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Associations Between IQ, Total and Regional Brain Volumes and Demography in a Large Normative Sample of Healthy Children and Adolescents

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Abstract

In the course of efforts to establish quantitative MRI-based norms for healthy brain development (Brain Development Cooperative Group, 2006), previously unreported associations of parental education and temporal and frontal lobe volumes with full scale IQ and its verbal and performance subscales were discovered. Our findings were derived from the largest, most representative MRI sample to date of healthy children and adolescents, ages 4 years 10 months to 18 years 4 months. We first find that parental education has a strong association with IQ in children that is not mediated by total or regional brain volumes. Second, we find that our observed associations between temporal gray matter, temporal white matter and frontal white matter volumes with full scale IQ, between 0.14 to 0.27 in children and adolescents, are due in large part to their correlations with performance IQ and not verbal IQ. The volumes of other lobar gray and white matter, subcortical gray matter (thalamus, caudate nucleus, putamen and globus pallidus), cerebellum and brainstem do not contribute significantly to IQ variation. Third, we find that head circumference is an insufficient index of cerebral volume in typically developing older children and adolescents. The relations between total and regional brain volumes and IQ can best be discerned when additional variables known to be associated with IQ, especially parental education and other demographic measures, are considered concurrently.

INTRODUCTION

Developmental brain mechanisms that mediate the association of parental demographic factors with IQ remain poorly understood. IQ is a composite measure of diverse cognitive functions that is associated with brain development and environmental factors. Since the work of Alfred Binet in the late 1800s, adult IQ to brain size correlation estimates have been inconsistent, ranging from 0 to ~0.6 with central tendency ~0.3 to 0.4 (Andreasen, et al., 1993; McDaniel, 2005; Vernon, Wickett, Bazana, & Stelmark, 2000; Witelson, Beresh, & Kigar, 2006). Full

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scale IQ and its performance (PIQ) and verbal (VIQ) subscales have been associated with assessments of brain development and demographic factors (Fisch, Bilek, Horrobin, & Chang, 1976; Gale, O'Callaghan, Bredow, & Martyn, 2006; Gale, O'Callaghan, Godfrey, Law, & Martyn, 2004; Ounsted, Moar, & Scott, 1988; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Shaw, et al., 2006; Weinberg, Dietz, Penick, & McAlister, 1974). Brain structure volumes change significantly across childhood and adolescence with cross-sectional and longitudinal age (Giedd, et al., 1999; Lenroot & Giedd, 2006) and these changes may be associated with variations in IQ test performance. It is also known that the volumetric variances of human brain structure sizes change markedly throughout life, differ within and between individuals (Sowell, et al., 2003), increase within and between males and females during puberty (Sowell, et al., 2003) and may have far reaching behavioral, pathological and social significance (Rutter, Caspi, & Moffitt, 2003; Shaw, et al., 2006). Maternal education likely affects brain development of their offspring and VIQ by predominantly genetic, but also modest shared environmental influences (Neiss M & Rowe, 2000). Developmental brain research has yet to reliably quantify the associations between parental demographic factors and regional gray and white matter brain volumes mediated by variations in total brain volume, structural connectivity and functional connectivity .

Brain growth can be measured accurately by *in vivo* magnetic resonance imaging (MRI), allowing investigation of the influence of brain growth on IQ and the influences of demographic, hormonal, cellular and genetic factors on healthy brain development from early childhood through adolescence and into adulthood (Hulshoff Pol, et al., 2006; Juraska & Markham, 2004; Zinkstok, et al., 2006). Due to the lack of any previous MRI study in which sampling was planned and completed to create a normatively representative sample of healthy children and adolescents, there are deficiencies in our understanding of how IQ in children may be associated with brain development and parental and offspring demographic factors. At present, our knowledge of key associations between these variables in neurodevelopmental disorders is limited because pathology and its correlates can be discerned only in relation to typical development. In this paper, we employ MRI and clinical measurements from the largest, most representative sample of typically developing children collected to date to further determine how brain structure sizes and demographics are associated with IQ.

METHODS

Participants

Through application of strict inclusion and exclusion criteria (Brain Development Cooperative Group, 2006), the Brain Development Cooperative Group acquired a sample of children and adolescents from across the United States using an epidemiologic sampling plan that combined cross-sectional and accelerated longitudinal study design principles (Brain Development Cooperative Group, 2006; Harezlak, Ryan, Giedd, & Lange, 2005). Family income levels and race/ethnicity proportions within each income level were matched to their joint distribution as determined by the US Census 2000 in each cell of a 3×7 table of income levels by race/ethnicity groupings. Because there is a plethora of co-factors that could be associated with assessments of brain structure, the Brain Development Cooperative Group decided to balance the sample with respect to age, sex, income and race/ethnicity, shown previously to relate to brain structure in the preceding order of importance. Siblings were excluded from the sample. Handedness was determined by observing hand preferences for writing and responses to seven gestural commands (e.g., show me how you use a hammer, throw a ball). Participants were classified as either right-handed (at least 7 out of 8 right-handed responses) or non-right-handed (Waber, de Moor et al., 2007); handedness was not studied in the present analysis. Informed consent/assent was obtained from all participants. Institutional Review Boards approved all protocols at parent institutions.

Family Income

Family income was employed as a surrogate for “socioeconomic status”. For the purposes of this study, due to regional income variability, adjusted family income (AFI) was defined as $AFI = ((A / B) / C) * D$, where A was the midpoint of each family’s self-reported income bracket, B was the US Housing and Urban Development (HUD) adjustment factor for family size, C was the local median family income for the Metropolitan Statistical Area (MSA) in which the family resided at the time of the interview, and D was the US median family income.

Parental Education

Parental education was defined as the highest level of education completed by either the mother or the father.

IQ Assessment

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) measured intelligence in children 6 years of age and older. For younger children (4 years and 10 months to 5 years and 11 months), only a General Conceptual Ability (GCA) score from the Differential Ability Scale (Elliott, 1990) was available. Verbal IQ (VIQ) was assessed by the Vocabulary and Similarities subtests (VIQ), performance IQ (PIQ) by the Matrix Reasoning and Block Design subtests, and full scale IQ (FSIQ) by the sum of VIQ and PIQ.

