

Heritability of brain ventricle volume: Converging evidence from inconsistent results

William S. Kremen^{a,b,c,*}, Matthew S. Panizzon^a, Michael C. Neale^d,
Christine Fennema-Notestine^{a,e}, Elizabeth Prom-Wormley^d, Lisa T. Eyler^{a,c}, Allison Stevens^f,
Carol E. Franz^a, Michael J. Lyons^g, Michael D. Grant^g, Amy J. Jak^{a,c}, Terry L. Jernigan^a,
Hong Xian^h, Bruce Fischl^f, Heidi W. Thermenos^{f,i}, Larry J. Seidman^{f,i}, Ming T. Tsuang^{a,b,c},
Anders M. Dale^{e,j}

^a Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, USA

^b Center for Behavioral Genomics, University of California, San Diego, La Jolla, CA 92093, USA

^c VA Health Care System, San Diego, CA 92093, USA

^d Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA 23219, USA

^e Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA

^f AA Martinos Center, Department of Radiology, Massachusetts General Hospital, Boston, MA 02129, USA

^g Department of Psychology, Boston University, Boston, MA 02215, USA

^h VA Medical Center and Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO 63108, USA

ⁱ Harvard Medical School, Boston, MA 02215, USA

^j Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA

Abstract

Twin studies generally show great consistency for the heritability of brain structures. Ironically, the lateral ventricles—perhaps the most reliably measured brain regions of interest—are the most inconsistent when it comes to estimating genetic influences on their volume. Heritability estimates in twin studies have ranged from zero to almost 0.80. Here we aggregate heritability estimates from extant twin studies, and we review and reinterpret some of the findings. Based on our revised estimates, we conclude that lateral ventricular volume is indeed heritable. The weighted average heritability of the revised estimates was 0.54. Although accumulated environmental insults might seem most logical as the predominant cause of age-related ventricular expansion, the data strongly suggest that genetic influences on lateral ventricular volume are increasing with age. Genetic influences accounted for 32–35% of the variance in lateral ventricular volume in childhood, but about 75% of the variance in late middle and older age. These conclusions have implications for the basic understanding of the genetic and environmental underpinnings of normative and pathological brain aging.

© 2012 Elsevier Inc. All rights reserved.

Keywords: Aging; Alzheimer's Disease; Endophenotype; Genetics; Lateral ventricles; Mild cognitive impairment; Structural MRI; Twins

Elucidating the genetic and environmental influences on brain structure and on brain structure changes over time is important for the basic understanding of brain aging. Although more work is needed to determine the extent of

genetic and environmental influences on brain structure, results to date across different studies are generally consistent for most measures that have been examined (reviewed by Glahn et al., 2007; Peper et al., 2007; Schmitt et al., 2007a). That is, the heritability—the proportion of phenotypic variance due to genes—of different regions of interest (ROIs) has been similar across studies.

One notable exception is the lateral ventricles. There has been substantial variability of heritability estimates in twin

* Corresponding author at: Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive (MC 0738), La Jolla, CA 92093, USA. Tel: +1 858 822 2393; fax: +1 858 822 5856.

E-mail address: wkremen@ucsd.edu (W.S. Kremen).

Table 1
Heritability of lateral ventricular volume (ordered by average age of sample)

Study	Sample size		a^2	Adjusted a^2	c^2	e^2	Age mean (range)
	No. twin pairs	Participant breakdown					
Peper et al. (2009) ^a	103	45 MZ pairs, 58 DZ pairs	0.35 ^a	—	0.35	0.30	9 (9–10)
Schmitt et al. (2007b) ^b	163	127 MZ pairs, 36 DZ pairs, 158 unrelated singletons	0.32	0.17	0.39	0.29	11 (6–19)
Chou et al. (2008)	66	38 MZ pairs, 28 DZ pairs	0.07 [0.42]	—	0.39 [0.08]	0.54 [0.50]	24 (20–26)
Baaré et al. (2001)	112	54 MZ pairs, 58 DZ pairs, 34 siblings	0.00 [0.46]	—	0.59 [0.27]	0.41 [0.27]	31 (19–69)
Wright et al. (2002) ^c	19	9 MZ pairs, 10 DZ pairs	0.00	—	0.48	0.50	31 (19–54)
Reveley et al. (1984) ^d	36	18 MZ pairs, 18 DZ pairs	0.82	0.68	0.02	0.16	38 (—)
Kremen et al. (2010) ^e	202	110 MZ pairs, 92 DZ pairs	0.78	0.79 or 0.75	0.00	0.22	55 (51–59)
Carmelli et al. (2002) ^f	139	72 MZ pairs, 67 DZ pairs	0.74	—	0.00	0.26	72 (69–80)

a^2 = additive genetic influences (heritability); c^2 = common (shared) environmental influences; e^2 = unique environmental influences. Adjusted a^2 = heritability estimates after adjusting for covariates as specified in b, d, and e; other studies did not include adjusted values. Estimates in square in brackets are revised estimates based on our reanalysis.

