

A pediatric twin study of brain morphometry

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Background: Longitudinal pediatric neuroimaging studies have demonstrated increasing volumes of white matter and regionally-specific inverted U shaped developmental trajectories of gray matter volumes during childhood and adolescence. Studies of monozygotic and dizygotic twins during this developmental period allow exploration of genetic and non-genetic influences on these developmental trajectories. **Method:** Magnetic resonance imaging brain scans were acquired on a pediatric sample of 90 monozygotic twin pairs, 38 same-sex dizygotic twin pairs, and 158 unrelated typically developing singletons. Structural equation modeling was used to estimate the additive genetic, common environment, and unique environment effects, as well as age by heritability interactions, on measures of brain volumes from these images. **Results:** Consistent with previous adult studies, additive genetic effects accounted for a substantial portion of variability in nearly all brain regions with the notable exception of the cerebellum. Significant age by heritability interactions were observed with gray matter volumes showing a reduction in heritability with increasing age, while white matter volume heritability increased with greater age. **Conclusion:** Understanding the relative contributions of genetic and nongenetic factors on developmental brain trajectories may have implications for better understanding brain-based disorders and typical cognitive development. **Keywords:** Brain development, brain imaging, pediatric, twin, behavioral genetics.

Magnetic resonance imaging (MRI), with its lack of ionizing radiation and capacity to provide exquisitely accurate details of *in vivo* brain anatomy, has become a valuable tool for investigating the neurobiological basis of psychiatric disorders. The safety and feasibility of MRI have also allowed for longitudinal studies of children and adolescents and the mapping of changes in brain anatomy during development. A logical scientific progression from characterizing the paths of development in health and illness is to begin to discern what potential factors may influence these trajectories, for good or ill. Studies of monozygotic (MZ) and dizygotic (DZ) twins are useful to explore the relative contributions and interactions of genetic and nongenetic parameters associated with these factors.

Imaging studies of adult twins have found genetic factors to account for 66–90% of total cerebral volume (Baare et al., 2001; Bartley, Jones, & Weinberger, 1997; Carmelli et al., 1998; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000; Wright, Sham, Murray, Weinberger, & Bullmore, 2002) and similarly high heritabilities are reported for individual gray and white matter volumes (Baare et al., 2001; Posthuma et al., 2003), as well as mid-sagittal corpus callosum area (Pfefferbaum et al., 2000; Scavougeras, Kigar, Jones, Weinberger, & Witelson, 2003). A single pediatric study of 34 MZ and 32 DZ pairs (some with and some without reading dis-

ability) reported similar heritability of brain morphometric measures (Pennington et al., 2000).

Of growing interest is whether the relative contributions of genetic and nongenetic factors change over the course of development, a phenomenon that may be linked to the timing of gene expression and related to the age of onset of various neuropsychiatric disorders and to cognitive development more broadly.

In this study, we examine heritability estimates of regionally specific gray and white matter brain structures during childhood and adolescence, and investigate age by heritability interactions for each of these brain regions.

Methods

Subjects

The twins and singletons were recruited as part of an ongoing longitudinal brain imaging project being conducted at the Child Psychiatry Branch of the National Institute of Mental Health. Parents of prospective participants were interviewed by phone and asked to report their child's health, developmental and educational history. Subjects were excluded if they had ever required special services in school, taken psychiatric medications, received mental health treatment, or had any other trauma or condition known to affect gross brain development. Inclusion criteria included a minimum gestational age of 29 weeks and a minimum birth weight of 1500 grams for both members of each twin

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pair. Approximately 80% of families responding to the ads met inclusion criteria. During their visit to the National Institutes of Health (NIH), subjects underwent a clinical interview, a physical examination, and neuropsychological testing, including assessment of general intellectual functioning. All participants scored greater than 70 on measures of IQ, which included the Wechsler Abbreviated Scales of Intelligence and estimated scores derived from the vocabulary and block design subtests of the Wechsler Intelligence Scales for Children and the Wechsler Adult Intelligence Scales. We obtained verbal or written assent from the child and written consent from the parents for their participation in the study. The National Institute of Mental Health Institutional Review Board approved the protocol.

