Cerebral Cortex September 2007;17:2163–2171
doi:10.1093/cercor/bhl125
Advance Access publication November 21, 2006

Relationships between IQ and Regional Cortical Gray Matter Thickness in Healthy Adults

Katherine L. Narr[1], Roger P. Woods[2], Paul M. Thompson[1], Philip Szeszko[3], Delbert Robinson[3], Teodora Dimtcheva[1], Mala Gurbani[1], Arthur W. Toga[1,2] and Robert M. Bilder[2,4]

[1]Laboratory of Neuro Imaging and [2]Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, Geffen School of Medicine at the University of California, Los Angeles (UCLA), Los Angeles, CA, USA, [3]Department of Psychiatry Research, The Zucker Hillside Hospital, North-Shore Long Island Jewish Health Systems, Glen Oaks, NY, USA and [4]Jane and Terry Semel Institute for Neuroscience and Human Behavior, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Prior studies show positive correlations between full-scale intelligence quotient (FSIQ) and cerebral gray matter measures. Few imaging studies have addressed whether general intelligence is related to regional variations in brain tissue and the associated influences of sex. Cortical thickness may more closely reflect cytoarchitectural characteristics than gray matter density or volume estimates. To identify possible localized relationships, we examined FSIQ associations with cortical thickness at high spatial resolution across the cortex in healthy young adult (age 17–44 years) men ($n = 30$) and women ($n = 35$). Positive relationships were found between FSIQ and intracranial gray and white matter but not cerebrospinal fluid volumes. Significant associations with cortical thickness were evident bilaterally in prefrontal (Brodmann's areas [BAs] 10/11, 47) and posterior temporal cortices (BA 36/37) and proximal regions. Sex influenced regional relationships; women showed correlations in prefrontal and temporal association cortices, whereas men exhibited correlations primarily in temporal–occipital association cortices. In healthy adults, greater intelligence is associated with larger intracranial gray matter and to a lesser extent with white matter. Variations in prefrontal and posterior temporal cortical thickness are particularly linked with intellectual ability. Sex moderates regional relationships that may index dimorphisms in cognitive abilities, overall processing strategies, or differences in structural organization.

Keywords: cerebral cortex, cognition, frontal, intelligence, magnetic resonance imaging, sex

Introduction

The essence of human intelligence has been a topic of considerable interest for many centuries. With the advent of imaging technologies and their advancement in recent decades, unique opportunities have emerged to study the neurobiological correlates of intellectual ability. To date, empirical evidence from imaging data, that allows the in vivo assessment of brain structure and function, has confirmed positive links between brain size and general intellectual ability. Estimated population correlations between brain size and general intelligence, termed *g* by Spearman (1904), are approximately 0.33 (McDaniel 2005). These relationships persist in spite of age (Reiss et al. 1996; McDaniel 2005) but are stronger in adults and than in children (Wilke et al. 2003; McDaniel 2005). Correlations also appear to be moderated by sex, although brain size–intelligence associations are reported in both males and females (Gur et al. 1999; McDaniel 2005). Relationships between brain size and general intelligence, both separately identified as heritable traits (Tramo et al. 1998; Baare et al. 2001; Posthuma et al. 2002), have been shown to be almost entirely genetically mediated (Thompson et al. 2001; Posthuma et al. 2002; Toga and Thompson 2005). Because genes appear to influence both phenotypes, a better understanding of how these traits are linked may help elucidate the means of genetic transmission that is not yet known.

For studies assessing associations with intracranial tissue volumes, the majority of data suggests that higher standardized intelligence scores are associated with larger cerebral gray matter volumes (Andreasen et al. 1993; Reiss et al. 1996; Gur et al. 1999). Positive relationships are also reported for white matter volumes (Gur et al. 1999; Haier et al. 2004), but negative findings exist (Andreasen et al. 1993). Although evidence supports nontrivial associations between cerebral gray matter and intelligence, few imaging studies have attempted to resolve whether structural variation in specific brain regions are associated with general intelligence and the regional specificity of existing findings is mixed. Moreover, relationships between intelligence and regional changes in brain tissue characteristics appear to be influenced by brain maturation across development. For example, in healthy children, associations between intelligence scores and cerebral gray matter, which develop with age (Wilke et al. 2003), have been localized in coarsely defined prefrontal regions (Reiss et al. 1996) and within the anterior cingulate in a study using voxel-based morphometry (VBM) methods (Wilke et al. 2003). Another VBM investigation of adolescents (age range: 12–21 years) again reported significant positive associations between FSIQ and gray matter density in cingulate cortices, whereas correlations in orbitofrontal (Brodmann's areas [BAs] 10, 11, and 47) and middle frontal cortical regions were further identified (Frangou et al. 2004).

Volumetric regions of interest studies in healthy adults also show correlations with full-scale intelligence quotients (FSIQs) in prefrontal regions (Flashman et al. 1997), although correlations are additionally reported with temporal lobe areas (Andreasen et al. 1993; Flashman et al. 1997). In a VBM study assessing correlations throughout the brain volume, Haier et al. (2004) found significant associations between higher FSIQ scores and increased gray matter density in prefrontal (BA 9, 10, 46), temporal (BA 21, 37, 22, 42), parietal (BA 43, 3), and occipital (BA 19) cortices in healthy adults. Although results concerning the spatial localization of gray matter–intelligence relationships are disparate and existing data are sparse, associations within frontal (Reiss et al. 1996; Flashman et al. 1997; Wilke et al. 2003; Frangou et al. 2004; Haier et al. 2004), temporal (Andreasen et al. 1993; Flashman et al. 1997; Haier et al. 2004), and, to a lesser extent, parietal and occipital (Haier et al. 2004) regions are most replicated. Whereas structural variations of thalamus and cerebellum appear involved at the subcortical level (Andreasen et al. 1993; Frangou et al. 2004). Regional

discrepancies in findings may reflect differences in methodological approaches (regions of interest vs. VBM approaches), correction strategies for addressing interindividual differences in brain size, and differences in the demographic characteristics of the samples studied. For example, the registration errors associated with VBM, which are required to generate a measurable signal, may compromise the ability to accurately localize regional changes in structural morphology (Bookstein 2001; Honea et al. 2005; Thacker 2005) and subsequent associations with intelligence scores. Differences in the standardized measures used to assess general intellectual ability, how strongly individual intelligence tests relate to the general factor of intelligence (*g*) (Colom et al. 2006), and the level of intellectual ability within study groups may also potentially impact the magnitude and regional specificity of results.

The thickness of the cortex, ranging between 1.5 and 4.5 mm in different cortical regions (Parent and Carpenter 1995), reflects cytoarchitectural characteristics of the neuropil including the density and arrangement of neurons, neuroglia, and nerve fibers. Measures of cortical thickness, although shown to relate to other local measures of gray matter (Narr, Bilder, et al. 2005), may more closely link with cognition and/or intellectual ability than volumetric or intensity-based gray matter concentration measures. Only one published study to date has examined correlations between general intelligence and cortical thickness. This investigation addressed the trajectory of change in the thickness of the neocortex from early childhood to early adulthood and found that relationships between FSIQ and cortical thickness were negative in early childhood (age range: 3.8–8.4 years) but that these relationships shifted toward positive correlations predominantly in frontal and temporal cortical regions in late childhood and in older subjects (age range: 8.6–29 years) (Shaw et al. 2006).