^a Based on log transformed data; $a^2 = 0.00$, $c^2 = 0.64$, and $e^2 = 0.36$ when based on untransformed data.

^b Adjusted = adjusted for total brain volume.

^c Values for a^2 , c^2 and e^2 do not add up to 1.00, but are as reported in the original article.

^d Computed tomography study; like our revised estimates, the results of this study are based on Falconer estimates; adjusted = adjusted for height and gender; age range was not provided (SD = 12.3 for MZs and 10.6 for DZs).

^e Based in log transformed data; estimates are based on average of left and right lateral ventricles; adjusted = adjusted for age, site, and total brain volume; or age, site, and estimated intracranial volume.

^f Based in log transformed data; estimates are based on average of left and right lateral ventricles.

studies of left and right lateral ventricular volumes, ranging from zero to nearly 0.80. As can be seen in Table 1, the heritability of lateral ventricular volume based on magnetic resonance imaging (MRI) has been reported in five adult twin samples (including our own) and two child and adolescent twin samples. There was also an earlier computed tomography study using an adult twin sample. We restrict this summary to twin studies because they provide a suitable way of differentiating genetic and family environmental sources of resemblance (Kendler and Neale, 2009). Adoption studies can also disentangle these sources of variance, but we are unaware of adoption studies with the necessary neuroimaging data.

Given that lateral ventricular expansion is a ubiquitous, albeit nonspecific, feature of normal brain aging (Pfefferbaum et al., 2004), it is perhaps intuitive to think that enlargement would be due primarily to accumulated environmental insults over the lifespan. However, the wide variability in the heritability estimates casts doubt on this explanation. The inconsistent results are particularly puzzling given the relative consistency of other brain structure heritability estimates plus the fact that the lateral ventricles are one of the easiest ROIs to delineate and measure reliably. This inconsistency leaves us with some as yet unresolved questions: Is the volume of the ventricles under some degree of genetic control or not? If it is, does the degree of genetic control differ as a function of age? If it is not under genetic control, what accounts for the high heritability reported in some studies? Is it just sampling and methodological differences across studies or something more systematic?

Clarifying the extent of genetic and environmental influences on lateral ventricular volume is an essential first step

in determining whether ventricular volume or expansion may also be a useful endophenotype. Ventricular expansion is greater than normal in many aging-related disorders. If it is under significant genetic control and not simply secondary to growth or shrinkage of surrounding brain tissue, a thorough understanding of brain aging will require the elucidation of the genetic factors that influence normal and pathological age-related lateral ventricular expansion. Thus, despite being nonspecific, lateral ventricular volume might be a useful endophenotype and an appropriate phenotype for genetic association studies. We sought to re-evaluate the extant twin studies of the lateral ventricles in an effort to account for the highly discrepant heritability findings, and to determine whether the well-known age-related increase in the volume and variability of the lateral ventricles is associated with changes in genetic or environmental factors.

1. Methods

1.1. Samples included

We identified a total of eight samples, including our own, in which the heritability of the lateral ventricles was estimated. With only eight samples plus the fact some data (e.g., variances) were not available from every study, we decided against conducting a formal meta-analysis. However, similar to a meta-analysis, we were able to calculate weighted averages of the results. In addition, we reanalyzed and reinterpreted data from two studies. Herein we describe the reanalyses and the rationale behind them. Our final conclusions are based on these revised results combined with the original results from other studies.

Table 1 shows demographic and descriptive data from the eight independent samples in which the heritability of lateral ventricular volume was reported. In some cases, there were multiple articles that included heritability estimates from the same samples. To avoid duplication, we referenced only one article per sample in Table 1. The reference selected was generally the one with the largest sample size. There were six studies of adults and two of children and adolescents.

1.2. Twin modeling

The results of these studies are based primarily on standard univariate twin analyses. The standard model, often referred to as an “ACE” model, estimates the proportion of phenotypic variance due to additive genetic effects (A), common or shared environmental effects (C), and unique environmental effects (E) (Eaves et al., 1978; Neale and Cardon, 1992). Note that the (A) component of the model corresponds to the heritability. Common environmental influences are those that make twins similar to one another; unique environmental influences are those that make twins different. Measurement error is assumed to be random, so it is uncorrelated within twin pairs and therefore forms part of the unique environmental variance. Twin studies include both monozygotic (MZ) twins who share 100% of their genes, and dizygotic (DZ) twins who, on average, share 50% of their genes. The basic univariate ACE model consists of: 1) additive genetic factors, which correlate 1.0 for MZ twins and 0.5 for DZ twins; 2) common environmental factors, which correlate 1.0 across twins regardless of zygosity; and 3) unique environmental factors, which are uncorrelated across twins. The fit of the full ACE model to the data may then be compared with a saturated model that fits the data perfectly. The fit of reduced models (i.e., dropping either or both of the A or C components) can also be tested. If there is not a significant reduction in fit, the reduced model is considered more parsimonious because it accounts for the data with fewer parameters. Testing model fits is usually carried out by means of maximum-likelihood-based structural equation modeling (Neale et al., 2003).