One hundred twenty-seven pairs of typically developing same-sex twins (mean age = 11.6, SD = 3.3; age range = 5.6–18.7; 74 male pairs [58%], 53 female pairs) and 158 unrelated typically developing singletons (mean age = 11.3, SD = 3.5; age range = 5.2–18.7; 94 males [59%], 64 females) underwent MRI scans. Of the 127 twin pairs, 90 [71%] were MZ (mean age = 11.9, SD = 3.0; age range = 5.8–18.7; 52 male pairs [58%], 38 female pairs), and 37 were DZ (mean age = 10.9, SD = 3.7; age range = 5.6–18.2; 22 male pairs [59%], 15 female pairs). Zygosity was determined by DNA analysis of buccal cheek swabs using 9–21 unlinked short tandem repeat loci for a minimum certainty of 99%, by BRT Laboratories, Inc. (Baltimore, MD).

MRI acquisition

All images were acquired on the same General Electric 1.5 Tesla Signa Scanner located at the NIH Clinical Center in Bethesda, Maryland. A three-dimensional spoiled gradient recalled echo sequence in the steady state sequence, designed to optimize discrimination between gray matter, white matter and CSF, was used to acquire 124 contiguous 1.5 mm thick slices in the axial plane (TE/TR = 5/24; flip angle = 45 degrees, matrix = 256 × 192, NEX = 1, FOV = 24 cm, acquisition time 9.9 min). A Fast Spin Echo/Proton Density weighted imaging sequence was also acquired for clinical evaluation.

Image analysis

The native MRI scans were registered into standardized stereotaxic space using a linear transformation (Collins, Neelin, Peters, & Evans, 1994) and corrected for non-uniformity artifacts (Sled, Zijdenbos, & Evans, 1998). The registered and corrected volumes were segmented into white matter, gray matter, cerebro-spinal fluid and background using a neural net classifier (Zijdenbos, Forghani, & Evans, 2002). The tissue classification information was combined with a probabilistic atlas to provide region of interest measures (Collins, Holmes, Peters, & Evans, 1995). The output measures of this process that have shown high agreement with conventional hand tracing measures, and were included in this analysis, are the midsagittal area of the corpus callosum, the gray and white matter volumes of the total cerebrum, frontal, temporal, and parietal lobes, the caudate nucleus, the cerebellum, and the lateral ventricles.

Statistical analysis

Because MZ twins share 100% of their polymorphic genes and DZ twins share approximately 50% of their polymorphic genes, a comparison of MZ and DZ concordance rates allows estimation of the extent to which variance in a trait, like brain morphometry, is genetically mediated (Neale & Cardon, 1992). Since the role of the shared environment is not expected to differ significantly between MZ and DZ groups with respect to the phenotypes of interest, the expected variance and covariances for an observed variable can be written:

$$\text{Var}_T = a^2 + c^2 + e^2$$

$$\text{Cov}_{MZ} = a^2 + c^2$$

$$\text{Cov}_{DZ} = 1/2a^2 + c^2$$

where a^2 is genetic variance, c^2 is shared (i.e., familial) environmental variance, e^2 is unique (i.e., individual specific) environmental variance, and Var_T represents the total observed phenotypic variance. These simultaneous equations can easily be solved for each individual variance component; $a^2 = 2 * (\text{Cov}_{MZ} - \text{Cov}_{DZ})$, $c^2 = (2 * \text{Cov}_{DZ}) - \text{Cov}_{MZ}$, and $e^2 = \text{Var}_T - a^2 - c^2$ (Falconer estimation). Of particular interest is a^2 , since it represents the broad sense heritability, i.e., the proportion of the phenotypic variance attributable to additive genetic effects.

