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DEVELOPMENTAL SEX DIFFERENCES IN THE RELATION OF NEUROANATOMICAL CONNECTIVITY TO INTELLIGENCE

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Abstract

Recent neuroimaging research has shown sex-related differences in the relationship between brain structure and cognitive function. Anatomical studies have shown a greater reliance for cognitive function on white matter structure in adult females, and a greater reliance on gray matter structure in adult males. Functional neuroimaging studies have also shown a greater correlation between brain connectivity and cognitive function in females. However, this relationship is not present in young childhood (5 years old) but appears during the developmental period. Here sex differences in structure-function relationships and their developmental trajectory are investigated using diffusion tensor imaging (DTI) on a large cohort of over 100 normal children ages 5–18. Significant sex-X-IQ interactions on fractional anisotropy (FA), a marker for white matter organization, were seen in the left frontal lobe, in fronto-parietal areas bilaterally, and in the arcuate fasciculus bilaterally, with girls showing positive correlations of FA with IQ, and boys showing a negative correlation. Significant sex-X-IQ-X-age interactions on FA were also seen in the left frontal lobe and in fronto-parietal areas bilaterally, showing a developmental effect. These results strongly corroborate previous findings regarding sex differences in structure-function relationships regarding intelligence. Results also indicate that a naïve interpretation of “more is better” with respect to FA may not be accurate, especially in adult males.

Keywords

Diffusion Tensor MRI; Sex Differences; Brain Growth and Development; Age Factors

Introduction

An increasing body of neuroimaging literature is demonstrating sex-related differences in brain structure and in its relation to cognitive function (e.g. (Allen, Damasio, Grabowski, Bruss, & Zhang, 2003; Gur et al., 1999; Luders et al., 2006)). An interesting finding is that women display a greater dependence on white matter structure for cognitive function. Global white matter volume correlates more strongly with intelligence in women; while global gray matter volume correlates more strongly in men (Gur et al., 1999). A voxel-based morphometry (VBM) study (Haier, Jung, Yeo, Head, & Alkire, 2005) showed many more

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regions in women in which regional white matter volume correlated with intelligence relative to men; the reverse was true in men, in whom there were more regions where regional gray matter volume correlated with intelligence. Magnetic resonance spectroscopy (MRS) studies (Pfleiderer et al., 2004; Jung et al., 2005) have also demonstrated white matter regions in which N-acetyl-aspartate (NAA) concentrations correlate with intelligence in women but not in men. Since the white matter contains mostly axons, which connect the different regions of the brain to each other, one might also expect sex-related differences in the relationship of brain connectivity to intelligence. Functional neuroimaging studies (Schmithorst & Holland, 2006, 2007) have shown a greater dependence on functional connectivity in females in early adulthood/late adolescence (18 years), although this is likely moderated by specific information processing demands (Schmithorst & Holland, 2007).

An important auxiliary question related to sex differences in brain structure and their relation to intelligence and cognitive function is the developmental aspect. How do the differences seen in adult men and women develop throughout childhood? Are these differences “hard-wired”, so to speak, in infants' or children's brains? Or do they develop, over time, throughout the normal course of maturation? Neuroimaging studies cannot completely unravel the “nature vs. nurture” question, as boys and girls are subject to differing environmental influences, which will affect their brain development in different ways. Nevertheless neuroimaging studies can provide information on possible differing developmental trajectories between boys and girls, which can inform the debate. While adult women have greater relative gray matter compared to men, the reverse situation is present in children under the age of 12, where girls have greater relative white matter volume (De Bellis et al., 2001). A sex-X-age interaction in development is seen, in which boys show a greater rate of increase of relative white matter volume and a greater rate of decrease of relative gray matter volume. Boys and girls are approximately equal in relative white and relative gray matter volume around age 11–12; after that point the relative volumes approach their adult values. In accordance with these results, the functional connectivity studies cited above (Schmithorst & Holland, 2006, 2007) show not only a sex-X-IQ interaction but also an age-X-sex-X-IQ interaction between functional connectivity and intelligence. Younger boys show a positive correlation between functional connectivity and IQ, which changes into a negative correlation after approximately 12 years of age; younger girls show no significant correlation between connectivity and IQ, while older girls display a positive correlation.

