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The Genetic Association Between Neocortical Volume and General Cognitive Ability Is Driven by Global Surface Area Rather Than Thickness

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Total gray matter volume is associated with general cognitive ability (GCA), an association mediated by genetic factors. It is expectable that total neocortical volume should be similarly associated with GCA. Neocortical volume is the product of thickness and surface area, but global thickness and surface area are unrelated phenotypically and genetically in humans. The nature of the genetic association between GCA and either of these 2 cortical dimensions has not been examined. Humans possess greater cognitive capacity than other species, and surface area increases appear to be the primary driver of the increased size of the human cortex. Thus, we expected neocortical surface area to be more strongly associated with cognition than thickness. Using multivariate genetic analysis in 515 middle-aged twins, we demonstrated that both the phenotypic and genetic associations between neocortical volume and GCA are driven primarily by surface area rather than thickness. Results were generally similar for each of 4 specific cognitive abilities that comprised the GCA measure. Our results suggest that emphasis on neocortical surface area, rather than thickness, could be more fruitful for elucidating neocortical–GCA associations and identifying specific genes underlying those associations.

Keywords: cognition, cortex, genetic correlation, heritability, twins

Introduction

Understanding the phenotypic and genetic relationship of brain structure to general cognitive ability (GCA) is of central importance with respect to neuroscience, neuropsychology, psychiatry, neurology, and genetics. Here, we use the term GCA to refer to measures that are essentially composite indices of different specific cognitive abilities, whether they are derived from a summation or average of individual test scores or from the first factor or principal component from a factor analysis of individual test scores. Total brain volume and total gray matter volume are positively correlated with GCA (Thompson et al. 2001; Posthuma et al. 2002; McDaniel 2005; van Leeuwen et al. 2009). However, given that higher cognitive functions are mediated to a large extent by neocortical regions, several researchers have focused specifically on neocortex–GCA associations. In many earlier studies of this relationship, the phenotype of interest was neocortical volumes (Jung and Haier 2007) (In this article, we do not refer to voxel-based morphometry (VBM) studies. These provide volumetric (density) measures so they do not distinguish between cortical thickness and surface area. Moreover, because VBM studies typically find only very small clusters of voxels to be significant, they tend to be inconclusive with regard to heritability. Suppose that a small cluster within the amygdala was significantly heritable. Concluding that the size of the entire amygdala was heritable would be an inference that is beyond the data. On the other hand, it seems rather unlikely that the size of only a tiny subregion within the amygdala is influenced by genes while the size of the rest of the structure is influenced only by environmental factors.). Neocortical gray matter volume is the product of surface area and thickness, but at the global level neocortical surface area and thickness develop relatively independently (Rakic 1988, 2009). According to the radial unit hypothesis, neocortical surface area is a function of the numbers of cortical columns, whereas neocortical thickness is determined by the number of neurons in a column (Rakic 1988, 2009).

Both brain structure and GCA are highly heritable, that is, a substantial proportion of the observed variance in these traits is due to genes (Bouchard and McGue 2003; Schmitt et al. 2007; Kremen et al. 2010). Because all of the variance is not due to genes, these heritability estimates indicate that environmental factors also contribute to individual differences in these phenotypes. It has also been demonstrated that at the global level, neocortical surface area and thickness are genetically as well as phenotypically uncorrelated (Panizzon et al. 2009; Winkler et al. 2010). More than 10 years ago, Posthuma et al. (2002) demonstrated that the cerebral gray matter volume–GCA association was due entirely to genetic factors. This finding has since been replicated (van Leeuwen et al. 2009), but over a decade after the initial findings by Posthuma et al. we are not aware of any studies that have examined the genetic and environmental influences underlying the relationship between GCA and neocortical volume as opposed to total brain or cerebral gray matter volume. Moreover, because the 2 global dimensions of neocortical volume are independent, the genetic relationship between GCA and neocortical volume would still be uninformative with respect to neocortical

thickness versus surface area. Thus, despite the substantial genetic influences on both GCA and brain structure, the underlying genetic and environmental relationship between GCA and the major cortical dimensions of surface area and thickness remains entirely unknown.

For that matter, even the phenotypic relationship of GCA to cortical thickness versus surface area is unclear and warrants further study. Significant positive thickness–GCA correlations have been found in some studies (Narr et al. 2007; Choi et al. 2008; Joshi et al. 2011; Karama et al. 2011, 2013), but not others (Shaw et al. 2006; Goh et al. 2011; Tamnes et al. 2011; Bjuland et al. 2013; Colom et al. 2013; Fleischman et al. 2013). Surface area–GCA associations have been less frequently examined. Significant positive phenotypic surface area–GCA correlations were also found in some (Colom et al. 2013; Fjell et al. 2013; Fleischman et al. 2013; Yang et al. 2013) but not all (Skranes et al. 2013) studies. Thus, there is a rather mixed picture regarding the relationship between GCA and cortical thickness or surface area.

Surface area increases appear to be the primary driver of the increased size of the human cortex relative to that of other species, whereas cross-species thickness differences are comparatively small (Rakic 2009; Hill et al. 2010). Indeed, there is an ~10-fold increase in cortical surface area in the human brain compared with the macaque brain, and an ~1000-fold increase in the human brain compared with the mouse brain (Rakic 2009; Hill et al. 2010). In contrast, there is only a 2- to 3-fold cortical thickness difference between the human and mouse brain (Rakic 2009). Hence, there is reason to think that surface area would be more important than thickness with respect to the substantially greater cognitive capacity of humans.

The primary goal of the present study was to examine the extent of these phenotypic and genetic relationships. We used the classical twin design (Eaves et al. 1978; Neale and Cardon 1992) to examine the phenotypic and genetic relationships between neocortical volume and GCA. We then decomposed the phenotypic and genetic relationship between cortical volume and GCA in analyses of the relationship of global measures of neocortical thickness and surface area with GCA. We hypothesized that total surface area, but not mean thickness, would be associated with GCA at both the phenotypic and genetic levels. We also predicted that the phenotypic relationship with surface area would be mediated primarily by genetic factors. In addition, we performed the same sets of phenotypic and genetic analyses on each of 4 specific cognitive components that comprise the GCA measure used in the present study.