To corroborate and extend previous findings, in this study, we first set out to examine relationships between FSIQ scores and brain tissue compartments in healthy adults of average intelligence quotient (IQ). Our primary goal, however, was to newly explore the patterns of relationships between FSIQ and regional changes in cortical thickness in young adults across a relatively narrow age range, while also characterizing the influences of sex. Cortical pattern–matching methods were employed to spatially align homologous regions of cortex across individuals, allowing relationships between FSIQ and regional variations in cortical thickness to be examined at high spatial resolution across the cortical mantle (Thompson et al. 2001; Narr, Bilder, et al. 2005; Narr, Toga, et al. 2005). Based on prior assessments of gray matter density and/or volume, we predicted that relationships would be most prominent within frontal and temporal neocortical regions. Notably, because brain size and age may influence the relationships between FSIQ and cortical gray matter (Gur et al. 1999; Haier et al. 2005), both variables were included in statistical analyses. The effects of sex on the slopes of FSIQ–cortical thickness associations were explicitly examined.

Methods

Subjects

Study participants included 30 male (mean age: 27.9 ± 7.1 years) and 35 female (mean age: 28.5 ± 7.5 years) healthy individuals. Subjects participated as healthy volunteers for a larger study aimed at examining structural neuropathology in schizophrenia (Narr, Bilder, et al. 2005; Narr, Toga, et al. 2005) and were recruited through local newspaper advertisements and community word of mouth. All participants were determined to have no history of psychiatric illness as assessed by clinical interview using the Structured Clinical Interview for Axis I DSM-IV Disorders, Non-patient Edition (SCID-NP). Study exclusion criteria included serious neurological or endocrine disorders, any medical condition or treatment known to affect the brain, or meeting Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for mental retardation. The North Shore—Long Island Jewish Health System Institutional Review Board (IRB) approved all procedures, and informed written consent was obtained from all subjects. Additional approval for image processing and analysis was received from the University of California, Los Angeles (UCLA) IRB.

Intelligence Assessments

To assess general intellectual ability, we employed the Wechsler adult intelligence scale (Wechsler 1981). This test, which demonstrates high reliability and validity, quantifies intelligence according to age-based norms that have been shown to correlate with academic and life success, measures of work performance, and occupational level (Jensen 1998). FSIQ is a composite score obtained from 11 subtests in verbal and performance categories where the FSIQ is standardized in a US population sample to have a mean of approximately 100 and standard deviation of approximately 15. In this investigation, FSIQ scores ranged between 74 and 139 (mean FSIQ = 100.2 ± 11.7 for male subjects and mean FSIQ = 100.0 ± 13.6 for female subjects).

Image Acquisition and Preprocessing

High-resolution 3-dimensional (3D) spoiled gradient recalled magnetic resonance images were obtained on a 1.5-T scanner (General Electric, Milwaukee, WI) as a series of 124 contiguous 1.5-mm coronal brain slices (256 × 256 matrix, 0.86 mm × 0.86 mm in-plane resolution). Image volumes passed through a number of preprocessing steps that included correction of head tilt and alignment by reorienting each volume into the standard position of the ICBM-305 average brain (Mazziotta et al. 1995) using a 6 parameter rigid-body transformation with no scaling (Narr et al. 2002; Narr, Bilder, et al. 2005), removal of nonbrain tissue and the cerebellum (interrater reliability for scalp editing procedures, $r_i = 0.99$), correction of intensity nonuniformity due to magnetic field inhomogeneities (Zijdenbos and Dawant 1994; Sled and Pike 1998), and tissue segmentation where voxels were classified as most representative of gray matter, white matter, and cerebrospinal fluid (CSF) using a partial volume correction method (Shattuck et al. 2001). The cortical surfaces of each hemisphere, comprising of 65 536 surface points, were then extracted (MacDonald et al. 1994), and 29 sulcal and gyral landmarks were manually identified on each surface rendering using previously validated anatomical delineation protocols (Ballmaier et al. 2004; Sowell et al. 2004). Interrater reliability estimates demonstrated less than a 2 mm root mean square difference in the matched 3D locations of sulcal landmarks traced on 6 test brains compared with a gold standard arrived at by a consensus of raters (Narr, Bilder, et al. 2005; Narr, Toga, et al. 2005).

Cortical Pattern Matching

Previously detailed cortical pattern–matching methods were used to spatially relate homologous regions of cortex between subjects, allowing cortical thickness to be estimated at spatially equivalent hemispheric locations across individuals (Thompson et al. 2001; Sowell et al. 2004; Narr, Bilder, et al. 2005; Narr, Toga, et al. 2005). Briefly, for matching procedures, a surface-warping algorithm uses the manually derived sulcal/gyral landmarks as anchors to compute a 3D vector deformation field that records the amount of x, y, and z coordinate shift (or deformation) required to match the same cortical surface locations in each subject with reference to the average anatomical pattern of the entire study group. These methods reparameterize (regrid) the hemispheric surface without imposing any scaling, so that the same anatomy bears spatially equivalent coordinate locations at all 65 536 surface points across subjects.

Cortical Thickness

Because the cortical pattern–matching algorithms spatially relate homologous cortical surface locations between individuals, anatomically comparable measures of cortical thickness may be obtained and

compared at different regions across the cortex from each subject. Cortical thickness was measured by referencing tissue-classified brain volumes using an implementation of the 3D Eikonal equation (Sapiro 2001). The thickness of the cortex was defined as the shortest distance in 3D, without crossing CSF voxels, from the cortical white–gray matter boundary to the outer gray–CSF hemispheric surface at all hemispheric surface points (Sowell et al. 2004; Thompson et al. 2004; Narr, Bilder, et al. 2005; Narr, Toga, et al. 2005). Notably, when gray matter surfaces are adjacent, the algorithm progressively codes distance values until meeting a voxel already assigned a distance code. Thus, although opposing gray matter banks not separated by CSF may receive the same thickness value, a spatial filter of radius 8 mm was applied to the coded distance values so that no practical difference could result from misattributing the thickness to one side of the sulcus or the other.

Statistical Analyses

For descriptive purposes, analyses of variance were employed to characterize sex and age effects for intracranial tissue volumes. Linear regression analyses were used to examine relationships between FSIQ and overall intracranial volumes, intracranial gray matter, white matter, and CSF while removing the variance associated with sex and age from the data. For each tissue compartment (intracranial gray matter, white matter, and CSF), analyses were additionally performed after including overall intracranial volume as a nuisance variable.

The same statistical model above was used to examine relationships between FSIQ and regional variations in cortical thickness using the statistical package R (http://www.r-project.org/), again with and without controlling for overall intracranial volume. Because a prior VBM study showed that the regional specificity of FSIQ–gray matter relationships differs in men and women (Haier et al. 2005), differences in the slopes of these relationships were examined using sex as the independent variable. To follow up the presence of interaction effects, FSIQ–cortical thickness relationships were mapped within male and female groups separately.

