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A Bivariate Twin Study of Regional Brain Volumes and Verbal and Nonverbal Intellectual Skills During Childhood and Adolescence

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Abstract

Twin studies indicate that both intelligence and brain structure are moderately to highly heritable. Recent bivariate studies of adult twins also suggest that intelligence and brain morphometry are influenced by shared genetic factors. The current study examines shared genetic and environmental factors between brain morphometry and intelligence in a sample of children and adolescents (twins, twin siblings, and singletons; n = 649, ages 4–19). To extend previous studies, brain morphometric data were parsed into subregions (lobar gray/white matter volumes, caudate nucleus, lateral ventricles) and intelligence into verbal and nonverbal skills (Wechsler Vocabulary and Block Design subtests). Phenotypic relationships between brain volumes and intelligence were small. Verbal skills shared unique environmental effects with gray matter volumes while nonverbal skills shared genetic effects with both global and regional gray and white matter. These results suggest that distinct mechanisms contribute to the small phenotypic relationships between brain volumes and verbal versus nonverbal intelligence.

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Keywords

Twin; Magnetic resonance imaging; Brain; Intelligence; Verbal; Nonverbal

Introduction

Research investigating the genetic contributions to individual differences in intellectual ability dates to the mid-nineteenth century and Galton's (1869) famous study of the heredity of “genius” (Plomin et al. 1997a). Numerous twin, adoption and molecular genetic studies currently are focused on the genetic and environmental contributions to variation in intelligence and its neuroanatomic underpinnings, but few have utilized bivariate methods to identify shared and unique influences, particularly during childhood and adolescence. Such research has the potential to inform studies seeking to develop novel biomedical or educational interventions aimed at augmenting cognitive functioning of individuals with intellectual disabilities or other learning difficulties. We present data on a sample of typically developing pediatric twins, their siblings, and unrelated, non-twins, referred to as ‘singletons’ from this point forward. Our analyses investigate the shared genetic and environmental covariance between individual differences in brain volumes (white and gray matter overall; frontal, temporal, and parietal lobes; and the caudate and lateral ventricles) and verbal (word knowledge) and nonverbal (visuo-spatial) skills.

Univariate twin studies of intelligence and specific cognitive abilities

Twin studies of general intelligence indicate that the variance attributable to genetic effects (i.e., heritability) is moderate (approximately 50%) and increases from 20% in infancy to 40% in childhood to 60% in adulthood. In contrast, estimates of shared environmental influences decrease from approximately 60% in infancy to negligible values in adulthood (for review, see McGue et al. 1993). A recent multi-site study of over 10,000 twin pairs comprised of children, adolescents, and young adults corroborated these earlier findings of increasing genetic influences on general intelligence with increasing age (Haworth et al. 2009). In a review of studies of specific cognitive abilities (that have included both children and adults), Plomin and Craig (1997) report heritability estimates of approximately 65% for verbal ability and 55% for visuo-spatial ability. Adoption studies suggest that heritability estimates for verbal and visuo-spatial abilities, similar to heritability estimates for overall intellectual ability, increase from early to later childhood (Plomin et al. 1997b). The consistency in these findings is likely due to the fact that verbal ability, as measured by Vocabulary or similar subtests, and visuo-spatial ability, as measured by Block Design or similar subtests, often are moderately to highly predictive of full scale IQ (e.g., Sattler 1992).

Univariate twin studies of brain volumes

Twin studies of brain volumes indicate that heritability is relatively high and age-specific (for review, see Peper et al. 2007; Schmitt et al. 2007). Many of these studies have examined total brain volumes, often quantifying gray matter and white matter separately, but to date, only three have examined lobar-level structures (Carmelli et al. 2002; Geschwind et al. 2002; Wallace et al. 2006). Two of these studies analyzed results from 72 monozygotic (MZ) pairs and 67 dizygotic (DZ) pairs of older adult twins (Carmelli et al. 2002; Geschwind et al. 2002) and one analyzed results from a pediatric sample including 90 MZ twin pairs and 38 DZ twin pairs (Wallace et al. 2006). Across all three studies, heritability values for lobar-level structures were generally more variable and lower than those for global indices of brain volume. When comparing brain structures common to these studies (frontal, temporal, and parietal), lobar-level volumes were more heritable in the pediatric

(additive genetic influences = .77–.88) than in the older adult (additive genetic influences = .40–.75) samples.