For all regions of interest, we calculated cross-twin correlations for both MZ and DZ, which provide descriptive evidence of genetic influences on phenotypes when MZ correlations are significantly larger than DZ correlations. Additionally, we split the group into younger and older age groups based on median age (11.36) and recalculated cross-twin correlations for all structures, which provide preliminary information on changes in heritability with age.

More sophisticated methods to quantify genetic and non-genetic influences combine structural equation modeling (SEM) and path analysis to provide estimates of the latent influences of additive genetic (A), common environmental (C), and unique environmental (including measurement error) (E) effects on observed phenotypes (Figure 1a). The paths between latent variables and the observed phenotype (a, c, and e) are analogous to partial regression coefficients in a multiple regression (i.e., beta weights). Expected covariances for these models can be derived from the rules of path analysis (Loehlin, 1998). SEM approaches offer numerous advantages over Falconer estimation, including flexibility in testing a variety of hypotheses, allowing for more explicit testing of the significance of parameters, the lack of nonsensical parameter estimates (such as variance component proportions greater than one or less than zero), the ability to include data from singletons to improve precision in total variance estimates, and simultaneous regression of phenotypic means on other observed variables (Neale & Cardon, 1992; Loehlin, 1998). Further, with the addition of individual-specific moderator variables, the standard ACE model can be expanded to account for interactions between A, C, and E with a second observed variable, such as age (Purcell, 2002). This expanded model design is shown in Figure 1b, in which the

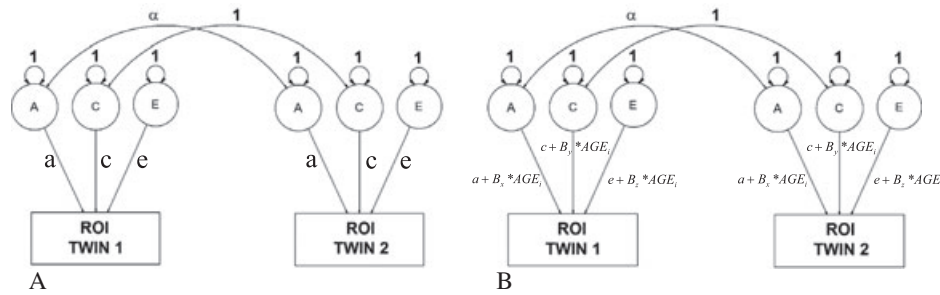


Figure 1 Graphical representation of structural equation modeling with genetically informative data. Latent variables are denoted by circles, while observed variables are shown as squares. In a twin paradigm, three latent variables are identified, denoted A (additive genetic), C (shared environment), and E (unique environment). Causal paths are denoted as single-headed arrows, while correlations are shown with double-headed arrows (a double-headed arrow to the same variable denotes a variance). Figure 1a represents a classical ACE model. Figure 1b shows a modified model allowing for age interactions with each variance component (with interaction parameters $\beta_X, \beta_Y,$ and $\beta_Z,$ representing age interaction with genetic, shared environmental, and unique environmental variance, respectively). α represents the genetic correlation between twin pairs; equal to unity in MZ pairs and .5 in DZ pairs

strength of the latent variables on phenotype is linearly modulated by age.

Modified univariate ACE twin models were constructed in Mx, a SEM software package that combines a matrix algebra interpreter with optimization capability (*Mx: Statistical Modeling: Version 5th edition*. Richmond, VA: Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, 1999). The effect of age and sex on mean phenotypic values was simultaneously modeled. Using maximum likelihood optimization (Edwards, 1972), the best-fit model for each neuroanatomic region was identified. From these maximum likelihood parameters, we calculated broad sense heritability estimates (i.e., the proportion of the variance due to genetic effects) for each structure and corresponding likelihood-based 95% confidence intervals (Neale & Miller, 1997). Both classical ACE models and age-moderated model parameter estimates (using mean age to generate a single population statistic) produced comparable heritability estimates and confidence intervals. Additionally, because the difference in maximum likelihood between any model and a nested submodel follows a χ^2 distribution with degrees of freedom equal to the difference in the number of parameters between models, we were able to directly test the statistical significance of genetic and shared environmental effects and heritability \times age interactions by removing the interaction parameters and comparing model fit. Though several tests were performed, given the correlated nature of the data and the modest sample sizes, we used an α of .05 as the threshold for statistical significance.