Notably, for the main effects examined here (i.e., mapping regional relationships between FSIQ and cortical thickness), testing the null hypothesis that the slope (b) is zero is equivalent to testing the null hypothesis that the correlation coefficient (r) is zero (Swinscow and Campbell 2001). That is, there is a one-to-one mathematical mapping between the P value for a nonnegative slope and the r value that quantifies the correlation. For within-sex mapping of FSIQ–cortical thickness relationships, regional partial correlation coefficients (r values) and the corresponding probability maps (P values) are both shown. In the presence of interactions (e.g., the differential effect between males and females on the relationship between FSIQ and cortical thickness), this mathematical equivalence no longer holds so that 2 distinct hypotheses can potentially be addressed. The first of these hypotheses is that the slopes of the relationship between dependent and independent variables differ in the 2 groups, a hypothesis that is readily addressed in the context of the linear regression model described above. The second hypothesis is that the magnitude of the correlations (i.e., the proximity of the points to a straight line) differs between the 2 groups. Although conceptually straightforward, this second hypothesis is computationally problematic because the correlations at each of the 65 536 points analyzed are correlated with one another. This invalidates the assumptions of the Fisher z-test that would otherwise be used for testing for differences in correlations statistically. Although alternative statistical methodologies that take into account the fact that the correlations are correlated exist (Olkin and Finn 1990; Bilker et al. 2004), they are only suitable for circumstances where the number of such correlated correlations is small and are rarely used. In the current context, these methods are computationally impractical. Therefore, rather than additionally addressing the issue of whether the magnitude of correlations differ by sex using formal statistical significance testing, we have provided in Figure 3 (bottom left) maps that directly show the differences in the correlations.

For all regional analyses of FSIQ–cortical thickness relationships, statistical mapping results were projected onto the 3D group-averaged hemispheric surface models where significant results are indexed in color. An uncorrected 2-tailed alpha level of $P < 0.05$ was determined as the threshold for interpreting statistical mapping results. However, because regression analyses were performed at thousands of homologous cortical surface coordinate points, permutation testing was used to test the overall significance of regional FSIQ–cortical thickness relationships and to confirm regional sex interaction effects. Because we predicted a priori that FSIQ–cortical thickness relationships would be present primarily in frontal and temporal neocortical regions, as based on prior results using different morphometric measures, permutation testing was performed only within these regions, whereas other regional effects were treated as exploratory. Frontal and temporal regions of interest were constructed using an average anatomical atlas. The number of cortical points showing significant FSIQ–cortical thickness relationships at a statistical threshold of $P < 0.01$ using the reduced model (i.e., controlling for sex and age, or sex, age, and intracranial volume) was then compared with the number of significant surface points that occurred by chance within each region of interest in a thousand new randomized analyses. Similarly, residuals from the reduced model were used to permute sex interaction effects for the slopes of FSIQ–cortical thickness relationships while controlling for the other terms in the model (Anderson and Legendre 1999; Anderson and Braak 2003).

Table 1
Means and standard deviations of demographic variables and intracranial tissue volumes

	Females (n = 35), Mean (SD)	Males (n = 30), Mean (SD)
Age	28.51 (7.56)	27.93 (7.09)
FSIQ	100.03 (13.67)	100.27 (11.71)
Percent dextral (%)	97	100[a]
Intracranial volume (cm^3)	1127.80 (88.23)	1260.05 (107.03)
Intracranial gray matter (cm^3)	588.49 (57.09)	654.53 (64.06)
Intracranial white matter (cm^3)	402.20 (45.01)	449.99 (52.51)
Intracranial CSF (cm^3)	137.09 (25.11)	155.51 (27.81)

[a]Handedness information was not available for 4 male subjects.

Results

Intracranial Tissue Volumes

The means and standard deviations for intracranial tissue volumes are shown in Table 1. Results revealed significant effects of sex (males larger) and age (decreases with age) for intracranial gray ($F_{1,64}$ = 21.19, $P < 0.001$ and $F_{1,64}$ = 14.20, $P < 0.001$, respectively) and white matter volumes ($F_{1,64}$ = 17.21, $P < 0.001$ and $F_{1,64}$ = 4.74, $P < 0.03$). Effects of sex (males larger), but not age, were observed for intracranial CSF volumes ($F_{1,64}$ = 8.28, $P < 0.005$) and overall intracranial volumes ($F_{1,64}$ = 29.32, $P < 0.001$). After correcting for overall intracranial volume, sex effects were absent for all intracranial tissue compartments, although significant age effects were observed for intracranial gray matter ($F_{1,64}$ = 43.16, $P < 0.001$), white matter ($F_{1,64}$ = 17.52, $P < 0.001$), and CSF ($F_{1,64}$ = 3.95, $P < 0.05$).

Regression analyses showed significant positive correlations between FSIQ and overall brain volume, r = 0.36, degrees of freedom (df) = 61, $P < 0.004$; intracranial gray matter, r = 0.37, df = 61, $P < 0.004$; and intracranial white matter volume, r = 0.26, df = 61, $P < 0.04$; significant associations were absent for CSF volumes, r = 0.12, df = 61, $P > 0.05$. As expected, after removing the variance associated with brain size, correlations between FSIQ and intracranial gray matter, r = 0.09, df = 60, $P > 0.05$, and white matter, r = 0.02, df = 60, $P > 0.05$, were no longer significant. Notably, regression analyses also revealed significant correlations between overall brain size and all brain tissue compartments (intracranial gray matter: r = 0.87, $P < 0.0001$; intracranial white matter: r = 0.78, $P < 0.0001$; and intracranial CSF: r = 0.55, $p < 0.0001$). Because overall brain size and intracranial tissue

compartments are highly correlated, in order to determine the factors contributing most to the variance in FSIQ scores, post hoc stepwise regression analyses were performed. After modeling the combinations of terms shown to significantly associate with FSIQ (overall intracranial volume, intracranial white, and gray matter), the greatest amount of variance was explained by including only intracranial gray matter in the model ($r = 0.33$, $df = 64$, $P < 0.007$), and the inclusion of the other variables did not serve to improve the model using a liberal exclusion criteria of $P > 0.1$.

The slopes of FSIQ–tissue volume relationships were not shown to differ by sex (gray matter: $F_{1,64} = 0.74$, $P > 0.05$; white matter: $F_{1,64} = 1.67$, $P > 0.05$; and CSF: $F_{1,64} = 0.08$, $P > 0.05$). Regression plots in Figure 1 show associations between FSIQ scores and intracranial volumes after partialling out sex and age.

