A key characteristic of sex differences in the developing brain: Greater Variability in Brain Structure of Boys than Girls

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ABSTRACT

In many domains, including cognition and personality, greater variability is observed in males than in females in humans. However, little is known about how variability differences between sexes are represented in the brain. The present study tested whether there is a sex difference in variance in brain structure using a cohort of 643 males and 591 females aged between 3 and 21 years. The broad age-range of the sample allowed us to test if variance differences in the brain differ across age. We observed significantly greater male than female variance for several key brain structures, including cerebral white matter and cortex, hippocampus, pallidum, putamen and cerebellar cortex volumes. The differences were observed at both upper and lower extremities of the distributions and appeared stable across development. These findings move beyond mean levels by showing that sex differences were pronounced for variability, thereby providing a novel perspective on sex differences in the developing brain.

Keywords: brain structure; development; sex differences; variability; X-chromosome

Many prior studies have reported sex differences in brain structure, but the regional patterns observed are not consistent across studies. In addition, it is unclear how regional sex differences relate to global brain size differences or how this pattern may change with development (Sacher et al. 2012; Koolschijn and Crone 2013; Ruigrok et al. 2014; Marwha et al. 2017). Therefore, sex differences in brain structure are currently not well understood. One possible shortcoming of most previous studies is that the focus has been on mean group differences, whereas much less is known about variance differences between males and females. It has however repeatedly been observed that variability differs between sexes across a variety of other domains, including cognitive abilities and personality traits, and also physical properties including body weight and height, even in the absence of mean differences, with males consistently showing greater variability than females (Arden and Plomin 2006; Johnson et al., 2008; Borkenau et al. 2013; Hyde 2014; Baye and Monseur 2016, Lehre et al. 2009). That is to say, males may in these cases be overrepresented at both ends of the distribution. A pertinent question concerns whether this is also the case for the human brain, but this has not yet been empirically addressed.

Prior studies have provided important, but inconclusive evidence for sex differences in brain structure. For example, a meta-analysis showed that males have on average 8-13 % larger volume for a range of brain measures (e.g., total brain volume, white matter volume) than females (Ruigrok et al. 2014). However, the reported size and directionality of regional sex differences in brain volumes are inconsistent across studies, likely partly explained by how the difference in overall brain size is accounted for (Giedd et al. 2015; Mills et al. 2016). Also, it should be noted that even raw volume sex differences are relatively small compared to the inter-individual variability in brain morphology, e.g. ~30% for total brain volume (Allen et al. 2002). Based on this and the observation that the magnitude of sex differences in mean volumes differs

substantially between regions of the brain, it has been highly debated to what degree the male and female brain can be distinguished (Glezerman, 2016; Del Giudice et al., 2016; Rosenblatta, 2016) or whether they are more alike than different (Joel et al. 2015).

These conclusions appear to stand in sharp contrast with epidemiological studies that show large sex differences in the prevalence of many neurodevelopmental disorders, e.g. Tourette syndrome (90% males), autism spectrum disorder (80% males), ADHD (80% males), schizophrenia (73% males), depression (63% females), anxiety disorder (67% females), and anorexia nervosa (93% females) (Bao and Swaab 2010). In general, these male-biased disorders are characterized by an early onset, while the female-biased disorders more often show age of onset in adolescence and show lower heritability estimates than the male-biased disorders (Costello et al. 2003). Moreover, there is evidence that females are protected against some mutations that are related to male biased disorders. For example, females need a larger number and more severe mutations to show clinical symptoms of autism spectrum disorder (Jacquemont et al. 2014) or ADHD (Taylor et al. 2016). This is also in line with the observation that not only the prevalence, but also symptoms and the course of several mental disorders are more severe in males. Males with schizophrenia for example, have been found to show poorer premorbid functioning, earlier onset, and more cognitive deficits, in addition to more severe structural brain abnormalities than females with schizophrenia (Goldstein et al. 2002). The mechanisms involved in these sex differences in vulnerability and protective effects remain unknown, but we suggest that assessing brain morphology beyond mean differences is an essential step in a better understanding of underlying mechanisms related to sex differences in the brain.