If MZ correlations are substantially more than double the DZ correlations, nonadditive (dominant/epistatic) genetic influences may also be operating. However, none of the studies had sufficient power to differentiate between additive and nonadditive genetic variance. In our data, broad heritability estimates (additive + nonadditive) were extremely similar to estimates based on the (A) component in the corresponding ACE models, as were the heritability estimates based on (AE) models.

Another approach to twin analysis is to implement the formulas of Falconer (1960). The Falconer estimate of heritability is derived by doubling the difference of the MZ and DZ twin correlations [$h^2 = 2*(r_{MZ} - r_{DZ})$]. The estimate of common environmental variance is double the DZ correlation minus the MZ correlation [$c^2 = 2* r_{DZ} - r_{MZ}$], and the

estimate of unique environmental variance is $1 - r_{MZ}$. These estimates were used in our reanalysis of two of the data sets because we did not have the raw data needed to conduct structural equation modeling.

2. Results

2.1. The extant literature does not adequately account for discrepant findings

It is clear from Table 1 that there is tremendous variability across studies in the heritability estimates for lateral ventricular volume. These range from 0.00 to 0.75. We now consider what might account for this substantial variability in the original estimates. Methodological differences in image acquisition or measurement might account for some differences, but considering the fact that the lateral ventricles are measured with very high reliability, it does not seem plausible that method differences could account for such extreme heritability differences. Sex differences might account for the differences across studies. Our sample (Kremen et al., 2010) and that of Carmelli et al. (2002) were both all-male samples. Baaré et al. (2001) found no sex differences for several brain structure measures that they compared, and reviews of MRI twin studies have not suggested substantial sex differences (Glahn et al., 2007; Peper et al., 2007; Schmitt et al., 2007a). Moreover, if the heritability of lateral ventricular volume was high only in men as it was in the two all-male samples, the findings of zero heritability in some mixed-sex samples would not be possible.

Age differences constitute another possible explanation. The lateral ventricles are very small in childhood, and larger mean volumes (as are found later in life) would be likely to be associated with larger variances (Østby et al., 2009). The patterns observed from childhood to young adulthood (Østby et al., 2009), and in comparisons of childhood to later life in our Fig. 1 strongly support the notion that the variance of lateral ventricular volumes increases with age. However, the explanation of increasing heritability with age does not fit neatly with the results reported in the extant studies. The weighted average heritability estimate of about 0.33 in children and adolescents (Peper et al., 2009; Schmitt et al., 2007b) compared with the weighted average of 0.76 in middle-aged and older adults (Carmelli et al., 2002; Kremen et al., 2010) might suggest a substantial increase in heritability with age. By contrast, heritability estimates were 0.00 in two samples with average ages of 31 (Baaré et al., 2001; Wright et al., 2002), and only 0.07 in a young adult sample with a mean age of 24 (Chou et al., 2008). If heritability is truly increasing with age, it is difficult to see how the estimates in the two samples covering wide age ranges ((Baaré et al. 2001) [19–69] and (Wright et al. 2002) [19–54]) could be zero. Also, heritability in a computed tomography study was much higher (0.82) in a sample with an average age of 36 (Reveley et al., 1984).

In sum, based on the literature as it is currently presented,

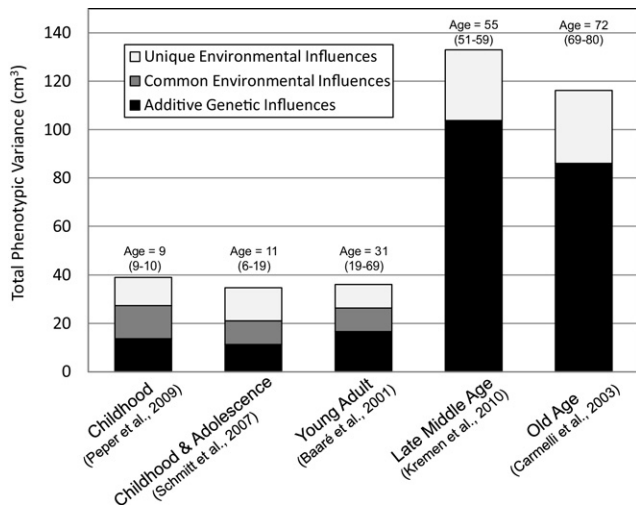


Fig. 1. Variance components of lateral ventricular volume in different child and adult age groups. Total phenotypic (nonstandardized) variances are shown, and are broken down into additive genetic (a), common environmental (c), and unique environmental (e) components. E includes measurement error. The values shown are not adjusted for total brain volume or intracranial volume.

it does not appear that methodological, age, or sex differences can account for the lack of consistency with regard to heritability of lateral ventricular volume. However, our re-consideration of some of these findings has led us to conclude that lateral ventricular volume is heritable and that heritability estimates do increase with increasing age of the studied samples.