Head Circumference

Maximal occipitofrontal head circumference (HC) was measured by paper tape and adequate reliability was established across all sites.

Imaging

Structural magnetic resonance images of brain anatomy were collected at 1.5 Tesla without sedation under a 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence (Brain Development Cooperative Group, 2006). We applied an automated tissue segmentation algorithm to obtain volumes of gray matter (GM), white matter (WM) and cerebrospinal fluid and for regional brain structure extraction (Collins, Holmes, Peters, & Evans, 1995). Careful human interactive quality control was performed for all acquired images; images failing this step were excluded from the analysis. Total brain volume (TBV) was defined as the sum of the lobar GM and WM, subcortical GM, cerebellum, brainstem and cerebrospinal fluid (CSF) volumes. Volumes were estimated for the intracranial cavity (ICC), frontal, temporal, parietal and occipital lobar WM and GM, subcortical GM (thalamus, caudate nucleus, putamen and globus pallidus), cerebellum and brainstem. For more detail, visit www.NIH-PediatricMRI.org.

Biostatistical power

Effect sizes reported previously in the literature (Lange, Giedd, Castellanos, Vaituzis, & Rapoport, 1997) determined minimum sample sizes to detect regional associations with 80% power at a false positive rate of 5% and where coefficients of variation (standard deviation expressed as a percentage of the mean) themselves varied between 9.4 (putamen) to 19.3 (amygdala) in a non-representative sample similar in age range (Giedd, et al., 1996). Coefficient of variation is more useful than standard deviation when comparing an ensemble of measurements having different means and different variability and when mean and variance appear correlated (van Belle, Heagerty, et al. 2004), as is the case for brain structure sizes (Lange, Giedd et al. 1997; Kennedy, Lange et al. 1998; Caviness, Lange et al. 1999). For the cross-sectional baseline scans analyzed in this report, we have a minimum of 80% power to

detect age-dependent volumetric differences in all measured structures with the current sample size at all ages.

Biostatistical Analysis

All missing data were treated as missing at random. Two-sample t-tests, preceded by F-tests for equality of variance, and univariate linear regressions were conducted in our initial data explorations prior to formal model selection. False positive error rate was set at 0.05 for each test. A robust smoothing algorithm (Cleveland, 1981) was applied to scatter-plots of age by HC, TBV and ICC, with kernel width tuning held constant for all plots, to produce model-free summary curves. All regional brain volumes and AFI were expressed as deviations from their sampling means scaled to unit variance. We tested differences in IQ-volumetric correlations in males, females and age groups by use of R. A. Fisher's z-transform (van Belle, Heagerty, et al. 2004).

Data analysis proceeded in three sequential sections. Section 1 was a series of association analyses between IQ, family income and parental education. Section 2 expanded Section 1 by adding total and regional brain volumes. Section 3 further extended Sections 1 and 2 by adding formal regression analysis.

Analytic stages of regression models (Section 3)—Due to the range of hypotheses of varying complexity currently tested in the field, we conducted our section 3 analysis in three stages. Each stage included a sex-stratified analysis, allowing different residual variation for males and females, and a combined analysis treating sex as an additional covariate with pooled residual variance. In stage 1, we investigated relations between TBV and PIQ, VIQ and FSIQ while covarying for age and sex. In stage 2, we replaced TBV with the volumes of the cortical lobes, subcortical GM and cerebellum by regression models. Relative analyses were also performed, in which we represented regional volumetric proportions of TBV as deviations from their means scaled to unit variance. In stage 3, we applied the same analyses as in stage 2 to lobar GM and lobar WM separately. The main associations of age, sex and AFI were fixed by study design and hence included in all models in accordance with the marginality principle (Venables & Ripley, 2002). In this paper, we occasionally use the term “effect” according to its statistical definition, being the magnitude of the estimated coefficient (parameter) in a regression model. Regression effects are equivalent in significance to the estimated partial correlations from such models. In all three stages, candidate covariates were treated simultaneously in separate models for each brain structure. We employed the Akaike Information Criterion (AIC) (Akaike, 1974) to obtain the best-fitting yet simplest models. The AIC includes or excludes factors by allowing them to compete with each other based on their explanatory power. Simultaneous consideration of the ensemble of covariates that may be associated with IQ and regional brain volumes, including parental education and TBV does not obfuscate the association of each covariate with IQ measurements. Multi-covariate models provide more accurate and precise interpretations of each covariate's concurrent association in the presence of the others (van Belle, Heagerty, et al. 2004). All data analysis was performed in R version 2.9.0 (04/17/09 build) whose results are equivalent to those produced by SAS.

RESULTS

Participant Demographics and IQ

Figure 1 is a record of how we started with our full sample of MRI images to identify our subsample of $N = 285$ participants for the present study. Table 1 and Table 2 contain participant demographics, means, standard errors and ranges of their IQ scores and discrepancies between their VIQ and PIQ scores.

Section 1. Associations Between IQ, Family Income and Parental Education Adjusted Family Income, Verbal IQ, Performance IQ and Full Scale IQ

Adjusted Family Income, Verbal IQ, Performance IQ and Full Scale IQ: Verbal IQ: We observed statistically significant increases in mean VIQ between participants whose AFIs were in the low versus higher ranges, of 6.6 points from low to medium AFI ($p = 0.0001$) and of 5.5 points from low to high AFI ($p = 0.01$). VIQ was subdivided into three subgroups based on its sampling distribution to arrive at three nearly equi-sized participant groups, low (less than 107), medium (from 107 to 114) and high (greater than 114). No significant VIQ group-AFI associations were found.

Performance IQ: We observed that the PIQ-AFI association was stronger than the VIQ-AFI association. Mean PIQ was found to increase by nearly 6 points from low to medium AFI ($p = 0.0003$) and by over 7 points from low to high AFI ($p = 0.0002$). We also subdivided PIQ into three subgroups based on its sampling distribution to arrive at three nearly equi-sized participant groups, low (less than 104), medium (from 104 to 115) and high (greater than 115), with PIQs in the lowest AFI range and exhibited the strongest associations.