Several prior studies have speculated about possible genetic underpinnings for the emergence of sex differences in variability. It has for instance been suggested that the lack of two parental X-chromosomal copies in males may directly relate to greater variability and vulnerability in males compared to females (see for review (Arnold 2012)). If this is true one could theoretically expect that any trait related to X-linked genes would express greater diversity in females than males. While 100% of cells in males would express a X-linked trait, female brain tissue would show two variants of the trait. We question whether this can be observed in the brain, by comparing inter-regional anatomical correlations in males and females.

Only a limited number of studies have focused on sex related variability in brain structure in humans of which samples where small (Lange et al., 1997) or included adults (Ritchie et al., 2017). A large population based study including developing individuals is currently lacking. Hence, the present study compared sex differences in variability in regional brain volumes estimated by magnetic resonance imaging (MRI) scans from 1234 individuals aged 3-21 years (52% males) recruited from the general population at nine different sites across the United States. This large population based sample provided us with sufficient power to test variance differences in the brain, and also provided a possibility to test for emergence of variance difference over development. Even though prior studies suggested a potential genetic determinacy, it remains an open question whether variance differences would already be observed in early childhood or would emerge when children develop into teenagers and adults. Another important question concerns the nature of these variability differences, e.g. whether variability differences would be observed at both extremities of the distribution. To assess sex differences in tail distributions in brain volumes we used quantile distance functions, a nonparametric method that estimates the

distance between male and female distributions (Lehre et al. 2013). Last, we compared interregional correlation between males and females and hypothesize stronger correlations in males.

We examined global brain volumes in addition to regions of interest (ROIs) that have been indicated to show mean or developmental differences between sexes (Lenroot et al. 2007; Ruigrok et al. 2014) and/or have been associated with male biased developmental disorders (Giedd et al. 2015). These ROIs included the volumes of cerebral cortex and white matter, cerebellar cortex and white matter, accumbens, caudate, pallidum, putamen, amygdala, hippocampus, and thalamus. In a follow-up analysis, cortical surface area and thickness were examined separately, as these components of cortical volume are influenced by different genes and develop differently (Wierenga et al. 2014; Vijayakumar et al. 2016; Tamnes et al., 2017).

MATERIALS AND METHODS

Participants

Data used in the preparation of this article were obtained from the Pediatric Imaging, Neurocognition, and Genetics (PING) Study database (http://ping.chd.ucsd.edu/). PING was launched in 2009 by the National Institute on Drug Abuse (NIDA) and the Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD). The primary goal of PING has been to create a data resource of highly standardized and carefully curated magnetic resonance imaging (MRI) data, comprehensive genotyping data, and developmental and neuropsychological assessments for a large cohort of developing children. The scientific aim of the project is, by openly sharing these data, to amplify the power and productivity of investigations of healthy and disordered development in children, and to increase understanding of the origins of variability in neurobehavioral phenotypes.

Initially over 1700 participants were enrolled in the PING study, collected at one of nine sites and 13 different scanners in the United States (for details see (Jernigan et al. 2016)). Each data collection site's Office of Protection of Research Subjects and Institutional Review Board approved the study. Written parental informed consent was obtained for all participants, in addition child assent was obtained for all participants older than 7 years. Participants had no diagnosis of neurological disorders; history of head trauma; preterm birth (less than 36 weeks); diagnosis of autism spectrum disorder, bipolar disorder, schizophrenia, mental retardation or contraindications for MRI (such as dental braces, metallic or electronic implants, or claustrophobia). For a detailed description of the data collection we refer the reader to (Jernigan et al. 2016).

The sample for the current study was limited to 1234 participants aged between 3 and 21 years (52% males) with complete acceptable data on imaging measures

(see Table 1 for demographics). There was no significant difference in variability of age between males and females (p = .9491). The imaging acquisition protocol, structural preprocessing, quality control, and analysis protocols were developed specifically to meet the challenges associated with multisite imaging and imaging of children. Similar proportions of males and females participated across the entire age range (Figure 1).

Imaging Data Acquisition and Processing

For complete details of the image acquisition and processing methods used in the creation of the PING dataset, please see (Jernigan et al. 2016). In brief, at 9 sites and 13 3T scanners, a standardized multiple-modality MRI protocol was implemented. The protocol included a high-resolution sagittal three-dimensional inversion recovery spoiled echo T1- weighted volume optimized for maximum grey/white matter contrast (flip angle = 8°; receiver bandwidth = ± 31.25kHz, freq = 256, phase =192, slice thickness =1.2mm, FoV = 24 cm; TE = 3.5 ms; TR = 8.1 ms; TI =640 ms). These volumes were acquired using prospective motion correction (PROMO), as described in (White et al. 2010). This procedure has been showed to effectively reduce effects of subject motion (Brown et al. 2010; Kuperman et al. 2011). Descriptions of the specific scanner models used at each site can be found in (Fjell et al. 2012).