2.2. Re-analysis and reinterpretation of some existing data

(Baaré et al. 2001) conducted one of the larger MRI twin studies, and they included non-twin siblings which increases the power of the twin design. In this very well conducted study, the authors found zero heritability for the lateral ventricles. In their Table 3, they reported the following correlations: MZ males = 0.72; MZ females = 0.74; DZ males = 0.52; DZ females = 0.44; DZ opposite sex = 0.53; twin-sibling males = 0.72; twin-sibling females = 0.89; twin-sibling opposite sex = 0.53. These correlations are consistent with what would be expected for a moderately heritable trait with additive genetic influences (MZ correlations higher than, but not more than double, the DZ correlations) except for the twin-sibling correlations for male and female pairs. Surprisingly, the latter are as high, or higher, than the MZ correlations and about 0.20–0.40 higher than the DZ correlations. If lateral ventricular volume is not heritable, one would not expect these correlations to be different from the twin correlations. But, there is no obvious genetic model or other theory to explain why sibling correlations would be meaningfully higher than the DZ twin correlations. In addition, MZ and DZ twin correlations should not differ in magnitude if a trait is not heritable. But

these MZ and DZ correlations do not appear to be similar in magnitude.

Based on the data for the twin participants only, Falconer heritability estimates in the Baaré et al. sample would be approximately 0.40 for men and 0.60 for women. Averaging the two MZ correlations and the three DZ correlations would yield a Falconer heritability estimate of 0.46. Thus, including twins only results in nearly one half of the variance being accounted for by genetic influences, whereas adding in a small number ($n = 34$) of nontwin siblings changes the heritability estimate to zero. The Falconer approach does not provide confidence intervals, but the difference in the MZ and DZ correlations based on (Fisher's 1921) z-prime transformation was highly significant ($z = 2.80$, $p = 0.005$).

In the study of (Chou et al. 2008), an ACE model resulted in nonsignificant heritability of 0.07. This near-zero heritability estimate is surprising given their MZ correlation of 0.50 and DZ correlation of 0.29, which (as the authors noted) suggests moderate heritability. These correlations would yield a Falconer heritability estimate of 0.42. As with the Baaré et al. study, this revised estimate suggests moderate heritability. Owing to the smaller sample size, the difference between the MZ and DZ correlations did not reach statistical significance based on a two-tailed test ($z = 1.61$, $p = 0.11$). Again, the dramatic difference in the two estimates suggests that further inquiry is warranted.

By estimating the data points in Figure 7 of Chou et al. (2008), we calculated very similar correlations ($r_{MZ} = 0.51$ and $r_{DZ} = 0.26$). Our estimates led to essentially the same pattern: a Falconer heritability estimate of 0.50, but a substantially lower ACE model heritability estimate of 0.17. In simulations, we found this type of discrepancy occurred when MZ and DZ variances were different. In the data estimated from the Chou et al. figure, the MZ variance was approximately 1.7 times greater than the DZ variance. With this variance difference, ACE model fits became worse in a clear linear fashion as we sequentially increased the sample sizes. When the samples reached between 60 and 70 twin pairs per group, the ACE model had a significantly poorer fit compared with the fully saturated model. Although it was logical for Chou et al. to accept their ACE model because it had an adequate fit to the data, our reanalysis strongly suggests that the absence of a significant reduction in model fit was due to insufficient power to detect a significant difference in variances between MZ and DZ twins. Such a variance difference violates an assumption of the model (Neale and Cardon, 1992).

In considering power and sample size, we also note that heritability estimates in the smaller studies in Table 1 may be unstable on account of the small sample sizes. Twin studies, in particular, require large samples to obtain reliable heritability estimates (Thompson et al., 2001; Visscher et al., 2008; Visscher, 2004). Elsewhere, we have shown that heritability estimates for brain structure based on several

small samples—each consisting of 10 MZ and 10 DZ pairs—are highly inconsistent (Supplementary Fig. 1 in Rimol et al., 2010). This situation creates difficulties for MRI twin studies because even the largest extant MRI twin studies will lack power for certain analyses. This may seem counterintuitive to many imaging researchers because samples that are extremely large for MRI studies may be considered rather small for the purpose of twin analysis.