White matter microstructure can be investigated using MRI, using diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI) (see (Basser & Jones, 2002) for a review of DTI). A previous DTI study (Schmithorst, Wilke, Dardzinski, & Holland, 2005) showed correlations between fractional anisotropy (FA) and intelligence in a normal pediatric population, in frontal and occipito-parietal regions; however the population consisted of mostly girls. In order to investigate possible differences in white matter microstructure between boys and girls and their relationship to intelligence, we performed DTI on a cohort of over 100 normal children ages 5–18. More highly organized fiber bundles, indicative of greater functional connectivity, will show higher FA due to the greater anisotropy. Given the previous results regarding functional connectivity, our prediction is that we should find regions in younger boys with a positive correlation between FA and intelligence, but in older boys with a negative correlation between FA and intelligence; we should also find regions in older girls with a positive correlation between FA and intelligence, but not in younger girls (and possibly even regions with a negative correlation). We do not have a firm prediction regarding mean diffusivity (MD). While changes in fiber density will reflect in changes in MD, MD is also affected by changes in the intracellular compartment related to normal development (Baratti, Barnett, & Pierpaoli, 1999).

Materials and Methods

This study is a reanalysis of DTI data published previously (Schmithorst, Holland, & Dardzinski, 2008) investigating developmental differences in white matter microstructure between boys and girls using DTI. The data is reanalyzed here to investigate whether there also exist sex-related developmental differences in the relationship of white matter microstructure to cognitive function. We refer the reader to our previous paper for the details regarding the scanning and data analysis procedures but provide a summary of the relevant details here.

Institutional Review Board approval was obtained for the study, informed consent was obtained from one parent or guardian, and assent was obtained from children over the age of 8. Subjects were prescreened for standard MRI exclusion criteria such as the presence of orthodontic braces. Other exclusion criteria included: failure to score within a normal range on a neurological examination; failure to maintain a C- average in school; positive history for neurologic or psychiatric disease; a previous clinically indicated MRI scan; any treatment (including medication) for any neurological or psychiatric conditions; learning disability; head trauma with loss of consciousness; birth at < 38 weeks gestational age.

DTI and neurocognitive data were successfully acquired from 106 children (54F, 52 M). Neurocognitive testing was performed under the supervision of a board certified pediatric neuropsychologist. Subjects received the Wechsler Preschool and Primary Scale of Intelligence, Revised (WPPSI-R), the Wechsler Intelligence Scale for Children, Third Edition (WISC-III), or the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III).

MRI scans were acquired on a Bruker 3T Medspec 30/60 system. A single-shot spin-echo echo-planar-imaging (EPI) DTI sequence was used with the following parameters: TR/TE = 6070/87 ms, FOV = 19.2 cm × 25.6 cm, slice thickness = 5 mm, matrix = 64 × 128, Δ = 40 ms, δ = 18 ms, diffusion gradient strength = 30 mT/m, b-value = 710 s/mm². For 47 subjects, the FOV in the readout (L–R) direction was 25.6 cm instead of 19.2 cm. Twenty-five diffusion gradient directions were used, determined using an electrostatic repulsive model (Jones, Horsfield, & Simmons, 1999). To minimize distortion due to gradient eddy currents, an automated gradient preemphasis adjustment routine was employed (Schmithorst & Dardzinski, 2002). A T1-weighted MP-RAGE scan was also acquired, for anatomical coregistration, with the following parameters: TI/TR/TE = 550/15/4.5 ms, FOV = 19.2 cm × 25.6 cm × 19.2 cm, matrix = 128 × 256 × 128.

The raw DTI datasets were corrected for geometric distortion artifacts arising from main magnetic field (B0) inhomogeneity using the multiecho reference method (Schmithorst, Dardzinski, & Holland, 2001). The DTI tensor components were computed from each DTI dataset using the Robust Estimation of Tensors by Outlier Rejection (RESTORE) method (Chang, Jones, & Pierpaoli, 2005). The RESTORE technique rejects data points corrupted by gross motion or by motion during the application of the diffusion gradients. Fractional anisotropy (FA) and mean diffusivity (MD) maps were computed from the DTI tensor components.

Spatial normalization and segmentation were performed using routines in SPM5 (Wellcome Dept. of Cognitive Neurology, London, UK), using pediatric templates (Wilke, Schmithorst, & Holland, 2003) to increase accuracy. The T1-weighted anatomical images from each subject were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) probability maps (in native space). The FA maps were co-registered to the white matter probability maps using a rigid body transformation, to correct for possible subject motion between the time of acquisition of the whole-brain anatomical scan and the DTI scan. The white matter maps were normalized to the white matter pediatric template, in Montreal

Neurologic Institute (MNI) space, and resampled to 2 mm isotropic resolution. Using the same transformation parameters, the FA and MD maps were also normalized into the MNI space, and also resampled to 2 mm isotropic resolution.