Phenotypic correlation between intelligence and brain volumes

Several studies have investigated the correlation between total brain volume and intelligence. McDaniel (2005) completed a meta-analysis of 37 samples, comprising 440 child and 1,090 adult participants, and reported an average correlation of .33 between intelligence and total brain volume. This correlation was reported to be higher for females than males and higher for adults than children. To the best of our knowledge, no study has reported correlations between brain volumes and verbal or visuo-spatial skills in a sample of typically developing children and adolescents. However, a few studies have examined these relations in adults. For example, Posthuma et al. (2003) reported no significant correlations between total gray matter, total white matter, or cerebellar volumes and the Verbal Comprehension Index (of which Vocabulary is one of three subtests) of the Wechsler Adult Intelligence Scale-III (r = .06, .01, and .03, respectively); however, they did find small, significant correlations between the Perceptual Organization Index (of which Block Design is one of three subtests) and both total gray matter and cerebellar volumes (r = .20 and .18, respectively). These findings are consistent with earlier research (Flashman et al. 1998) in which small, non-significant correlations between Verbal IQ and lobar volumes (r from .06 to .19) and somewhat larger, significant correlations between Performance IQ and lobar volumes (r from .15 to .28) were found. In this latter study, no significant correlations between Vocabulary and any brain measure (frontal, temporal, occipital, parietal, cerebellar, and whole brain volumes) were reported; however, small significant correlations were reported between Block Design and all of the aforementioned brain volumes except frontal lobar volumes (r from .21 to .28).

Bivariate twin studies of brain structure and intelligence

We are aware of four previous reports (based on two adult samples) that have used twin modeling to investigate the shared genetic and environmental relations between brain structure and intelligence. These include both brain volume (Posthuma et al. 2002, 2003) and voxel-based methods (Hulshoff Pol et al. 2006; Thompson et al. 2001). Consistent with investigations of singletons, a small to moderate phenotypic relationship has been observed between brain structure and IQ. The limited data available suggest that a substantial portion of this is due to shared genetic influences. In a study of adults, the phenotypic relationship between cerebellar volume and performance on the Perceptual Organization index was underpinned by both genetic and unique environmental influences. In contrast, significant genetic and environmental correlations between brain volume and Verbal Comprehension were not found. The first bivariate study to utilize voxel-based methods, focusing on gray matter densities and general intellectual ability, demonstrated significant shared genetic contributions (Thompson et al. 2001). Extending these findings, a subsequent investigation (Hulshoff Pol et al. 2006) showed significant genetic effects on the phenotypic relationship between nonverbal intellectual skills (Performance IQ) and localized gray and white matter densities. Shared genetic effects between brain structure and verbal ability (Verbal IQ) were also present, but to a lesser extent.

Because childhood and adolescence are periods of dynamic structural brain development (e.g., Lenroot et al. 2007) and explosive growth in educational attainment and cognitive skill acquisition, the examination of shared genetic and environmental covariances between brain structure and intellectual functioning during this age range is particularly important. Thus, the current study investigates these covariances in a young typically developing sample using finer-grained measurements of both brain volume and intellectual functioning than have been used previously.

Methods

Participants

A total of 649 typically developing individual twins, siblings of twins, and singletons (see Table 1 for demographic characteristics) 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 (NIMH; Giedd et al. 2009). The same-sex twins comprised 107 MZ pairs, 53 DZ pairs and 23 unmatched individual twins. BRT Laboratories and Proactive Genetics determined zygosity through DNA analysis of buccal cheek swabs using 9–21 unlinked short tandem repeat loci for a minimum certainty of 99%. Prospective participants were excluded if they had ever required special services in school, taken psychiatric medications, received mental health treatment, or had any condition known to affect gross brain development. Inclusionary criteria were a gestational age of at least 29 weeks, a minimum birth weight of 1,500 g, and a summary IQ score of 70 or greater. The groups were comprised of predominantly Caucasian participants (88%). We obtained verbal or written assent from the child and written consent from the parents or adult participants. The NIMH Institutional Review Board approved the protocol.

Measures of verbal and nonverbal intellectual skills

Vocabulary and Block Design subtest scores were obtained using the Wechsler Scales. Given the age range of the participants and that study enrollment has been ongoing for 19 years, different versions of the Wechsler Scales had been administered. The majority of participants (n = 551) completed the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999); the remainder completed these subtests from the Wechsler Intelligence Scale for Children (Wechsler 1974, 1991; n = 78), the Wechsler Preschool and Primary Scale of Intelligence (Wechsler 1967, 1989, 2002; n = 17), or the Wechsler Adult Intelligence Scale (Wechsler 1981; n = 3). Administration procedures for the two subtests are very similar across instruments. For the Vocabulary sub-test, participants are asked to provide the definitions of words of increasing difficulty (for younger and less able participants, in some cases, picture vocabulary items precede oral vocabulary items). For the Block Design subtest, participants copy a series of geometric designs utilizing colored blocks and completion is timed.