2.3. Comparison of phenotypic (nonstandardized) variance components

It is possible for heritability to increase without any change in genetic variance. For example, in a study of reading ability, we found that heritability increased substantially as a function of parental education, but the increasing heritability was due to reductions in common environmental variance with no change in additive genetic variance (Kremen et al., 2005). When variance components are standardized to yield proportions of variance, if one increases another must decrease. Consequently, the only way to see the determinants of differences in heritability is to look at the actual (nonstandardized) amounts of phenotypic variance components. These are shown in Fig. 1 for the large (> 100 twin pairs) samples. These phenotypic variances were based on unadjusted ventricular volumes, but the pattern is the same for the available adjusted results. As can be seen in the figure, the amount of total variance in the middle-aged (132.98 cm³) and older (116.21 cm³) adults is between three and four times greater than that of the children and adolescents (39.01 cm³ [(Peper et al., 2009)]; 35.09 cm³ [(Schmitt et al., 2007b)]) or the younger adults (36.11 cm³ [(Baaré et al., 2001)]). Compared with the child and adolescent samples, the unique environmental variance averaged 2.36 times greater in the middle-aged and older adult samples but the genetic variance averaged 7.70 times greater. Compared with the young (based on mean age) adult sample, the unique environmental variance averaged 3.05 times greater in the middle-aged and older adult samples, and the genetic variance averaged 5.71 times greater. Thus, based on Fig. 1, the most plausible scenario is that increased heritability in middle-aged and older adults is due to increasing genetic influences on lateral ventricular volume with age.

2.4. Summary of results across studies

The original estimates plus our revised Falconer estimates are shown in Table 1. With the exception of the small Wright et al. study, the revised estimates tend to increase with average age in each study from 0.32–0.35 in children and adolescents to 0.74–0.75 in late middle age and older adulthood. The weighted (according to sample size) average heritability of the revised unadjusted estimates for these samples was 0.54. Excluding the computed tomography study changed the weighted average by less than 0.01. The weighted average was 0.17 for common environmental vari-

ance and 0.28 for unique environmental variance. These sum to 0.99 due to a rounding error.

3. Discussion

3.1. Lateral ventricle volume is heritable and its heritability increases with age

Based on these data, including our revised analyses, we conclude that lateral ventricular volume is heritable, and that its heritability does increase with age from childhood to at least late middle age. Figure 1 shows that the total phenotypic variance increases substantially from childhood to middle and older age, but it is a disproportionate increase in genetic variance that primarily accounts for the heritability increase. Figure 1 also suggests that the increase in heritability and in phenotypic variance may level off after late middle age. Consistent with these conclusions, an earlier report based on the cross-sectional child and adolescent sample showed a significant age x heritability interaction for lateral ventricular volume from age 6–19 (Wallace et al., 2006); both genetic and unique environmental variance increased significantly with age, with much larger increases in genetic than in unique environmental variance.

It could be argued that measurement error is greater in children than in adults because the lateral ventricles can be very small and more difficult to measure in children. Greater measurement error would increase the unique environmental variance, thereby reducing heritability in children. However, as shown in Fig. 1, the amount of actual unique environmental variance is greater in midlife and older adults. It also seems highly unlikely that all the E estimates in childhood reflect measurement error.

Our findings and conclusions seem to argue against the “common sense” notion that age-related ventricular enlargement is due to the direct effect of accumulated environmental insults over time. Increasing genetic variance being associated with age-related volume increases of the lateral ventricles might suggest the influence of new genes later in life. In a rare and important longitudinal analysis, Pfefferbaum et al. (2004) found no change in heritability of lateral ventricular volume in a 4 year follow-up of a subset of the sample reported on by Carmelli et al. (2002). A genetic correlation of 1.00 and a unique environmental correlation of 0.91 indicated that no new genes and virtually no new environmental factors were influencing ventricular volume at the follow-up. By contrast, 73% of the variance in change scores over the 4-year period was accounted for by unique environmental factors. Thus, in these older adults, individual differences in ventricular volume at a given point were primarily due to genetic influences, whereas differences in the amount of change over time were largely due to environmental influences. There was also no change in phenotypic variance over this 4-year interval, but other changes in heritability might be observed with a longer time interval. It is possible, for example, that increases in the incidence of

diseases in old-old adults would result in increased environmental variance leading to decreased heritability of lateral ventricle volume. Possible selection bias is also an unavoidable possibility in such a study; these analyses were based on 71 intact pairs from the 139 pairs in the earlier report of (Carmelli et al. 2002).

3.2. Limitations

Our report and reanalyses have some limitations that should be addressed. There were demographic differences in the samples included in our review with some including men only, some with very narrow age ranges, and others with wide age ranges. As such, we cannot be certain as to whether findings would generalize to other populations. Most of the results were based on ventricular volumes that were unadjusted for brain, head, or body size. As such, the heritability estimates might reflect some of the variance contributing to overall brain size. Three studies did report adjusted values, and those are also shown in Table 1. These adjusted values do not alter our overall conclusions, but it would be informative to have both adjusted and unadjusted data in all of the samples. In the child and adolescent sample (Schmitt et al., 2007b), heritability went from 0.32 to 0.17 after adjusting for total brain volume; in our middle-aged Vietnam Era Twin Study of Aging (VETSA) sample heritability, after adjusting for total brain volume, changed minimally from 0.78 to 0.79. Adjusting for either total brain volume or intracranial volume is likely to be very similar in children, but these could produce different results in late middle-aged adults because of expansion of sulcal cerebrospinal fluid. However, adjusting for estimated intracranial volume (which includes sulcal cerebrospinal fluid) in the VETSA sample still resulted in a similar heritability of 0.75 (Kremen et al., 2010). Therefore, the difference between these two samples might reflect the greater influence of developmental factors in the children and adolescents compared with late middle-aged adults.

