Published in final edited form as:

Alzheimer Dis Assoc Disord. 2009 ; 23(3): 218–223. doi:10.1097/WAD.0b013e31819cadd8.

Bivariate Heritability of Total and Regional Brain Volumes: the Framingham Study

Anita L. DeStefano, PhD^{1,2}, Sudha Seshadri, MD^{2,3}, Alexa Beiser, PhD^{1,2}, Larry D. Atwood, PhD^{1,2,3}, Joe M. Massaro, PhD^{1,3,4}, Rhoda Au, PhD^{2,3}, Philip A. Wolf, MD^{2,3}, and Charles DeCarli, MD⁵

¹Department of Biostatistics, Boston University of Public Health, Boston MA

²Department of Neurology, Boston University School of Medicine, Boston, MA

³National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, MA

⁴Department of Mathematics and Statistics, Boston University, Boston, MA

⁵Department of Neurology and Center for Neuroscience, University of California at Davis, Sacramento, California

Abstract

Heritability and genetic and environmental correlations of total and regional brain volumes were estimated from a large, generally healthy, community-based sample, to determine if there are common elements to the genetic influence of brain volumes and white matter hyperintensity volume. There were 1538 Framingham Heart Study participants with brain volume measures from quantitative magnetic resonance imaging (MRI) who were free of stroke and other neurological disorders that might influence brain volumes and who were members of families with at least two Framingham Heart Study participants. Heritability was estimated using variance component methodology and adjusting for the components of the Framingham stroke risk profile. Genetic and environmental correlations between traits were obtained from bivariate analysis. Heritability estimates ranging from 0.46 to 0.60, were observed for total brain, white matter hyperintensity, hippocampal, temporal lobe, and lateral ventricular volumes. Moderate, yet significant, heritability was observed for the other measures. Bivariate analyses demonstrated that relationships between brain volume measures, except for white matter hyperintensity, reflected both moderate to strong shared genetic and shared environmental influences. This study confirms strong genetic effects on brain and white matter hyperintensity volumes. These data extend current knowledge by showing that these two different types of MRI measures do not share underlying genetic or environmental influences.

Keywords

heritability; quantitative MRI; brain volume; white matter hyperintensity

Introduction

Volumetric magnetic resonance imaging (MRI) can provide quantitative measures of total and regional brain volumes and white matter hyperintensity (WMH) volumes that may serve as

intermediate phenotypes for genetic studies of usual brain aging, as well as cerebrovascular and neurodegenerative disease.

Previous studies have mostly examined genetic influence on brain volume using a twin pair study design or a relatively small sample size in selected samples (see Peper et al 2007 and Schmitt et al for review)^{1, 2}. These selected samples include elderly male WWII veteran twins³, adolescents with reading disability⁴, and persons with schizophrenia.⁵ Substantial heritability of total brain volume, with estimates ranging from 0.65 to 0.97, has been observed.¹ Genes also appear to influence lobar volumes, although the heritability (0.32 to 0.75) is lower than that for total brain volume.³ While some studies find large genetic influence on lateral ventricular volume^{6, 7} others indicate that twin similarity is due to common environment rather than genetics.^{5, 8} Thompson et al examined genetic influence in twins using three-dimensional cortical maps, as opposed to lobar volumes, and determined that there is a strong genetic influence on cortical volume in frontal regions and in Broca's and Wernicke's language areas.⁹

A limited number of studies have conducted multivariate analyses in twins to assess if there are common genetic and environmental influences on brain regions^{4, 8, 10, 11}. Although there were consistent findings of strong genetic correlation, for grey and white matter for example, there were also features, such as lateral ventricular volume, which showed no evidence of genetic correlation with other measures. These findings suggest multiple lines of genetic and environmental factors contribute to neuroanatomy.