Although different versions of the Wechsler scales were used, performance on these tests is thought to be comparable. Based on data reported in the Wechsler Abbreviated Scale of Intelligence manual (Wechsler 1999), typically developing children who completed both the Wechsler Abbreviated Scale of Intelligence and the Wechsler Intelligence Scale for Children —Third Edition obtained very similar mean subtest scores (within 1 point of each other). Furthermore, these subtest scores were highly correlated, with a magnitude (r = .72–.74) similar to reported test–retest reliability values (r = .80–.84). These data provide support for our including subtest scores from various versions of the Wechsler scales. While one study raised questions about the comparability of the abbreviated and full versions of the adult Wechsler scales (Axelrod 2002), it used very different participants—a heterogeneous clinical sample recruited from a veteran's hospital. Given that our participants were typically developing children/adolescents and that very few of them completed the full adult version of the Wechsler scale, we do not believe that the use of different versions of the Wechsler scales is problematic in our study.

Magnetic resonance imaging (MRI) acquisition

All MRI scans were acquired on the same General Electric 1.5 Tesla Signa Scanner located at the National Institutes of Health Clinical Center in Bethesda, Maryland. A three-dimensional spoiled gradient recalled echo sequence in the steady state, designed to

optimize discrimination between gray matter, white matter, and cerebrospinal fluid, was used to acquire 124 contiguous 1.5-mm thick slices in the axial plane (TE/TR = 5/24 ms; flip angle = 45 degrees, matrix = 256 × 192, NEX = 1, FOV = 24 cm, acquisition time 9.9 min).

Image analysis

The native MRI scans were registered into standardized stereotaxic space using a linear transformation (Collins et al. 1994) and corrected for nonuniformity artifacts (Sled et al. 1998). The registered and corrected volumes were segmented into gray matter, white matter, cerebrospinal fluid and background using a neural net classifier (Zijdenbos et al. 2002). The tissue classification information was combined with a probabilistic atlas to provide volumetric measures (Collins et al. 1995) of gray and white matter volumes of the total cerebrum, frontal, temporal, and parietal lobes, the lateral ventricles (see Fig. 1), and the caudate nucleus (not shown). These measures have shown high agreement with conventional hand tracing measures.

Statistical analysis

Univariate variance component analyses were conducted on Vocabulary and Block Design scores and volumetric measures in order to characterize the relative influence of genetic and environmental factors prior to conducting the bivariate analyses (Neale and Cardon 1992). These heritability estimates were obtained using all available twin, sibling, and singleton data. In these analyses the total variance (σ^2_P) was partitioned into additive genetic (σ^2_A), shared environmental effects (σ^2_C), and non-shared or unique environmental (σ^2_E) effects. The total variance was thus parameterized as: $\sigma^2_P=\sigma^2_A+\sigma^2_C+\sigma^2_E$, while the covariance terms were parameterized as: $\mathrm{Cov}_{MZ}=\sigma^2_A+\sigma^2_C$ and $\mathrm{Cov}_{DZ/Sibling}=.5\sigma^2_A+\sigma^2_C$. Univariate ACE, CE, AE and E only models were fitted to test the significance of additive genetic and shared environmental effects. Optimization of this data used maximum likelihood (Edwards 1984) by calculating twice the negative log-likelihood of the raw data for each twin pair and summing across all pairs. The use of maximum likelihood in measuring model fit allows for hypothesis testing between an original model (ACE) and its nested models (AE, CE and E only). Because the variance component estimates are zero-bounded, the difference between an original model and its respective submodels follows a 50:50 mixture of zero and a χ^2 distribution with degrees of freedom equal to the difference in model parameters (df = 1).

Two series of analyses were conducted to examine the genetic and environmental covariation between brain volume and (1) Vocabulary and (2) Block Design performance. The statistical significance of genetic and environmental correlations was assessed by comparing twice the log-likelihood of the full Cholesky model to that of a submodel in which the genetic or environmental correlation between morphometric measures and Wechsler subtest scores was set to zero. Under certain regularity conditions, such differences are asymptotically distributed as chi-squared with one degree of freedom. A third sub-model tested the significance of the phenotypic correlation by setting all three genetic and environmental correlations between the Wechsler subtests and brain volumes to zero. Genetic and environmental covariances were used to estimate both the total covariance and phenotypic correlations (Posthuma et al. 2003) as well as to determine relative and absolute contributions of each factor to the relationship between brain volumes and Vocabulary and Block Design subtest scores.