Full Scale IQ: Mean FSIQ increased significantly with AFI, by about 7 points from low to medium AFI ($p < 0.00001$) and by about 8 points from low to high AFI ($p < 0.0001$). FSIQ was also subdivided into three subgroups based on its sampling distribution to arrive at three nearly equi-sized participant groups, low (less than 106), medium (from 106 to 115) and high (greater than 115). We observed a nearly 2 point increase from low to medium AFI in participants with mid-level FSIQ ($p = 0.005$).

Parental Education, Verbal IQ, Performance IQ and Full Scale IQ

Parental Education, Verbal IQ, Performance IQ and Full Scale IQ: Verbal IQ: We detected a significant increase in mean VIQ between participants whose parental educations were in the lower versus higher ranges. The largest increase in participant VIQ occurred when parental education increased from the high school graduate to the college graduate level. VIQ was observed to increase by 14–15 points if their parents completed college or further higher education compared to those whose parents were only high school graduates from ($p < 0.00001$). Inspection of the statistical effects of parental education in the participant VIQ subgroups showed significant increases of 7–8 points in VIQ with parental education increases only in participants having VIQs in the lowest range ($p = 0.006$) and of 5–8 points in the highest range ($p = 0.03$).

Performance IQ: We observed that PIQ increased significantly with increasing parental education. Mean PIQ was found to increase by 8–10 points ($p = 0.004$) and mean FSIQ by 12–13 points ($p < 0.00001$) in participants whose parents completed college or further higher education compared to those whose parents graduated from high school only. Inspection of the statistical effects of parental education in the PIQ subgroups showed a significant 6–8 point change only in participants whose PIQs were in the lowest range ($p = 0.01$).

Full Scale IQ: The association between parental education and FSIQ was found to be less significant ($p < 0.05$) than that with PIQ and was seen only in participants whose FSIQs were in the lowest and highest ranges.

Section 2. Associations Between IQ, Total and Regional Brain Volumes, Intracranial Cavity Volume and Head Circumference—Table 3 contains marginal, conditional and joint correlations between FSIQ, VIQ, PIQ, TBV, total lobar GM volume, total lobar WM volume, ICC volume and HC. Each Pearson correlation was computed with and

without possible age and sex dependencies. We observed low but statistically significant FSIQ-volumetric correlations, the highest found in TBV and total lobar GM (0.22 – 0.23) and the lowest found in total lobar WM (0.14); Table 3, lower right triangle, first column. The observed brain and head size correlations with FSIQ were due in the main to their significant correlations with PIQ and not VIQ.

Associations between Total and Regional Brain Volumes, Intracranial Cavity and Head Circumference in Children and Adolescents: Volumetric correlations in two “younger” and “older” age groups, 4:10–11:1 and 12:0 – 18:4 years of age (Table 3, lower left and center triangles) indicated that the correlations of TBV with HC were highest in the younger children (0.40–0.79) and decreased in the older group (0.26–0.45). In contrast, the correlation between TBV and ICC remained high across the developmental period (0.93–0.96). Age-dependent HC- and ICC-volumetric correlation decreases were anticipated because, as shown in Figure 1, the cross-sectional age trajectories of TBV, ICC, and HC are similar when children are young but diverge during early adolescence when brain and intracranial cavity growth cease but head growth continues.

IQ and Total Brain Volume: We subdivided TBV into three groups, low (less than 2 SDs from the mean), medium (between - 2 SDs and 2 SDs from the mean) and high (greater than 2 SDs from the mean). We observed lower-powered positive VIQ-TBV increases in the subgroup analysis. Mean PIQ was found to increase by 15 points for participants with medium TBV compared to those with low TBV ($p < 0.0001$). Further subgroup analysis showed that the VIQ-TBV association was significant only in the low PIQ subgroup, by 11 points ($p = 0.007$). PIQ also showed significant upward shifts with increased TBV. Mean VIQ increased by 13 points for participants with medium compared to low TBV ($p = 0.045$). No VIQ subgroup exhibited a significant shift. As in PIQ, mean FSIQ was found to increase by 15 points for participants with medium TBV compared to those low TBV ($p = 0.003$). On average, participants having low VIQ and medium TBV were found to have 7 more VIQ points than those with low VIQ and low TBV ($p = 0.041$). No other FSIQ subgroup showed a significant shift.

Dissociations of IQ, Total and Regional Brain Volumes, Intracranial Cavity and Head Circumference by Age and Sex: We observed numerous differences between male and female measures of brain size, head size and measures of intelligence.

Dissociations of Total and Regional Brain Volumes and Head Circumference: Analyses of additional conditional correlations by sex (Table 3, lower left and center triangles) and of joint correlations by age and sex together (Table 3, four triangles in its upper left quadrant) identified many significant differences between male and female measures of brain size, head size and intelligence. The most salient dissociation between TBV and HC occurred between younger and older males, a dramatic drop in correlation from 0.79 to 0.26 ($p < 0.0000001$). Age-dependent changes in GM and WM associations with HC contributed roughly equally to this dissociation in males only ($p < 0.001$). Additional sexually dimorphic dissociations were evident among age group transitions, showing decreased HC-WM correlation in younger females (0.31) compared to younger males (0.61, $p = 0.018$).

Dissociations of Intelligence, Total and Regional Brain Volumes, Intracranial Cavity and Head Circumference: The strongest and most consistent associations between IQ measures and brain volumetrics were found in PIQ correlations with TBV, lobar GM and lobar WM. The highest correlation found was between PIQ and TBV for males aged 4:10 – 11:11 years (0.32) and the lowest between PIQ and lobar WM overall (0.18). A major dissociation of IQ and brain volumetrics was observed in the older age group, where only PIQ exhibited correlations with TBV, lobar GM and ICC (0.25–0.26).