Tissue classification and anatomical labeling was performed on the basis of the T1- weighted MR image using the well-validated and well-documented Freesurfer v5.3.0 software (http:// surfer.nmr.mgh.harvard.edu/). This software encompasses tools for cortical surface reconstruction, subcortical segmentation, cortical parcellation, and estimation of various measures of brain morphometry. Technical details of the automated reconstruction scheme are described elsewhere (Dale et al. 1999; Fischl et al. 1999; 2002). In addition to the standard processing pipeline, extensions made at the UCSD MultiModal Imaging Laboratory

(MMIL) were implemented. These include maps of relative cortical surface area changes and genetically informed cortical parcellations (Jernigan et al. 2016). For the present study, volumes of the cerebral cortex and white matter, cerebellar cortex and white matter, accumbens, caudate, pallidum, putamen, amygdala, hippocampus, and thalamus were included as ROIs. All ROIs were averaged across hemisphere within subject. For follow-up analyses, cerebral cortex total surface area and average thickness were assessed.

Quality control

An important part of the data processing is the quality control procedure, which is critical for imaging data in developmental samples (Mills and Tamnes 2014). Details of this procedure can be found in Jernigan et al. (2016). In short, raw images of each scan session were automatically checked for completeness and protocol compliance. Next, T1-weighted images were examined for evidence of excessive motion and rated as either acceptable and processed in Freesurfer or recommended for rescan. Processed scans were also examined by checking subcortical volumetric segmentations, cortical areal parcellations, and white and pial surface reconstructions. The proportion of individuals that failed to pass QA are described in detail by Brown et al. (2012) for a subset of the sample used in the current study. The final sample of the current study included 1234 scans.

Statistical analysis

Variance ratio

Differences in variance between males and females were examined by first controlling for age and scan site. This was done using a random forest regression model (Breiman 2001), which is implemented in R-package randomForest, and can accommodate models with interactions and non-linear effects. Letting y_i

denote the observed outcome for observation number *i* and $\hat{y}_i$ its predicted outcome, the residuals were then formed:

$$r_i = y_i - \hat{y}_i .$$

The standard deviations SD_{males} and $SD_{females}$ were computed separately for males and females, and used to form the test statistic

$$T = SD_{males} / SD_{females} .$$

For each outcome, a permutation test of the hypothesis that the sex specific standard deviations were equal was performed. This was done by random permutation of the sex variable among the residuals. Using *B* permutations, the p-value for the k-th outcome (ROI) was computed as

$$p_k = \sum_{b=1}^{B} I(T_b \geq T) / B ,$$

where $I(T_b \geq T)$ is an indicator function that is 1 when $T_b \geq T$, and 0 otherwise. Thus, the p-value is the proportion of permuted test statistics (T_b) that were greater than the observed value *T* of the test statistic above. Here B was set to 10,000.

A combined test of difference in variance across the different outcomes was performed, using the test statistic

$$T = -\sum_{k} \log(p_k)$$

with the permutation distribution of *T* constructed as described in (Pesarin and Salmaso 2010).

Quantile Distance Function

In order to assess the nature of the variability difference between males and females quantile distance functions were estimated for each ROI using quantile regression forests (Meinshausen 2006), implemented in the quantregForest R

library (Lehre et al. 2013). As a first step quantile distribution functions are estimated for males and females separately. Let *q* be a probability between 0 and 1. The quantile function specifies the values at which the volume of a ROI will be at or below any given *q*. The quantile function for males is given as $Q(q \mid males)$ and for girls as $Q(q \mid females)$. The quantile distance function is then defined as:

$$D(q) = Q(q \mid males) - Q(q \mid females)$$

For illustration purposes we show these quantile distance functions as shift functions for each 10th quantile i.e. decile, where mean differences between males and females were removed (Rousselet al., 2017). This function describes how the distribution of females should be re-arranged to match the distribution of males. If the shift function is a straight line parallel to the x axis, this would indicate a stable difference between the sexes across the distribution and thus no difference in variability. A positive slope on the other hand would indicate greater male variance. More specifically this would show that the largest males are relatively larger than the largest females, and the smallest males are relatively smaller than the smallest females. A negative slope of the shift function would indicate larger variability in females at both ends of the distribution.