A Cholesky factorization allows for the decomposition of the genetic and environmental covariance matrices for measures of brain structure and Wechsler subtest performance. The diagonal elements of either an A or E matrix produces the variances due to that specific effect for each of the individual measures while the off-diagonal element produces the

covariances due to either of the effects. The Cholesky decomposition calculates A and E matrices as the product between a lower triangular matrix and its transpose. The production of separate genetic and environmental variance/covariance matrices are positive semi-definite which is consistent with the idea that variation is caused by factors that operate in a linear additive fashion.

The genetic and environmental covariances between measures of brain structure and Wechsler subtest scores were used to calculate genetic correlations to indicate the degree to which genetic effects are shared between the two measures. The genetic correlation between two measures is defined as.

$$r_{x,y} = \frac{A_{xy}}{\sqrt{(A_x \times A_y)}}$$

where A_{xy} is the genetic covariance between each measure of brain structure (x) and a subtest score (y) and A_x and A_y represent the heritability of x and y. The environmental correlation is similarly defined using measures of environmental variance and covariance. Shared environmental effects were non-significant in univariate analyses of Wechsler subtest performance and measures of brain volume (Table 3). Therefore, bivariate genetic models decomposed the covariance between these measures into genetic and unique environmental variance.

The false discovery rate (FDR), set at $q = .05$, was utilized to control for multiple comparisons (Benjamini and Hochberg 1995). Because previous analyses of brain volume measures have shown significant effects of age and sex (Giedd et al. 1999; Lenroot et al. 2007), all analyses included sex, and the linear, quadratic, and cubic effects of age as fixed effects in the means models. Maximum likelihood analyses of individual observations (as implemented in Mx 1.66; Neale et al. 2006) were used for all analyses.

Results

Descriptive statistics

Prior to variance component estimation, group differences in Vocabulary and Block Design scores and brain volumes were examined. Performance on the Vocabulary and Block Design subtests differed significantly between groups (see Table 2). For Vocabulary, MZ twins had significantly lower scores and singletons had significantly higher scores compared to the entire sample. For Block Design, MZ twins had significantly lower scores. These group differences were not expected to bias estimates of genetic and environmental effects since there were no differences in group means or variances between MZ and DZ twins. There were no significant differences in brain volume means or variances between MZ twins, DZ twins, singletons, and siblings of twins, with the exception of the lateral ventricles (see Table 2). Mean differences were assessed using PROC MIXED in SAS (SAS version 9.1.3; SAS Institute, Cary, NC) to account for the random residual effects of twin and family resemblance on the simplifying assumption of constant correlation between measures within families and sibling groups.

Univariate analyses

For Vocabulary and Block Design scores and all brain volumes, there were no significant differences in model fit between the full ACE model and models where shared environmental effects were removed (see Table 3). There was a significant decrease in model fit for models excluding additive genetic effects. Therefore, all subsequent model

fitting was conducted using a model including both additive genetic and unique environmental effects.

Bivariate analyses

Vocabulary and brain volumes—Table 4 displays the standardized genetic and environmental covariance estimates and the phenotypic correlations between Vocabulary scores and total/regional brain volumes. Most phenotypic correlations were significant but small. In general, the unique environmental correlations between gray matter brain volumes and performance on the Vocabulary subtest were significant. However, the contribution of the unique environment to the total covariance was less than the genetic contribution. A significant genetic correlation was also detected between the caudate nucleus and Vocabulary scores; however, after FDR correction for multiple comparisons (q = .05), only unique environmental correlations for frontal gray matter, gray matter ? white matter, and total gray matter remained significant.

Block design and brain volumes—Table 5 displays the standardized genetic and environmental covariance estimates and the phenotypic correlations between Block Design scores and total/regional brain volumes. Phenotypic correlations between most brain volumes and Block Design scores were significant but weak. There were significant genetic correlations between Block Design performance and all brain volume measures except the lateral ventricles; the environmental correlations were non-significant. All of these genetic correlations remained significant after FDR correction for multiple comparisons. Furthermore, just as with Vocabulary, there was greater genetic contribution to the total covariance between brain volumes and Block Design performance compared to the contribution of environmental effects.