To guard against possible spurious results from morphological (as opposed to white matter microstructural differences), and artifacts from partial volume effects and imperfect spatial normalization, a very conservative approach was taken for the voxelwise analysis. Analysis was restricted to only those voxels with a white matter probability of > 0.9 and a FA of > 0.25 , and globally, the analysis was restricted to only those voxels in which this criterion was met in 60 subjects or more. This conservative approach has the effect of limiting the analysis to the larger white matter tracts.

A General Linear Model (GLM) voxelwise analysis (Worsley & Friston, 1995) was used, modified to account for the different scan protocol and electronics upgrade midway through the data acquisition period, as detailed in our previous paper. This procedure necessitated discarding data from one subject (the only subject for which the original scanner architecture was used with a larger voxel size). A three-way ANCOVA design was used: the two regressors of interest are sex-X-IQ interaction and sex-X-age-X-IQ interaction; nuisance variables are main effects of age, sex, and IQ, age-X-sex interaction, and age-X-IQ interaction. T-score maps were converted into Z-score maps, spatially filtered using a Gaussian filter of width 3 mm, and restricted to voxels inside the white matter mask to prevent “bleeding” into gray matter or CSF regions. A threshold of $Z = 10$ with spatial extent threshold of 150 voxels was used. These values of magnitude and spatial extent threshold were selected in order to obtain statistically significant results ($p < 0.01$) corrected for multiple voxel comparisons; corrected p-values were estimated using a Monte Carlo method (Ledberg, Akerman, & Roland, 1998), since the filter width was not significantly larger than a single voxel.

For each region with a significant sex-X-IQ or age-X-sex-X-IQ interaction on FA or MD, the centroid of the region was found and converted from MNI to Talairach coordinates using the **mni2tal** procedure (available at <http://nil.wustl.edu/labs/kevin/man/answers/mnispac.html>), and the average FA or MD values across the regions were found and analyzed separately for display purposes. For the regions with a sex-X-IQ interaction, the data was separated out into boys and girls, and the correlation coefficient (R value) of FA/MD vs. IQ was computed separately for boys and girls. For the regions with a sex-X-age-X-IQ interaction, the data was separated out into younger (age < 12 years) boys, older (age ≥ 12 years) boys, younger girls, and older girls. Cohen's f^2 was also computed as a measure of the magnitude of the effect size for each region.

Results

There was no significant difference between boys and girls for age (girls = 12.4 ± 3.5 [range 5.7 – 18.3 years], boys = 12.1 ± 3.6 years [range 5.8 – 18.7 years]; $p > 0.6$, student's T-test), Full-Scale IQ (girls = 111.1 ± 15.4 , boys = 110.7 ± 11.7 ; $p > 0.8$, student's t-test), Verbal IQ (girls = 112.2 ± 15.2 , boys = 111.3 ± 12.1 ; $p > 0.7$, student's t-test), or Performance IQ (girls = 107.9 ± 16.1 , boys = 108.3 ± 11.7 ; $p > 0.8$, student's t-test), or handedness, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) (6 left-handed boys, 2 left-handed girls, 1 ambidextrous boy; $p > 0.2$, χ^2 contingency test).

Four regions displayed a significant sex-X-IQ interaction on FA (Figure 1, Table 1): the right arcuate fasciculus, right fronto-parietal white matter, a left frontal region, and a left fronto-parietal region including part of the left arcuate fasciculus. Separating out the data

between boys and girls (Table 1), these regions show a negative correlation of FA with IQ in boys, and a positive correlation of FA with IQ in girls (all correlations significant at nominal one-tailed $p < 0.05$). A graphical representation of this data is presented in Figure 2.

Six regions displayed a significant sex-X-IQ interaction on MD (Figure 3, Table 2), including large frontal-parietal-occipital areas in both hemispheres. In these regions, boys displayed a negative correlation of MD with IQ, with no significant correlation seen in girls. Sex-X-IQ interactions were also seen in the left inferior longitudinal fasciculus, the left corticospinal tract, the splenium of the corpus callosum, and the right occipital lobe. In the left hemisphere areas (inferior longitudinal fasciculus and cortico-spinal tract), boys displayed a significant or near-significant negative correlation of MD with IQ while girls displayed a positive correlation. In the right occipital lobe, girls displayed a positive correlation of IQ with MD, while no significant effect was seen in boys. Results are graphed in Figure 4.