Variance change with age

To study the age effects on variability we used the residuals of the predicted outcome of the random forest model described earlier:

$$r_i = y_i - \hat{y}_i$$

The absolute value of these was then used as the response in a linear regression model with an age by sex interaction.

Anatomical correlation analysis

Anatomical correlation analysis assesses the inter-regional anatomical associations by defining the statistical similarity between two ROIs. The Pearson correlation coefficient between any two regions *i* and *j* was assessed for males and females separately. This produces two group correlation matrices M_{ij} and F_{ij} where $i, j = 1, 2, \mathrm{K}\ , N$, and is the number of brain regions, here *N* = 11.

Sex specific means and standard deviations were removed, by performing sex specific standardization. The significance of the differences between M_{ij} and F_{ij} was assessed by the difference in their Fisher's z-transformed values, and *p*-values were computes using permutations as above.

RESULTS

Sex differences in mean and variability of brain volumes

As a background analysis we first assessed whether the investigated brain regions showed mean volume differences between males and females, by using 10,000 random permutations and accounting for scan site and age using random forest analysis. All ROIs showed significantly larger volume in males than females ($p < 0.001$), effects sizes (Cohen's d) range from 0.033 (caudate volume) to 0.083 (cerebral white matter volume). The effects also remained significant after accounting for intra cranial volume, with exception of the caudate (p= .539).

Our first research question was whether there are sex differences in variance of brain structure. In order to test whether variability in brain volumes differed between males and females we estimated the log transformed variance ratios. A positive variance ratio is indicative of greater variability in males than females. We accounted for mean sex difference, scan site and age using random forest analysis. First, a combined test of sex difference in variance across all the included volumetric outcomes was performed using permutation testing (10,000 permutations). This analysis confirmed a general greater variance in boys than girls as indicated by a significant combined *p*-value (p=0.0034). The next step was to follow up on this effect with post-hoc analyses for each brain region separately, following the same method described above. The results showed that all ROIs had greater variance in males than females as indicated by positive log transformed variance ratios (Figure 2). The ROIs for which boys show significantly greater variance in volume than girls were cerebral white matter (p<.0001), hippocampus (p=.0017), pallidum (p=.0202), cerebellar cortex (p=.0011), putamen (p=.0335), and cerebral cortex (p= .0414). Follow-up analyses revealed that the variance difference in cerebral cortex volume was reflected in cortical surface area (p= .0035) but not thickness (p= .9688).

Together, these results indicate that there is greater male variability in brain structure, beyond mean differences.

Greater variance in boys at both extremities

To further explore the nature of the significant variability differences between the sexes, we examined whether they were expressed at both upper and lower extremities of the volume distributions for cerebral white matter, hippocampus, pallidum, cerebellar cortex, putamen and cerebral cortex. To assess this effect, cumulative distribution functions were estimated using the quantile function. This function estimates the value at which a given volume will be at or below a given probability between 0 and 1. We estimated quantile functions separately for boys and girls. Next, the quantile distance function was assessed as the difference between these functions (Figure 3). The functions were adjusted for scan site and age using the quantile regression forest model.

Boys on average had larger volumes than girls for all ROIs that showed significant variance differences between males and females, which can be observed as positive values at quantile .5 (median) in each distance function in Figure 3. Furthermore, the upward deflections in these functions indicate larger variability in boys at both upper and lower extreme ends of the distributions. The right part of any given quantile distance function show that boys with large volumes have relatively even larger volume than girls with large volumes (compared to the median volume difference, dotted line). While the left part of the plot shows that boys with small volumes have relatively smaller volume compared to girls with small volumes, i.e. at the distribution ends boys have relatively larger and smaller volumes, respectively.

Variance difference between sexes is stable across development

Next, we explored whether the differences in variance of brain volumes between boys and girls differed across the age-range 3-21 years. To do so we used a linear regression model to test for age by sex interaction effects on the residual ROI volume values after accounting for mean sex difference, age and scan site. None of the ROIs showed significant interaction effects between age and sex on variance. This suggests that the variability difference between males and females is stable across age from childhood to young adulthood.