Substantial heritability of WMH has been observed in elderly male twins ($h^2=0.73$)¹², in sib pairs in which the proband were Alzheimer's disease cases ($h^2=.49$)¹³ as well as in the offspring cohort and surviving members of the original cohort of the Framingham Heart Study (FHS), which represents a generally healthy, younger population ($h^2=.55$).¹⁴ A genome-wide linkage analysis for WMH volume in the FHS cohorts identified a significant linkage peak (LOD=3.69) on chromosome 4.¹⁵ It is unknown whether the gene in this linkage peak, or on other regions of the human genome, influence WMH via non-vascular aging related changes or through genetic influence on cerebrovascular risk or both.

The first goal of the current study is to examine the heritability of total and regional brain volumes in the FHS cohorts to determine if the strong genetic influence observed in select populations or twin studies is also seen in a younger, healthy, community-based sample that includes extended familial relationships. The second goal is to determine if there are common elements to the genetic influence of brain volume and WMH volume, or if the heritability observed in these phenotypes is due to distinct sets of genes.

Methods

Subjects and Outcome Variables

The FHS was established in 1948 with the enrollment of 5209 men and women residing in Framingham, Massachusetts.¹⁶ In 1971, 5124 offspring of the original participants and their spouses¹⁷ commenced the Framingham Offspring cohort. Original cohort participants undergo biennial examinations and the Offspring undergo examinations every four years. Starting in 1999 brain MRIs were obtained on surviving study participants. The original cohort members contain many individuals who are related as siblings or first cousins. After ascertainment of the offspring cohort family relationships among participants were systematically constructed resulting in the identification of pedigrees including extended pedigrees with two or three generations of related individuals and first, second and third degree relationships including numerous siblings, half-sibling, parent-offspring, first cousin and avuncular relationships as well as more distant relationships¹⁸. All individuals gave informed consent and the Boston

University Institutional Review Board approved all protocols. Participants were imaged on a Siemens Magnetom 1 tesla field strength magnetic resonance machine using a double spin-echo coronal imaging sequence of 4 mm contiguous slices from nasion to occiput. After the MR scan was obtained digital information was transferred to a central location and was processed under the supervision of a single individual (CD) who was blinded to gender, age, familial relationships and clinical status of the participants. Image quantification consisted of mathematical modeling of image pixel intensities¹⁹ after removal of non-brain tissues and correction of image intensity inhomogeneities²⁰. Image segmentation proceeded in two steps, first by segmentation of brain from non-brain and then by identification of white matter hyperintensities (WMH)^{21,22}. Further analysis included standardized analysis of lobar brain regions as previously reported for this cohort²³. Operators trained in the anatomy of the hippocampus outlined all hippocampi. The hippocampus included the CA1 - CA4 fields, dentate gyrus, and the subicular complex using an operator guided ROI approach are image realignment along the axis of the left hippocampal formation. The borders of the hippocampus were manually traced on contiguous 1.5 mm coronal slices in the anterior to posterior direction. While the borders are traced on the coronal slices, the corresponding sagittal and axial views are presented to the operator and can be relied on to verify hippocampal boundaries. Anatomical guidelines determined boundaries for the hippocampus²⁴. The fimbria were excluded from the superior boundary of the hippocampus. The inferior boundary of the hippocampus was the white matter of the parahippocampal gyrus. The lateral boundary was the inferior (temporal) horn of the lateral ventricle, taking care in posterior sections to exclude the tail of the caudate nucleus. The posterior boundary of the hippocampus was the first slice in which the fornices were completely distinct from any gray/white matter of the thalamus. The number of voxels for each ROI were multiplied by the voxel size in milliliters to obtain measures of the total cranial, supratentorial parenchymal (total) brain, lateral ventricular, temporal horn, frontal lobe, parietal lobe, temporal lobe, occipital lobe, hippocampal and WMH volumes.