Section 3. Comprehensive Linear Regression Models

Stage 1: Table 4 contains results from stage 1 regression analyses. Highly significant effects of parental education, with college graduation as baseline, were evident in IQ for males and females separately and combined. Mean VIQ was observed to decrease by about 18 points in males whose most highly educated parent holds only a high school diploma ($p < 0.001$) and by about 11 points if that parent attended some college but does not hold a college degree ($p = 0.001$). In females, corresponding but more moderate VIQ decreases were observed, of 10 and 6 points ($p \sim 0.03$) and in the sex-combined analysis. Standardized increases in AFI were associated with increased PIQ of 3 points per SD in females ($p = 0.001$) and of 2 points in the combined sample ($p = 0.008$).

The statistical effects of unit increases in TBV on IQ remained significant after adjustments for age-related associations and when all significant demographic associations were considered concurrently. A unit SD increase in TBV was associated with increased PIQ of about 3 points in males ($p = 0.002$). This increase was not observed in females separately but was reflected in the sex-combined analysis ($p = 0.001$). FSIQ was observed to increase with unit increases in TBV of about 3 points in males ($p = 0.002$), of about 2 points in females ($p = 0.026$), and of about 3 points in the combined sample ($p < 0.001$).

Stage 2: Table 5 contains findings from our stage 2 regression analysis, in which TBV was partitioned into frontal, temporal, parietal and occipital, subcortical GM and cerebellar volumes. Parental education and AFI associations were found to be similar to those evident in the TBV analysis (Table 4) yet less pronounced in males and females when analyzed separately, as anticipated from results previously reported herein. IQ was associated with frontal and temporal lobe volumes only (Table 5A). In males, PIQ was found to increase by 3 points with each SD unit increase in frontal lobe volume ($p = 0.004$) and FSIQ increased nearly 3 points with each SD unit variance increase in temporal lobe volume ($p = 0.0004$). In females, a unit increase in temporal lobe volume was associated with increased PIQ of about 2 points ($p = 0.014$), increased VIQ of nearly 5 points ($p = 0.022$) and increased FSIQ of about 5 points ($p = 0.004$). The full sample exhibited increases in PIQ of nearly 3 points with unit increases in temporal lobe volume ($p < 0.001$) and in FSIQ of 4 points ($p = 0.007$). No IQ-volume association persisted in corresponding relative analyses of regional volume to TBV ratios (Table 5B). We also observed increases in PIQ of between 2–3 points associated with AFI in males, females and the full sample ($p \sim 0.005$).

Stage 3: Table 6 contains a summary of our regression analysis from stage 3, which investigated relations between IQ and all tissue-segmented regional brain volumes. Increases in male VIQ were associated with SD unit increases in frontal GM of about 5 points ($p = 0.047$), and with unit increases of temporal WM of over 5 points ($p = 0.036$); Table 6A. Increases in PIQ were associated with unit increases in frontal WM of over 3 points in males only ($p = 0.002$), and with unit increases in temporal GM and WM of about 2 points in the combined sample ($p \sim 0.045$). FSIQ increases of over 4 points were associated with unit increases in temporal WM in females and the combined sample. Of all brain regions, temporal GM, temporal WM and frontal WM volumes had the most widely distributed associations across the IQ measures in both absolute (Table 6A) and relative (Table 6B) terms. IQ appeared to be unrelated to other regional brain volumes.

DISCUSSION

Although qualitative relations between child IQ, total brain volume and parental education are well known, the quantitative contributions of child total brain volume and parental demographic factors to variation in child IQ are inconsistent and not known. To our knowledge,

ours is the first study to examine simultaneously the associations between IQ and total and regional brain volumes, age, sex, family income and parental education and in a large representative sample of typically developing children and adolescents. First, we find that total and regional brain volumes do not mediate the strong association between parental education and child IQ. Second, we find that child and adolescent performance IQ, not verbal IQ, contributes in part to our observed correlations, between 0.14 to 0.27, of full scale IQ with temporal gray matter, temporal white matter and frontal white matter volumes. The volumes of other lobar, subcortical and subtentorial structures, when measured at our macroanatomic spatial and tissue imaging resolution, do not contribute significantly to variation in IQ when one acknowledges, concurrently, the association between IQ and parental education levels. We find that associations between VIQ and PIQ and total and regional brain volumes, parental education and family income are not uniform across the brain or the sexes. Third, we find that head circumference is an inadequate index of cerebral volume in typically developing older children and adolescents.

Parental Education

Our results demonstrate the importance of measuring parental education in studies designed to analyze the relations of IQ and total and regional brain volumes. The influence of parental education on IQ has been shown previously for children 4–8 years of age (Gale, et al., 2006; Gale, et al., 2004). The majority of studies examining the relationship of IQ to brain variables have considered full scale IQ only. We found different associations between parent education and brain morphometry on verbal, performance and full scale IQ.

In our analysis, the associations of parental education with childhood IQs are larger than IQ associations with unit increases in TBV and regional brain volumes. The influence of parental education on IQ in children is not mediated by total or regional brain volume measured in our cross-sectional design. Parental education levels are not correlated with any of the brain volumes examined in the children. Parental education may be associated with genetic and non-genetic mechanisms to influence other aspects of brain development that are associated with VIQ and PIQ in children. Genetic mechanisms may influence the correlation between IQ and education in parents and the heritability of IQ (Toga & Thompson, 2005). Non-genetic pathways may include associations between maternal education and prenatal care, nutrition during infancy and early childhood (Isaacs et al., 2008) through their enrichment of the environment and experiences to which a child is exposed during postnatal development. Parental education likely has significant associations with aspects of brain development in children other than total and regional brain volumes. Longitudinal growth trajectories, white matter microstructure, patterns of brain activation and neural network connectivity all appear to be related to IQ (Schmithorst & Holland, 2006; Schmithorst, Wilke, Dardzinski, & Holland, 2005; Shaw, et al., 2006).

IQ and Brain Size in Children, Adolescents and Adults

Our findings replicate past studies that found significant correlations between TBV and IQ and highlighted the importance of frontal and temporal lobes in this relationship. The large NIH sample is, however, the most representative sample of the entire United States population with respect to income and race/ethnicity to date; previous study findings are derived from non-representative samples. Hence, more important than replication, the quantitative findings reported here may be taken as normatively representative and employed for predictive and diagnostic purposes.