Materials and Methods

Participants

Participants were 534 middle-aged men from the Vietnam Era Twin Study of Aging (VETSA; Kremen et al. 2006, 2013). Mean age was 55.70 years old (SD = 2.62; range: 51–60), and mean level of educational attainment was 13.80 years (SD = 2.11; range: 8–20). After quality control, we had analyzable neocortical data on 515 individuals including 131 monozygotic (MZ) and 96 dizygotic (DZ) male twin pairs and additional 61 individual twins. Zygosity determination was based on 25 microsatellite markers for 92% of the participants. It was determined by questionnaire and blood group for the remaining 8%; this method had 95% agreement with the DNA-based method in this sample.

The VETSA MRI sample used in this study is a subsample of participants from the main VETSA study, which includes a total of 1237 twins. More detailed description of the VETSA study as well as the VETSA MRI subsample can be found elsewhere (Kremen et al. 2006, 2013). VETSA participants are similar to American men in their age range in terms of health and sociodemographic characteristics (National Health and Nutrition Examination Survey) (Schoenborn and Heyman 2009; Kremen et al. 2006, 2013). All VETSA participants served in the military ~35 years prior to the study; nearly 80% reported no combat experience. Overall, the participants who underwent brain imaging did not differ from the VETSA participants who did not undergo the MRI protocol in terms of sociodemographic characteristics (Panizzon et al. 2009).

Data for this study were collected at 2 sites: university of California, San Diego, and Boston University. Brain imaging at the Boston site was performed at the Massachusetts General Hospital. All participants gave written informed consent to be in the study. The study protocol was approved by the Institutional Review Boards at the participating institutions.

General Cognitive Ability Measure

GCA was measured with Armed Forces Qualification Test (AFQT). The AFQT is a 50-min paper-and-pencil test consisting of 4 components: verbal ability (vocabulary); arithmetic, spatial processing (mental folding and unfolding of boxes); and reasoning about tools and mechanical relations. The AFQT has a high correlation (~0.85) with Wechsler IQ—the most common GCA measure—and in the VETSA sample its 35-year test–retest reliability was 0.74 (Lyons et al. 2009). AFQT scores are percentiles, but analyses were performed based on the percentile scores transformed into their normal deviates. The current AFQT score obtained during the VETSA was used in the present analyses. Cognitive testing and neuroimaging were conducted on back-to-back days.

Image Acquisition and Processing

Images were acquired on Siemens 1.5 T scanners. Two sagittal T1-weighted MPRAGE sequences were employed with a TI = 1000 ms, TE = 3.31 ms, TR = 2730 ms, flip angle = 7°, slice thickness = 1.33 mm, and voxel size 1.3 × 1.0 × 1.3 mm. To increase the signal-to-noise ratio, the 2 MPRAGE acquisitions were rigid-body registered to each other (motion corrected) and then averaged. Volume segmentation (Fischl et al. 2002; Fischl, Salat, et al. 2004) and cortical surface reconstruction (Dale and Sereno 1993; Dale et al. 1999; Fischl et al. 1999, 2002; Fischl, Salat, et al. 2004; Fischl, van der Kouwe, et al. 2004) were based on the publicly available FreeSurfer software package. The cortical surface was covered with a polygonal tessellation and smoothed to reduce metric distortions. The three-dimensional cortical surface was reconstructed to measure thickness and area at each surface location or vertex using a semi-automated approach in the FreeSurfer software package. There are over 160 000 vertices in total for each hemisphere. The vertices are contiguous triangles that form the cortical surface.

After the initial surface model was constructed, a refinement procedure was applied to obtain a representation of the gray/white boundary. This surface was then deformed outwards to obtain an explicit representation of the pial surface. The resulting cortical surface model was manually reviewed and edited for technical accuracy. Minimal manual editing was performed according to standard, objective editing rules. These semi-automated measures have a high correlation with manual measures in vivo and ex vivo (Fischl and Dale 2000; Walhovd et al. 2005).

Cortical parcellation was performed according to the system of Desikan et al. (2006) and implemented in FreeSurfer. Surface area of each parcellation unit was calculated as the sum of the areas of all vertices within that unit. Total surface area was calculated as the sum of the areas of all parcellation units. Cortical thickness was calculated as the average distance between the gray/white boundary and the pial surface within each parcellation unit (Fischl and Dale 2000). Mean cortical thickness was calculated as the weighted average thickness of all parcellation units, weighted by the area of each parcellation unit. MRI image acquisition and processing is explained in more detail in Kremen et al. (2010) and Eyler et al. (2012).

Statistical Analysis

In the twin design, the variance of a phenotype can be accounted for by additive genetic influences (A), common environmental influences

(C), and unique environmental influences (E). The resulting model is referred to as an ACE model. The A effects correlate 1.0 in MZ twin pairs, who are assumed to share all of their genes, whereas these effects correlate 0.5 in DZ twin pairs who share on average half of their segregating genes. Because the C effects refer to all environmental effects that make members of a twin pair alike, they correlate 1.0 both in MZ and DZ twin pairs. The E effects are uncorrelated both in MZ and DZ twin pairs as these refer to all environmental effects that make members of twin pair different; E includes measurement error as well.

Because VETSA participants were in their 50s and had mostly not lived together in the same household for decades, one might wonder how it is possible to distinguish between genetic and common environmental influences. To address this question, it is important to emphasize that A, C, and E are latent variables. They do not refer to specific genes or specific environmental events. For example, we do not know which specific genes or how many genes are involved, but the twin method still makes it possible to accurately estimate the total amount of variance in a phenotype that is accounted for by genetic influences. The same is true for environmental factors. C, which refers to common environmental variance, is often mistaken for the effects of being in the same family or the same household. Although those effects may well be included in the C component, C represents the effect of all environmental factors that make twins similar. These could be childhood environmental factors with long-lasting effects or more current environmental factors such as both twins living in an urban environment. In response to an authoritarian father disciplining both twins, 1 twin might become submissive and the other might react aggressively. In this case, the same environmental event would be part of the E—not the C—variance because its effect was to make the twins different (Neale and Cardon 1992; Carey 2003).