Four regions also displayed a significant age-X-sex-X-IQ interaction on FA (Figure 5, Table 3). In the fronto-parietal regions bilaterally, younger boys show a positive correlation of FA with IQ while older boys show a negative correlation; in girls, younger girls show no significant correlation while older girls show a positive correlation of FA with IQ. A similar effect is seen in a left frontal region, except that the younger boys show no significant correlation. In the cortico-spinal tract (at a level inferior to the internal capsule), boys maintain a negative correlation of IQ with FA throughout development; younger girls have a strong positive correlation while older girls have no significant correlation. Results are graphically shown in Figure 6.

Widespread regions of the brain were seen to exhibit an age-X-sex-X-IQ interaction on MD (Figure 7, Table 4). Due to the widespread nature of the effect, the post-hoc analysis was separated out only into left and right hemispheres (graphically shown in Figure 8). Younger girls display a negative correlation of IQ with MD; this effect disappears during the developmental period. Younger boys display a positive correlation of MD with IQ in the left hemisphere and no significant correlation in the right hemisphere; however older boys display a negative correlation of MD with IQ in both hemispheres.

Discussion

A previous study (Schmithorst, Wilke, Dardzinski, & Holland, 2002) investigating changes of FA and MD with age during normal development (using the same age range as in this study) found regionally specific areas with increasing FA, but widespread regions with decreasing MD. This led to the hypothesis of at least two major changes occurring in the brain during normal development: 1) denser and more ordered packing of fiber tracts; and 2) intracellular changes including greater membrane concentration and surface-to-cell volume ratio. Process 1) will lead to an increase in FA, while process 2) will lead to a decrease in MD (Baratti et al., 1999). However, differences in packing or ordering of fiber tracts will also reflect in differences in MD, and the direction of the change in MD is not uniquely determined. For instance, if a highly ordered fiber bundle becomes even more highly ordered and dense, this would reflect in a decrease in MD (in addition to an increase in FA) due to the more highly restricted extracellular space. In a region with many crossing fiber tracts, however, if some of the crossing tracts disappear as a result of selective gray matter pruning, this would reflect in an increase in FA (due to the increase in ordering) but also in an increase in MD, due to a less restricted extracellular space.

Our results show that the developmental changes described above do not necessarily result in improved cortical function, and this effect is moderated by sex-related developmental

differences. In boys there are several regions showing a negative correlation of FA with IQ, or an interaction effect showing a developmental change from a positive to a negative correlation of FA with IQ. This indicates that a developmental trend towards more highly ordered fiber tracts is not beneficial in males in all brain regions. In girls there are several regions showing a positive correlation of MD with IQ, and the overall effect seen in younger girls throughout the brain of a negative correlation between MD and IQ disappears during development. While this could indicate that intracellular changes towards greater membrane concentration/surface-to-cell volume ratio is not beneficial for cognitive function in females, the MD changes could also be the result of other factors, as described above.

We first consider implications for brain development in girls. Functional neuroimaging studies (Schmithorst & Holland, 2006, 2007) point to an increasing reliance on functional connectivity with age for cognitive function. Anatomical studies also show that adult females display a greater correlation between intelligence and global and regional white matter volume (Gur et al., 1999; Haier et al., 2005). Consistent with these findings, girls develop a positive correlation of FA with intelligence in associative and commissural regions bilaterally, including a large fronto-parietal region encompassing part of the arcuate fasciculus. The FA findings point to increased fiber organization being a critical component underlying cognitive function in the developing female brain.

However, adult females also display a smaller proportion of white matter (normalized for whole brain volume) (De Bellis et al., 2001) compared to males; this finding also shows a developmental effect in most regions (De Bellis et al., 2001), with the particular exception of the left inferior frontal gyrus (Blanton et al., 2004). Thus in addition to increased reliance on organization and connectivity, there is also a relatively more constrained white matter space compared to boys. This would reflect in increased tortuosity and hence lower FA values. In white matter associative regions, girls display lower FA relative to boys overall, with however greater increases with age in associative regions in the right hemisphere (Schmithorst et al., 2008).