Log-transformed data were used in some studies but not in others as noted in Table 1. This too may limit comparisons. In the child sample of Peper et al. (2009), heritability was 0.35 based on log-transformed data, but it was 0.00 for the nonlog-transformed measure. The authors suggested that a log transformation might produce multiplicative rather than additive genetic and environmental effects. However, because the non-normally distributed, nontransformed data violate an assumption of the model testing, we chose to focus on the results based on the transformed data. Even if we used the 0.00 heritability estimate for this (the youngest) sample, it would not change our overall conclusions. We also used log-transformed data in the VETSA (Kremen et al., 2010), but the heritability estimate (0.78) was virtually unchanged compared with nontransformed data (0.81). The corresponding numbers for estimates adjusted for age, site and intracranial volume were 0.75 and 0.79.

We also acknowledge that using only the twin data from the twin–sibling study of Baaré et al. (2001), and using Falconer estimates for both the Baaré et al. (2001) and Chou et al. (2008) study could be called into question. However, the highly discrepant patterns that we pointed out in these samples suggest that it is reasonable to consider their overall findings to be mixed. Most importantly, we implemented an alternative approach to the data that is bolstered by the fact that it allowed a coherent and parsimonious explanation of a set of findings that have thus far been inexplicably variable. A statistical test of our hypothesis would require a multigroup collaboration that is beyond the scope of this report, but we do acknowledge that further empirical testing—particularly long-term longitudinal assessments covering a variety of age ranges—will be needed to formally examine the validity of our proposed interpretation of the data. Toward that end, we have begun the first longitudinal follow-up of our late middle-aged VETSA twins.

3.3. Implications

The degree of genetic versus environmental control of lateral ventricular volume is important for the basic understanding of the factors influencing structural brain development, and it may be particularly important with respect to certain neuropsychiatric disorders. For example, in aging-related disorders of cognition such as Alzheimer's disease or mild cognitive impairment, or in psychotic disorders such as schizophrenia, parenchymal shrinkage and ventricular enlargement is common (Fox et al., 2000; Nestor et al., 2008; Wright et al., 2002). Some of the key questions are whether these two processes are determined by the same or different sets of genetic influences, and whether change in one or both is more environmentally determined. The size of brain regions surrounding the ventricles is highly heritable (Kremen et al., 2010; Peper et al., 2007; Schmitt et al., 2007a), but a genetic factor analysis in VETSA participants showed that a ventricular factor was largely genetically independent of other surrounding gray matter structure factors (Eyer et al., in press). In the child and adolescent sample, corpus callosum area was found to be influenced by genetic effects that were largely independent of other structures including the lateral ventricles (Schmitt et al., 2007b). These findings of independent genetic effects on the lateral ventricles combined with the evidence presented for increasing genetic influences on lateral ventricular volume with age argue against the notion that ventricular volume is simply a secondary consequence of age-related parenchymal shrinkage. The findings of Pfefferbaum et al. (2004) suggest that, at least in older adults, stability of lateral ventricular volume is largely due to genetic effects whereas change is largely due to unique environmental effects. Understanding how these processes may change across a longer age span and what specific genes are involved will be important for a full understanding of brain aging.

A closely related issue is the potential usefulness of the

lateral ventricles as an endophenotype, i.e., a genetically-mediated characteristic that is along the pathway between a disorder and genotypes that influence the disorder (Gottesman and Gould, 2003). If the volume of the lateral ventricles is strongly influenced by genes, then it may warrant consideration as an endophenotype. In support of the endophenotype concept, ventricular enlargement does differentiate normal older adults, those with mild cognitive impairment, and those with Alzheimer's disease (Chou et al., 2009; Nestor et al., 2008). Genetic association studies have provided additional evidence for genetic influences on lateral ventricular volume. Neuregulin 1 and catechol-O-methyltransferase polymorphisms have each been associated with lateral ventricular volume in first-episode patients with nonaffective psychoses (Crespo-Facorro et al., 2007; Mata et al., 2009), with neuregulin 1 polymorphisms accounting for 7% of the variance in lateral ventricular volume (Mata et al., 2009). Mata et al. suggested that lateral ventricular enlargement, which is also present in unaffected relatives, might be an endophenotype for schizophrenia. These findings of specific genes being associated with lateral ventricle volume bolster the conclusions of the present analyses, and are consistent with the notion that lateral ventricular enlargement could serve as a morphological brain endophenotype for aging-related neurocognitive disorders as well as other conditions.

Disclosure statement

Anders M. Dale is a founder and holds equity in CorTechs Laboratories, Inc., and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. All other authors state that there are no actual or potential conflicts of interest.

