

Table 3c. Phenotypic and Genetic Correlations between Left and Right Ventricular and Subcortical Volumes and Test of Whether Genetic Correlation Can Be Constrained to Unity

	<i>Phenotypic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Genetic Correlation between Left and Right Hemisphere (95% Confidence Interval)</i>	<i>Uncorrected p^a</i>
Lateral ventricle	0.90 (0.88, 0.92)	0.98 (0.96, 1.00)	.02
Inferior lateral ventricle	0.65 (0.59, 0.70)	0.92 (0.82, 1.00)	.05
Thalamus	0.92 (0.91, 0.94)	0.98 (0.96, 1.00)	.03
Caudate	0.94 (0.93, 0.95)	0.99 (0.98, 1.00)	.02
Putamen	0.89 (0.87, 0.91)	0.98 (0.96, 1.00)	.02
Pallidum	0.72 (0.67, 0.76)	0.87 (0.81, 0.92)	<.0005 ^b
Hippocampus ($n = 422$)	0.83 (0.80, 0.86)	1.00 (0.97, 1.00)	.50
Amygdala	0.77 (0.73, 0.80)	0.99 (0.94, 1.00)	.38
Accumbens	0.42 (0.34, 0.50)	0.54 (0.35, 0.67)	<.0005 ^b

^a $p < .0005$ (Bonferroni-corrected for 75 measures) indicate that r_g cannot be constrained to equal 1 and therefore suggest different genetic factors acting on each hemisphere (lateralized genetic influences).

^bSignificant after Bonferroni correction for multiple (75) regional comparisons.

of heritabilities differs in homologous left versus right hemisphere regions. Confidence intervals provided in the studies of Yoon et al. illustrate this point in that, as in most results in this study, there was substantial overlap between every corresponding left and right confidence interval. Given the smaller sample size in the Geschwind et al. study, it is highly likely that those confidence intervals would also be substantially overlapping. Our finding of a greater heritability on the left than right for the volume of the inferior lateral ventricle was surprising and warrants further investigation.

Among measures of cortical size, including surface area and thickness, the same genetic factors that relate to individual differences in one hemisphere seem to be acting on the other hemisphere, as evidenced by very large interhemispheric genetic correlations that were statistically indistinguishable from being perfectly correlated ($r_g = 1.0$). This was also generally the case for subcortical volumes, including for the hippocampus, which generally shows a phenotypic rightward volume bias (Shi, Liu, Zhou, Yu, & Jiang, 2009), and for the ventricles. Genetic correlations between volumes of left and right pallidum and left and right accumbens were the only measures that had genetic correlations significantly lower than 1.0 after Bonferroni correction for multiple comparisons. Although genetic factors play a large role in determining individual differences in size of these two structures in both hemispheres, our evidence suggests that some of the genes influencing left hemisphere volume may differ from those influencing right hemisphere volume. Asymmetries of volume or surface features of the BG are inconsistently reported (Renteria, 2012), but there is some suggestion that alterations of structural and functional laterality in accumbens and pallidum might be related to schizophrenia (Qiu et al., 2009), mood symptoms in bipolar disorder (Caligiuri et al., 2003), and paw preference in rodents (Budilin, Midzyanovskaya, Shchegolevskii, Ioffe, & Bazyan, 2008). It is unknown whether there are age-related alterations in volume or functional asymmetry in these regions. Further work is needed to replicate our findings and to identify genes that might contribute uniquely to either left or right hemisphere size in these regions.

Given that the genetic contributions to size variations are generally shared between the two hemispheres, individual differences in laterality scores could not, by definition, be heritable. Our findings suggest that to the extent that people vary in the degree of size asymmetry between homologous cortical and subcortical regions (as indicated by proportionately large *SDs* around measures of asymmetry, e.g., an *SD* of 0.08 for a mean laterality score $[(L - R)/(L + R)]$ of 0.09 for the pars opercularis surface area and an *SD* of 0.03 for a mean laterality score of -0.03 for the hippocampus), these variations are primarily determined by unique environmental factors. The large role for environmental factors in size asymmetries is consistent with the conclusions of a recent review of this literature (Bishop, 2013) as well as prior studies showing low heri-

tability for functional motor asymmetry as indexed by hand use preference (Medland et al., 2009; Warren, Stern, Duggirala, Dyer, & Almasy, 2006).