Given the positive correlation between global/regional white matter volume and intelligence in adult women (Gur et al., 1999; Haier et al., 2005), an increasingly constrained white matter space appears to have a deleterious effect on overall intelligence, and could also reflect in increased white matter density. Consistent with this interpretation, girls develop a positive correlation of MD (reflecting decreased density) with IQ in the right occipital lobe, the left inferior longitudinal fasciculus, and the left cortico-spinal tract; throughout the rest of the brain, a negative correlation of MD (reflecting increased white matter density) with intelligence is eliminated. We also interpret the MD findings as possibly indicating that the elimination of unnecessary crossing fiber tracts may also play a key role in the development of the necessary brain architecture. During the developmental gray matter pruning phase, ineffective and/or inefficient cortical connections should also be removed. Removal of these connections would also reflect in decreased white matter density, and greater MD.

We now consider implications for brain development in boys. In boys, a negative correlation of FA with IQ develops with age in the same regions in which girls develop a positive correlation of FA with IQ. The negative correlation of FA with IQ is consistent with boys' development of a negative association between intelligence and functional connectivity (Schmithorst & Holland, 2006, 2007).

An unexpected finding however was that an overall negative correlation of MD with intelligence also develops in boys. This change is not consistent with less dense and/or organized fiber tract connections, especially considering the relatively larger and less constrained white matter volume in boys. Given the widespread region in the which age-X-

sex-X-IQ interaction on MD, we believe these results reflect a global maturational process. These results could reflect a beneficial global maturational change in the intracellular compartment (Baratti et al., 1999), involving possibly an increased concentration of macromolecules (Tower & Bourke, 1966) and also a greater surface-to-cell volume ratio caused by an increased proliferation of processes and organelles (Caley, 1971). While this global maturational change occurs both in boys and girls, its relation to MD values will be affected by sex-related differences in axonal diameter and possibly shape as well. Microstructural differences in axonal shape and size in the corticospinal tract have been previously seen between adult (elderly) men and women in a post-mortem study (Zhou, N. Goto, J. Goto, Moriyama, & He, 2000). It has been hypothesized that the corpus callosum in adult men contains fewer but thicker myelinated fibers (Westerhausen et al., 2004); this result has been corroborated by a post-mortem study involving rats, in which thicker myelin sheaths in the corpus callosum were detected in males (Kim, Ellman, & Juraska, 1996). Fewer, but thicker and more myelinated axons, would become more sensitive to changes in the intracellular compartment, due to the greater intracellular fraction. Another intriguing hypothesis is that, due to differences in axonal diameter and shape, boys may be more sensitive to myelination processes and this may reflect in decreased MD due to a greater proliferation of myelinating glia in the extracellular compartment. It has been hypothesized (Fields, 2005) that myelination may in fact be a mechanism for plasticity during development. Unfortunately, DTI does not provide a direct marker for myelination and further research will be necessary to investigate this hypothesis further.

Another unexpected finding was the difference between younger and older girls in the relationship between intelligence and FA in the lower corticospinal tract, and the negative correlation between FA and intelligence in this regions in boys throughout the developmental period. A previous study found lower FA in this region in trained musicians compared with non-musicians (Schmithorst & Wilke, 2002), which was interpreted as the effects of fine motor practice (analogous to findings in functional MRI of decreased activation in the motor cortex in trained performers). We therefore hypothesize that our results may represent experience-related developmental differences in the motor pathways associated with IQ, although further research will also be necessary to further elucidate this finding.

Our results put into some question the assumption that higher FA necessarily implies better cortical function. Our first study (Schmithorst et al., 2005) showed a positive correlation of FA with IQ; however, the sample population was significantly biased toward females. However, here we are able to show, in older boys (and likely adult men as well), significant negative correlations ($|R| > 0.5$ in the fronto-parietal regions) between FA and IQ. These results corroborate the hypothesis (Haier, 1993) that elimination of inefficient synaptic connections is a critical component of the development of the brain in males.

A strength of the study design is that it avoids problems associated with transferability of results (Rivkin, 2000). Unlike studies involving subjects clinically referred for MR exams and only classified retrospectively as normal, in this study all subjects were recruited for a normal cross-sectional study and scored within the normal range on neurological/neuropsychological measures. Thus, the results are generalizable to the normal pediatric population.

