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SHORT COMMUNICATION

Brain structure mediates the association between height and cognitive ability

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Abstract

Height and general cognitive ability are positively associated, but the underlying mechanisms of this relationship are not well understood. Both height and general cognitive ability are positively associated with brain size. Still, the neural substrate of the height-cognitive ability association is unclear. We used a sample of 515 middle-aged male twins with structural magnetic resonance imaging data to investigate whether the association between height and cognitive ability is mediated by cortical size. In addition to cortical volume, we used genetically, ontogenetically and phylogenetically distinct cortical metrics of total cortical surface area and mean cortical thickness. Height was positively associated with general cognitive ability and total cortical volume and cortical surface area, but not with mean cortical thickness. Mediation models indicated that the well-replicated height-general cognitive ability association is accounted for by individual differences in total cortical volume and cortical surface area (highly heritable metrics related to global brain size), and that the genetic association between cortical surface area and general cognitive ability underlies the phenotypic height-general cognitive ability relationship.

Keywords Cognitive ability · Cortical surface area · Cortical thickness · Height · Magnetic resonance imaging · Twins

Introduction

Both height and general cognitive ability (GCA) are predictors of health outcomes, and there is a positive height-GCA correlation of 0.10–0.20 (Silventoinen et al. 2012; Keller et al. 2013; Marioni et al. 2014). There has been widespread interest in the association between height and cognitive ability from the development of preterm infants (Sammallahti et al. 2014) to aging-related dementia (Russ et al. 2014). Height is highly heritable, but is also considered to reflect early life events and is often regarded as a proxy for early brain development. Still, the neural substrate of the height-cognitive ability association is unclear. Understanding its neural underpinnings may shed light on pathways to normative and abnormal development and aging.

Both height and GCA have substantial heritability and their association is largely due to shared genetic effects (Silventoinen et al. 2012; Marioni et al. 2014). Both are positively correlated with brain volume (which is also highly heritable), and these associations are also largely due to shared genetic effects (Posthuma et al. 2000, 2002). Studies have examined head size or global brain measures with respect to height (Taki et al. 2012; Adams et al. 2016).

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Association between brain volume and GCA remains when controlling for height (Andreasen et al. 1993) and a map-based study in children using cortical volume (CV) measures of gray matter indicated some overlapping regional brain volume-height and brain volume-GCA correlations (Taki et al. 2012). Still, no studies have investigated if cortical structure mediates the association between height and GCA.

During the past decade, studies of GCA-cortical relationships have moved from CV measures to investigations of cortical thickness (CT) and surface area (CSA) separately, two metrics that are phenotypically and genetically uncorrelated at the global level (Panizzon et al. 2009; Vuoksimaa et al. 2015). However, we are unaware of any investigations of the role that CT and CSA play in the relationship between height and GCA. A twin design could further explicate the genetic/environmental underpinnings of these associations.

In a sample of 515 middle-aged male twins (51–60 years) with data on GCA, height and neuroimaging with 1.5T MRI, we investigated whether cortical structure mediates the height-cognitive ability association and the genetic underpinnings of those relationships. Using the same sample, we have previously reported that GCA is positively correlated with total cortical CSA, but not with mean CT and that total CSA is much more strongly related to cortical, whole brain, and intracranial volumes in comparison to mean CT (Vuoksimaa et al. 2015). Further, we have also shown that both GCA and height are associated with greater CSA in regions that are relatively high-expanded across evolution and human development, whereas CT in these regions was not related to height (Vuoksimaa et al. 2016). These observations, together with other studies including brain structure, cognition and height, e.g., (Andreasen et al. 1993; Taki et al. 2012), led us to hypothesize that the height-GCA association would be accounted for by cortical CSA, rather than CT.

We studied the global cortical metrics of total CV and CSA and mean CT in relation to GCA and height. Associations of GCA with total cortical volume, total CSA and mean CT (including their shared genetic effects) have been reported previously in Vuoksimaa et al. (2015). Associations of height with global cortical size measures and GCA in this sample are reported here for the first time. Our analyses included mediation models and trivariate Cholesky decomposition with height, cortical size and GCA.

Methods and materials

Participants

Participants were 534 middle-aged men (51–60-year-olds; $M = 55.7$; SD = 2.6) from the Vietnam Era Twin Study of Aging (VETSA) (Kremen et al. 2006, 2013). After quality control, we had measures of total cortical gray matter volume and surface area and cortical thickness on 515 participants (Vuoksimaa et al. 2015). The sample consisted of 131 monozygotic (MZ) and 96 dizygotic (DZ) full twin pairs and 61 individuals without a co-twin. Our sample of over 500 participants is well powered to detect small height-GCA correlation of about 0.10–0.20 as suggested by earlier literature.