Sex differences in anatomical correlations

Finally, we investigated whether females showed greater diversity than males in regional volumes across the brain. To do so anatomical correlation matrices were estimated to compare inter-regional anatomical associations in males and females, a method previously applied in several structural MRI studies (see e.g.). Pearson correlations were calculated for each ROI combination. Next, the anatomical correlation matrix for females was subtracted from the anatomical correlation matrix for males, yielding a difference matrix (Figure 4). Stronger anatomical correlations for males than females are indicated in blue (indicative of larger homogeneity across regions in males and greater diversity in females), while stronger correlations for females are displayed in yellow (indicative of larger homogeneity in females and greater diversity in males). There were 45 unique correlations coefficients of which 55% showed stronger correlations in males than females. This percentage was larger for anatomical correlations between ROIs that showed significantly greater male volume variance (cerebral white matter, hippocampus, cerebellar cortex, pallidum, putamen and cerebral cortex): 60% of these ROI pairs showed stronger anatomical correlation in males than females.

We further explored significant differences for each ROI pair using 10,000 permutations, where sex was permuted. Ten pairs showed significant difference in anatomical correlation between males and females (shown on the left lower

side of the difference matrix in Figure 4), of which 7 were male biased. These results indicate that there is, in line with our hypothesis, somewhat larger homogeneity across regions in brain volumes in the male brain and greater diversity in the female brain.

DISCUSSION

The present study shows that looking beyond mean effects in the brain provides new insights into differences between males and females. We observed greater brain structure variability in males compared to females in a large sample of children and adolescents. This observation is in line with findings in adults (Ritchie et al, 2017) and supports the greater male variability hypothesis. More specifically, four key findings in this study support this hypothesis. First, a combined significant effect indicated larger variance in males than females across investigated brain volumes, and region specific analyses showed the same effect for multiple brain structures. Second, the quantile distance models indicated that males show relatively more extreme values at both the upper and lower ends of the distributions. Third, we observed that the greater male variance does not show a significant interaction effect with age. This suggests that the sex differences in brain structure variability are stable across the age-range 3-21 years. Last, stronger structural anatomical correlations were observed for males compared to females, especially between brain regions that showed significant difference in variance between the sexes, indicating larger homogeneity of brain volumes in males than females. The methods and results provide new avenues for linking sex differences in the human brain with behavior, mental disorders and genetic influences.

This study showed global, as well as regional specific findings for greater male variance in brain structure. Among the brain regions investigated, the largest difference in variance between sexes was observed for cerebral white matter

volume. The region with the second largest sex variance effects was the hippocampus, followed by the cerebellar cortex, pallidum, and putamen. Interestingly, several of these structures have been linked to male biased disorders, including schizophrenia; for example the cerebellar vermis showed more severe abnormalities in males than females (Frazier et al. 2007; Womer et al. 2016). Hence, this study may provide new strategies to identify brain regions involved in these disorders. Furthermore, cerebral cortex volume also showed a male biased variability effect. Follow-up analysis indicated that this difference was reflected in cortical surface area but not thickness; separate determinants of cortical volume that have previously been shown to have distinct sources of genetic influences (Panizzon et al. 2009; Kremen et al. 2013). The current study concurs with the previous findings of moderate to high and distinct genetic contributions to individual differences in these brain structures (see review (Gu and Kanai 2014)), although it cannot be ruled out that early socialization effects may have contributed to the greater male variability observed. Future studies could further investigate this by investigating a larger and younger sample.

The results from this study may have important implications for understanding mental disorders, several of which are more prevalent in males than in females. Specifically, the finding that males are over represented in both upper and lower extremities of volume distributions complements studies that investigate traits as quantitative distributions rather than dichotomous variables. For example, a growing number of studies investigate not only negative but also positive tails of normally distributed traits, e.g. extreme low and extreme high hyperactivity (Greven et al. 2016). Additionally, genetic epidemiology studies indicated that ADHD reflects the extreme ends of one or more traits that are continuously distributed throughout the population (Chen, Zhou, et al. 2008). Despite the high heritability rates observed for many developmental disorders, linking single genes to qualitative measures of psychiatric disorders has shown to be extremely

challenging (Uher 2009). Rather, the inheritance of multiple genes (polygenic liabilities) has been hypothesized to quantitatively contribute to the expression of traits associated with these disorders (Plomin et al. 2009). Herewith, both low and high polygenic liabilities may be associated with adaptive or desired traits, however the mid-range may represent a favorable trade-off between advantages and disadvantages (Nettle 2006). For example, the opposite end of the hyperactivity trait, i.e. extreme low hyperactivity, may be associated with behavioral rigidity.