Results

Descriptive statistics

Cross-twin correlations are reported in Table 1. Correlations for most structures were quite high, suggesting strong familial correlations for brain volumes. MZ correlations were substantially higher

Table 1 Cross-twin correlations for neuroanatomic regions of interest. Correlations for monozygotic (MZ) and dizygotic (DZ) twin pairs are given, as are correlations in these groups after splitting them into younger (Y) and older (O) age groups

	MZ	DZ	MZY	DZY	MZO	DZO
Total cerebrum	.91	.44	.89	.58	.91	.21
Total gray matter	.84	.41	.81	.56	.86	.22
Total white matter	.91	.53	.82	.43	.92	.53
Frontal gray matter	.82	.46	.77	.55	.84	.43
Frontal white matter	.90	.47	.79	.31	.91	.44
Total frontal lobe	.89	.45	.84	.51	.90	.37
Parietal gray matter	.80	.29	.80	.45	.80	.07
Parietal white matter	.90	.46	.83	.39	.91	.45
Total parietal	.88	.30	.86	.45	.87	.16
Temporal gray matter	.83	.45	.74	.62	.86	.23
Temporal white matter	.91	.65	.80	.62	.93	.60
Total temporal	.92	.53	.87	.65	.92	.34
Caudate nucleus	.83	.39	.72	.42	.88	.38
Corpus callosum	.84	.32	.90	.37	.76	.20
Lateral ventricles	.68	.40	.65	.66	.69	-.14
Cerebellum	.86	.73	.86	.81	.83	.41

than DZ correlations and were often close to being twice as large, indicating that familial correlations are produced predominantly by genetic effects rather than shared environmental sources. In general, the difference between MZ and DZ correlations was greater in the older subgroups after splitting by age. These estimates, however, are limited by small sample sizes of the subgroups.

AIC/E models

As indicated in Table 2, the heritability for total cerebrum and lobar volumes (including gray and white matter subcompartments) ranged from .77 to .88, with virtually none of the variance attributable to shared environmental effects. Similarly, heritability for our subcortical gray matter structure, the caudate nucleus, volume was .80. Although confid-

Table 2 Heritability estimates for identified brain regions, based on maximum likelihood optimization of the full age moderated model. a^2 , c^2 , and e^2 represent the proportion of the variance in volume due to genetic, shared environmental, and unique environmental sources, respectively. Additionally, Chi-squared tests of the significance of genetic (A) and shared environmental (C) variance components were performed by comparing the fit of models with and without their corresponding parameters, and are provided on the right. Since the unique environment includes a contribution from measurement error, it cannot be removed from the model. Heritability estimates of these full models (i.e., including interactions) were virtually identical to traditional ACE models (not shown)