Acknowledgements

This work was supported by National Institute on Aging (AG022381, AG018384, AG018386, AG022982); National Center for Research Resources (P41-RR14075; NCRB Birn Morphometric Project BIRN002); National Institute for Biomedical Imaging and Bioengineering (R01EB006758); National Institute for Neurological Disorders and Stroke (R01 NS052585-01); Mental Illness and Neuroscience Discovery (MIND) Institute, part of the National Alliance for Medical Image Computing (nemic), funded by the National Institutes of Health through the NIH Roadmap for Medical Research Grants U54 EB005149. Additional support was provided by the Autism and Dyslexia Project funded by the Ellison Medical Foundation. The US Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable

assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

References

- Baaré, W.F.C., Hulshoff Pol, H.F., Boomsma, D.I., Posthuma, D., de Geus, E.J.C., Schnack, H.G., van Haren, N.E.M., van Oel, C.J., Kahn, R.S., 2001. Quantitative genetic modeling of variation in human brain morphology. *Cereb. Cortex* 11, 816–824.
- Carmelli, D., Swan, G.E., DeCarli, C., Reed, T., 2002. Quantitative genetic modeling of regional brain volumes and cognitive performance in older male twins. *Biol. Psychol.* 61, 139–155.
- Chou, Y.Y., Lepore, N., Avedissian, C., Madsen, S.K., Parikshak, N., Hua, X., Shaw, L.M., Trojanowski, J.Q., Weiner, M.W., Toga, A.W., Thompson, P.M., 2009. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *Neuroimage* 46, 394–410.
- Chou, Y.Y., Lepore, N., Chiang, M.C., Avedissian, C., Barysheva, M., McMahon, K.L., de Zubicaray, G.I., Meredith, M., Wright, M.J., Toga, A.W., Thompson, P.M., 2008. Mapping genetic influences on ventricular structure in twins. *Neuroimage* 44, 1312–1323.
- Crespo-Facorro, B., Roiz-Santianez, R., Pelayo-Teran, J.M., Perez-Iglesias, R., Carrasco-Marin, E., Mata, I., Gonzalez-Mandly, A., Jorge, R., Vazquez-Barquero, J.L., 2007. Low-activity allele of Catechol-O-Methyltransferase (COMT) is associated with increased lateral ventricles in patients with first episode non-affective psychosis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 1514–1518.
- Eaves, L.J., Last, K.A., Young, P.A., Martin, N.G., 1978. Model-fitting approaches to the analysis of human behavior. *Heredity* 41, 249–320.
- Eyler, L.T., Prom-Wormley, E., Fennema-Notestine, C., Panizzon, M.S., Neale, M.C., Jernigan, T.L., Fischl, B., Franz, C.E., Lyons, M.J., Stevens, A., Pacheco, J., Perry, M.E., Schmitt, J.E., Spitzer, N.C., Seidman, L.J., Thermenos, H.W., Tsuang, M.T., Dale, A.M., Kremen, W.S., in press. Genetic Patterns of Correlation Among Subcortical Volumes in Humans: Results From a Magnetic Resonance Imaging Twin Study. *Brain, Hum Mapp.*
- Falconer, D.S., 1960. *Introduction to Quantitative Genetics*. Ronald Publishing, New York.
- Fisher, R.A., 1921. On the probable error of a coefficient of correlation deduced from a small sample. *Metron* 1, 3–32.
- Fox, N.C., Cousins, S., Schill, R., Harvey, R.J., Rossor, M.N., 2000. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: Power calculations and estimates of sample size to detect treatment effects. *Arch. Neurol.* 57, 339–344.
- Glahn, D.C., Thompson, P.M., Blangero, J., 2007. Neuroimaging endophenotypes: Strategies for finding genes influencing brain structure and function. *Hum. Brain Mapp.* 28, 488–501.
- Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am. J. Psychiatry* 160, 636–645.
- Kendler, K.S., Neale, M.C., 2009. "Familiality" or heritability (letter to the editor). *Arch. Gen. Psychiatry* 66, 452–453.