Even without knowing the specific genetic or environmental factors, these latent variable components can be decomposed algebraically. Suppose the correlation for phenotype X is 0.70 between MZ twins. MZ twins share all of their genes and, by definition, all of whatever aspects of the environment make them similar. Hence, it is only unique environmental factors that can make them different. Therefore, 1 minus the MZ correlation, or 0.30 must be the amount of variance in phenotype X that is due to unique environmental factors. This is the case mathematically, without knowing any of the specific genes or environmental factors.

Analyses were performed using the maximum-likelihood based, structural equation modeling software Mx (Neale et al. 2004). To determine the relative contribution of genetic and environmental influences on both the individual measures and the covariance between measures, we fit Cholesky decompositions to the data. All variables were normally distributed, meeting a basic assumption of these parametric analyses. The univariate ACE model is easily extended to a bivariate or trivariate setting in which the sources of genetic and environmental covariance can also be examined. We began with trivariate models that include GCA, total surface area, and mean thickness. Bivariate models included GCA and 1 of the neuroanatomic measures. We refer to the trivariate Cholesky as the "ACE–ACE–ACE" Cholesky, and we refer to the bivariate Cholesky as the "ACE–ACE" Cholesky. These designations indicate that the models include the A, C, and E variance components for each variable. Reduced models in which particular components were set to zero (e.g., "ACE–AE") were then tested relative to these full Cholesky decompositions.

Model comparisons were based on the likelihood-ratio χ^2-test, which is calculated as the change in −2 log likelihood (−2LL) from the ACE–ACE or the ACE–ACE–ACE Cholesky to the reduced model, and is distributed as a χ^2 with degrees of freedom equal to the difference in parameters between the models. Nonsignificant P values (>0.05) indicate that the reduced model does not yield a significant change in the model fit and therefore provides an essentially equally good fit to the data while using fewer parameters.

We also used these models to compute phenotypic, genetic, common environmental, and unique environmental correlations between GCA and neocortical volume in a bivariate model as well as between GCA and neocortical total surface area and mean thickness in a trivariate model. Phenotypic correlations are the standard sets of correlations universally used by researchers and statisticians. It is well known that phenotypic correlations represent shared variance between 2 traits, but many researchers may not be thinking about the fact that these correlations represent a composite of the shared genetic and environmental sources of variance. In non-genetically informative studies, it is not possible to differentiate these sources of covariance. However, in the twin method, it is possible to separate genetic, common environmental, and unique environmental variance components underlying individual differences in a given trait. It is thus possible to examine only the shared *genetic* variances between 2 traits. The genetic correlation represents this shared genetic variance, i.e., the extent to which the same genetic factors influence 2 different phenotypes (Neale and Cardon 1992). Common environmental correlations and unique environmental correlations are analogous to genetic correlations with respect to those variance components.

The effects of age and scanner were regressed out of the neocortical measures prior to all analyses; that is, residual scores, after covarying age and scanner, were used in the analyses. We did not adjust for total brain volume because correcting the two-dimensional measure of surface area and the one-dimensional measure of thickness with the three-dimensional volume measure would create an overcorrection, and one that would be very different for surface area and thickness (Wierenga et al. 2013). In the present sample, total brain volume was correlated 0.91 ($P < 0.00001$) with surface area but only 0.14 ($P < 0.002$) with thickness. Thus, controlling for total brain volume would have a dramatically different meaning with respect neocortical thickness and surface area. It would remove very little variance for thickness but almost all of the variance for surface area. As such, it effectively makes it impossible to detect different relationships for mean neocortical thickness and total surface area. Adjusting for global effects is important when the goal is to examine relative regional differences, but that is not the case in the present study. However, because of this very differential relationship, we believe that total brain volume or total neocortical volume are still inappropriate covariates when examining regional differences (see Discussion).

Results

Descriptive Statistics

Table 1 shows the means and SDs for cognitive and neuroanatomic characteristics of the sample. The average GCA percentile score was 63. This score is equivalent to a Wechsler IQ score of 104–105, which is just slightly above average.

General Cognitive Ability

Table 2 shows the phenotypic, genetic, and unique environmental correlations between the measures. These correlations were derived from the best-fitting genetic models and therefore reflect statistics derived from both bivariate and trivariate

Table 1
Descriptive statistics for neocortical and cognitive measures ($N = 515$)

	Mean (SD)
Neocortical measures	
Volume (cm^3)	321 (30)
Surface area (cm^2)	1623 (133)
Thickness (mm)	1.98 (0.08)
Cognitive measures	
AFQT total score (GCA)	63 (21)
AFQT verbal ability	84 (17)
AFQT arithmetic	62 (27)
AFQT tool/mechanical reasoning	63 (25)
AFQT spatial processing	48 (27)

Note: AFQT, Armed Forces Qualification Test. All AFQT scores are percentiles. GCA, general cognitive ability.

Table 2
Correlations for general cognitive ability, total neocortical volume, total neocortical surface area, and mean neocortical thickness

	General cognitive ability	Total neocortical volume	Total neocortical surface area	Mean neocortical thickness
Phenotypic correlations				
GCA	1.00			
Volume	**0.22 (0.12; 0.31)**	1.00		
Surface area	**0.21 (0.11; 0.30)**	**0.88 (0.85; 0.90)**	1.00	
Thickness	0.08 (−0.02; 0.18)	**0.43 (0.34; 0.50)**	−0.02 (−0.12; 0.08)	1.00
Genetic correlations				
GCA	1.00			
Volume	**0.25 (0.12; 0.39)**	1.00		
Surface area	**0.24 (0.11; 0.38)**	**0.89 (0.87; 0.91)**	1.00	
Thickness	0.09 (−0.06; 0.24)	**0.41 (0.30; 0.50)**	−0.01 (−0.13; 0.11)	1.00
Unique environmental correlations				
GCA	1.00			
Volume	**0.24 (0.08; 0.40)**	1.00		
Surface area	**0.21 (0.04; 0.37)**	**0.69 (0.59; 0.77)**	1.00	
Thickness	0.10 (−0.08; 0.26)	**0.63 (0.52; 0.72)**	−0.11 (−0.27; 0.06)	1.00

Note: Statistically significant correlations ($P < 0.05$) are in bold; 95% confidence intervals are shown in parentheses. GCA–volume correlations were derived from the bivariate genetic model (see Table 3, Model 2). GCA–surface area correlations and GCA–thickness correlations were derived from the trivariate genetic model (see Table 3, Model 4). Volume–surface area and volume–thickness correlations were derived from a trivariate genetic model including these 3 measures. GCA, general cognitive ability.