Structure	a^2	c^2	e^2	A		C	
				χ^2	p	χ^2	p
Total cerebral	.89 (.67 .92)	.00 (.00 .22)	.11 (.08 .16)	51.5	<.0001	.0	1.0000
Total gray matter	.82 (.50 .87)	.00 (.00 .31)	.18 (.13 .26)	26.2	<.0001	.0	1.0000
Total white matter	.85 (.56 .90)	.01 (.00 .28)	.15 (.10 .22)	35.6	<.0001	.0	1.0000
Frontal gray matter	.77 (.36 .83)	.00 (.00 .38)	.23 (.17 .32)	16.5	.0003	.0	1.0000
Frontal white matter	.84 (.52 .89)	.00 (.00 .31)	.16 (.11 .23)	34.3	<.0001	.0	1.0000
Total frontal	.84 (.56 .89)	.00 (.00 .27)	.16 (.11 .23)	34.2	<.0001	.0	1.0000
Parietal gray matter	.78 (.41 .86)	.02 (.00 .37)	.20 (.14 .29)	20.2	<.0001	.0	.9915
Parietal white matter	.85 (.63 .90)	.00 (.00 .22)	.15 (.10 .22)	39.6	<.0001	.2	.8900
Total parietal	.86 (.62 .90)	.00 (.00 .24)	.14 (.10 .20)	39.9	<.0001	.0	1.0000
Temporal gray matter	.80 (.45 .86)	.00 (.00 .34)	.20 (.14 .28)	22.1	<.0001	.0	1.0000
Temporal white matter	.82 (.40 .89)	.02 (.00 .44)	.16 (.11 .23)	27.9	<.0001	.0	.9965
Total temporal	.88 (.60 .91)	.00 (.00 .27)	.12 (.09 .17)	44.3	<.0001	.0	1.0000
Caudate Nucleus	.80 (.56 .85)	.00 (.00 .22)	.20 (.15 .29)	28.7	<.0001	.0	1.0000
Corpus callosum	.85 (.41 .89)	.00 (.00 .43)	.15 (.11 .22)	26.9	<.0001	.0	1.0000
Lateral ventricles	.31 (.00 .67)	.24 (.00 .58)	.45 (.33 .60)	9.5	.0088	6.5	.0379
Total cerebellum	.49 (.13 .83)	.30 (.00 .64)	.21 (.16 .29)	8.9	.0118	1.6	.4532

Brackets indicate 95% confidence intervals.

ence intervals overlap widely, cerebral white matter regions appeared to have slightly higher a^2 values when compared to their gray matter counterparts; consistent with this finding, a strong genetic influence on corpus callosum area was also observed ($a^2 = .85$).

Direct hypothesis testing using submodels found that genetic contributions were highly statistically significant (see Table 2) and shared environment effects were not significant for any of the regions (χ^2 range .0–1.6, p -value range 1.0–.45) except the lateral ventricles ($\chi^2 = 6.5$, $p = .0379$).

Lateral ventricular volume measures are qualitatively different than the other brain region measures in that the ventricles are fluid filled cavities and their size and shape are largely determined by a multitude of neighboring tissue structures. Lateral ventricular volume measures tend to have different distributions than solid tissue measures and have the highest coefficient of variation of any of our brain measures (Lange, Giedd, Castellanos, Vaituzis, & Rapoport, 1997). The heritability pattern for lateral ventricular measures was also different from the gray and white matter tissue measures in that its variance was divided approximately equally among a^2 , c^2 , and e^2 .

The most clearly distinctive heritability pattern of any structure we examined was for the cerebellum with an additive genetic effect of .49. Unlike the lateral ventricles, the distinctiveness of cerebellum heritability cannot be attributed to solid/fluid differences or to figure/ground issues with neighboring structures.

Age \times heritability interactions

Total variance attributable to both additive genetic and unique environmental factors increased with age, though the proportion of that increased variance attributable to genetic or non-genetic factors differed between structures. Specifically, for white matter additive genetic effects account for a greater proportion of the variance with increasing age, whereas for gray matter unique environment effects account for a greater proportion of the variance with increasing age (see Figures 2 and 3).

To test the statistical significance of age \times heritability interactions a likelihood-ratio chi-square test was used to assess how well the model, which includes age by A/C/E interactions, fits the data, as compared to a model that does not include the age interactions.