Statistical Mapping Results

Statistical maps in the left panel of Figure 2 show significant correlations between FSIQ and regional variations in cortical thickness after removing the partial effects of sex and age. The right panel (shaded) shows results after additionally including overall intracranial volume as a nuisance variable. Probability values associated with significant positive or negative partial correlations are indexed in color. Significant positive associations between FSIQ and cortical thickness were evident in prefrontal (anterior–ventral prefrontal and frontopolar cortices; BA 10/11 and 47) and temporal cortices (inferior temporal, fusiform, and parahippocampal cortices; BA 20, 37, and 36) bilaterally. Associations were more spatially diffuse in the right hemisphere including anterior middle temporal (BA 21) and extrastriate occipital (BA 19) cortical regions. Only small and very localized associations were observed within cingulate cortices. Results were more spatially concentrated and less pronounced after controlling for overall brain volume (Fig. 2, right panel), although significant correlations were identified within the same regions. No brain region exhibited significant negative correlations between FSIQ and cortical thickness. Permutation testing confirmed the significance of FSIQ–cortical thickness relationships within frontal and temporal brain regions after removing the partial effects of sex and age (corrected P values: $P < 0.03$ and $P < 0.02$, respectively). However, permutation testing did not confirm regional results when intracranial volume was additionally included in the model (corrected P values: $P < 0.09$ and $P < 0.11$).

Figure 3 (top left) shows statistical mapping results comparing the slopes of FSIQ–cortical thickness relationships between males and females after removing the partial effects of age. Sex effects were observed within frontopolar (rostral superior and middle frontal gyral regions; BA 10/11), caudal middle temporal

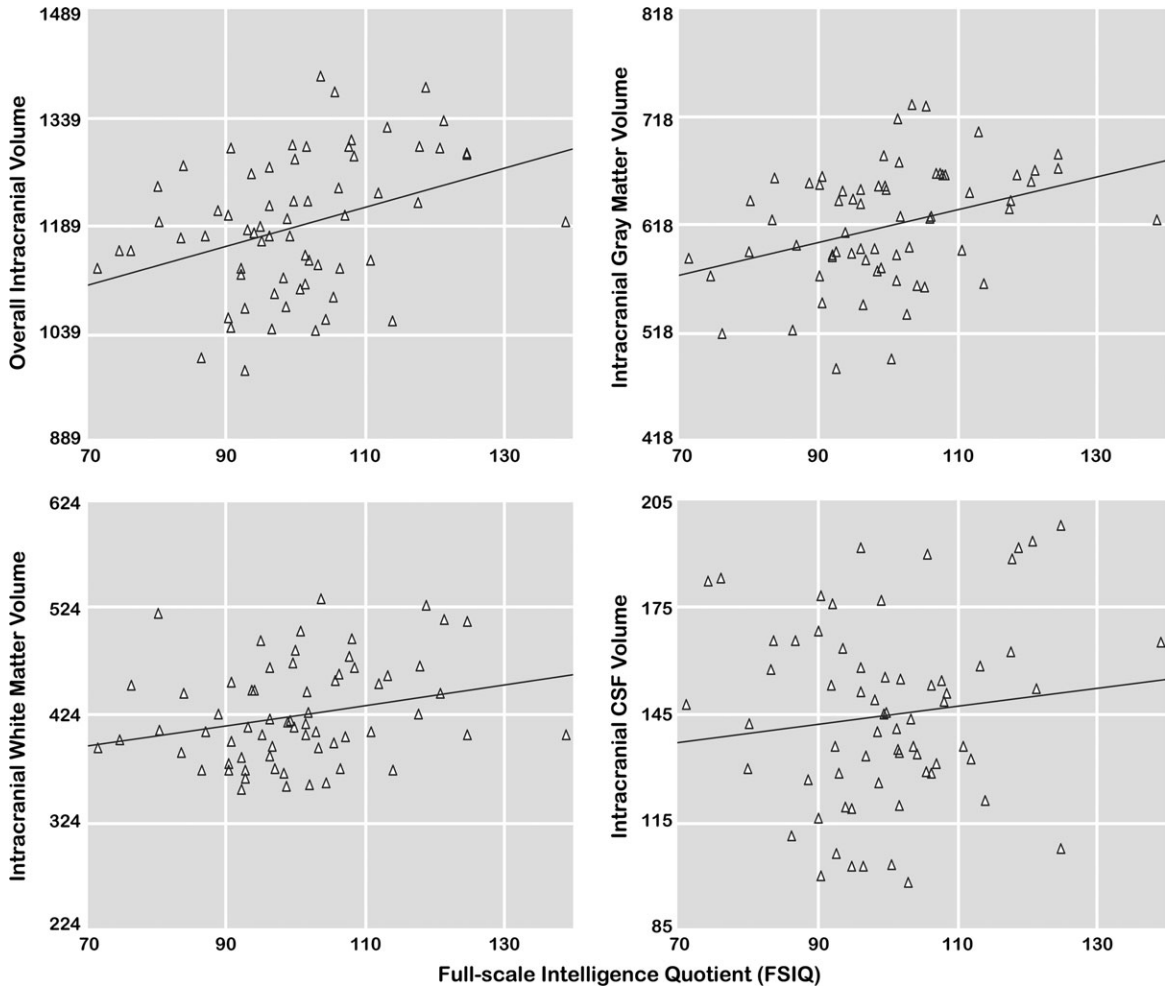

Figure 1. Partial regression plots, controlling for sex and age, showing relationships between FSIQ and overall intracranial volumes (cm^3) (top left), intracranial gray matter volumes (cm^3) (top right), intracranial White volumes (cm^3) (bottom left), and intracranial CSF volumes (cm^3) (bottom right).

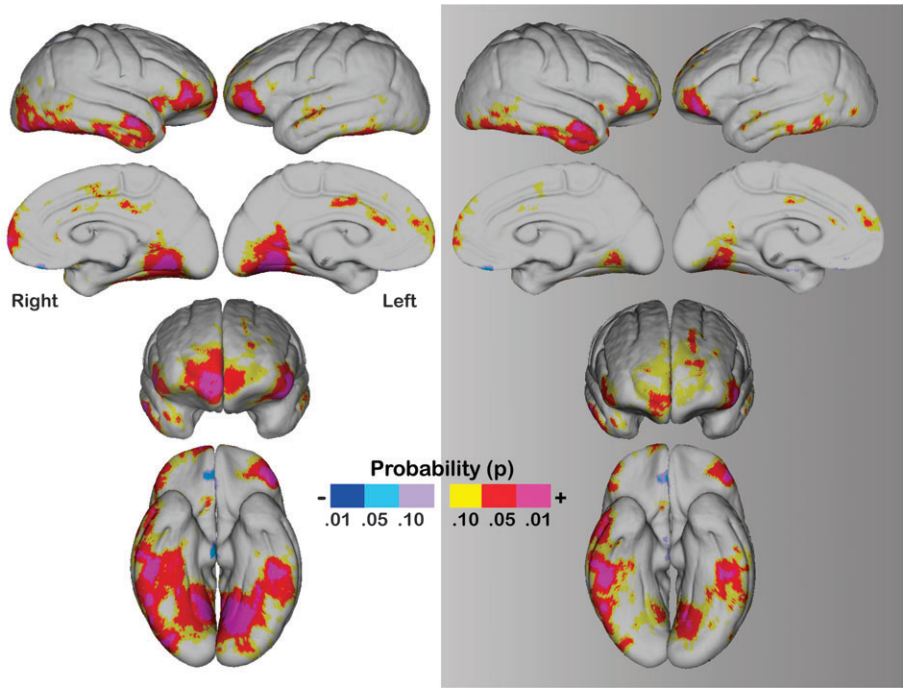

Figure 2. Statistical maps show the regional significance of relationships between FSIQ and cortical thickness after removing the partial effects of sex and age (left) and after additionally removing the partial effects of overall intracranial volume (right, shaded). Positive probability values shown in hot colors (red, pink) on the color bar encode the significance of positive relationships. Negative probabilities in cold colors (blues) on the color bar encode the significance of negative relationships, although negative relationships between FSIQ and cortical thickness were not observed in any region in the above analyses.