In the same way both very large and very small brain volumes may be associated with extreme ends of quantitative traits. And if males at both ends of the distribution show relatively more extreme brain volumes, they may be at higher risk. Perhaps it is this higher representation of males in both extremities, rather than mean differences in brain structures, that may be associated with higher prevalence of several developmental disorders in males than females. A better understanding of variability and extreme ends of distributions in brain structures may help to better understand risk factors and identify neurobiological phenotypes associated with developmental disorders.

An important step in unraveling the nature of greater male variability has been to identify whether differences in variability are already present at birth (Arden and Plomin 2006). The present paper observed that the variance difference between sexes in brain volumes is stable across the range of 3 to 21 years of age, even after controlling for age related mean changes in brain structure. This suggests that variability differences in brain structure are already present early in development. The early presence of a sex difference in variability supports a genetic contribution to larger male variability rather than social cultural effects (Hyde 2014). This is in contrast with a variety of observed mean differences between males and females; for example, sex differences in math performance

have been shown to be highly associated with cultural variation in opportunity structures for girls (Else-Quest et al. 2010), although this has recently been debated (Stoet and Geary, 2015). In sum, our findings are consistent with the notion that genetic mechanisms moderate greater male variability. However, it cannot be ruled out that alternative explanations are at play, as our sample for example did not include newborns and infants, and our study may have been underpowered to study age effects on variability differences between sexes.

The finding of larger homogeneity in regional volumes across the male brain, indicated by stronger anatomical correlations in males than females, indirectly supports a specific role for the X-chromosome in greater male variability. Foremost, the pattern of brain correlations observed is in line with the mosaic pattern of X-inactivation in females, in comparison to the single X-chromosome in males. This finding is supported by twin studies that observed the opposite pattern: dizygotic male twin pairs (inheriting a single maternal X-chromosomes at random) showed a much lower within twin correlation than female dizygotic twin pairs (sharing at least one paternal X-chromosome) for a number of global brain volumes (Baaré et al. 2001). Another line of evidence supporting the notion that the number of X-chromosomes is related to sex differences in variability comes from studies that show that in species where females are the heterogametic sex (e.g. birds and butterflies), females have significant higher variability in e.g. body size than males (Reinhold and Engqvist 2013). Further evidence that supports that the number of X-chromosomes relate to sex differences comes from disorders that are observed to have increased lethality levels in males, e.g. Rett syndrome, Aicardi syndrome, and neural tube deficits (Ryan et al. 1997; Chen, Watkins, et al. 2008). These studies indicate a direct link between vulnerability and the presence of a single X-chromosome, independent of Y-chromosomal or gonadal effects, as these X-linked disorders were also present in the absence of Y-chromosomes. It is thought that in females the effect of a (lethal) mutation on

one of the X-chromosomes could be compensated by the second parental copy. In females, both copies of X-chromosomes have been shown to be expressed in the brain, through a process called X-chromosome silencing. This process is indicated to occur at random, such that neighboring nerve cells may have different expressions of the two X-chromosomes (Wu et al. 2014). Hence, mutations in X-linked genes would be expressed in 50% of the cells in females, while expression rates would be 100% in males. Interestingly, skewed X-inactivation patterns have been observed in some of the syndromes mentioned above. For example, in females with Rett syndrome the X-chromosome that contains the affected gene is inactivated in 80% of the cells (Plenge et al. 2002; Amos-Landgraf et al. 2006). In a similar fashion, (non-lethal) X-linked traits may result in increased representation at the extreme ends of a distribution and herewith increased variability, as males are fully dependent on their maternal X-chromosome copy, and all X-linked genes will be fully expressed. Although not yet tested in the human brain, this line of research suggests that there may be a genetic influence for why there could potentially be more variance in the brain of males compared to females.