The correlation between full scale IQ and cerebral volume in the typically developing children in our study is small but significant (0.20 – 0.27), in general agreement with the correlations reported in the literature in older children and adolescents, and, as expected, lower than in

adults. In our study of the NIH sample, the FSIQ-TBV correlation is due to the significant correlation with PIQ and contributions from both lobar gray matter and lobar white matter volumes. Associations between FSIQ and lobar gray matter volume have been reported (Posthuma, et al., 2002; Reiss, et al., 1996). Verbal IQ is correlated to a much lesser degree with TBV, total lobar gray matter and white matter volumes in the children we studied. Our tissue-specific analyses show that the IQ-lobar GM volume associations are most prominent in frontal and temporal lobes. This finding is in agreement with multiple studies, mostly in adults, showing a link between IQ and these volumes (Frangou, Chitins, & Williams, 2004; Reiss, et al., 1996; Shaw, et al., 2006; Thompson, et al., 2001), although some studies find more widely distributed lobar GM involvement (Colom, Jung, & Haier, 2006; Haier, Jung, Yeo, Head, & Alkire, 2004; Wilke, Sohn, Byars, & Holland, 2003). The frontal and temporal lobes develop later than other regions of the brain, are important in complex cognitive processes such as language and executive function, and, as IQ, show increasing heritability with age during development (Lenroot, et al., 2007). No other brain regions appear to be involved in the relationship as directly.

Performance IQ, Temporal GM, Frontal GM and Frontal WM

Our findings suggest that aspects of brain development resulting in increased brain size, particularly increased lobar GM and lobar WM volumes, are more strongly associated with PIQ than VIQ. Non-volumetric aspects of brain development, such as the quality of proximal and distal brain connectivity and neural transmission, may be more important in the development of VIQ. Verbal IQ is more affected than full scale IQ by environmental exposures during fetal and postnatal development (Hibbeln et al., 2007; Horwood et al., 2001; Isaacs et al., 2008). Early nutrition, particularly in pre-term babies and better brain growth with early calorie and nutrient loading, may provide a more complex environment and early stimulation related to income and educational variables combined with better food sources during a critical period of early brain growth that, in turn, relates to intellectual development. It may be that these environmental exposures have relatively greater associations with qualitative aspects of brain development, related to VIQ, than on volumetric aspects of brain development, related to PIQ.

Most studies examining the relation of regional brain volume and IQ have considered gray matter only. Our findings from the large representative sample to date highlight the importance of frontal and particularly temporal WM volume when interpreting IQ variation in children and adolescents. The association between IQ and frontal lobe WM volume was seen in males and in males and females with relative WM volume. The role of white matter in intellectual performance has been suggested by studies that have found an association between voxel-based WM microstructure and measures of cortico-cortical connectivity and IQ (Lerch, et al., 2006; Schmithorst & Holland, 2006; Schmithorst, et al., 2005). Various aspects of intellectual function are known to involve intra- and inter-hemispheric communication between widely distributed cortical regions (Shaw, 2007). Our results suggest that WM connectivity with frontal and temporal cortices may play a critical role in IQ variation in children and adolescents.

Sexual dimorphisms

Consistent with past studies, we find sexual dimorphisms in relations between IQ and brain volume, supporting the evidence that developmental processes linking brain function and IQ may be different in males and females (Schmithorst & Holland, 2006). We also demonstrate the utility of sex-stratified and sex-combined approaches to investigate these dimorphisms. We find multiple, intriguing age-related associations that support the observations of other investigators (Schmithorst & Holland, 2006; Shaw, et al., 2006; Wilke, et al., 2003) and emphasize the need for further developmental approaches for the study of brain-IQ relations (Shaw, 2007).

Head Circumference

Although head circumference is used frequently as a measure of brain size, we find that it is an inadequate surrogate for cerebral volume in older typically developing children. The HC-TBV correlation of 0.59 for the children in our sample is smaller than correlations reported previously (Bartholomeusz, Courchesne, & Karns, 2002; Gale, et al., 2004; Hazlett, et al., 2005; Piven, Arndt, Bailey, & Andreasen, 1996). Very young children aged less than 4 years, 10 months were not included in the analysis presented here. The trajectories of TBV and HC diverge in adolescence when total brain growth ends and HC continues to increase. This differential growth pattern accounts for decreasing correlations of HC and TBV from childhood to adolescence (Lainhart, Lazar, Bigler, & Alexander, 2005). Some samples used to measure the correlation of HC and TBV have included individuals with autism (Hazlett, et al., 2005; Piven, et al., 1996), who as a group are known to have increased HC variance compared to typical individuals (Lainhart, et al., 2006).

The main caution that results from the HC-TBV correlation found in the NIH MRI sample is that head circumference is an insufficient index of TBV in typically developing older children and adolescents. In pediatrics, since the 1970s, it has been well known that the absence of hydrocephalus and gross abnormalities of head shape, head circumference was a practical, low-cost surrogate for brain size particularly during early childhood, where significant disturbances in whole-brain growth are accompanied by abnormal changes in head circumference. As seen in the NIH data (Figure 1), the maxima of TBV, ICC and HC occur, on average, at different ages. Total brain volume is the first to reach its maximum, and plateaus thereafter. Intracranial cavity volume reaches its maximum at a slightly older age, followed by the head circumference maximum which continues to increase (Aylward et al., 2002) due to increased skull and scalp thickness. When total brain volume decreases gradually in adulthood, head circumference and intracranial cavity volume remain relatively constant (Lainhart, et al., 2005) and thus diminishing their value as reliable surrogates of age-related developmental changes in total brain volume in older children and adolescents.

Limitations

Age-related changes found in this study are based on cross-sectional data and need to be confirmed or denied by longitudinal analyses (Shaw, 2007). The sampling distribution of parental education favors college and graduate level education that may limit generalization to less advantaged children and families and may also help explain why IQ scores in this sample are higher than average. Matching parental education proportions to those in the US Census 2000, in addition to AFI and race/ethnicity, would, however, have compromised sampling feasibility and reduced sample size given available resources. Relations between cortical thickness and cognitive ability (Karama, Ad-Dab'bagh et al. 2008) have not been addressed in this paper.