(BA 21), occipitotemporal (BA 37), and inferior parietal (BA 7) gyral regions. Statistical mapping results additionally including overall intracranial volume in the model are not shown, although the regional pattern of effects were extremely similar to those observed before intracranial size correction. Permutation testing confirmed the significance of interaction effects within frontal and temporal regions both with and without partialling out overall intracranial volume (corrected P values: $P < 0.04$ and $P < 0.02$ before and $P < 0.03$ and $P < 0.04$ after intracranial volume correction for frontal and temporal regions, respectively).

To follow up interaction effects, FSIQ–cortical thickness associations were mapped within females and males separately after removing the partial effects of age (Fig. 3, top right). Statistical maps revealed highly significant FSIQ–cortical thickness relationships in females within frontopolar and bordering prefrontal regions (BA 10/11 and 47) and within inferior temporal (BA 20), lateral occipitotemporal, and fusiform (BA 37 and 36) gyral regions. In male subjects, localized correlations were less pronounced in temporal cortices and predominantly observed in medial temporo-occipital BA 37 (bordering BA 19 and 30), whereas significant correlations in prefrontal cortical regions appeared absent. Negative correlations between FSIQ and cortical thickness were observed in a discrete area of the left inferior parietal cortex (BA 7) in male subjects. The spatial patterns of regional significance were similar within each sex when intracranial volume was additionally included as a nuisance variable (results not shown).

Maps showing the magnitudes of correlation coefficients within female and male subjects are shown in the bottom right panels of Figure 3 that correspond to the female and male probability maps shown directly above. Sex differences in the magnitude of correlations between FSIQ and cortical thickness were assessed by subtracting regional correlation coefficients in male subjects from correlation coefficients in females at homologous cortical locations (Fig. 3, bottom left). Hot colors indicate regions where females show larger partial correlation coefficients compared with males, and cool colors reflect regions where males show larger correlations with respect to females. Although subtraction maps reflect sex differences in the magnitudes, as opposed to the slopes, of relationships between FSIQ and cortical thickness, regional difference profiles were similar in spatial pattern to interaction effects (top left above). Correlations were greater in magnitude within frontopolar (BA 10/11), caudal middle temporal (BA 21), occipitotemporal (BA 37), and inferior parietal (BA 7) gyral regions in females compared with males. In males, correlations appeared larger only in spatially discrete medial temporo-occipital regions.

Discussion

Our data show that larger brain volumes are associated with greater intellectual ability, in line with established findings (McDaniel 2005). As further confirmed, positive relationships extend to intracranial gray matter (Andreasen et al. 1993; Reiss et al. 1996; Gur et al. 1999; Haier et al. 2004) and white matter tissue compartments (Gur et al. 1999; Haier et al. 2004), whereas associations between FSIQ and intracranial CSF appear minimal or absent (Andreasen et al. 1993). Overall intracranial size and tissue compartment measures, however, are themselves correlated, and when overall intracranial size is taken into account, relationships between FSIQ and intracranial gray or white matter are below the threshold of significance. The genetic factors contributing to brain size, which is known to