As seen in Table 3, for total WM the A*age interaction was significant ($\chi^2 = 4.7$, $p = .03$) whereas the E*age interaction was not ($\chi^2 = .6$, $p = .44$). For total GM the E*age interaction was significant ($\chi^2 = 5.4$, $p = .02$), whereas the A*age interaction was not ($\chi^2 = 1.9$, $p = .16$). GM and WM lobar divisions generally followed this pattern, with all WM subdivisions having significant A*age effects and Frontal GM and Temporal GM having significant E*age effects (parietal GM did not have significant A*age or E*age effects).

The caudate nucleus did not follow the same pattern as the cortical GM structures in that almost all of its increased variance was driven by A*age. The corpus callosum area variance did not

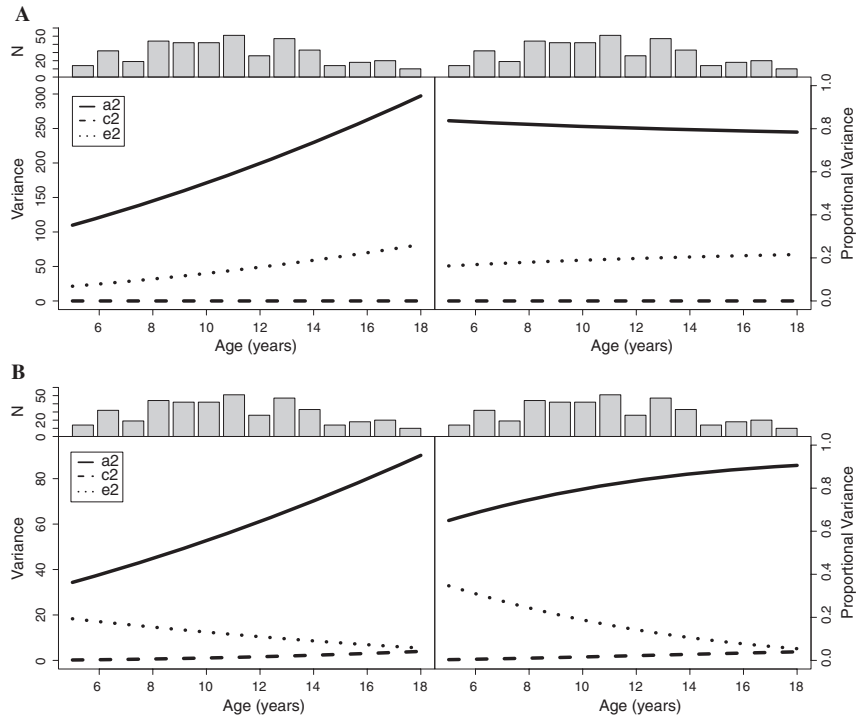


Figure 2 The total and proportion of variance in temporal lobe volume attributed to A, C, and E by age for 128 twin pairs (98 MZ, 38 DZ). Temporal lobe GM (A) heritability in the graph on the right decreases with increasing age whereas temporal lobe WM (B) heritability increases