In the current study, we only examined one type of laterality with respect to brain structure (i.e., left–right differences in homologous regions), so it remains to be seen if individual differences in global human asymmetries, such as Yakovlevian torque, that can also be assessed with careful surface-based MRI measures (Lyttelton et al., 2009), are more determined by genetic factors, as might be suggested by a recent finding based on width measurements in vervet monkeys (Fears et al., 2011). It is also possible that individual variation in left–right differences for other types of measures may be determined by genetic factors. For example, in a diffusion tensor imaging study, Jahanshad et al. (2010) found heritabilities ranging from 0 to .42 for left–right differences in one measure of anisotropy (hyperbolic tangent of geodesic anisotropy), although only the anterior thalamic radiation difference was significant. It is also possible that genetic factors could play a significant role in functional asymmetries that exist even in the absence of structural asymmetries.

The present results were observed in a sample of both left- and right-handed individuals. Although it has been suggested that handedness and brain laterality are linked (Haberling, Badzakova-Trajkov, & Corballis, 2013; Annett, 1985), there have been mixed findings regarding the role of genetic or environmental factors in this association (Haberling et al., 2013; Geschwind et al., 2002). A full examination of these issues was beyond the scope of the present article, but the inclusion of both right- and left-handed individuals and, therefore, both concordant and discordant twin pairs allows our findings about brain laterality to generalize to the full population and gives the most accurate estimates of genetic and environmental influences. Furthermore, when the analyses were repeated with a sample that included only right-handers (data not shown), findings were broadly similar, although some heritability estimates (e.g., for the laterality scores in the pallidum and accumbens) were not significant in the right-handed subsample, perhaps because of reduced power of the smaller sample size.

Our larger sample afforded adequate power to find significant regional heritability (Kremen et al., 2010), significant differences in magnitudes of heritability within hemispheres (Eyler, Prom-Wormley, Panizzon, et al., 2011), and meaningful variations in genetic correlations between regions (Chen et al., 2012). Yet, in the current study, we failed to observe any evidence of differences in the magnitude of heritability in homologous left and right hemisphere brain regions, different genetic influences for homologous left and right hemisphere regions except in volume of select subcortical regions, or significant heritability of left–right size differences except in those regions. Furthermore, findings were not different when adjusting values for global size measures, suggesting that the absence of lateralized effects was not because of a masking

of regional effects by global factors. These findings contradict the seemingly widely held view that genetic influences play a significant role in individual differences in cerebral laterality, at least for the structural brain measures we assessed. However, we think the actual data across studies are nevertheless consistent with the view that genetic factors do not play much of a role in determining individual differences in structural brain asymmetry (Bishop, 2013). Our findings also argue for use of bilateral brain phenotypes when looking for associations with particular genes, because the power to detect such associations is likely to be higher for the combined measure than for left or right measures alone.

Although it is possible that small lateralized genetic effects of one of these types could be observed with a much larger sample, it seems unlikely that such small effects would be particularly useful in understanding human development and behavior. It is also possible that there are genetic influences determining variation in structural asymmetry in some specific regions (e.g., language regions) whose boundaries do not correspond with the regions we have measured. On the basis of our results, it seems unlikely that different genes influence left and right hemisphere regions or that the degree of genetic influences is meaningfully different in the left and right hemisphere. There are, however, some known consistencies in left–right size differences across people and a great deal of phenotypic variation in our measures of laterality. Although genetic influences on individual variation in left–right differences were not observed for most measures, we should point out that this does not necessarily imply that genes are not involved in left–right patterning in development. For example, it is very likely that genes directly influence the development of the heart on the left side of the body, but a twin study would not reveal genetic influences on variation because this trait is shared by almost every individual. Furthermore, it could be that the genes that influence development of laterality do not have allelic variations between individuals and therefore would not contribute to individual variation in the degree of laterality. Still, our results, in concert with the growing body of evidence linking abnormalities of laterality to brain disorders or differences in aging outcomes, point to the importance of discovering the nature and timing of the environmental factors that influence individual differences in brain asymmetry. One can speculate that unique environmental influences such as gaining expertise in a given task that preferentially involves one hemisphere or the other (e.g., playing a musical instrument, playing tennis, or learning a second language) may contribute to different patterns of regional laterality. Unilateral brain insults, such as mild strokes or traumatic injuries, could also play a role. Finally, gene expression differences between individuals could likely contribute, because gene expression is largely a stochastic process, which can vary from cell to cell and person to person even in the context of identical DNA (Raj & van Oudenaarden, 2008), and becomes more random with

age (Bahar et al., 2006). Carefully designed developmental studies will need to be conducted to fully understand the environmental determinants of structural asymmetries.

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