Zygosity determination was based on 25 microsatellite markers for majority of the participants (92%). Questionnaire and blood group-based zygosity determination was used for the remaining participants (8%). Questionnaire and blood group based classification has 95% agreement with the DNA-based method indicating that most of the twin pairs with non-DNA-based zygosity determination are correctly classified.

Data on GCA and neuroimaging were collected on back-to-back days. Height was assessed in stocking feet with a stadiometer, rounded to the nearest half inch and then converted to cm. Height and GCA data were acquired on the same day. Data were collected at two sites: University of California, San Diego and Boston University (neuroimaging at the Massachusetts General Hospital). Ethical approval was obtained from all participating institutions and all participants gave written informed consent.

General cognitive ability (GCA) measure

GCA was measured with Armed Forces Qualification Test (AFQT). The AFQT is a 50-min paper-and-pencil test consisting of items measuring verbal ability (vocabulary); arithmetic, spatial processing (mental folding and unfolding of boxes); and reasoning about tools and mechanical relations. The total score on the AFQT has a correlation ~0.85 with Wechsler IQ and in the VETSA sample test–retest reliability was 0.74 over 35 years and 0.73 over 42 years (Lyons et al. 2009, 2017). AFQT yields a percentile score but in the analyses we used a variable whereby the percentile scores were transformed into their normal deviates (Lyons et al. 2009).

Image acquisition and processing

Detailed descriptions of MR image acquisition and processing can be found in (Kremen et al. 2010) and (Eyler et al. 2012). Briefly, 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 $1.3 \times 1.0 \times 1.3$ mm. To increase the signal-to-noise ratio, the two MPRAGE acquisitions were rigid-body registered to each other (motion corrected) and then averaged.

Volume segmentation (Fischl et al. 2002, 2004a) and cortical surface reconstruction (Dale and Sereno 1993; Dale et al. 1999; Fischl et al. 1999, 2004b) were performed using

the publicly available FreeSurfer software package, version 3.0.1b running on a 32-bit CentOS-based Linux system. 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. The cortical surface was covered with a triangular tessellation, which was then smoothed to reduce metric distortions. A refinement procedure was then applied to obtain a more accurate 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).

Total surface area was calculated as the sum of the areas of all vertices across the cortex. Cortical thickness was calculated as the average distance between the gray/white boundary and the pial surface within each vertex (Fischl and Dale 2000). Mean cortical thickness was calculated as the average thickness of the whole cortex. Total cortical volume was calculated as a product of total cortical surface area and mean cortical thickness.

Bootstrapped mediation models

We ran a multilevel mediation model in Stata (ml_mediation) with family as a cluster variable (i.e., robust standard errors accounting for the clustered within-family twin data). GCA was a dependent variable, total CV or CSA was a mediator variable and height was independent variable. The effects of age and scanner (different scanners were used in Boston and San Diego data collection sites) were regressed out of total CV and CSA before the analysis.

All variables were standardized with a mean of 0 and standard deviation of 1. A bootstrapped method with 1000 replications was used to derive 95% confidence intervals. Path estimates that do not include zero in the confidence intervals were considered as statistically significant. We also ran an additional mediation model whereby height and total CSA variables were considered as mediator and independent variables, respectively.

Biometrical genetically informative twin analyses

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 (see Supplementary material for more specific description about the twin modeling and its assumptions). We began with trivariate models that included additive genetic (A), common environmental (C) and unique environmental (E) variance components for GCA, total CSA, and height. This starting point was called as the "ACE–ACE–ACE" Cholesky. Next, a reduced ACE-AE-AE Cholesky decomposition in which the C effects for total CSA and height were fixed to be zero was tested relative to the full ACE–ACE–ACE Cholesky decomposition. We have previously used the Cholesky decompositions in the context of GCA, total CSA and mean CT. Our previous work (Vuoksimaa et al. 2015) showed that C effects were 0.17 for GCA, but the lower bound of the 95% confidence interval included zero indicating that C effects could also be fixed to zero in the case of GCA. However, we kept the C component for GCA in the subsequent models because we believe that the magnitude of C effect was too large to be fixed at zero. It is important to note that all covariance between twins is accounted either by A or C effects. Thus, fixing C to zero would inflate the magnitude of A effects. Our approach of keeping the C effect for GCA is, therefore, a conservative approach which reduces the possibility that genetic covariation between traits is confounded by the C effects. We computed phenotypic, genetic (representing the shared genetic variance between variables) and unique environmental (represent the shared individual-specific environmental variance between variables) correlations between GCA, total CSA and height (Neale and Cardon 1992).