MRI measures were available on 245 original cohort and 2014 offspring cohort participants. Individuals with stroke, dementia or other neurological conditions known to alter brain MRI (n=72) were excluded. Although stroke and other neurological conditions may have a genetic component, they also have a marked effect on brain volume which may skew heritability estimates associated with typical brain volume variability. Our goal is to assess heritability of brain volumes in 'normal' aging. Volumetric measures were analyzed as a ratio to total cranial volume to adjust for individual variability in head size. The ratio of WMH volume, lateral ventricular volume, and temporal horn volume to total cranial volume were skewed and were natural log transformed for analysis. An age-specific (within 10-year age groups) z-score for the log transformed ratio of WMH volume was obtained as previously described.¹⁵

Two levels of covariate adjustment were considered. The first level included adjustment for age, age squared where appropriate²³ and sex. The second level of covariate adjustment included the previous covariates plus the individual elements of the Framingham stroke risk profile score (FSRP)^{25, 26}, which provides an estimate of a participant's 10-year risk for stroke and are known to affect the extent of WMH and brain volume, even among cognitively normal individuals^{27, 28}, potentially confounding bivariate heritability estimates. Covariate measures from the exam prior to brain MRI were used. Final traits for heritability analysis were studentized residuals obtained from linear regression analysis of each outcome variable on the covariates. Covariate information was unavailable on 41 individuals; adjusted brain MRI measures were computed for 2,146 participants.

Statistical Analysis

Univariate and bivariate heritability was estimated using the variance component model implemented in SOLARv2.1.4.²⁹ Specifically, a mixed model was fit that included fixed

effects for covariates and additive effects for additive polygenic (g) and residual error (e) terms. The variance, V_p , of the observed trait can be partitioned into genetic plus environmental components, $V_g + V_e$, and heritability is the ratio of V_g to V_p . Under this model, the covariance between two subjects equals twice the kinship coefficient times V_g . The variance component approach allows exact modeling of the covariance structure for the large extended pedigrees available in the Framingham Heart Study. Common environmental effects can be modeled with this approach but were not included in the model because data is not available as to whether or when individuals shared a household. Non-biological relationships (eg step-siblings) are not accounted for in this model with the exception of spouses connected in the pedigree via biological offspring. To assess significance of heritability, the polygenic model is compared to a sporadic model in which the additive genetic effect is constrained to zero. The variance component model can be extended to bivariate analysis that simultaneously maximizes the model over two outcome variables³⁰. Bivariate heritability analysis utilizes two traits simultaneously as outcome variables and provides an estimate of the genetic correlation and environmental correlation between the two traits. These correlations range from -1.0 to 1.0 and indicate whether the observed correlation between traits is due to genetic factors, environmental factors or a combination of both. Phenotypic (total) correlation among traits was computed by two methods: 1) Pearson correlation ignoring the relationship among individuals and 2) based on the environmental and genetic correlations from SOLAR which correctly account for family relationships. Phenotypic correlations were nearly identical by the two methods and only the Pearson correlation results are presented due to the ease of p-value computation for this approach. The variance component methods are sensitive to departures from normality³¹. For residuals with high kurtosis (temporal horn volume, temporal lobe volume) winsorized residuals, in which values >3.5 (<-3.5) were set to 3.5 (-3.5), were analyzed.

Univariate and bivariate heritability analyses utilized 1538 individuals with brain MRI measures who were members of families with at least two FHS participants. A subset of 778 individuals meeting the same family structure criteria were used for estimates of heritabilities involving hippocampal measures.

Results

Estimates for single trait heritability and for genetic and environmental correlations between traits were similar when adjusting for age and sex or when additionally adjusting for the components of the FSRP. Therefore, only results using the complete covariate set are shown. Table 1 shows the univariate heritability estimates for the brain volume measures. Heritability ranges from 0.28 to 0.55. Pearson correlations among the brain MRI traits are shown in Table 2. Significant correlation (either positive or negative) is observed among most traits with the exception of WMH with a maximum correlation of .07 with the other measures.