CONCLUSIONS

Our findings contribute to the understanding of neural-environmental associations with IQ in healthy children and may also inform brain-behavior-environment studies of developmental disorders in childhood. Unique relations between IQ, parental education, total brain volume, regional brain volumes, income and sex in children with developmental disabilities, such as autism, need to be investigated and compared to our findings in typically developing healthy children. Causal pathways linking IQ, brain development and parental education need to be understood at genetic and non-genetic levels in both typically developing children and in children with atypical development. In addition to IQ, associations between parental education and brain morphometry with other skills and abilities, such as social cognition, also need to be

investigated. These future studies will lead to a better understanding of what can be done to improve cognitive functioning in health, disease and disorder in childhood.

BRAIN DEVELOPMENT COOPERATIVE GROUP AUTHORSHIP LIST

The MRI Study of Normal Brain Development is a cooperative study performed by six pediatric study centers in collaboration with a Data Coordinating Center (DCC), a Clinical Coordinating Center (CCC), a Diffusion Tensor Processing Center (DPC), and staff of the National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the National Institute for Neurological Diseases and Stroke (NINDS), Rockville, Maryland.

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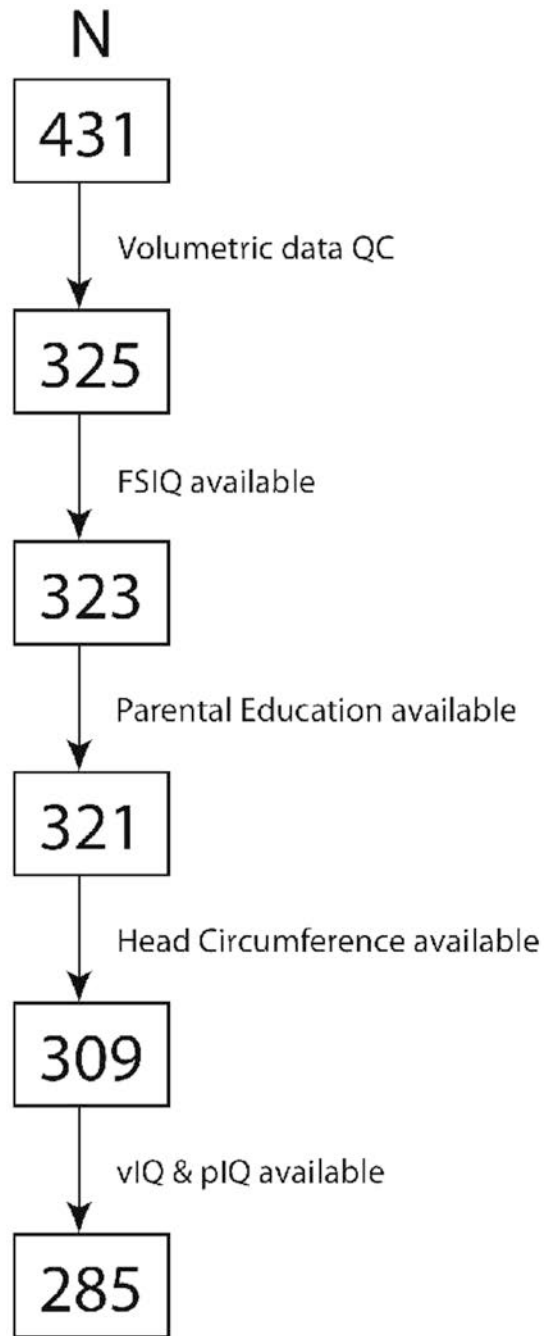


Figure 1.
Participant accrual and sample inclusion stages.