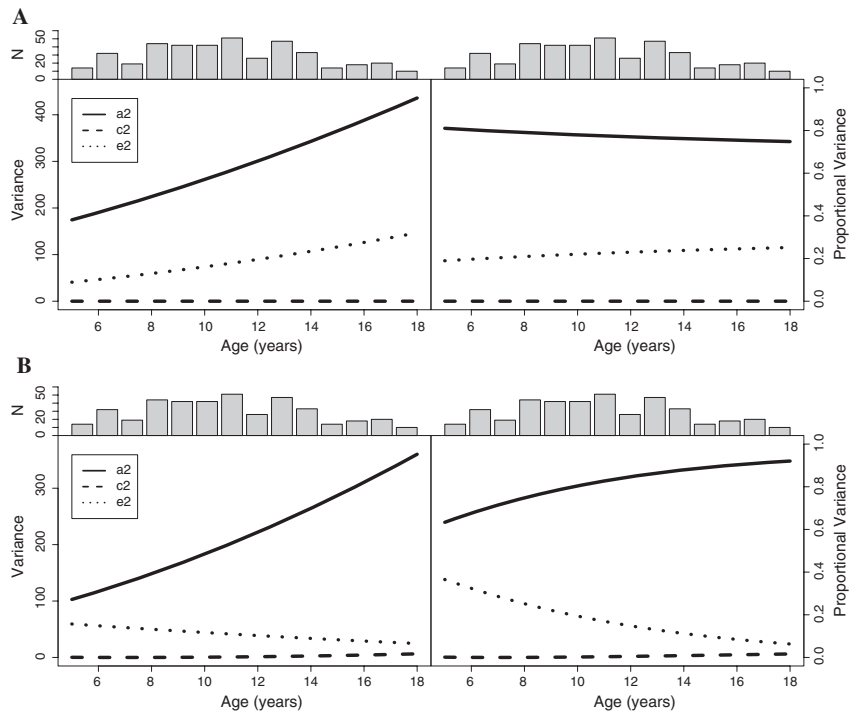


Figure 3 The total and proportion of variance in frontal lobe volume attributed to A, C, and E by age for 128 twin pairs (98 MZ, 38 DZ). Frontal lobe GM (A) heritability decreases with increasing age whereas frontal lobe WM (B) heritability increases

significantly increase with age and neither A*age nor E*age effects were significant. Lateral ventricular volume showed the greatest increase in variance with age, with strong contributions from both

A*age and E*age. The cerebellum volume variance showed the least change with age ($\chi^2 = 1.5, p = .68$) and neither the A*age or E*age terms were significant.

Table 3 Age \times heritability interactions for indicated brain morphometric measures. For each structure, maximum likelihood estimates for the variance components of full ACE- $\beta_x\beta_y\beta_z$ models are given. Chi-squared tests of age invariance (i.e., heteroscedasticity) were performed by removing all age interaction parameters (i.e., β_x , β_y , and β_z) simultaneously from the full model. Tests of gene by age and (unique) environment by age interactions were performed on models in which nonsignificant shared environment interaction parameters were removed

	Parameter estimates						Age invariance ¹		Gene * age		Environment * age	
	a	c	e	β_x	β_y	β_z	χ^2_3	p	χ^2_1	p	χ^2_1	p
Total cerebrum	58.54	.01	20.82	2.43	.00	.85	6.9	.0752	4.0	.0447	1.14	.2857
Total gray matter	41.09	.01	10.11	1.27	.01	1.41	11.0	.0119	1.9	.1648	5.43	.0198
Total white matter	24.44	8.20	18.32	1.10	-.98	-.25	4.7	.1927	4.7	.0307	.6	.4386
Frontal gray matter	10.26	.01	4.19	.59	.01	.44	14.8	.0020	4.2	.0398	4.35	.0370
Frontal white matter	6.74	1.61	8.75	.68	-.23	-.21	9.6	.0223	9.4	.0022	2.13	.1444
Total frontal	14.59	.19	11.29	1.24	-.20	.11	10.9	.0124	8.4	.0037	.11	.7401
Parietal gray matter	6.46	3.56	2.86	.28	-.17	.18	8.1	.0446	2.2	.1362	2.56	.1096
Parietal white matter	4.99	4.97	3.04	.24	-.48	.02	6.2	.1014	5.0	.0248	.07	.7913
Total parietal	10.36	1.62	4.57	.51	-.11	.17	8.5	.0362	4.8	.0286	1.02	.3125
Temporal gray matter	7.88	.01	2.92	.52	.00	.34	14.6	.0022	5.0	.0251	3.91	.0480
Temporal white matter	4.46	.17	5.03	.28	-.12	-.15	8.5	.0366	6.5	.0110	4.11	.0426
Total temporal	11.35	.01	4.74	.74	.00	.23	11.0	.0117	6.9	.0086	1.59	.2073
Caudate nucleus	.31	.00	.48	.05	.00	.00	10.1	.0177	9.3	.0023	.17	.6801
Corpus callosum	76.28	.01	17.49	-1.05	.01	.86	3.6	.3131	1.2	.2674	2.99	.0838
Lateral ventricles	5.43	3.54	1.28	-.71	-.09	.18	50.7	<.0001	11.4	.0007	6.91	.0086
Total cerebellum	7.86	6.58	3.20	-.11	-.12	.10	1.5	.6800	1.1	.3055	.95	.3297