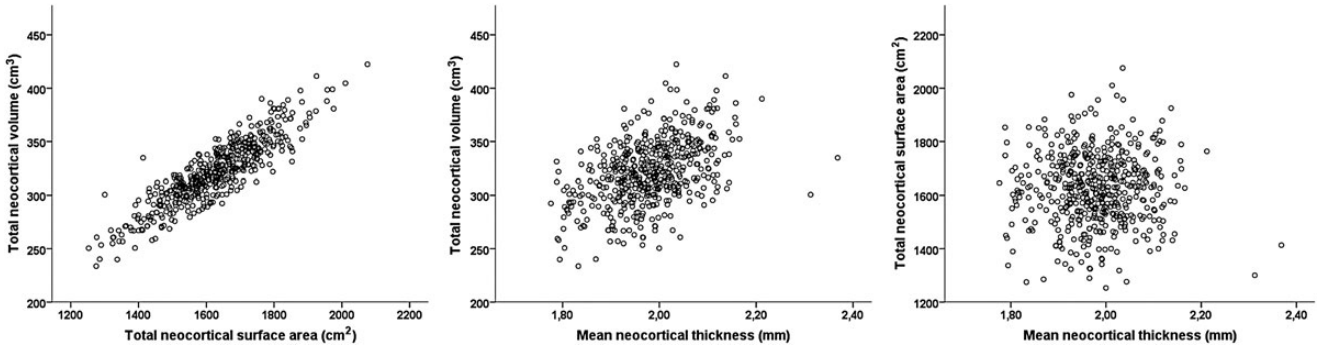

Figure 1. Scatterplots for total neocortical volume–total neocortical surface area, total neocortical volume–mean neocortical thickness, and total neocortical surface area–mean neocortical thickness.

analyses. Common environmental correlations are not shown because the best-fitting models did not include common environmental influences for any of the cortical measures. Total neocortical surface area and mean neocortical thickness were uncorrelated both phenotypically and genetically. As can be seen in Table 2, both the phenotypic and genetic neocortical volume–surface area correlations were significantly greater than the corresponding neocortical volume–thickness correlations, as indicated by the non-overlapping 95% confidence intervals. These volume–surface area correlations were approximately double in magnitude compared with the volume–thickness correlations. Figure 1 shows the scatterplots depicting the relationships between the 3 neuroanatomic measures. Figure 2 shows the scatterplots depicting the relationship between GCA and each of the 3 neuroanatomic measures.

We tested bivariate genetic models to examine the relationship between GCA and neocortical volume. The reduced ACE–AE model, in which C effects were retained for GCA and dropped for neocortical volume, was the best-fitting bivariate model (Table 3, Model 2). Table 4 shows the standardized variance components derived from the bivariate models. Based on the best-fitting model, the heritabilities were 0.62 for GCA and 0.92 for neocortical volume. There were significant phenotypic, genetic, and unique environmental correlations between GCA and neocortical volume (Table 2).

Next, we tested the trivariate models with GCA, total neocortical surface area, and mean neocortical thickness. The ACE–AE–AE model, in which the C effects were dropped for both surface area and thickness, had an excellent fit to the data, and was the best-fitting trivariate model (Table 3, Model 4). The standardized variance components for the trivariate models are shown in Table 5. Based on the ACE–AE–AE model, heritabilities were 0.61 for GCA, 0.94 for total surface area, and 0.80 for mean thickness. As can be seen in Table 2, there were significant phenotypic and genetic correlations between GCA and total neocortical surface area but those correlations were nonsignificant for mean neocortical thickness.

As seen in Tables 4 and 5, in the reduced models, we dropped the C effects from the neocortical measures because they were nonsignificant and accounted for a small amount of the variance (only ~5% or less) in these phenotypes. The C effects were also nonsignificant for GCA, but they accounted for 15% of the variance. We were concerned that dropping this parameter (i.e., fixing it to zero) would artificially inflate the A estimate. Therefore, we took the more conservative approach of retaining it in the reduced models even though it was nonsignificant so that we would avoid overly biased estimates of A and of the shared genetics variance between GCA and neocortical measures. Thus, the reduced models included A, C, and E variance components for GCA, but only A and E variance

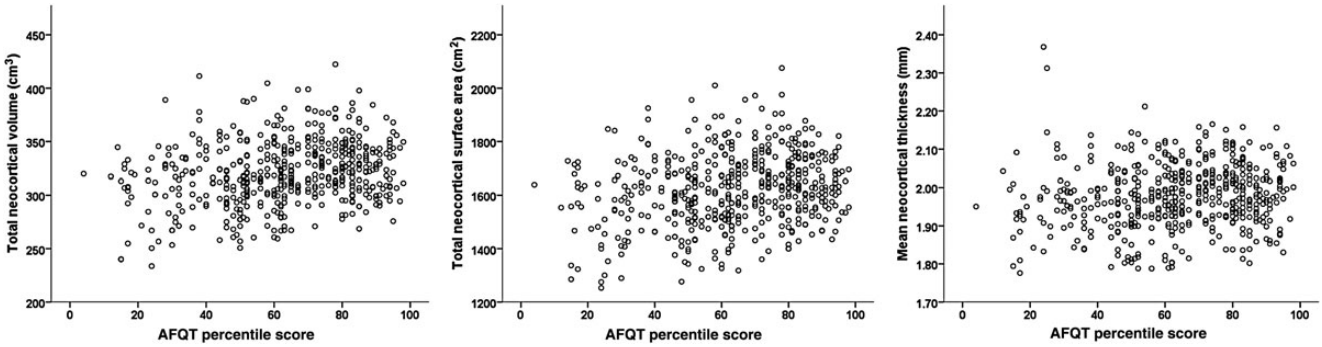

Figure 2. Scatterplots for total neocortical volume–general cognitive ability (GCA), total neocortical surface area–GCA, and mean neocortical thickness–GCA. General cognitive ability was measured with the AFQT.