Discussion

In this article we report the bivariate relationship between verbal (word knowledge) and nonverbal (visuo-spatial) intellectual skills and brain volume in a typical pediatric sample of twins, their siblings, and singletons. Several unique features of this study include the focus on (a) children and adolescents in an extended twin design, (b) regional brain volumes, and (c) separate consideration of verbal and nonverbal intellectual skills, as measured by the Vocabulary and Block Design subtests of the Wechsler scales. Small phenotypic correlations between brain volumes (overall gray and white matter as well as regional volumes) and subtest performance were found. Modest but significant unique environmental correlations were found between gray matter volumes and Vocabulary subtest performance. Results for the Block Design subtest indicated small genetic correlations with both gray and white matter volumes.

Our findings of high heritability of word knowledge, visuo-spatial abilities and brain volumes are consistent with previous univariate analyses (for reviews, see Plomin et al. 1997a; Peper et al. 2007; Schmitt et al. 2007). Also observed were small but consistent phenotypic correlations between both verbal and visuo-spatial intellectual skills and brain volumes (e.g., Flashman et al. 1998; Posthuma et al. 2003).

Although the phenotypic correlations between verbal/visuo-spatial skills and brain volumes were consistently low and positive, the genetic and environmental contributions to these relationships varied. The covariance between Block Design performance and both gray and white matter volumes appears to be due to additive genetic factors. These findings are consistent with at least one previous study (Hulshoff Pol et al. 2006) which showed significant genetic correlations between Performance/nonverbal IQ, including the Block Design subtest, and discrete (voxel-level) gray and white matter measurements (densities).

However, another study (Posthuma et al. 2003) did not find significant genetic correlations between Perceptual Organization (which also includes the Block Design subtest) and total gray or white matter volumes in an adult sample, but instead reported this association with cerebellar volumes, which were not quantified here.

In contrast, unique environmental influences appear to underlie the association between Vocabulary performance and lobar gray matter volumes. This was unexpected because prior studies have reported that variation in verbal ability is more strongly influenced by common rather than unique environmental factors during childhood (e.g., Byrne et al. 2006). Unique environmental influences may be playing a greater role because our sample included older adolescents and unique environmental effects on verbal ability become more prominent later in development (see Plomin et al. 1997a). Lastly, it is noteworthy that our failure to find a genetic correlation between verbal ability and brain structure is consistent with the two adult studies previously testing this association (Hulshoff Pol et al. 2006; Posthuma et al. 2003).

Limitations and future directions

Brain lobar volumes are likely not the optimal level of anatomic resolution for description of structural and functional relationships, and this may have contributed to the relatively small magnitude of the correlations we observed between brain structures and cognitive ability. Future research should investigate the genetic and environmental relationships between intellectual skills and more functionally relevant measures of brain anatomy, such as cortical thickness in specific regions of interest (Shaw et al. 2006) or measures of connectivity (Lerch et al. 2006; Nagy et al. 2004; Schmitt et al. 2008). Furthermore, based on our findings and previous studies with adults in which relations between brain volumes and verbal/visuo-spatial skills were examined (Flashman et al. 1998; Posthuma et al. 2003), it appears that a ‘bigger is better’ conceptualization of brain structure may be an oversimplification, particularly during childhood and adolescence when brain structure undergoes both linear (mostly white matter) and nonlinear (mostly gray matter) changes (Lenroot et al. 2007). Because this phenotypic relationship is dynamic and captured best via longitudinal designs (Shaw et al. 2006), we may have been limited in our ability to detect genetic and environmental correlations between brain structure and intellectual skills in this sample spanning early childhood through late adolescence. Thus, future research should examine their contributions to brain developmental trajectories associated with differing levels of intellectual functioning in a longitudinal framework.

While our findings suggest that different genetic and environmental influences underpin the phenotypic relationship between brain volumes and verbal versus visuo-spatial skills, the present study did not directly model their unique and shared contributions (e.g., in the context of a trivariate model). Given that both Vocabulary and Block Design performance are highly predictive of general intellectual ability (Sattler 1992) but only moderately correlated with one another (r = .33 in the present study), we would anticipate both independent and common genetic and environmental correlations with regional brain volumes. We plan to assess these relationships further in future analyses.