The bivariate trait heritabilities are shown in Table 3 with genetic correlations estimates in the cells above the diagonal and environmental correlation estimates in cells below. A non-zero genetic correlation implies that the two traits are influenced by the same genes. A positive genetic correlation indicates that the two traits both increase or decrease together in response to a genetic influence; a negative genetic correlation indicates that one trait increases and the other trait decreases in response to the same genetic influence. The same interpretation holds true for the environmental correlation and trait responses to non-genetic, environmental factors.

The strongest single trait heritability estimates, ranging from 0.46 to 0.60, were observed for total brain, WMH, hippocampal, temporal lobe, and lateral ventricular volumes. Moderate, yet significant, heritability was observed for the other measures.

The bivariate analyses yielded strong genetic and environmental correlation among some traits and no correlation among others. Total brain volume demonstrated a moderate to strong genetic relationship with all other measures except WMH, occipital and hippocampal volumes. As expected, relationships between total brain volume and cerebral spinal fluid (CSF) measures (i.e. temporal horn volume and lateral ventricular volume) were high, but inverse. Although genes control approximately half the variability observed for total brain volume and WMH volume, bivariate analysis yielded a genetic correlation (r_g) between them equal to 0.02, which indicates that the genes controlling these traits are distinct. In contrast, there may be common genetic influences on WMH volume and specific brain regions such as frontal lobe volume ($r_g=0.30$) and parietal lobe volume ($r_g=-0.39$).

Brain regions which appear to share genes in common include temporal horn volume, which demonstrated a positive genetic correlation to lateral ventricular, and a negative genetic correlation to frontal lobe volume. The strongest genetic correlation observed was between hippocampal volume and temporal lobe volume ($r_g=0.76$). There was also a strong inverse genetic relationship between occipital lobe volume and parietal lobe volume ($r_g=-.59$).

The pattern of environmental correlation observed for total brain volume among the other measures was similar to the genetic pattern, with the genetic correlations being slightly stronger. Significant environmental correlations were observed for total brain volume with frontal lobe ($p<.001$), temporal lobe ($p=.01$), and parietal lobe ($p=.001$) volumes. For total brain volume with hippocampal ($p=.06$), lateral ventricle ($p=.07$), and temporal horn ($p=.09$) volumes we observed non-zero environmental correlations which did not differ from zero with this sample size. In contrast, there was no evidence of environmental factors in common between total brain volume and WMH volume ($r_e=0.00$, $p=1.0$). There is evidence of environmental influences in common between WMH volume and frontal lobe volume ($r_e=-0.17$) and, parietal lobe volume ($r_e=0.24$). In general, there were as many significant environmental correlations as genetic correlations among brain volume measures.

Discussion

We confirm the strong genetic component contributing to variability in brain volume measures. Moreover, bivariate heritability estimates show the expected positive associations between total and regional brain volumes. Inverse associations between brain and CSF measures were also observed, which is expected given that loss of brain tissue without change in intracranial volume will lead to expansion of CSF spaces. These results suggest that generalized atrophy (loss of brain volume and expansion of CSF spaces) may be under common genetic influence. Some regional specific genetic influences, however, may also be present. For example, hippocampal and temporal lobe measures shared the highest bivariate association (genetic correlation = 0.76). This finding is particularly intriguing given the age-related presence of Alzheimer's disease pathology in these two regions.³²⁻³⁴ It is also possible that the genetic correlation of these anatomically linked structures reflects genetic influence on a common developmental pathway. We cannot distinguish between genetic influence on initial volumes and genetic influence on change in volume with the current cross-sectional study design. WMH volumes, by comparison, seem to have genetic influences generally independent of brain volume indicating that brain atrophy and WMH formation may result from different biological processes.