Table 3
Bivariate (GCA, total neocortical volume) and trivariate (GCA, total neocortical surface area, mean neocortical thickness) model-fitting results

Model	−2LL	LRT	d.f.	Δd.f.	*P* value
Bivariate models					
1. ACE–ACE Cholesky	2477.296	—	1019	—	—
2. ACE–AE	2477.296	0.001	1021	2	0.9999
Trivariate models					
3. ACE–ACE–ACE Cholesky	3761.942	—	1524	—	—
4. ACE–AE–AE	3763.246	1.304	1529	5	0.934
5. ACE–AE–AE, r_g between thickness and GCA = 0	3764.566	1.320	1530	1	0.251
6. ACE–AE–AE, r_g between surface area and GCA = 0	3776.075	12.829	1530	1	0.001

Note: Model 1 is the comparison model for Model 2; Model 3 is the comparison model for Model 4; Model 4 is the comparison model for Models 5 and 6. GCA, general cognitive ability; −2LL, −2 log likelihood; LRT, likelihood-ratio χ^2-test; Δd.f., change in degrees of freedom; A, additive genetic variance; C, common environmental variance; E, unique environmental variance; r_g, genetic correlation.

Table 4
Standardized variance components for bivariate model (GCA, total neocortical volume)

Model	General cognitive ability	Total neocortical volume
Full (ACE–ACE Cholesky)[a]		
	A = 0.62 (0.35; 0.82)	A = 0.92 (0.75; 0.94)
	C = 0.15 (0.00; 0.41)	C = 0.00 (0.00; 0.18)
	E = 0.22 (0.17; 0.30)	E = 0.08 (0.06; 0.10)
Reduced (ACE–AE)[b]		
	A = 0.62 (0.36; 0.82)	A = 0.92 (0.89; 0.94)
	C = 0.16 (0.00; 0.40)	C = 0.00
	E = 0.22 (0.17; 0.30)	E = 0.08 (0.06; 0.10)

Note: GCA, general cognitive ability; A, additive genetic variance; C, common environmental variance; E, unique environmental variance.
[a]From Model 1 in Table 3.
[b]From Model 2 in Table 3.

components for neocortical volume, total surface area, and mean thickness.

For the trivariate model, we tested further reduced models where the genetic correlation between GCA and either total surface area or mean thickness was fixed at zero. Excluding the genetic correlation between GCA and mean thickness from the model resulted in virtually no change in model fit (Table 3, Model 5). In sharp contrast, the fit to the data was extremely poor after excluding the genetic correlation between GCA and surface area from the model (Table 3, Model 6).

Finally, we used information derived from the model testing to determine the genetic contribution to the phenotypic

Table 5
Standardized variance components for trivariate model (GCA, total neocortical surface area, mean neocortical thickness)

Model	General cognitive ability	Total neocortical surface area	Mean neocortical thickness
Full (ACE–ACE–ACE Cholesky)[a]			
	A = 0.63 (0.35; 0.82)	A = 0.90 (0.68; 0.95)	A = 0.74 (0.49; 0.84)
	C = 0.15 (0.00; 0.41)	C = 0.05 (0.00; 0.27)	C = 0.06 (0.00; 0.30)
	E = 0.22 (0.17; 0.29)	E = 0.06 (0.04; 0.08)	E = 0.20 (0.15; 0.27)
Reduced (ACE–AE–AE)[b]			
	A = 0.61 (0.36; 0.82)	A = 0.94 (0.92; 0.96)	A = 0.80 (0.73; 0.85)
	C = 0.16 (0.00; 0.40)	C = 0.00	C = 0.00
	E = 0.23 (0.17; 0.29)	E = 0.06 (0.04; 0.08)	E = 0.20 (0.15; 0.27)

Note: GCA, general cognitive ability; A, additive genetic variance; C, common environmental variance; E, unique environmental variance.
[a]From Model 3 in Table 3.
[b]From Model 4 in Table 3.

Table 6
Standardized variance components of specific cognitive abilities for trivariate model

Verbal ability	Arithmetic	Tool/mechanical reasoning	Spatial processing
A = 0.36 (0.01; 0.62)	A = 0.44 (0.14; 0.73)	A = 0.27 (0.001; 0.65)	A = 0.63 (0.37; 0.72)
C = 0.16 (0.00: 0.47)	C = 0.22 (0.00; 0.48)	C = 0.33 (0.00; 0.59)	C = 0.00 (0.00; 0.22)
E = 0.48 (0.37; 0.61)	E = 0.34 (0.26; 0.44)	E = 0.40 (0.31; 0.52)	E = 0.37 (0.28; 0.48)

Note: A, additive genetic variance; C, common environmental variance; E, unique environmental variance.
Based on Model 1 (ACE–AE–AE) for each specific cognitive ability in Table 8.

correlation, that is, the proportion of the observed correlation that is mediated by genetic factors. This contribution is calculated as the product of the genetic correlation and the square roots of the heritabilities of each phenotype divided by the phenotypic correlation (Neale and Cardon 1992). The observed correlations between each cortical measure and GCA were mediated primarily by genetic factors. The proportion of the observed correlations that were mediated by genetic factors was 86% for neocortical volume and 86% for total surface area.

Specific Cognitive Components

After examining GCA, we examined the relationship of each of the 4 cognitive components of the AFQT with total neocortical surface area and with mean thickness. Table 6 shows the standardized variance components for each of the AFQT cognitive components. Heritabilities were modest for verbal ability,

Table 7
Correlations for specific cognitive abilities and total neocortical surface area/mean neocortical thickness

	Verbal ability	Arithmetic	Tool/mechanical reasoning	Spatial processing
Phenotypic correlations				
Surface area	**0.17 (0.08; 0.27)**	**0.20 (0.11; 0.29)**	0.08 (−0.02; 0.18)	**0.15 (0.05; 0.24)**
Thickness	0.08 (−0.02; 0.17)	**0.12 (0.02; 0.21)**	0.01 (−0.09; 0.10)	0.06 (−0.04; 0.15)
Genetic correlations				
Surface area	**0.25 (0.08; 1.00)**	**0.29 (0.14; 0.56)**	0.11 (−0.10; 1.00)	**0.17 (0.04; 0.30)**
Thickness	0.08 (−0.14; 0.57)	0.14 (−0.04; 0.36)	0.12 (−0.11; 1.00)	0.05 (−0.10; 0.20)
Unique environmental correlations				
Surface area	0.16 (−0.01; 0.32)	0.08 (−0.09; 0.25)	0.16 (−0.01; 0.32)	0.11 (−0.07; 0.27)
Thickness	0.12 (−0.04; 0.28)	0.12 (−0.05; 0.28)	**−0.18 (−0.33; -0.01)**	0.07 (−0.10; 0.24)

Note: Statistically significant correlations ($P < 0.05$) are in bold; 95% confidence intervals are shown in parentheses. Cognitive ability–surface area correlations and cognitive ability–thickness correlations were derived from the trivariate genetic model (see Table 8, Model 1 for each specific cognitive ability).