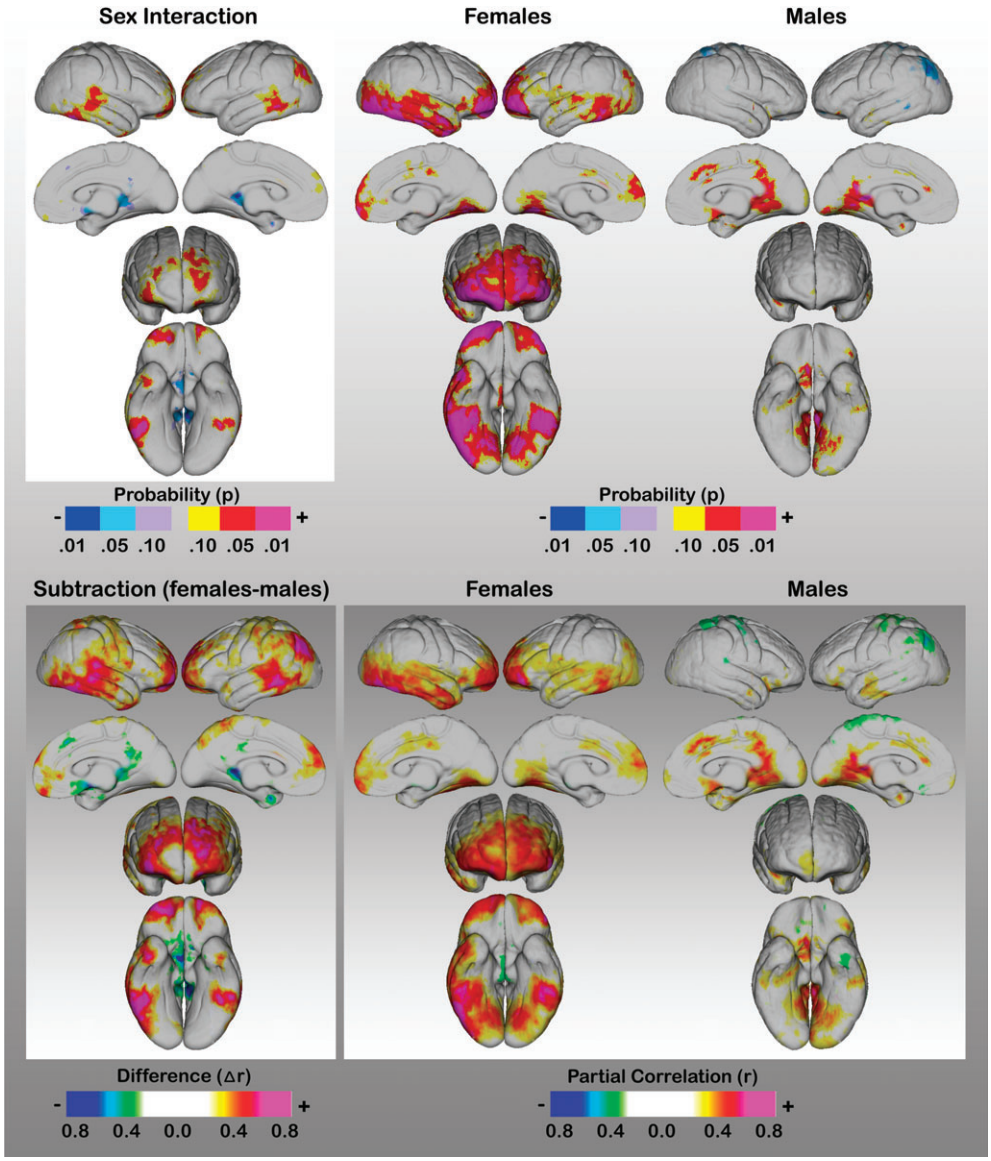

Figure 3. Statistical maps in the top left corner show significant interactions between males and females in the slopes of regional FSIQ–cortical thickness relationships (after removing the partial effects of age from the data). Positive probability values (hot colors) indicate greater slopes in females with respect to males, whereas negative probability values (cool colors) indicate greater slopes in males. Top center and top right statistical maps show the regional significance of FSIQ–cortical thickness relationships within female and male groups separately. Positive probability values (hot colors) encode positive relationships. Negative probabilities (cool colors) encode negative relationships. Bottom center and bottom left statistical maps show the magnitude of partial correlation coefficients between FSIQ and cortical thickness (after partialling out age effects) within females and males separately, which correspond to the same sex probability maps shown directly above. Positive *r* values (hot colors) index positive FSIQ–cortical thickness relationships; negative *r* values (cool colors) index negative FSIQ–cortical thickness relationships. Statistical maps in the bottom left show differences in the magnitude of correlations between males and females where *r* values in males are subtracted from *r* values in females at homologous cortical locations. Positive values (hot colors) index larger correlations in females with respect to males; negative values (cool colors) index larger correlations in males compared with females.

be highly heritable (Posthuma et al. 2002), overlap with the genetic factors accounting for variations in gray and white matter volumes (Baare et al. 2001). Therefore, genes expressed in gray and white matter, which make up approximately 80–90% of total brain volume in humans (Zhang and Sejnowski 2000), account to a large extent for variations observed in overall intracranial size. Our post hoc stepwise regression analyses indicate that when including overall intracranial, gray, and white matter volumes in the model, gray matter is the best predictor of variations in FSIQ scores. Thus, because gray matter contains neurons, axons, and dendritic trees and spines that act as the units of brain function and sites of information transfer, respectively, relationships between intracranial volume and FSIQ may reflect primary relationships with gray matter and to a slightly lesser extent with white matter properties.

Functional imaging studies demonstrate that distributed brain regions linked by cortical networks are activated during higher cognitive functioning. Overlap of brain activity in some specific cortical regions, particularly in prefrontal, parietal, and/or temporo-occipital networks, has been shown to relate to general intelligence (Duncan and Owen 2000; Gray et al. 2003; Haier et al. 2003; Lee et al. 2006). Although relationships between intelligence and gray matter volume are well replicated, fewer investigations have focused on localizing the

structural homologues of general intelligence. In spite of discrepancies in findings that may relate to differences in image analysis methods and the demographic characteristics of subjects studied, gray matter volume or density increases in prefrontal (Flashman et al. 1997; Frangou et al. 2004; Haier et al. 2004), medial and lateral temporal (Andreasen et al. 1993; Flashman et al. 1997; Haier et al. 2004), and in parietal (Haier et al. 2004) cortical regions appear most linked with improved performance on standardized intelligence tests in adolescent and adult samples. To date, only one published study has examined relationships between FSIQ and regional variations in cortical thickness specifically (Shaw et al. 2006). This investigation, focused on identifying cross-sectional and longitudinal changes in FSIQ–cortical thickness relationships across development, reported positive correlations between intelligence in cortical thickness after the age of 8 years, peaking in late childhood, that remained evident in prefrontal and temporal cortical regions in subjects within the adolescent–early adult age range. This prior investigation also showed, via longitudinal assessment, that more intelligent children demonstrate more dynamic changes in cortical thickness over development particularly in prefrontal cortices.

The cortex consists of layers of cells, also organized into columns that vary in cortical depth (~1 to 4.5 mm) as dependent on number of layers, the types of neurons and glial cells, and their size and density. The cytoarchitectural characteristics defining cortical thickness vary within different cortical regions (Economo and Parker 1929) and may represent a more regionally relevant survey of structural integrity than gross measures of gray matter volume. Because laminar thickness varies across the cortical mantle, associations can be compared across individuals only at homologous cortical locations. After employing cortical pattern–matching methods to align anatomy across subjects, we found significant relationships between FSIQ and cortical thickness predominantly in prefrontal (BA 10/11 and 47) and temporal (BA 37 and 36) cortical regions where findings remained present irrespective of brain size corrections. These results largely agree with a previous study using VBM methods to correlate intelligence with gray matter density throughout the brain in a smaller, high-IQ adult sample (Haier et al. 2004). Our findings are also consistent with the cross-sectional results of Shaw et al. (2006) reporting significant correlations between greater intelligence and increased cortical thickness predominantly frontal and temporal cortices within the late adolescent–early adulthood age group studied.

Specific links between FSIQ and cortical thickness within prefrontal BA areas 10 and 11 (and bordering association area 47), spanning the rostral portions of the inferior and superior frontal gyri extending medially, are not surprising given that these regions are sometimes collectively referred to as the center of biological intelligence and are involved in higher cognitive functions like problem solving, planning, sequencing, reasoning, and judgment. In the temporal lobe, cortical association area 37, spanning portions of the inferior temporal gyrus laterally and fusiform gyrus medially, participates in the analysis of visual form, motion, and the representation of objects. Observations of specific links with FSIQ in this region and within proximal visual association area 36 suggest variations in laminar thickness influence visual analysis abilities that are central to most cognitive processes, especially those assessed with standardized intelligence testing. Interestingly a positron emission tomographic study showed that brain activations associated with a nonreasoning condition (passively viewing videos) were greater within temporo-occipital regions (BA 37/19) in subjects with higher scores on a *g*-loaded test and that connectivity was increased between this region and prefrontal regions (Haier et al. 2003). Furthermore, a functional magnetic resonance imaging study showed positive correlations between FSIQ and verb-generation task-associated brain activity in BA 19 as well as in frontal and temporal areas in children (Schmithorst and Holland 2006).