There are several other lines of evidence that support the notion that X-chromosome linked genes play a substantial role in the brain and herewith may directly influence sex variability differences in cognition and behavior, independent of e.g. social factors or sex steroids. For example, a disproportionately large number of genes related to 'mental retardation' have been linked to protein-coding genes on the X-chromosome (Zechner et al. 2001). In addition, X-linked genes show high expression rates in brain tissue compared to rates in somatic tissue (Graves et al. 2002; Nguyen and Disteche 2005). These findings suggest that X-linked genes play a disproportionate large role in shaping the human brain. We speculate that brain regions observed to show male biased

variability might have particularly high expression rates of X-linked genes in the developing human brain in vivo.

It should be noted that this study is inherently limited by several factors. First, our study design may have been limited in detecting developmental effects as we used a cross-sectional dataset of participants 3-21 years old. Hence, future large studies including longitudinal data are warranted to further look into when variability differences between the sexes occur and how these develop. Second, head motion during MRI acquisition can affect morphometry estimates (Reuter et al. 2015; Ducharme et al. 2016). In addition, individual differences in psychological traits have been linked to head motion (Kong et al. 2014), and some of these traits, such as impulsivity, are more prevalent in boys than girls. This stresses the importance of the quality control procedures applied in this study in addition to the use of prospective motion correction procedures during acquisition. We acknowledge that our data may nevertheless be influenced by motion effects. However, the quantile distance functions show that at both ends of the distributions males showed more extreme values. As head motion typically results in underestimations of tissue volumes (Reuter et al. 2015), we believe it is unlikely that motion effects could account for our findings. Third, we did not directly address the influence of genetic factors in sex variability differences. Future studies including twin models could address the hypothesized genetic mechanisms involved.

This study provides new avenues for studies of sex differences in the human brain. Our results show greater variance in brain volumes in males compared to females. This observation is in line with previous findings for behavioral traits, such as greater male variability in cognition and general intelligence (Arden and Plomin 2006; Baye and Monseur 2016). Furthermore, sex differences in brain volume variability were observed to be stable across development, and males

also showed greater homogeneity across regional brain volumes than females. Our findings indirectly support the hypothesis that the X-chromosome might play an essential role in shaping brain structure and sexual dimorphisms in the brain. We encourage future studies to investigate sex differences in brain variability, including studies of young children and clinical groups, as well as studies of brain microstructure and functional activation patterns. Our study provides a novel perspective that looks beyond mean sex differences in order to better understand brain - and eventually behavioral - differences between males and females and how these emerge and develop.

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TABLES

Table 1. Demographic variables PING dataset

Site	Sex	N	Mean age	(SD)	Age range			
a	F	57	15.394	(4.354)	4.080	-	21.000	
	M	57	14.963	(4.028)	7.420	-	20.920	n.s.
b	F	11	13.682	(2.913)	7.670	-	17.670	
	M	17	10.612	(3.603)	5.580	-	15.920	*
c	F	48	14.632	(4.631)	3.750	-	20.920	
	M	62	14.712	(3.735)	5.420	-	21.000	n.s.
d	F	59	12.453	(5.426)	3.170	-	20.750	
	M	59	12.185	(4.956)	3.420	-	21.000	n.s.
e	F	19	12.744	(3.629)	6.580	-	17.580	
	M	25	12.567	(3.131)	6.330	-	16.830	n.s.
f	F	57	13.296	(6.149)	3.670	-	20.920	
	M	69	10.760	(5.969)	3.170	-	20.750	*
g	F	115	10.360	(4.984)	3.080	-	20.500	
	M	127	10.793	(4.943)	3.000	-	20.670	n.s.
h	F	30	13.944	(3.809)	6.750	-	20.920	
	M	35	13.155	(4.875)	4.170	-	20.000	n.s.
i	F	68	8.459	(3.401)	3.250	-	17.830	
	M	67	8.922	(3.658)	3.580	-	20.250	n.s.
j	F	55	10.068	(3.705)	3.420	-	19.830	
	M	65	11.224	(3.927)	3.420	-	21.000	n.s.
k	F	9	7.730	(1.49)	6.080	-	11.000	
	M	4	10.373	(0.494)	9.830	-	10.830	**
l	F	8	14.679	(3.132)	8.920	-	18.500	
	M	6	14.360	(4.832)	8.830	-	20.750	n.s.
m	F	55	13.549	(4.271)	6.080	-	20.670	
	M	50	14.698	(3.533)	6.670	-	20.580	n.s.
Total	F	591	12.074	(5.046)	3.080	-	21.000	
	M	643	12.04	(4.826)	3.000	-	21.000	n.s.