Table 8
Trivariate (specific cognitive abilities, total neocortical surface area, and mean neocortical thickness) model-fitting results

Trivariate models	−2LL	LRT	d.f.	Δd.f.	*P* value
Verbal ability					
1. ACE–AE–AE	3863.070	—	1529	—	—
2. ACE–AE–AE, r_g between thickness and GCA = 0	3863.666	0.596	1530	1	0.440
3. ACE–AE–AE, r_g between surface area and GCA = 0	3871.557	8.487	1530	1	0.004
Arithmetic					
1. ACE–AE–AE	3820.549	–	1529	–	–
2. ACE–AE–AE, r_g between thickness and GCA = 0	3823.041	2.492	1530	1	0.114
3. ACE–AE–AE, r_g between surface area and GCA = 0	3834.682	14.133	1530	1	0.001
Tool/mechanical reasoning					
1. ACE–AE–AE	3845.270	—	1529	—	—
2. ACE–AE–AE, r_g between thickness and GCA = 0	3846.415	1.145	1530	1	0.285
3. ACE–AE–AE, r_g between surface area and GCA = 0	3846.532	1.262	1530	1	0.261
Spatial processing					
1. ACE–AE–AE	3852.090	—	1529	—	—
2. ACE–AE–AE, r_g between thickness and GCA = 0	3852.568	0.479	1530	1	0.489
3. ACE–AE–AE, r_g between surface area and GCA = 0	3858.894	6.804	1530	1	0.009

Note: Model 1 is the comparison model for Models 2 and 3.
−2LL, −2 log likelihood; LRT: likelihood-ratio χ^2-test; Δd.f.: change in degrees of freedom; A, additive genetic variance; C, common environmental variance; E, unique environmental variance; r_g, genetic correlation.

arithmetic, and tool/mechanical reasoning (0.27–0.44). The heritability of the spatial processing component was higher (0.63), and it was the only cognitive component with no C effects.

The phenotypic, genetic, and unique environmental correlations of each component with surface area and thickness are shown in Table 7. The results for verbal ability, arithmetic, and spatial processing paralleled the results for GCA. The 1 exception was that there was a small, but significant phenotypic correlation between neocortical thickness and arithmetic ($r = 0.12$); however, the genetic correlation was nonsignificant. There were no significant phenotypic or genetic correlations for tool/mechanical reasoning.

As can be seen in Table 8, the trivariate genetic models for each cognitive component also closely parallel the results for GCA. For 3 of the 4 components, there was a significant reduction in model fit when the genetic correlation between the cognitive component and neocortical surface area was fixed at zero, but there was not a significant change in model fit when the genetic correlation between the component and neocortical thickness was fixed at zero.

Discussion

We began with an examination of the phenotypic and genetic relationships between neocortical volume and GCA. Our results were strikingly consistent with the results of Posthuma et al. (2002) for cerebral gray matter volume. Their phenotypic and genetic correlations were 0.25 and 0.29, respectively; ours were 0.22 and 0.25. They found that the observed correlation was mediated entirely by genetic factors. In our sample, genetic factors accounted for most (86%), but not all, of the observed correlation. Therefore, we have shown a very similar relationship for a different, but related, phenotype. Demonstrating this consistency for these volumetric results was also important for supporting the argument that our results for surface area and thickness are unlikely to be due to unusual characteristics of our sample. In our analysis of the relationship of neocortical thickness and surface area with GCA, we found that, total surface area, but not mean thickness, had a significant phenotypic correlation with GCA. It is not necessarily the case that genetic associations parallel phenotypic associations but we did observe the same pattern at the genetic level in, what is to our knowledge, the first genetic analysis of these relationships. Thus, the phenotypic relationship between cortical volume and GCA is driven primarily by neocortical surface area rather than thickness, and that phenotypic association is largely mediated by genetic factors (i.e., 86% of the observed GCA-surface area correlation was due to genetic factors).

It is possible that the relationship of GCA to surface area and thickness might be driven more by particular cognitive components than others, but the genetic model testing indicated that the relationships were mostly similar for 3 of the 4 specific

components. There was a mixed result for the tool/mechanical reasoning component in that it had no significant phenotypic or genetic correlations with surface area. In contrast to the overall pattern, 1 component—arithmetic—had a small, but significant phenotypic correlation with mean thickness. There was also a significant negative unique environmental correlation between tool/mechanical reasoning and thickness. This was the only negative correlation between a cognitive and a neuroanatomic measure. Although the latter 2 correlations could be Type 1 errors, they might also suggest that thickness is related to some other specific cognitive abilities not assessed with our measure of GCA.

Although we are unaware of any other genetic studies of this issue, there are phenotypic studies using a map-based approach in which significant positive correlations between regional cortical thickness and GCA have been reported (Narr et al. 2007; Choi et al. 2008; Joshi et al. 2011; Karama et al. 2011, 2013). On the other hand, several phenotypic map-based studies did not find significant regional thickness–GCA correlations (Shaw et al. 2006; Bjuland et al. 2013; Colom et al. 2013) although 1 of these (Goh et al. 2011) reported negative regional thickness–GCA correlations. In phenotypic map-based analyses of surface area–GCA relationships, Colom et al. (2013) and Fjell et al. (2013) found significant phenotypic associations, whereas Skranes et al. (2013) did not. The use of map-based approaches in these studies makes it hard to draw conclusions as to whether global mean thickness/total surface area or only some specific thickness/surface area regions were related to GCA.