Model comparisons were based on the likelihood-ratio χ^2-test, which is calculated as the change in -2 log likelihood (-2LL) from one model to another 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 solution 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. The effects of age and scanner were regressed out of the cortical measures prior to all analyses.

Results

Measured height ($M=177$ cm, SD $=6.7$ cm) was positively correlated with GCA ($r=0.10$, $p=0.022$), CV ($r=0.24$, $p<0.0001$) and CSA ($r=0.25$, $p<0.0001$), but not with CT ($r=0.04$, $p=0.41$). We previously reported the sample description and descriptive statistics for CSA, CT and GCA in (Vuoksimaa et al. 2015) where we also showed that the association between CV and GCA is driven by CSA rather than CT. Based on a trivariate Cholesky decomposition, phenotypic and genetic correlations, respectively, between cortical metrics and GCA as reported in Vuoksimaa et al. (2015) were: 0.22 and 0.25 for CV; 0.21 and 0.24 for CSA and 0.08 and 0.09 for CT. Since both height and GCA were associated with CV and CSA but not with CT, we used only CV and

CSA in subsequent analyses (see supplementary Tables 1 and 2 for regression models for height-GCA, height-CV, and height-CSA associations).

First, we ran a non-mediation model which indicated a significant association between height and GCA (Fig. 1a). We then ran a mediator model using CV as a mediator of the height-GCA association (Fig. 1b). In this model, CV significantly mediated the association between height and GCA. The direct effect of height on GCA was not significant ($\beta = 0.077$, 95% CI −0.040; 0.194), but the indirect effect of height on GCA through CV ($\beta = 0.050$, 95% CI 0.014; 0.087) accounted for 39% of the total effect ($\beta = 0.128$, 95% CI 0.005; 0.251) of height on GCA (Fig. 1b).

Next, we ran a mediator model with CSA as a mediator variable. CSA significantly mediated the association between height and GCA (Fig. 1c). In this model, the direct effect of height on GCA ($\beta = 0.080$, 95% CI −0.044; 0.205) was not significant (Fig. 1c) and the indirect effect of height on GCA through total CSA ($\beta = 0.048$, 95% CI 0.014; 0.082) accounted for 38% of the total effect ($\beta = 0.128$, 95% CI 0.003; 0.253) of height on GCA (Fig. 1c).

We also ran a mediator model with CSA as an independent variable and height as a mediator. In this model, the direct effect from CSA to GCA was significant ($\beta = 0.202$, 95% CI 0.092; 0.311), but the indirect effect of CSA to GCA through height was nonsignificant ($\beta = 0.019$, 95% CIs −0.014; 0.052) (Supplementary Fig. 1).

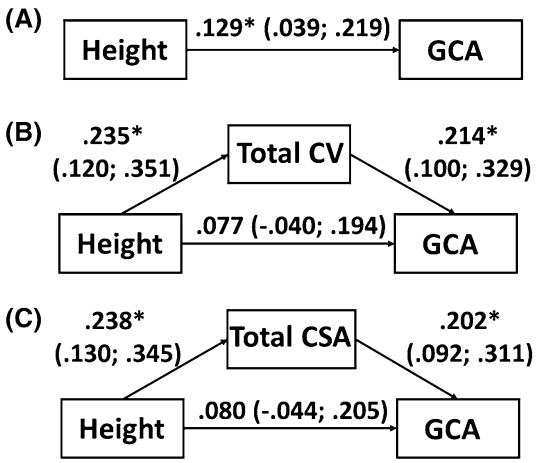

Fig. 1 Associations between height, cortical size and general cognitive ability (GCA). Path estimates with 95% confidence intervals in parentheses. **a** Path estimates for the effect of height on GCA. **b** Mediation model with total cortical volume (CV) as a mediator. Path estimates of direct and indirect effects from height to GCA. **c** Mediation model with total cortical surface area (CSA) as a mediator. Path estimates of direct and indirect effects from height to GCA. *Path estimates that do not include zero in the confidence intervals are considered as statistically significant path estimates. All variables standardized ($M = 0$, SD = 1)

Fixing C effects to zero for CSA and height did not result in a poorer fit relative to a full ACE-ACE-ACE Cholesky where all variables included A, C and E effects (model 2 vs model 1 in Table 1). Heritability estimates (95% CIs in parentheses) from the biometric trivariate Cholesky decomposition were: 0.59 (0.33;0.82) for GCA, 0.94 (0.92;0.96) for CSA, and 0.93 (0.91;0.95) for height (from model 2 in Table 1). Constraining the GCA-CSA genetic correlation to be zero did result in a poorer model fit (Table 1, model 3), but constraining the genetic correlation between height and GCA to be zero did not result in a poorer model fit (Table 1, model 4). In the best-fitting Cholesky decomposition (Table 1, model 4), phenotypic and genetic correlations between GCA and CSA were 0.19 (0.09;0.28) and 0.22 (0.09;0.36), respectively.