Future research should seek to extend these findings beyond twin modeling in the search for shared molecular markers. It may be that genes associated with general intellectual functioning, such as SSADH and CHRM2 (for review, see Payton 2006; Shaw 2007) also shape brain structure. However, thus far, genes associated with cognitive functioning have proven to explain only a very small proportion of variance in cognitive test performance (for review, see Payton 2006), and at least one study failed to find a significant association of genes influencing brain size with general cognitive and language abilities (Bates et al. 2008). Similar to existing twin research, these studies may be limited by cross-sectional designs that obscure the often nonlinear nature of brain development and its relationship with

cognitive abilities. Thus, studies of molecular markers may benefit from examining longitudinal trajectories of relationships between brain structure and intelligence.

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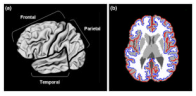

Fig. 1.
a Lateral view of lobar-level brain regions quantified for this study (*occipital lobe not labeled*); **b** Axial view of gray matter (*in light gray*) and white matter (*in white*) segmentation with lateral ventricles depicted in *dark gray*

Table 1

Demographic characteristics

	MZ		DZ		Singletons		Siblings of twins		Total	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	***p***
Sex										
Male	103	54.0	58	51.3	96	55.8	52	41.6	309	0.14
Female	121	46.0	61	48.7	121	44.2	37	58.4	340	
Ethnicity										
White	212	94.6	114	95.8	160	73.7[#]	87	97.8	573	<0.001
Other	12	5.4	5	4.2	57	26.3	2	2.2	76	
Handedness[a]										
Right	198	88.4	94	79.0[^]	194	89.4	72	80.9[^]	558	0.02
Non-right	26	11.6	25	21.0	23	10.6	17	19.1	91	
	M (SD)		*M* (SD)		*M* (SD)		*M* (SD)			
Age	12.1 (3.7)		10.1 (3.7)[*]		12.5 (3.8)[*]		11.8 (3.8)			<0.0001
Range	5.5–19.5		5.3–18.2		4.4–19.5		5.5–19.6			
SES[b]	43.8 (18.2)		44.5 (15.7)		40.7 (21.3)		41.3 (16.5)			0.25
Range	20–89		20–82		20–95		20–82			

[a] For all study participants, handedness was assessed by using the Physical and Neurological Examination for Soft Signs (PANESS; Denckla 1985)

[b] *SES* (Socioeconomic Status) was measured by using the Hollingshead Two-Factor Index (Hollingshead and Redlich 1958). Note that lower scores denote higher SES

[*] Groups carrying significant differences ($p < 0.05$) for a measure compared to the total sample

[#] Singletons have a lower proportion of white participants than all other groups as indicated by pair-wise chi-square analyses ($p < 0.001$)

[^] Pair-wise chi-square analyses indicate that DZs and Siblings of twins have a lower proportion of right-handed participants than Singletons and that DZs also have a lower proportion of right-handed participants than MZs ($p < 0.05$)

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Table 2

Means (SDs) for vocabulary, block design, and brain volumes

	MZ (*N* = 224)	**DZ (*N* = 119)**	**Singletons (*N* = 217)**	**Siblings of twins (*N* = 89)**	***p***
Vocabulary	11.4 (2.8)*	11.5 (2.6)	12.3 (3.0)*	12.0 (3.0)	0.03
Range	4–18	5–18	2–19	5–18	
Block design	11.3 (2.8)*	11.9 (3.0)	12.2 (2.9)	12.3 (3.0)	0.02
Range	4–19	3–19	4–19	5–19	
Gray matter + white matter	1172.5 (106.5)	1146.1 (105.9)	1164 (117.5)	1165.8 (118.6)	0.41
Range	894.7–1470.4	816.3–1417.7	891.3–1473.1	920.4–1495.6	
Gray matter	736.5 (66.2)	725 (70.1)	728 (78.1)	732.6 (75.1)	0.68
Range	430.5–910.3	492.9–904.5	563.1–935.8	583.3–981.6	
White matter	435.9 (55.8)	421.1 (53.3)	435.9 (54.4)	433.2 (55.9)	0.22
Range	322.3–586.4	286.7–576.9	302–612.9	329.4–605.4	
Frontal gray matter	232.3 (21.3)	228.8 (22.6)	230.5 (25.2)	231.2 (24.6)	0.78
Range	143.2–288.8	155.9–286.6	173–298.7	178.8–310.3	
Frontal white matter	167.3 (22.6)	161.6 (20.3)	167.4 (21)	167.1 (22.3)	0.21
Range	125.4–227.5	112.8–217.9	113.1–238.2	125.7–234.4	
Parietal gray matter	123.1 (13)	124.2 (13.2)	122.6 (15.4)	124 (14.8)	0.81
Range	89.8–154.8	95.1–167.9	91.6–169.6	93.7–177	
Parietal white matter	83.9 (11.8)	82.9 (11.3)	85 (11.2)	84.5 (11.9)	0.57
Range	58.2–115.1	56.9–114.6	57.6–120.6	62.1–125.6	
Temporal gray matter	190.5 (18.5)	186.5 (20.2)	187.8 (20.4)	189.7 (20)	0.52
Range	88.4–245.2	117.8–232.5	138.6–246.1	150.7–264.5	
Temporal white matter	94 (12.3)	91 (12.7)	93.9 (12.4)	93.6 (12.9)	0.35
Range	69.1–131	65.9–130.6	64.7–134.8	67.4–129.3	
Lateral ventricles	11.5 (6.6)*	10.2 (5.1)	10.6 (5.9)	8.4 (4.1)*	0.0001
Range	2.9–41.5	3–31.6	2.8–35.9	3.3–27.2	
Caudate nucleus	9.9 (1.1)	9.8 (1.1)	9.8 (1)	9.9 (1.1)	0.96
Range	7.7–13.7	7.3–12.3	7–12.6	7.4–13	