In addition to our current study, we are aware of 3 other studies that investigated the relationship between global measures of mean thickness or total surface area and GCA. In line with the current results, there was a positive phenotypic relationship between total surface area and GCA, but not mean thickness, in a study of older adults mostly over 80 years of age (Fleischman et al. 2013). In young adults mainly in their 20s, both total surface area and mean thickness were positively related to GCA (Yang et al. 2013). In contrast, mean thickness in a study with an age range of 8–30 years was negatively related to GCA; a breakdown by age groups revealed a significant negative correlation in children (8–14 years), but nonsignificant correlations in adolescents or young adults (Tamnes et al. 2011). Surface area measures were not included in this study.

Combining global and map-based studies, there were significant positive thickness–GCA correlations in 6 of 13 studies; results were more consistent for surface area, with significant positive surface area–GCA correlations in 5 of 6 studies. Considering only map-based studies, significant positive regional thickness–GCA correlations were found in 5 of 9 studies, whereas significant positive regional surface area–GCA correlations were found in 2 of 3 studies. More relevant to the present study is the results of studies—including the current study—that used global measures: significant positive total surface area–GCA correlations were found in 3 of 3 studies; and significant positive mean thickness–GCA correlations were found in only 1 of 4 studies. In 2 of the map-based studies (Shaw et al. 2006; Goh et al. 2011), and 1 of the studies using global measures (Tamnes et al. 2011), there were significant inverse correlations between thickness and GCA. Although Goh et al. found some inverse regional correlations with thickness, there was a significant positive correlation with total brain volume. Without conducting a meta-analysis, these results—combined with the current study—suggest that more research is needed to shed light on the mixed results for cortical thickness and that greater emphasis should be placed on neocortical surface area as a brain phenotype with respect to GCA.

With respect to aging or developmental changes, the cross-sectional associations that we observed in our late middle-aged adults may not necessarily be the same throughout the lifespan. GCA is highly heritable and very stable throughout the lifespan (Deary et al. 2000; Lyons et al. 2009), and the present results for cortical volume were quite consistent with the prior genetic studies of GCA–cerebral gray matter volume correlations in children and younger adults (Posthuma et al. 2002; van Leeuwen et al. 2009). Surface area and thickness are also highly heritable and relatively stable throughout life, but there also appears to be a dynamic relationship between them (Stiles and Jernigan 2010). There is evidence, for example, that during childhood the trajectories of surface area and thickness are not parallel. From early childhood to early adulthood mean cortical thickness appears to decrease linearly with age; total cortical surface area appears to increase until early adolescence and then decrease until early adulthood, but at a much slower rate than cortical thickness (Shaw et al. 2006; Brown et al. 2012; van Soelen et al. 2012; Alemán-Gómez et al. 2013). Continued reductions take place during normal adult aging (Salat et al. 2004; Kochunov et al. 2008).

The greater changes taking place during childhood and adolescence might partially account for some of the mixed findings in the studies that we summarized. Total surface area–GCA associations were consistent in young (Yang et al. 2013), middle-aged (current study), and older (Fleischman et al. 2013) adults, but results for thickness were more inconsistent in younger samples. For example, Karama et al. (2011) reported widespread positive regional thickness–GCA correlations in 6–18 year olds, whereas Tamnes et al. (2011) reported a negative correlation between mean thickness and GCA in 8–14 year olds and no correlation in older individuals (>14–30). The dynamics of cortical thickness–GCA associations may change over rather short periods during child development as suggested by the study of Shaw et al. (2006). Cortical thickness and GCA in that study were uncorrelated across the entire sample; however, thickness was negatively correlated with GCA in younger children, but switched to a positive relationship in later childhood and adolescence. Also, individuals with superior GCA compared with those with average GCA had a different pattern of cortical thickness changes from 7 to 16 years of age. However, it is still puzzling that other studies with a similar age range (e.g., Karama et al. 2011) found only positive thickness–GCA correlations.

Cortical thinning tends to be associated with atrophy and poorer cognitive function in older adults (Salat et al. 2004; Fjell et al. 2012). Cortical thinning during adolescence may also be associated with synaptic pruning (Rakic et al. 1994). As such, cortical thinning during this period may be associated with more efficient cognitive function, unless pruning was excessive. In a map-based study of surface area, neocortical regions that undergo the greatest areal expansion during childhood tended to be most strongly correlated with cognitive function (Fjell et al. 2013). It has been suggested that stretching of the cortex may be a mechanism for enhancing functional connectivity (Seldon 2007), but that some regional stretching—which increases surface area—may be accompanied by regional

thinning (Hogstrom et al. 2013). This phenomenon could partially explain the more consistent correlations between surface area and GCA in comparison to thickness and GCA. On the other hand, there is also evidence that neocortical regions undergoing the greatest areal expansion during childhood also tend to be the thickest (Hill et al. 2010). This might explain some of the regional thickness–GCA correlations that have been reported.

Although these interpretations seem to be contradictory, it is important to distinguish between cross-sectional and longitudinal studies. Cortical thinning over a 2-year period was associated with decline in GCA in children and adolescents; surface area changes were not associated with GCA change, perhaps because surface area change is much smaller during this period (Burgaleta, Johnson, et al. 2013). It is also worth noting that within-person thinning during childhood and adolescence does not necessarily mean thinner cortex at a given point in time. Individuals starting with a thicker cortex are still likely to remain thicker after pruning, something that would be more consistent with the positive rather than negative thickness-GCA correlations (if thickness is meaningfully related to GCA). Other evidence of the complex relationships that may be present between neocortical surface area and thickness comes from a study in which a leftward asymmetry for surface area but a rightward asymmetry for thickness was found in different auditory cortex regions (Meyer et al. 2013).