Discussion

The underlying mechanism of the well-replicated association between height and GCA has heretofore remained unclear. Our mediation models indicated that the height-GCA association is accounted for by brain size as characterized by individual differences in total CSA. Earlier studies have indicated some overlapping regional brain volume-height and brain volume-GCA correlations (Taki et al. 2012) and that the association between brain volume and GCA remains when controlling for height (Andreasen et al. 1993), but our study formally investigated if cortical size mediates the association between height and GCA. Going beyond examining global volumetric size measure, we also investigated mean CT and total CSA, two cortical

Table 1 Trivariate model fitting results for general cognitive ability (GCA), total cortical surface area (CSA), and height

Model	−2ll	LRT	*df*	Δ*df*	*p* value
1. ACE-ACE-ACE Cholesky	3569.826		1524		
2. ACE-AE-AE	3571.036	1.210	1529	5	0.944
3. ACE-AE-AE GCA-CSA $r_g = 0$	3584.029	12.993	1530	1	0.001
4. **ACE-AE-AE GCA-Height $r_g = 0$**	**3574.666**	**3.631**	**1530**	**1**	**0.057**

Model 1 is the comparison model for Model 2; Model 2 is the comparison model for Models 3 and 4

Model 4 includes A, C and E effects for GCA, A and E effect for CSA, A and E effects for height and significant CSA-GCA r_g, significant CSA-height r_g, but no significant GCA-height r_g

Best-fitting model shown in bold font

A additive genetic variance, *C* common environmental variance, *E* unique environmental variance, r_g genetic correlation, −2ll = −2 log likelihood, *LRT* likelihood-ratio χ^2-test, *df* degrees of freedom, *Δdf* change in degrees of freedom

metrics that are genetically and phenotypically uncorrelated across the life span (Panizzon et al. 2009; Winkler et al. 2010; Lyall et al. 2015).

Across adulthood, reductions in CV are related more to reductions in CT than CSA, suggesting that CSA may be a more stable cortical metric after childhood (Storsve et al. 2014). Our finding that CSA rather than CT is associated with height and GCA is supported by divergent trajectories of CSA and CT development; CSA continues to increase into adolescence/early adulthood whereas CT declines across postnatal development (Fjell et al. 2015; Walhovd et al. 2016; Forde et al. 2017; Remer et al. 2017). The associations between CSA and GCA emerge during early postnatal development and remain throughout life (Walhovd et al. 2016). In line with this, many studies have reported that at the global level it is CSA rather than CT that is associated with GCA across adulthood (Vuoksimaa et al. 2015; Cox et al. 2018; Ritchie et al. 2018). CT-GCA associations are less consistent across studies including findings of negative CT-GCA associations (Tamnes et al. 2011; Brouwer et al. 2014; Vuoksimaa et al. 2015).

Although we did not have neuroimaging data in young adulthood and our finding of CSA mediating the effect of height on GCA was based on a middle-aged sample, other studies have indicated stable CSA-GCA (Walhovd et al. 2016) and height-GCA (Harris et al. 2016) associations throughout life. Both height-GCA and CSA-GCA associations likely have origins in early development. Head growth in the first years of life reflects rapid growth in brain size, especially with respect to cortex. CSA undergoes remarkable growth from 0 to 2 years with an average 1.8-fold expansion in the first year of life (Li et al. 2013). Very low birth weight children have smaller CSA and lower GCA compared to those with normal birth weight (Solsnes et al. 2015). Birth weight within the normal range is positively associated with CSA (Walhovd et al. 2016). A study including 6–26-year-old twins showed that the within-twin pair differences in birth weight in both MZ and DZ twins were related to within-twin pair differences in CV (i.e., a co-twin with higher birth weight having greater CV), and these associations were driven more by within-pair differences in CSA rather than differences in CT (Raznahan et al. 2012). A Swedish study of over 200,000 men indicated that low birth weight, short birth length and small infant head circumference were all associated with poorer GCA at 18 years of age (Lundgren et al. 2001). In addition, short adult stature in those born small for gestational age was associated with poorer GCA, but catch-up growth during childhood correlated positively with young adult GCA in these individuals (Lundgren et al. 2001, 2011). Another study found that faster linear growth in childhood was related to taller height and higher education in adulthood in low and middle income countries (Adair et al. 2013). Together these studies stress the importance of early development with regard to height, brain structure, and cognitive ability in adulthood.