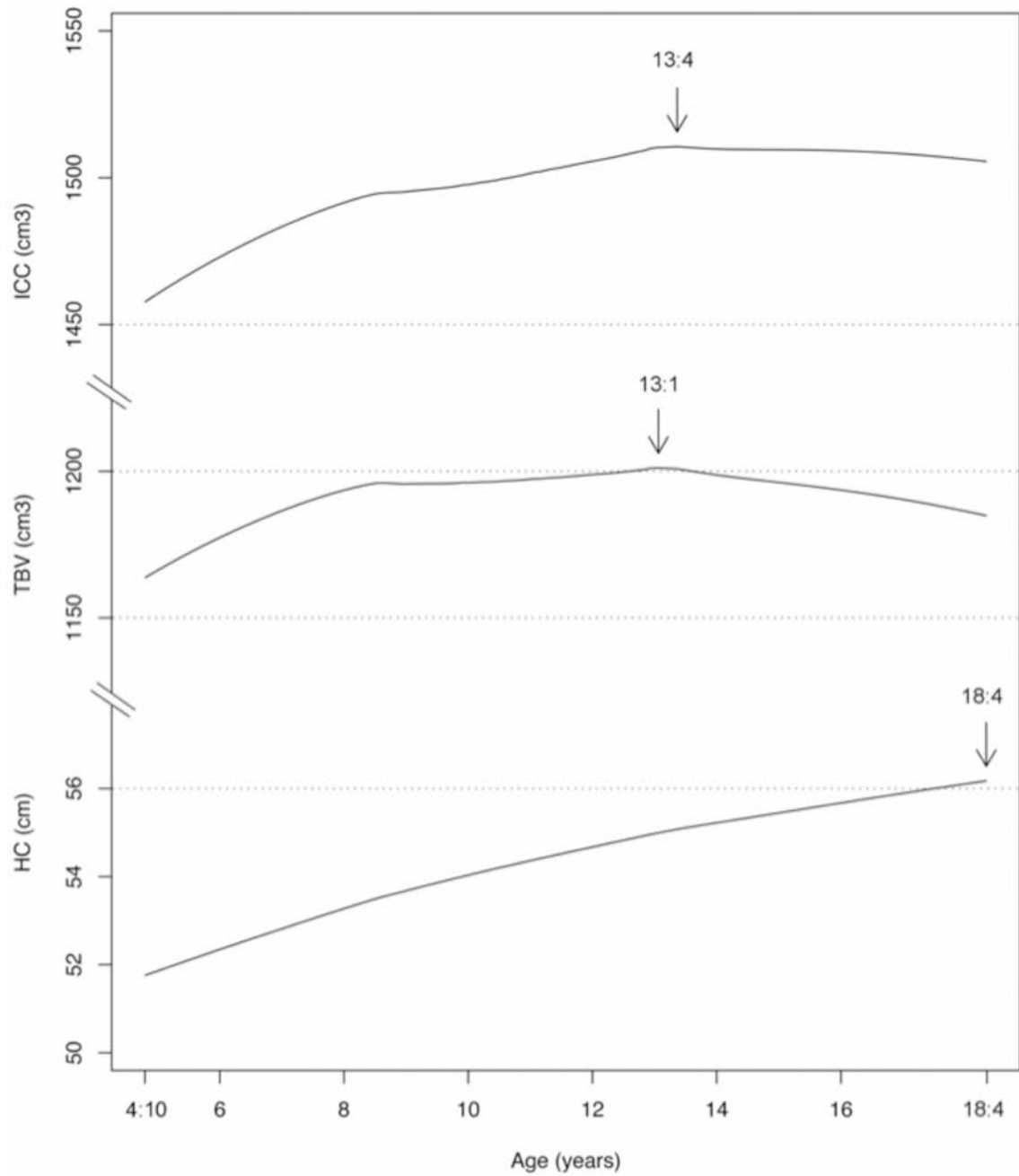


Figure 2. Empirical model-free curves for head circumference (HC), total brain volume (TBV) and intracranial cavity volume (ICC) by cross-sectional age. Arrows indicate curve maxima.

Table 1

Participant Demographics and IQ distribution

	Male	Female	Total
Sample size	143	166	309
Age (years)*	10.95 (0.32)	10.88 (0.28)	10.91 (0.21)
Age Range	4:10 to 18:4	4:11 to 18:3	4:10 to 18:4
Adjusted Family Income [†]	70,695 (2,478)	\$75,073 (2,619)	73,047 (1,816)
FSIQ	111 (1.02)	110 (0.92)	111 (0.68)
pIQ [‡]	111 (1.06)	108 (1.01)	110 (0.73)
PIQ [‡]	110 (1.20)	111 (1.04)	110 (0.79)
PIQ – pIQ discrepancy (%)			
Less than –14	13.8	11.0	12.3
Between –14 and 14	73.9	70.3	71.9
Greater than 14	12.3	18.7	15.8
Right-handed (%)	85.2	89.8	87.7
Parental Education**			
High School ^{††}	19	11	30
Some College	29	37	66
College	44	53	97
Some Graduate School	7	12	19
Graduate School	44	53	97
Total	143	166	309
Adjusted Family Income			
Low: Less than \$50,000	38	46	84
Medium: \$50,000 to \$100,000	80	75	155
High: Greater than \$100,000	25	45	70
Total	143	166	309

* Mean (SEM).

[†] Derived from tables provided by the US Department of Housing and Urban Development and the US Census 2000.

[‡] N = 285, total sample size; n = 155 females, n = 130 males.

** Highest level attained by either parent.

^{††} Includes one participant neither of whose parents completed high school.

Table 2

Means, standard errors and ranges of measures of intelligence.

Intelligence Measure	Male		Female		Total	
	mean (SEM)	range	mean (SEM)	range	mean (SEM)	range
Verbal IQ (Standard Score)	110 (1.20)	74–144	111 (1.04)	82–149	110 (0.79)	74–149
Performance IQ (Standard Score)	111 (1.06)	80–140	108 (1.01)	72–143	110 (0.73)	72–143
Full Scale IQ (Standard Score)	111 (1.02)	74–144	110 (0.92)	79–141	111 (0.68)	74–144

Table 3

Estimated Pearson Correlation Coefficients (N = 309*)

	4:10 – 11:11						12:0 – 18:4						Total									
	Intelligence			Brain Volumetrics			Intelligence			Brain Volumetrics			Intelligence			Brain Volumetrics						
	FSIQ	VIQ	PIQ	TBV	GM	WM	ICC	FSIQ	VIQ	PIQ	TBV	GM	WM	ICC	FSIQ	VIQ	PIQ	TBV	GM	WM	ICC	
Male	VIQ	0.86†						VIQ	0.88						VIQ	0.87						
	PIQ	0.81	0.40					PIQ	0.83	0.47					PIQ	0.82	0.43					
	TBV	0.29	0.20	0.32				TBV	0.17	0.06	0.27				TBV	0.23	0.14	0.28				
	GM	0.24	0.16	0.27	0.88			GM	0.14	0.04	0.23	0.89			GM	0.20	0.13	0.23	0.88			
	WM	0.17	0.09	0.21	0.75	0.37		WM	0.21	0.11	0.29	0.84	0.51		WM	0.17	0.09	0.24	0.80	0.44		
	ICC	0.26	0.14	0.32	0.96	0.81	0.77	ICC	0.19	0.07	0.30	0.95	0.85	0.81	ICC	0.23	0.11	0.30	0.95	0.83	0.78	
	HC	0.20	0.11	0.23	0.79	0.68	0.82	HC	0.13	0.14	0.09	0.26	0.24	0.35	HC	0.17	0.13	0.16	0.46	0.43	0.38	0.55
Female	VIQ	0.82						VIQ	0.87						VIQ	0.84						
	PIQ	0.81	0.33					PIQ	0.84	0.47					PIQ	0.82	0.38					
	TBV	0.24	0.20	0.20				TBV	0.20	0.13	0.21				TBV	0.22	0.18	0.20				
	GM	0.27	0.21	0.25	0.92			GM	0.26	0.19	0.25	0.87			GM	0.27	0.21	0.25	0.90			
	WM	0.13	0.12	0.10	0.82	0.54		WM	0.07	0.03	0.09	0.83	0.45		WM	0.11	0.09	0.09	0.82	0.51		
	ICC	0.20	0.19	0.15	0.94	0.84	0.81	ICC	0.20	0.14	0.19	0.93	0.77	0.82	ICC	0.20	0.17	0.16	0.94	0.81	0.81	
	HC	0.15	0.16	0.08	0.40	0.38	0.31	HC	0.04	0.06	-0.02	0.41	0.27	0.38	HC	0.09	0.11	0.03	0.41	0.34	0.34	0.53
Total	VIQ	0.84						VIQ	0.87						VIQ	0.85						
	PIQ	0.81	0.36					PIQ	0.84	0.46					PIQ	0.82	0.40					
	TBV	0.25	0.17	0.26				TBV	0.18	0.07	0.26				TBV	0.22	0.12	0.25				
	GM	0.26	0.16	0.27	0.92			GM	0.20	0.10	0.25	0.91			GM	0.23	0.14	0.26	0.91			
	WM	0.15	0.09	0.17	0.82	0.56		WM	0.15	0.05	0.21	0.87	0.60		WM	0.14	0.07	0.18	0.85	0.58		
	ICC	0.22	0.14	0.24	0.96	0.86	0.83	ICC	0.18	0.07	0.26	0.96	0.85	0.86	ICC	0.20	0.10	0.24	0.96	0.86	0.84	
	HC	0.18	0.14	0.16	0.59	0.54	0.48	HC	0.08	0.06	0.08	0.45	0.38	0.42	HC	0.13	0.10	0.11	0.51	0.46	0.45	0.60