*Groups with significant mean differences ($p < 0.05$) for a measure compared to the total sample

Table 3

Univariate model fit summary

	Full model	No A	No C	No AC	A	95% CI	C	95% CI	E	95% CI
Vocabulary	3137.27	<0.0001	1.00	<0.0001	0.64	(0.42; 0.78)	0.08	(0; 0.25)	0.28	(0.22; 0.38)
Block design	3118.95	<0.0001	1.00	<0.0001	0.75	(0.55; 0.81)	0	(0; 0.18)	0.25	(0.19; 0.33)
Gray matter + white matter	3118.95	<0.0001	0.90	<0.0001	0.91	(0.74; 0.94)	0	(0; 0.18)	0.08	(0.06; 0.1)
Gray matter	3169.00	<0.0001	0.49	<0.0001	0.83	(0.65; 0.92)	0.06	(0; 0.24)	0.11	(0.08; 0.15)
White matter	3032.88	<0.0001	1.00	<0.0001	0.89	(0.75; 0.92)	0	(0; 0.14)	0.11	(0.08; 0.15)
Frontal gray matter	3205.08	<0.0001	0.49	<0.0001	0.82	(0.64; 0.91)	0.05	(0; 0.24)	0.11	(0.08; 0.15)
Frontal white matter	3006.51	<0.0001	1.00	<0.0001	0.92	(0.76; 0.94)	0	(0; 0.16)	0.08	(0.06; 0.1)
Parietal gray matter	3156.09	<0.0001	0.34	<0.0001	0.61	(0.4; 0.82)	0.18	(0; 0.36)	0.21	(0.16; 0.29)
Parietal white matter	3073.19	<0.0001	0.94	<0.0001	0.74	(0.55; 0.88)	0.1	(0; 0.28)	0.15	(0.11; 0.2)
Temporal gray matter	3208.84	<0.0001	0.97	<0.0001	0.92	(0.78; 0.94)	0	(0; 0.13)	0.08	(0.06; 0.11)
Temporal white matter	3062.08	<0.0001	1.00	<0.0001	0.89	(0.77; 0.92)	0	(0; 0.12)	0.11	(0.08; 0.15)
Lateral ventricles	3399.24	<0.0001	1.00	<0.0001	0.65	(0.5; 0.73)	0	(0; 0.09)	0.35	(0.27; 0.46)
Caudate nucleus	3340.93	<0.0001	1.00	<0.0001	0.85	(0.71; 0.89)	0	(0; 0.12)	0.15	(0.11; 0.21)