- Kremen, W.S., Jacobson, K.C., Xian, H., Eisen, S.A., Waterman, B., Toomey, R., Neale, M.C., Tsuang, M.T., Lyons, M.J., 2005. Heritability of word recognition in middle-aged men varies as a function of parental education. *Behav. Genet.* 35, 417–433.
- Kremen, W.S., Prom-Wormley, E., Panizzon, M.S., Eyer, L.T., Fischl, B., Neale, M.C., Franz, C.E., Lyons, M.J., Pacheco, J., Perry, M.E., Stevens, A., Schmitt, J.E., Grant, M.D., Seidman, L.J., Thermenos, H.W., Tsuang, M.T., Eisen, S.A., Dale, A.M., Fennema-Notestine, C., 2010. Genetic and environmental influences on the size of specific brain regions in midlife: The VETSA MRI study. *Neuroimage* 49, 1213–1223.
- Mata, I., Perez-Iglesias, R., Roiz-Santianez, R., Tordesillas-Gutierrez, D., Gonzalez-Mandly, A., Vazquez-Barquero, J.L., Crespo-Facorro, B., 2009. A neuregulin 1 variant is associated with increased lateral ventricle volume in patients with first-episode schizophrenia. *Biol. Psychiatry* 65, 535–540.
- Neale, M.C., Boker, S.M., Xie, G., Maes, H.H., 2003. *Mx: Statistical Modeling*, 6th Ed. Department of Psychiatry, Medical College of Virginia, Richmond, VA.
- Neale, M.C., Cardon, L.R., 1992. *Methodology for Genetic Studies of Twins and Families*. Kluwer Academic, Dordrecht, the Netherlands.
- Nestor, S.M., Rupsingh, R., Borrie, M., Smith, M., Accomazzi, V., Wells, J.L., Fogarty, J., Bartha, R., 2008. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain* 131, 2443–2454.
- Østby, Y., Tamnes, C.K., Fjell, A.M., Westlye, L.T., Due-Tønnessen, P., Walhovd, K.B., 2009. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *J. Neurosci.* 29, 11772–11782.
- Peper, J.S., Brouwer, R.M., Boomsma, D.I., Kahn, R.S., Hulshoff Pol, H.E., 2007. Genetic influences on human brain structure: A review of brain imaging studies in twins. *Hum. Brain Mapp.* 28, 464–473.
- Peper, J.S., Schnack, H.G., Brouwer, R.M., Van Baal, G.C., Pjetri, E., Szekely, E., van Leeuwen, M., van den Berg, S.M., Collins, D.L., Evans, A.C., Boomsma, D.I., Kahn, R.S., Hulshoff Pol, H.E., 2009. Heritability of regional and global brain structure at the onset of puberty: a magnetic resonance imaging study in 9-year-old twin pairs. *Hum. Brain Mapp.* 30, 2184–2196.
- Pfefferbaum, A., Sullivan, E.V., Carmelli, D., 2004. Morphological changes in aging brain structures are differentially affected by time-linked environmental influences despite strong genetic stability. *Neurobiol. Aging* 25, 175–183.
- Reveley, A.M., Reveley, M.A., Chitkara, B., Clifford, C., 1984. The genetic basis of cerebral ventricular volume. *Psychiatry Res.* 13, 261–266.
- Rimol, L.M., Panizzon, M.S., Fennema-Notestine, C., Eyer, L.T., Fischl, B., Franz, C.E., Hagler, D.J., Lyons, M.J., Neale, M.C., Pacheco, J., Perry, M.E., Schmitt, J.E., Grant, M.D., Seidman, L.J., Thermenos, H.W., Tsuang, M.T., Eisen, S.A., Kremen, W.S., Dale, A.M., 2010. Cortical thickness is influenced by regionally-specific genetic factors. *Biol. Psychiatry* 67, 493–499.
- Schmitt, J.E., Eyer, L.T., Giedd, J.N., Kremen, W.S., Kendler, K.S., Neale, M.C., 2007a. Review of twin and family studies on neuroanatomic phenotypes and typical neurodevelopment. *Twin Res. Hum. Genet.* 10, 683–694.
- Schmitt, J.E., Wallace, G.L., Rosenthal, M.A., Molloy, E.A., Ordaz, S., Lenroot, R., Clasen, L.S., Blumenthal, J.D., Kendler, K.S., Neale, M.C., Giedd, J.N., 2007b. A multivariate analysis of neuroanatomic relationships in a genetically informative pediatric sample. *Neuroimage* 35, 70–82.
- Thompson, P.M., Cannon, T.D., Narr, K.L., van Erp, T., Poutanen, V.P., Huttunen, M., Lonnqvist, J., Standertskjold-Nordenstam, C.G., Kaprio, J., Khaledy, M., Dail, R., Zoumalan, C.I., Toga, A.W., 2001. Genetic influences on brain structure. *Nat. Neurosci.* 4, 1253–1258.
- Visscher, P.M., 2004. Power of the classical twin design revisited. *Twin Res.* 7, 505–512.
- Visscher, P.M., Gordon, S., Neale, M.C., 2008. Power of the classical twin design revisited: II detection of common environmental variance. *Twin Res. Hum. Genet.* 11, 48–54.
- Wallace, G.L., Schmitt, J.E., Lenroot, R., Viding, E., Ordaz, S., Rosenthal, M.A., Molloy, E.A., Clasen, L.S., Kendler, K.S., Neale, M.C., Giedd, J.N., 2006. A pediatric twin study of brain morphometry. *J. Child Psych. Psychiatry* 47, 987–993.
- Wright, I.C., Sham, P., Murray, R.M., Weinberger, D.R., Bullmore, E.T., 2002. Genetic contributions to regional variability in human brain structure: Methods and preliminary results. *Neuroimage* 17, 256–271.