* N = 297 for VIQ and PIQ

† Entries in bold-face are significant at the 0.05 level

Table 4

Linear model summaries, Stage 1. Key: Δ , change on IQ due to statistical effect; p , p -value. College graduation was the baseline for estimating statistical effects of parental education.

Male						
Estimated effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	3.6	0.049				
High School			-17.6	< 0.0001	-13.6	< 0.001
Some College			-11.3	< 0.001	-10.3	< 0.001
Total Brain Volume	3.1	0.002			3.0	0.002

Female						
Estimated effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	3.0	< 0.001				
High School			-9.7	0.030	-8.3	0.026
Some College			-6.4	0.033	-5.8	0.019
Total Brain Volume					1.9	0.026

Combined						
Estimated effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	2.1	0.008				
High School	-5.8	0.037	-13.6	< 0.00001	-10.8	< 0.0001
Some College	-4.2	0.031	-8.4	< 0.0001	-7.9	< 0.0001
Total Brain Volume	2.6	0.001			2.9	< 0.001

Table 5

Table 5A. Linear model summaries, Stage 2 absolute. Key: Δ, change on IQ due to statistical effect; p, p-value. College graduation was the baseline for estimating statistical effects of parental education.

Effect	Male					
	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
High School			-16.9	< 0.0001	-13.8	< 0.001
Some College			-10.3	0.001	-10.1	< 0.001
Frontal Lobe	3.0	0.004				
Temporal Lobe					2.8	0.004

Effect	Female					
	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	3.0	0.001			2.2	0.024
Some College					-5.7	0.019
Temporal Lobe	2.3	0.014	4.6	0.022	5.2	0.004

Effect	Combined					
	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	2.1	0.009				
High School			-13.0	< 0.0001	-10.3	< 0.0001
Some College			-7.9	< 0.0001	-7.4	< 0.0001
Temporal Lobe	2.7	<10 ⁻³			4.0	0.007

Table 5B. Linear model summaries, Stage 2 absolute. Key: Δ, change on IQ due to statistical effect; p, p-value. College graduation was the baseline for estimating statistical effects of parental education.

Male					
Effect	PIQ		VIQ		FSIQ
	Δ	p	Δ	p	Δ
Income	3.3	0.001			
High School			-17.3	< 0.0001	-13.2
Some College			-10.9	< 0.001	-9.5
					< 0.001
					0.001

Female					
Effect	PIQ		VIQ		FSIQ
	Δ	p	Δ	p	Δ
Income	3.3	<10 ⁻³			2.5
Some College			-5.9	0.049	-6.3
					0.012

Combined					
Effect	PIQ		VIQ		FSIQ
	Δ	p	Δ	p	Δ
Sex	3.5	0.012			
Income	2.3	0.005			
High School			-13.5	< 0.00001	-10.8
Some College			-8.4	< 0.0001	-7.8
					< 0.0001
					< 0.0001

Table 6

Table 6A. Linear model summaries, Stage 3 absolute, Key: Δ, change on IQ due to statistical effect; p, p-value. College graduation was the baseline for estimating statistical effects of parental education.

Effect	Male					
	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
High School			-15.9	< 0.001	-13.0	< 0.001
Some College			-10.5	0.001	-9.7	< 0.001
Frontal GM			4.9	0.047	2.8	0.014
Frontal WM	3.4	0.002				
Temporal WM			5.3	0.036		

Female

Effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
	Income	3.0	0.002			2.1
High School					-7.6	0.039
Some College					-5.6	0.020
Temporal WM					4.2	0.017

Combined

Effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
	Income	3.0	<10 ⁻⁴			
High School			-12.7	< 0.0001	-10.0	< 0.0001
Some College			-8.2	< 0.001	-7.5	< 0.0001
Frontal GM					2.2	0.017
Temporal GM	1.6	0.042				
Temporal WM	1.6	0.048			4.0	0.009

Table 6B. Linear model summaries, Stage 3 relative. Key: Δ, change on IQ due to statistical effect; p, p-value. College graduation was the baseline for estimating statistical effects of parental education.

Male						
Effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
High School			-15.4	< 0.001		0.001
Some College			-9.9	0.008		0.022
Frontal Lobe WM			-5.4	0.018		

Female						
Effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	4.2	< 0.0001	3.8	0.001	4.5	< 0.00001
Frontal Lobe WM					-5.4	0.005
Temporal Lobe GM	5.1	0.002				

Combined						
Effect	PIQ		VIQ		FSIQ	
	Δ	p	Δ	p	Δ	p
Income	2.1	0.040				
High School			-11.4	0.001	-9.3	0.001
Some College			-7.6	0.002	-7.0	0.001
Frontal Lobe WM			-8.7	0.001	-3.3	0.008
Temporal Lobe WM					3.5	0.024