As universally reported in the literature, men exhibited larger mean brain volumes than women. Because sex accounts for a large amount of the variance in brain size, after controlling for intracranial volume, sex effects for gray and white tissue volumes were no longer significant. Relationships between FSIQ and brain tissue volumes were not shown to differ between men and women. That is, although women possess smaller mean intracranial volumes and tissue contents, the slopes of FSIQ relationships were approximately parallel in both sexes. Although FSIQ represents abilities across several cognitive domains, individual IQ subtests are positively correlated and related by degree to general intelligence (*g*) by factor analysis (Neisser et al. 1996). The few studies relating separate intelligence subtests or factors to brain structure have shown little consistency, especially with regard to sex differences. For example, although both sexes showed overall FSIQ–brain size correlations, female-biased correlations were observed between brain size and verbal IQ, whereas performance IQ showed male-biased correlations (Andreasen et al. 1993). Another study, however, showed relationships between performance IQ, but not verbal IQ, in frontal, temporal, and parietal regions but failed to detect sex differences (Flashman et al. 1997). In contrast, postmortem data revealed relationships between verbal IQ and cerebral volume in women and in right-handed men, and exclusively in women for visuospatial ability (Witelson et al. 2006). Others have investigated whether crystallized (abilities dependent on acquired knowledge) or fluid intelligence (reasoning and problem solving), which is occasionally isolated as a separate factor, link more closely with structural brain variations with the evidence coming down on the side of fluid intelligence (Gray and Thompson 2004). Discrepancies in these results may stem from studying broad-based intelligence measures (e.g., verbal or performance IQ) versus employing cognitive subtests according to how closely they relate to general intelligence or *g*. Notably, investigators have recently shown that individual subtests with greater *g* loadings (i.e., tests that indicate greater average correlations with other tests in an intelligence battery) are associated with greater gray matter volumes throughout the brain and, for particular tests, with increased gray matter density in frontal, temporal, and parietal regions (Colom et al. 2006).

Although the slopes of the relationships between intracranial tissue volume measures and FSIQ were not shown to differ by sex in our investigation, the slopes of FSIQ–cortical thickness relationships were significantly different within prefrontal and posterior temporal neocortical regions and to a lesser extent in left lateral inferior parietal regions (Fig. 3, top left). Moreover, the largest differences between males and females in the magnitudes of regional correlation coefficients were observed within the same regions (Fig. 3, bottom left). When FSIQ–cortical thickness relationships were examined separately within each sex, only females showed significant relationships between FSIQ and cortical thickness in prefrontal cortices. Correlations were also more spatially diffuse in temporal cortices in females; males

showed significant correlations primarily in posterior medial temporal cortices (BA 37) and bordering regions. These findings contrast with VBM findings of strong FSIQ correlations in frontal and parietal regions in male subjects. Female-specific associations, however, were observed in prefrontal cortices (BA 10) as consistent with our results, but associations were not detected in temporal association regions (Haier et al. 2005). Men and women possess some regional differences in cortical thickness distributions where sex differences have been shown to be influenced by brain size correction methods (Luders et al. 2006). Thus, discrepancies in results may stem from differences in spatial normalization approaches, smoothing, and the gray matter indices (gray matter density vs. cortical thickness) examined. Shaw et al. (2006) did not report significant sex differences in cross-sectional examination of intelligence–cortical thickness relationships, although sex differences were not assessed exclusively within the adolescent–early adulthood group studied.

Although men and women are of similar intelligence, on average, men are reportedly better at visuospatial tasks, fitting with our observations of regionally specific FSIQ–cortical thickness relationships in temporo-occipital association areas that are important for the analysis of visual form (Kimura 1996). Women, however, generally perform better in tasks requiring verbal processing and memory involving frontal–temporal cortical networks. Spatially distinct relationships between FSIQ and cortical thickness in men and women may thus reflect sexual dimorphisms in some processing abilities. Alternatively, sex differences in regional relationships may reflect differences in processing strategies that do not depend on competence or reflect differences in neural circuitry and brain structural organization. Interestingly, although performance was similar across sexes, the patterns of brain activity associated with a variety of cognitive tasks were shown to differ between men and women (Bell et al. 2006). The focus of our study was to examine only the moderating influences of sex on global and regional relationships between brain tissue measures and general intellectual ability, thereby also avoiding the potential for inflated Type I error by excluding analyses of subtest scores that are shown to correlate with general intellectual ability to varying degrees. Future studies, however, may elucidate whether specific information processes, especially those shown to exhibit sex differences, are linked with variations in cortical thickness. On a final note, because there are many factors, such as differences in socio-economic and cultural backgrounds that cannot be dissociated from racial–ethnic class, potential influences of race toward the relationships between brain size and intelligence were not examined here.

Conclusion

Although the concept of general intelligence or "*g*" is disputed by some, the common view remains that this trait represents a major dimension of mental competence across a diverse range of cognitive abilities, which unequivocally serves to predict many aspects of life success. This study is the first to explore the regional specificity of relationships between cortical thickness and general intellectual ability in healthy adults of normal IQ within a relatively narrow age range, as well as the moderating effects of sex. Our results suggest that a common biological substrate influences both general intelligence and intracranial gray and white matter volumes, where variation in the thickness of prefrontal and temporal association cortices is particularly relevant to intellectual ability. Variations in intracranial tissue characteristics, particularly in prefrontal regions (Thompson et al. 2001), may thus prove useful as endophenotypes that may help to determine the overlapping genetic factors accounting for general intelligence. However, sex is shown to influence the regional relationships between general intelligence and cortical thickness. Women show significant associations in prefrontal and temporal association cortices, whereas men show associations primarily in temporal–occipital association cortices. It remains to be determined if sex-specific competences account for these regional differences or vice versa and/or whether regional differences in relationships between men and women represent differences in processing strategies or underlying structural organization.

Notes

This work was generously supported by research grants from the National Center for Research Resources (P41 RR13642), the National Institute of Mental Health (RO1 MH60374), the National Institutes of Health (NIH) Roadmap Initiative (P20 RR020750), the National Library of Medicine (R01 LM05639), the NIH Roadmap for Medical Research, Grant U54 RR021813 entitled Center for Computational Biology, a National Alliance for Research on Schizophrenia and Depression Young Investigator Award and Career Development Award (K01 MH073990-01A1, to KLN). Algorithm development was also supported by grants R21 EB01651, R21 RR019771, and AG016570 (to PT). *Conflict of Interest*: None declared.

Address correspondence to Dr Katherine L. Narr, Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Neuroscience Research Building, Suite 225, 635 Charles E. Young Drive South, Los Angeles, CA 90095-7334, USA. Email: narr@loni.ucla.edu.

References

Anderson MJ, Braak CJ. 2003. Permutation tests for multi-factorial analysis of variance. J Stat Comput Simul. 73:85–113.

Anderson MJ, Legendre P. 1999. An empirical comparison of permutation methods for tests of partial regression coefficients in a linear model. J Stat Comput Simul. 62:271–303.

Andreasen NC, Flaum M, Swayze V 2nd, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WT. 1993. Intelligence and brain structure in normal individuals. Am J Psychiatry. 150:130–134.

Baare WF, Hulshoff Pol HE, Boomsma DI, Posthuma D, de Geus EJ, Schnack HG, van Haren NE, van Oel CJ, Kahn RS. 2001. Quantitative genetic modeling of variation in human brain morphology. Cereb Cortex. 11:816–824.

Ballmaier M, O'Brien JT, Burton EJ, Thompson PM, Rex DE, Narr KL, McKeith IG, DeLuca H, Toga AW. 2004. Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. Neuroimage. 23:325–335.

Bell EC, Willson MC, Wilman AH, Dave S, Silverstone PH. 2006. Males and females differ in brain activation during cognitive tasks. Neuroimage. 30:529–538.