There is no obvious biological explanation for the inverse genetic and environmental correlations between parietal and occipital lobes. We utilize distinct anatomic boundaries for the frontal and temporal lobes, but the boundaries are less distinct between parietal and occipital. If one assumes that the posterior aspect of the brain is well defined then dividing the region along indistinct lines may introduce an inverse correlation as occipital volume plus

parietal must equal posterior brain volume. Although the estimated genetic contribution to total brain volume in the FHS was substantial (heritability=0.46), this estimate is lower compared to previous reports.^{5, 8, 10, 35} Lower heritability could reflect issues with measurement methodology. This is not likely the cause of the lower heritability estimates given that similar methodology has been applied by the same investigator (CD) in a twin sample which found high heritability for total brain volume.³ The current study utilized multigenerational pedigrees to estimate heritability as compared to the previous studies that are primarily based on twin cohorts. Genetic estimates based on twins may overestimate heritability¹, which may partially account for the smaller estimate obtained in this community based sample. The smaller estimate observed in the FHS may also reflect that participants included in the analysis ranged in age from 34 to 97 (mean=63.96 years) when brain MRIs were obtained. Finally, Framingham Heart Study participants with MRI are generally younger and healthier in comparison to participants for whom MRI is not available.²³ This may also lead to a conservative (lower) estimate of heritability as the population included in heritability analysis may not include the full range of brain volume heritability. These heritability estimates reflect genetic influences in a cognitively normal, healthy, community based sample.

Twin studies may be the gold standard for estimating heritability, however, extended pedigrees such as those in the Framingham Heart study are an important resource for genetic linkage and association analyses for gene identification. The number of subjects in the current study, 1538, is more than three times that of prior twin analyses.² The substantial heritability observed in the Framingham population supports the value of these extended pedigrees for gene identification studies.

The current study identified significant genetic correlation between lateral ventricular volume and total brain, frontal lobe and temporal lobe volumes, which is in contrast to other studies that found no genetic correlation with lateral ventricle volume^{2,8,10}. This difference may be due to age as the FHS subjects tended to be older than studies using pediatric samples¹¹ or adults less than 40 years of age^{8,10}. With increasing age and atrophy of the parenchyma there is an additional component added to the lateral ventricular volume. In young adults the volume you are born with may reflect genetic or as one study suggests shared maternal in utero environmental influences⁸. This may be independent of parenchymal size as skull size (intracranial volume) can vary during development. During aging, however, as the brain shrinks, the ventricles (and the subarachnoid space outside the brain) have to enlarge since the skull cannot shrink, the same genetic processes that result in atrophy would be expected to increase LV size in a similar matter, consequently resulting in shared genetic variance.

In conclusion this study confirms current knowledge regarding the strong genetic effects on brain and WMH volumes and extends current knowledge by showing that these two types of MRI measures appear to have differing underlying genetic influences. There also appears to be shared genetic influences on some brain regions, in particular temporal lobe and hippocampal structures, both known to be susceptible to Alzheimer's disease pathology. Genetic analyses using these latter regions as endophenotypes, therefore, could result in identification of novel Alzheimer's disease susceptibility genes. Chromosomal regions in which association is observed to multiple brain volume measures (e.g. hippocampal and temporal lobe volume) are likely to harbor genes with a significant influence on brain structure or function. Thus, the results of these bivariate analyses are likely to inform future genetic studies.

Acknowledgments

Funding/Support: the National Heart, Lung, and Blood Institute's Framingham Heart Study, National Institutes of Health (NIH/NHLBI contract N01-HC-25195) and grants: NIA #5RO1-AG16495, NIA #5RO1-AG08122 and NINDS #5R01-NS17950, Boston University Alzheimer's Disease Center P30 AG13846.

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Table 1

Heritability of brain MRI measures adjusted for individual components of the FSRP.