The study however is also subject to several limitations. An important limitation of the study is the inability to investigate smaller fiber tracts, due to partial volume effects, and much of the corpus callosum, due to significant inter-subject variability and hence poor coregistration of the brain in this area. We chose to employ a conservative approach to masking, which greatly reduces the possibility for spurious results yet may possibly result in failure to find

some significant differences. It is possible, therefore, that sex-related differences in the relationship of brain structure to cognitive function may exist in additional white matter regions. Another limitation is the upper age limit of the study population (18 years). It is likely that brain maturation continues beyond the 18th year of life, possibly until age 30 or even beyond, and there may also be sex-related differences in the relation of this maturational process to intelligence. In addition, the cognitive measure used (Full-Scale IQ) is only a proxy for general cognitive ability. There may be additional regions associated with differences in other specific cortical functions which have been investigated with DTI, for instance reading ability (Klingberg et al., 2000). Future research will investigate sex-related differences in specific aspects of cognitive function, including such important distinctions as fluid vs. crystallized intelligence.

Our results naturally await independent replication. Sex differences found in exploratory functional MRI studies have sometimes been found not to replicate (Haut & Barch, 2006), although DTI studies involve structural information alone and are not subject to confounds related to cognitive factors, as is the case with fMRI. While it was thought that a large sample size would be necessary, as sex-related effects were thought to be small in magnitude, our data in fact reveal rather large effect sizes (as seen by the Cohen's f^2 values); the effect sizes for sex-related differences in relation to IQ are larger than the effect sizes for sex differences alone (Schmithorst et al., 2008). Thus, it would be feasible to test for these effects in studies with significantly smaller sample sizes than the present study. For instance, an f^2 of 0.3 (typical for the sex-X-IQ interaction effects) should be detectable with an α of 0.05 and power of 0.8 with a sample size of 30, as shown using a “sensitivity power analysis” computed using a freely-available software program, G*Power 3.03 (Faul, Erdfelder, Lang, & Buchner, 2007). An f^2 of 0.4 (typical for the sex-X-age-X-IQ interaction effects) should be detectable with a sample size of under 25 subjects.

Finally, while the present neuroimaging studies, using fMRI, DTI, and other methodologies, provide strong evidence of differences in brain structure and development between males and females, and their relationship to cognitive function, they cannot at present unravel the “nature” vs. “nurture” question. Are sex differences innate (“nature”) and the observed differences predetermined? Or, are the sex differences the result of differing socialization and experiences between boys and girls (“nurture”), which could conceivably be significantly reduced or even perhaps reversed with differing socialization? A very interesting finding of the present study is that differences between 18-year-old men and women appear actually to be the *opposite* of differences between younger boys and girls, which might lend some support to the “nurture” hypothesis. Yet making a firm conclusion would certainly be premature.

Conclusion

Developmental sex-related differences in the relation of white matter microstructure to intelligence was investigated using DTI performed on a cohort of normal children ages 5–18. Girls develop a positive correlation of FA with IQ with age in frontal and fronto-parietal regions, while boys develop a negative correlation of FA in those regions. These results corroborate previous functional neuroimaging studies showing females developing a positive correlation between functional connectivity and IQ and boys developing a negative correlation between functional connectivity and IQ, and are consistent with previous studies showing adult females with greater correlations between intelligence and regional white matter volumes, and adult males with greater correlations between intelligence and regional gray matter volumes. Results also put into question the assumption that greater FA is always correlated with improved cognitive function, especially in adult males.

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Figure 1.

Regions with a significant sex-X-IQ interaction on FA in a cohort of 105 children ages 5–18. Slice locations (positive = right hemisphere; negative = left hemisphere) range from +41 mm (top left-hand corner) to –41 mm (bottom right-hand corner).

Figure 2. Scatterplots of FA vs. Wechsler Full-Scale IQ for the regions in Table 1 for girls (pink, asterisks) and boys (blue, triangles).

Figure 3. Regions with a significant sex-X-IQ interaction on MD in a cohort of 105 children ages 5–18. Slice locations (positive = right hemisphere; negative = left hemisphere) range from +41 mm (top left-hand corner) to –41 mm (bottom right-hand corner).

Figure 4. Scatterplots of MD ($\times 10^{-4}$ mm²/s) vs. Wechsler Full-Scale IQ for the regions in Table 2 for girls (pink, asterisks) and boys (blue, triangles).

Figure 5.

Regions with a significant sex-X-age-X-IQ interaction on FA in a cohort of 105 children ages 5–18. (Color code: yellow-red = girls > boys; blue = boys > girls.) Slice locations (positive = right hemisphere; negative = left hemisphere) range from +41 mm (top left-hand corner) to -41 mm (bottom right-hand corner).