With respect to development, it is also important to keep in mind that brain–cognition associations are unlikely to be unidimensional. Greater surface area does foster greater intellectual ability, but there are also individual differences in experience-dependent plasticity that in turn alter developmental trajectories and can have long-lasting effects (Gluckman et al. 2009; Hrvoj-Mihic et al. 2013). For example, late development of synaptic density in prefrontal cortex, which may serve to lengthen the period for developing higher level cognitive abilities (Hrvoj-Mihic et al. 2013), could be a partial reason for the changing relationships between cortical thickness and GCA from childhood to adolescence. Thickness–GCA relationships could also vary in adulthood, because later developing cortical association regions and region that manifest greater areal expansion in early childhood do show more thinning in young versus middle-aged adults (McGinnis et al. 2011). An effect on some cognitive functions that could be related to experience-dependent plasticity is suggested by findings from a sample from the same twin registry as participants in the present study. In that study, the impact of common environment on adult reading ability varied substantially as a function of presumed environmental context (Kremen et al. 2005). At the lowest level of parental education, common environment accounted for 52% of the variability in reading ability, but it did not account for any variance at the highest level of parental education. On the other hand, we found no such moderation effect for GCA in the present sample (Grant et al. 2010).

Individual structural differences in white matter tracts (Penke et al. 2012) and subcortical regions (Burgaleta, Macdonald, et al. 2013) also contribute to individual differences in cognitive abilities. There is also evidence that white matter damage is related to GCA in old age, after accounting for childhood GCA (Valdes Hernandez et al. 2013). Cortical thinning also takes place in normal aging, and it is related to changes in cognitive performance (Fjell et al. 2012). However, findings from the Lothian Birth Cohort suggest more stability than change with respect to associations with GCA. In that sample, the pattern of associations between current GCA and cortical thickness regions in older adult brains was quite similar to the pattern of associations between childhood GCA and cortical thickness in the same older adult brains (Karama et al. 2013). Older age has also been associated with surface area reductions (Hogstrom et al. 2013), but relatively little is known about the dynamics of changes in surface area and thickness and their relationship to changes in cognitive abilities during the latter half of the lifespan. We also cannot be certain that our results are generalizable to women; however, the cited prior studies of GCA–cortical associations have found little or no sex differences.

Some methodological considerations are also important with regard to interpretation of cortical–GCA associations. The basic geometry of the cortical ribbon would seem to mandate that cortical volume will be much more highly correlated with cortical surface area than with cortical thickness, but these relationships may vary over the course of development. Consistent with this idea, neocortical surface area in neonates has been shown to be related to volume according to a power law, whereas thickness was unrelated to volume (Xue et al. 2007). Few published studies of cortical–GCA associations have reported thickness/surface area–volume correlations. Cortical thickness was correlated 0.75 with cortical volume in the study of Karama et al. (2011) and 0.65 in the study of Colom et al. (2013); both studies used the same methods. In our data, the phenotypic cortical thickness–volume correlation was only 0.43, approximately one-half that of the surface area–volume correlation of 0.88. Using the same methods as in our study, Winkler et al. (2010) reported strikingly similar thickness–volume (0.43) and surface area–volume (0.89) correlations. Using a different method in the same study, Winkler et al. reported a thickness–volume correlation of 0.53 and a surface–area volume correlation of 0.76. Thus, 56% of the phenotypic variance in cortical volume is shared by thickness in the Karama et al. data, 42% in the Colom et al. data, 28% by 1 method in the Winkler et al. data, but 18% in our study and 18% in the study of Winkler et al. when using the same methods as the present study.

These different thickness–volume correlations suggest the possibility that methodological differences may contribute to inconsistencies across studies. Direct comparison of the different methods of measuring cortical thickness is needed in order to resolve these issues. It is possible that in some methods volume might be partially contributing to thickness estimates. Differences in partial volume effects in gray matter segmentation across different methods can affect estimation of cortical thickness (Lüsebrink et al. 2013). Thickness estimates could also vary if there were differences in gray–white contrast signal intensity across studies because that would, in turn, affect the determination of the gray–white boundary (Fischl and Dale 2000). Another possibility is that the different thickness–volume associations could be a function of age. For example, the mean ages were 12 (Karama et al. 2011) and 20 (Colom et al. 2013) in the samples with larger correlations, but they were 49 (Winkler et al. 2010) and 55 in the samples with smaller correlations.

Studies also varied as to whether or how the investigators adjusted for overall brain size. We have argued that controlling for total brain volume was problematic in the current study. Our finding that the correlation between total brain volume and neocortical surface area was 0.91, but was only 0.14 with thickness, also has implications for studies in which the focus

is region-specific differences in the relationship of cognition to neocortical surface area or thickness. To understand region-specific (relative) differences, it is necessary to control for global effects, but controlling for total brain volume or intracranial volume will have vastly different effects for surface area and thickness. Moreover, those effects may be different in children and adults as thickness–volume correlations may change during different periods of development. Therefore, it is our view that regional surface area relationships should be controlled for total surface area, and regional thickness relationships should be controlled for mean thickness.

In sum, the present findings have important implications for the study of normal and pathological aging as well as psychiatric and neurologic disorders. Considering neocortical gray matter, our results suggest that in healthy adults individual differences in surface area rather than in thickness do explain the individual differences in GCA, and this association is mostly due to shared genetic effects. A similar pattern was observed when we investigated the specific cognitive domains of verbal, arithmetic, and spatial processing abilities. However, in these domain-specific analyses, we also detected a small, but statistically significant, correlation between arithmetic ability and cortical thickness. The present findings and the discussion of other cerebral measures clearly indicate that neither neocortical surface area nor genetic factors are the only determinants of individual differences in cognitive ability differences. Moreover, there may be complex patterns of age-related changes in the relationship of neocortical surface area and thickness to GCA.

Nevertheless, the present results—based on global neocortical measures—constitute an initial step toward elucidating the genetic relationship between cortical structure and cognition. At the global level, neocortical thickness are surface area are independent, but their relationship may vary at the regional level (Hill et al. 2010; Hogstrom et al. 2013). A more complete understanding will necessitate examination of thickness and surface area regions of interest as well as continuous maps of the cortex and of other brain regions. Such analyses are currently underway in the VETSA sample. Finally, we note that although the ultimate goal of genetic analyses is to identify specific genes, the twin method is still particularly useful for elucidating the genetic underpinnings of brain–GCA associations because it can determine the nature of those associations before the specific genes involved are identified. Thus, the twin data indicate that for these purposes, the targeted phenotypes should be neocortical thickness and surface area rather than volume.

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Notes

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