Discussion

These data are the first reported from a large-scale pediatric neuroimaging twin study and demonstrate (1) A/C/E modeling data for pediatric brain morphometry with relatively high additive genetics effects for most structures; (2) age \times heritability interactions with additive genetic effects accounting for more of the proportion of variance in WM and less of the proportion of variance in GM with increasing age; and (3) a distinct pattern of heritability and age \times heritability for the cerebellum.

Age \times heritability interactions may be particularly relevant to investigations of gene, brain, and behavior relationships; however, we are unaware of other brain imaging studies that have addressed this issue. Increasing environmental effect on GM volumes is consistent with the notion of plastic synapses changing in response to activity. Speculatively, it would be interesting to assess whether the increasing heritability of WM volumes is related to increasing heritability with age reported by other investigators for phenotypic traits such as IQ (McCleary et al., 1997).

Many highly heritable neuropsychiatric disorders, notably those involving mood, anxiety, or psychosis, have peak age of onset during adolescence. A possibility to partially account for this phenomenon is age-dependent activation or expression of genes relevant to the disorders interacting with other maturational processes or environmental stressors to unleash the illness. Knowledge of when certain brain structures are particularly sensitive to genetic or environmental influences during development could also have important educational and/or therapeutic implications.

Although the wide confidence intervals merit cautious interpretation, the cerebellum is noteworthy as the structure with the lowest additive genetic effect. The unique developmental pattern of the cerebellum is further fortified by it being the most sexually dimorphic macroscopic brain structure during pediatric development and amongst the latest to reach peak volume (Lenroot et al., 2005). The potential for relatively strong environmental influences on cerebellar development is consistent with its preferential susceptibility to insults such as alcohol, lead, or anoxia and its role in modulating responses to environmental stimuli. The post-natal neurogenesis of cerebellar Purkinje cells may also confer susceptibility to environmental insult (Welsh et al., 2002), although the relationship between this process and volumetric changes remains to be elucidated.

Unlike the similarly high additive genetic effects for large brain regions reported in most adult twin studies, our pediatric cerebellar A/C/E findings are in contrast to those of an adult extended design (siblings of twins included) twin study of 256 family members from 111 twin families (Posthuma et al., 2000). In the adult study, cerebellar size was found to be highly heritable, driven by a low correlation among 17 DZ male twin pairs ($r = -.06$). This correlation, which was lower than that for opposite-sex siblings ($N = 21$, $r = .27$), was mainly due to two DZ male twin pairs with large intrapair differences. The correlations for MZ male twin pairs ($N = 32$, $r = .85$) and for MZ and DZ female twin pairs were similar to those in our pediatric study. Despite these methodologic issues, the pediatric specificity of the cerebellar findings are somewhat supported by a study of MZ twin pairs discordant for the narrow autism phenotype. Cerebral structures, regardless of tissue type, exhibited high intra-

class correlations, while the cerebellar region did not (Kates et al., 2004). Although the authors argue that relatively low cerebellar heritability may be autism specific, our findings indicate that it may instead be related to the use of a pediatric sample.

Studies of twins are an important approach to help discern influences on developmental brain trajectories in health and illness. Highly heritable brain morphometric measures provide biological markers for inherited traits, and may serve as targets for genetic linkage and association studies. These intermediate phenotypes may better serve to identify and inform gene-behavior relationships. A greater understanding of the forces which guide brain development will help provide a heuristic for developing and implementing more effective interventions in the treatment of brain-based disorders.

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