Figure 6.

Scatterplots of FA vs. Wechsler Full-Scale IQ for the regions in Table 3 for younger (age < 12 years, top frames) and older (age $\geq$ 12 years, bottom frames) girls (pink, asterisks) and boys (blue, triangles).

Figure 7. Regions with a significant sex-X-age-X-IQ interaction on MD in a cohort of 105 children ages 5–18. Slice locations (positive = right hemisphere; negative = left hemisphere) range from +41 mm (top left-hand corner) to –41 mm (bottom right-hand corner).

Figure 8. Scatterplots of MD ($\times 10^{-4}$ mm²/s) vs. Wechsler Full-Scale IQ for the regions in Table 4 for younger (age < 12 years, top frames) and older (age $\geq$ 12 years, bottom frames) girls (pink, asterisks) and boys (blue, triangles).

Table 1

Regions (from Figure 1) displaying a significant sex-X-IQ interaction on FA. Locations (X, Y, Z) in Talairach coordinates. (Boy R = correlation of FA with IQ in boys; Girl R = correlation of FA with IQ in girls).

X,Y,Z	# Voxels	Location	Boy R	Girl R	Cohen's f ²
-23, 27, 19	188	LFrontal	-0.37	0.41	0.32
31, -1, 28	169	RArcuate	-0.34	0.39	0.36
25, -33, 38	423	RFrontoParietal	-0.25	0.30	0.24
-26, -21, 40	664	LFrontoParietal	-0.39	0.23	0.39

Table 2

Regions (from Figure 3) displaying a significant sex-X-IQ interaction on MD. Locations (X, Y, Z) in Talairach coordinates. (Boy R = correlation of MD with IQ in boys; Girl R = correlation of MD with IQ in girls).

X,Y,Z	# Voxels	Location	Boy R	Girl R	Cohen's f^2
-40, -31, 1	237	LILF	-0.23	0.31	0.42
-22, -15, 5	261	LCST	-0.19	0.34	0.21
32, -72, 5	160	ROccipital	-0.07	0.23	0.41
1, -38, 19	227	Splenium	-0.12	0.20	0.26
27, -41, 34	1522	RFrontoParietalOccipital	-0.27	0.16	0.34
-25, -31, 37	1165	LFrontalParietalOccipital	-0.23	0.12	0.36

(Abbreviations: LILF = Left Inferior Longitudinal Fascicle; LCST = Left Cortico-Spinal Tract.)

Table 3

Regions (from Figure 5) displaying a significant age-X-sex-X-IQ interaction on FA. Locations (X, Y, Z) in Talairach coordinates. (Young Boy R = correlation of FA with IQ in younger (age < 12 years) boys; Young Girl R = correlation of FA with IQ in younger (age < 12 years) girls; Old Boy R = correlation of FA with IQ in older (age ≥ 12 years) boys; Old Girl R = correlation of FA with IQ in older (age ≥ 12 years) girls).

X,Y,Z	# Voxels	Location	Young Boy R	Young Girl R	Old Boy R	Old Girl R	Cohen's f ²
7, -19, -3	151	CST	-0.36	0.61	-0.40	-0.07	0.44
-22, 27, 21	231	LFrontal	0.12	0.13	-0.25	0.50	0.48
-32, -21, 35	216	LFrontoParietal	0.38	-0.12	-0.56	0.50	0.40
26, -32, 37	376	RFrontoParietal	0.43	-0.19	-0.53	0.29	0.74

(Abbreviations: CST = cortico-spinal tract).

Table 4

Regions (from Figure 7) displaying a significant age-X-sex-X-IQ interaction on FA. Locations (X, Y, Z) in Talairach coordinates. (Young Boy R = correlation of FA with IQ in younger (age < 12 years) boys; Young Girl R = correlation of FA with IQ in younger (age < 12 years) girls; Old Boy R = correlation of FA with IQ in older (age >= 12 years) boys; Old Girl R = correlation of FA with IQ in older (age >= 12 years) girls).

X,Y,Z	# Voxels	Location	Young Boy R	Young Girl R	Old Boy R	Old Girl R	Cohen's f ²
-26, -21, 30	3068	LHemisphere	0.30	-0.26	-0.39	0.14	0.70
25, -27, 32	3303	RHemisphere	-0.05	-0.31	-0.32	0.02	0.56