Multiple studies have shown that the association between height and GCA is explained to a large extent by genetic effects (Silventoinen et al. 2006, 2012; Keller et al. 2013; Marioni et al. 2014). Moreover, the associations of adult brain size and CSA with GCA are reported to be mostly genetic in origin (Posthuma et al. 2002; Vuoksimaa et al. 2015). A genome-wide association study (GWAS) of intracranial volume (a proxy measure of brain size) identified genetic variants that were also associated with adult height and both childhood and adulthood GCA (Adams et al. 2016). In short, there is a strong support for shared genetic effects among height, brain size and cognitive ability. Our study further specifies that the well-documented genetically-mediated positive association between height and cognitive ability is accounted for by cortical size as indicated by total CV and total CSA.

In the present study, we hypothesized that the association with CV would be driven almost entirely by CSA. Although our presentation of the analyses began with CV, it is important to note that we recommend against testing for an association with CV and, if significant, following up with tests for CSA and CT. Rather, the association with CV may obscure associations with CSA or CT, which are generally independent of one another. Therefore, it is important to test for associations with CSA and CT separately, regardless of whether there is an association with CV.

Growth hormone and insulin-like growth factor-1 (IGF-1) are regulators of childhood physical growth (Butler and Le Roith 2001) but are also implicated in brain development including brain growth and cortical maturation (D'Ercole et al. 1996; Narducci et al. 2018). Higher IGF-1 levels have also been reported to be associated with higher GCA (Gunnell et al. 2005). Together, these observations suggest the GH/IFG-1 axis as a candidate biological mechanism behind the height–CSA–GCA associations. Other factors may also explain the results of our study.

Limitations of our study include the all male middle-aged sample. We cannot generalize our results to women and to other age groups. However, a meta-analysis indicated that the brain size-GCA associations are evident both in men and women and in children, and in adults (Pietschnig et al. 2015). Moreover, studies have indicated positive height-GCA associations both in men and women and across the lifespan (Humphreys et al. 1985; Harris et al. 2016). Further studies in children could look at the developmental stage at which brain size mediates the height-cognition association. From a methodological standpoint, we note that scanner and software affect the estimates of CV, CSA and CT. Our data were acquired with 1.5T scanners and we used an older version of Freesurfer (same version that has been used in previous studies

from the same sample). Of the three cortical metrics used in our study, particularly CT estimates may be more prone to scanner, software or data quality effects (Walhovd et al. 2017), with data quality having a major impact on CT estimates (Ducharme et al. 2016). However, extensive quality control was performed on our data (resulting in usable CV, CSA and CT data from 515 individuals out of 534 participants with MRI data). Moreover, the finding that CSA rather than CT is associated with GCA is in line with many recent studies (Walhovd et al. 2016; Cox et al. 2018; Ritchie et al. 2018).

Adult height is one of the most heritable traits, but it has also been considered as an indicator of early life circumstances (NCD Risk Factor Collaboration (NCD-RisC) 2016). It should be noted that although genetic effects explained most of the variance in height, CSA and GCA and their interrelationships in our sample, environmental effects could play a greater role in a population with more restricted childhood nutrition and healthcare. Deficient childhood nutrition has deleterious effects on physical growth and brain development, which in turn affects cognitive development. In other words, genetic effects may play a greater role in an environment that is more optimal for development. Finally, the observed associations among height, brain size, and cognitive ability are small in magnitude, with correlations ranging from 0.1 to 0.25, i.e., each phenotype accounting for only about 1–4% of the variance in the other phenotype. Nevertheless, the associations between these traits are well replicated and our study increases the understanding of biological mechanisms underlying the height–cognitive ability association.

In conclusion, the literature supports the importance of distinguishing between the genetically, ontogenetically, and phylogenetically distinct cortical metrics of CSA and CT. Our results indicate that the well-replicated height-GCA association is accounted for by individual differences in CSA, but not CT, and that the genetic association between CSA and GCA underlies the phenotypic height-GCA relationship. Similar associations were also observed for CV, but those are driven almost entirely by CSA.

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Compliance with ethical standards

Conflict of interest AMD is a founder of and holds equity in CorTechs Laboratories, Inc., and also serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc., and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All other authors have no conflicts of interest to declare.

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