Volume measure	Heritability *
Total brain	0.46
Frontal lobe	0.26
Temporal lobe	0.55
Parietal lobe	0.30
Occipital lobe	0.32
Hippocampal	0.54
Lateral ventricular	0.60
Temporal horn	0.28
WMH	0.49

* standard error = 0.08 for all traits except hippocampal volume with standard error =0.13

Table 2

Pearson correlation among brain MRI measures*

	Total brain	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Hippocampal	Lateral ventricular	Temporal horn	WMH
Total brain		0.46[†]	0.43	0.31	-0.02	0.24	-0.43	-0.24	0.02
Frontal lobe			-0.27	-0.34	-0.23	0.13	-0.27	-0.22	-0.00
Temporal lobe				-0.05	-0.10	0.38	-0.30	-0.05	-0.03
Parietal lobe					-0.59	0.05	-0.04	0.09	-0.01
Occipital lobe						-0.06	-0.01	-0.11	0.04
Hippocampal							-0.20	0.04	-0.01
Lateral ventricular								0.37	-0.00
Temporal horn									0.07

* adjusted for age, sex and the individual components of the Framingham stroke risk profile.

[†] Bold indicates values are significantly different than zero (p<.05).

Table 3

Bivariate analysis of brain MRI measures *

	Total brain	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Hippocampal	Lateral Ventricular	Temporal horn	WMH
Total brain		0.37±0.14[†] p=0.04	0.55±0.09 p<0.001	0.40±0.13 p=0.008	0.11±0.15 p=0.47	0.19±0.15 p=0.23	-0.61±0.08 p<0.001	-0.41±0.14 p=0.01	0.02±0.12 p=0.88
Frontal lobe	0.49±0.07 p<0.001		-0.05±0.16 p=0.73	-0.37±0.17 p=0.06	-0.04±0.20 p=0.86	0.08±0.21 p=0.71	-0.35±0.13 p=0.02	-0.45±0.17 p=0.03	0.30±0.15 p=0.05
Temporal lobe	0.29±0.09 p=0.01	0.45±0.08 p<0.001		0.39±0.13 p=0.002	-0.26±0.13 p=0.06	0.76±0.12 p<0.001	-0.43±0.09 p=0.09	-0.04±0.15 p=0.69	0.08±0.11 p=0.45
Parietal lobe	0.28±0.08 p=0.001	-0.33±0.07 p<0.001	-0.37±0.07 p<0.001		-0.59±0.11 p=0.002	0.02±0.19 p=0.94	-0.15±0.13 p=0.24	0.26±0.19 p=0.17	-0.39±0.14 p=0.005
Occipital lobe	-0.12±0.09 p=0.17	-0.34±0.07 p<0.001	0.01±0.10 p=0.89	-0.59±0.05 p<0.001		-0.16±0.19 p=0.40	0.01±0.13 p=0.93	-0.36±0.20 p=0.07	0.21±0.14 p=0.14
Hippocampal	0.27±0.14 p=0.06	0.17±0.13 p=0.19	-0.11±0.17 p=0.50	0.03±0.13 p=0.79	0.05±0.13 p=0.71		-0.20±0.14 p=0.16	0.21±0.21 p=0.32	-0.04±0.15 p=0.80
Lateral ventricular	-0.22±0.10 p=0.07	-0.24±0.08 p=0.014	-0.09±0.12 p=0.52	0.05±0.10 p=0.57	0.01±0.10 p=0.94	-0.20±0.19 p=0.26		0.43±0.11 p=0.003	-0.04±0.11 p=0.67
Temporal horn	-0.15±0.08 p=0.09	-0.13±0.07 p=0.09	-0.05±0.08 p=0.68	0.02±0.07 p=0.81	0.00±0.08 p=0.96	-0.06±0.13 p=0.63	0.34±0.08 p<0.001		0.07±0.15 p=0.66
WMH	0.00±0.10 p=1.0	-0.17±0.08 p=0.046	-0.18±0.11 p=0.09	0.24±0.14 p=0.005	-0.10±0.09 p=0.27	-0.02±0.15 p=0.92	-0.03±0.11 p=0.76	0.07±0.09 p=0.41	

* adjusted for age, sex and the individual components of the Framingham stroke risk profile. Genetic correlations are on the upper diagonal and environmental correlations are on the lower diagonal.

[†] Bold indicates p-value < .05 for the test whether correlation differs from zero.