Table 4

Model fitting summary for vocabulary and brain volumes

		Model comparison p-values			Standardized covariance estimates				Correlation estimate	
	Full model	**No rA**	**No rE**	**No rP**	**A**	**95% CI**	**E**	**95% CI**	**rP**	**95% CI**
GMWM	3138.53	0.048	0.003*	0.0001*	0.09	(0; 0.18)	0.04	(0.01; 0.07)	0.13	(0.05; 0.22)
GM	3188.54	0.066	0.003*	<0.0001*	0.09	(−0.01; 0.18)	0.05	(0.02; 0.09)	0.14	(0.05; 0.22)
WM	3060.48	0.086	0.285	0.042*	0.08	(−0.01; 0.17)	0.02	(−0.02; 0.05)	0.10	(0.01; 0.18)
FGM	3219.21	0.055	0.002*	<0.0001*	0.09	(0; 0.18)	0.05	(0.02; 0.09)	0.14	(0.06; 0.23)
FWM	3029.50	0.023	0.221	0.009*	0.10	(0.01; 0.19)	0.02	(−0.01; 0.05)	0.13	(0.04; 0.21)
PGM	3178.07	0.117	0.031	0.002*	0.08	(−0.02; 0.17)	0.05	(0; 0.1)	0.13	(0.04; 0.21)
PWM	3104.55	0.018	0.469	0.06	0.11	(0.02; 0.2)	−0.01	(−0.05; 0.02)	0.10	(0.01; 0.18)
TGM	3237.09	0.028	0.027	0.001*	0.1	(0.01; 0.19)	0.03	(0; 0.06)	0.13	(0.05; 0.22)
TWM	3089.76	0.015	0.259	0.004*	0.12	(0.02; 0.21)	0.02	(−0.01; 0.06)	0.14	(0.05; 0.22)
LATVENT	3421.22	0.93	0.567	0.821	0	(−0.1; 0.1)	−0.02	(−0.07; 0.04)	−0.02	(−0.1; 0.07)
CAUD	3363.82	0.009	0.377	0.003*	0.13	(0.03; 0.22)	0.02	(−0.02; 0.06)	0.15	(0.06; 0.23)

rA-Genetic Correlation; rE-Unique Environmental Correlation; rP-Phenotypic Correlation; *GMWM* gray matter + white matter, *GM* gray matter, *WM* white matter, *FGM* frontal gray matter, *FWM* frontal white matter, *PGM* parietal gray matter, *PWM* parietal white matter, *TGM* temporal gray matter, *TWM* temporal white matter, *LATVENT* lateral ventricles, *CAUD* caudate nucleus

*Correlations significant after adjustment for multiple testing (q = .05)

Table 5

Model fitting summary for block design and brain volumes

		Model comparison *p*-values			Standardized covariance estimates				Correlation estimate	
	Full model	**No rA**	**No rE**	**No rP**	**A**	**95% CI**	***E***	**95% CI**	**rP**	**95% CI**
GMWM	3118.96	0.002*	0.748	0.004*	0.14	(0.05; 0.23)	0	(−0.02; 0.03)	0.14	(0.06; 0.23)
GM	3169.54	0.006*	0.302	0.002*	0.13	(0.04; 0.22)	0.02	(−0.02; 0.05)	0.15	(0.06; 0.23)
WM	3032.88	0.007*	0.351	0.027*	0.13	(0.03; 0.22)	−0.01	(−0.05; 0.02)	0.12	(0.03; 0.19)
FGM	3205.64	0.015*	0.235	0.004*	0.11	(0.02; 0.2)	0.02	(−0.01; 0.05)	0.13	(0.05; 0.22)
FWM	3006.51	0.016*	0.411	0.054	0.11	(0.02; 0.2)	−0.01	(−0.04; 0.02)	0.10	(0.01; 0.18)
PGM	3159.37	0.038*	0.491	0.024*	0.10	(0.01; 0.19)	0.01	(−0.03; 0.06)	0.11	(0.03; 0.2)
PWM	3074.20	0.007*	0.581	0.006*	0.13	(0.03; 0.22)	0.01	(−0.03; 0.05)	0.14	(0.05; 0.22)
TGM	3208.84	0.001*	0.259	<0.0001*	0.16	(0.07; 0.25)	0.02	(−0.01; 0.05)	0.18	(0.09; 0.26)
TWM	3062.08	0.0003*	0.226	0.002*	0.17	(0.08; 0.26)	−0.02	(−0.05; 0.01)	0.15	(0.06; 0.23)
LATVENT	3399.24	0.715	0.97	0.902	−0.02	(−0.12; 0.08)	0	(−0.06; 0.05)	−0.02	(−0.1; 0.07)
CAUD	3340.93	0.04*	0.094	0.002*	0.10	(0; 0.19)	0.03	(−0.01; 0.07)	0.13	(0.05; 0.21)

rA-Genetic Correlation; rE-Unique Environmental Correlation; rP-Phenotypic Correlation; *GMWM* gray matter + white matter, *GM* gray matter, *WM* white matter, *FGM* frontal gray matter, *FWM* frontal white matter, *PGM* parietal gray matter, *PWM* parietal white matter, *TGM* temporal gray matter, *TWM* temporal white matter, *LATVENT* lateral ventricles, *CAUD* caudate nucleus

*Correlations significant after adjustment for multiple testing (q = .05)