Bilker WB, Brensinger C, Gur RC. 2004. A two factor ANOVA-like test for correlated correlations: CORANOVA. Multivar Behav Res. 39: 565–594.

Bookstein FL. 2001. "voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage. 14:1454–1462.

Colom R, Jung RE, Haier RJ. 2006. Distributed brain sites for the g-factor of intelligence. Neuroimage. 31(3):1359–1365.

Duncan J, Owen AM. 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 23: 475–483.

Economo C, Parker S. 1929. The cytoarchitectonics of the human cerebral cortex. London: Humphrey Milford, Oxford University Press.

Flashman LA, Andreasen NC, Flaum M, Swayze I, Victor W. 1997. Intelligence and regional brain volumes in normal controls. Intelligence. 25:149–160.
Frangou S, Chitins X, Williams SC. 2004. Mapping IQ and gray matter density in healthy young people. Neuroimage. 23:800–805.
Gray JR, Chabris CF, Braver TS. 2003. Neural mechanisms of general fluid intelligence. Nat Neurosci. 6:316–322.
Gray JR, Thompson PM. 2004. Neurobiology of intelligence: science and ethics. Nat Rev Neurosci. 5(6):471–482.
Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE. 1999. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci. 19:4065–4072.
Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. 2004. Structural brain variation and general intelligence. Neuroimage. 23:425–433.
Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. 2005. The neuroanatomy of general intelligence: sex matters. Neuroimage. 25:320–327.
Haier RJ, White NS, Alkire MT. 2003. Individual differences in general intelligence correlate with brain function during nonreasoning tasks. Intelligence. 31:429–441.
Honea R, Crow TJ, Passingham D, Mackay CE. 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry. 162:2233–2245.
Jensen AR. 1998. The g factor: the science of mental ability. Westport (CT): Praeger.
Kimura D. 1996. Sex, sexual orientation and sex hormones influence human cognitive function. Curr Opin Neurobiol. 6:259–263.
Lee KH, Choi YY, Gray JR, Cho SH, Chae JH, Lee S, Kim K. 2006. Neural correlates of superior intelligence: stronger recruitment of posterior parietal cortex. Neuroimage. 29(2):578–586.
Luders E, Narr KL, Thompson PM, Rex DE, Woods RP, Deluca H, Jancke L, Toga AW. 2006. Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp. 27:314–324.
MacDonald D, Avis D, Evans AC. 1994. Multiple surface identification and matching in magnetic resonance imaging. Proc Soc Photo Opt Instrum Eng. 2359:160–169.
Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. 1995. A probabilistic atlas of the human brain: theory and rationale for its development (The International Consortium for Brain Mapping; ICBM). Neuroimage. 2:89–101.
McDaniel. 2005. Big-brained people are smarter: a meta-analysis of the relationship between in vivo brain volume and intelligence. Intelligence. 33:337–346.
Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, Robinson D, Sevy S, Gunduz-Bruce H, Wang YP, et al. 2005. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex. 15:708–719.
Narr KL, Cannon TD, Woods RP, Thompson PM, Kim S, Asunction D, van Erp TG, Poutanen VP, Huttunen M, Lonnqvist J, et al. 2002. Genetic contributions to altered callosal morphology in schizophrenia. J Neurosci. 22:3720–3729.
Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, Sevy S, Wang Y, Schrock K, Bilder RM. 2005. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry. 58:32–40.
Neisser U, Boodoo G, Bouchard TJ, Boykin AW, Brody N, Ceci SJ, Halpern DF, Loehlin JC, Perloff R, Sternberg RJ, et al. 1996. Intelligence: knowns and unknowns. Am Psychol. 51:77–101.
Olkin I, Finn J. 1990. Testing correlated correlations. Psychol Bull. 108:330–333.
Parent A, Carpenter MB. 1995. Human neuroanatomy. Baltimore (MD): Williams & Wilkins.
Posthuma D, De Geus EJ, Baare WF, Hulshoff Pol HE, Kahn RS, Boomsma DI. 2002. The association between brain volume and intelligence is of genetic origin. Nat Neurosci. 5:83–84.
Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB. 1996. Brain development, gender and IQ in children. A volumetric imaging study. Brain. 119 (5):1763–1774.
Sapiro G. 2001. Geometric partial differential equations and image analysis. Cambridge (UK): Cambridge University Press.
Schmithorst VJ, Holland SK. 2006. Functional MRI evidence for disparate developmental processes underlying intelligence in boys and girls. Neuroimage. 31(3):1366–1379.
Shattuck DW, Sandor-Leahy SR, Schaper KA, Rottenberg DA, Leahy RM. 2001. Magnetic resonance image tissue classification using a partial volume model. Neuroimage. 13:856–876.
Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, Evans A, Rapoport J, Giedd J. 2006. Intellectual ability and cortical development in children and adolescents. Nature. 440:676–679.
Sled JG, Pike GB. 1998. Standing-wave and rf penetration artifacts caused by elliptic geometry: an electrodynamic analysis of MRI. IEEE Trans Med Imaging. 17:653–662.
Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. 2004. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci. 24:8223–8231.
Spearman C. 1904. General intelligence objectively determined and measured. Am J Psychol. 15:201–293.
Swinscow TDV, Campbell MJ. 2001. Statistics at square one. 10th ed. London: BMJ Books.
Thacker NA. 2005. A critical analysis of voxel-based morphometry. Technical Report. http://www.tina-vision.net/docs/memos/2003-011.pdf, Tina Memo No 2003-011. p. 1–10.
Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Kaprio J, Khaledy M, et al. 2001. Genetic influences on brain structure. Nat Neurosci. 4:1253–1258.
Thompson PM, Hayashi KM, Sowell ER, Gogtay N, Giedd JN, Rapoport JL, de Zubicaray GI, Janke AL, Rose SE, Semple J, et al. 2004. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. Neuroimage. 23(Suppl 1):S2–S18.
Toga AW, Thompson PM, 2005. Genetics of brain structure and intelligence. Annu Rev Neurosci. 28:1–23.
Tramo MJ, Loftus WC, Stukel TA, Green RL, Weaver JB, Gazzaniga MS. 1998. Brain size, head size, and intelligence quotient in monozygotic twins. Neurology. 50:1246–1252.
Wechsler D. 1981. Wechsler adult intelligence scale, revised: manual. New York: Harcourt Brace Jovanovich.
Wilke M, Sohn JH, Byars AW, Holland SK. 2003. Bright spots: correlations of gray matter volume with IQ in a normal pediatric population. Neuroimage. 20:202–215.
Witelson SF, Beresh H, Kigar DL. 2006. Intelligence and brain size in 100 postmortem brains: sex, lateralization and age factors. Brain. 129:386–398.
Zhang K, Sejnowski TJ. 2000. A universal scaling law between gray matter and white matter of cerebral cortex. Proc Natl Acad Sci USA. 97:5621–5626.
Zijdenbos AP, Dawant BM. 1994. Brain segmentation and white matter lesion detection in mr images. Crit Rev Biomed Eng. 22: 401–465.