F=females; M=males; SD=standard deviation; *p<.05;**p<.01; n.s. = not significant

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FIGURE CAPTIONS

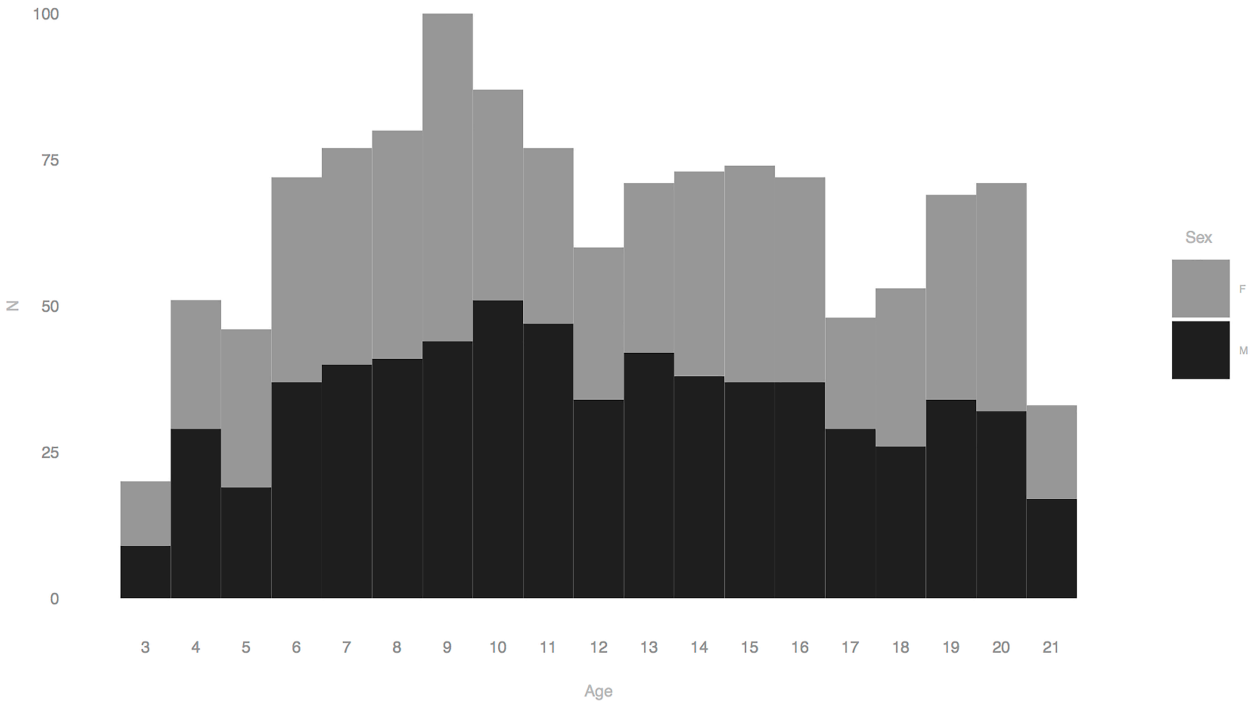
Figure 1. Equal distributions of males and females across the age range. The x-axis shows age from 3-21 years old for males (blue) and females (yellow) in a stacked histogram. In total, 643 males and 591 females between 3 and 21 years old were included in the sample.

Figure 2. Greater brain volume variance in males than females. (**a**) Grey matter regions of interest are indicated in a, note that cerebral white matter (a) and cerebellar white matter (j) are not displayed. (**b**) Log transformed variance ratio (x-axis) for all investigated brain regions averaged across hemispheres (y-axis). Variance ratio is estimated as the difference in variance between males and females after adjusting for mean sex difference, scan site and age. Positive values are indicative of larger variance in males than females, vice versa for negative values. All investigated brain regions showed positive values, i.e. larger variance in males. Permutation test (10,000 permutations) showed significant effects for volumes of cerebral white matter, hippocampus, cerebellar cortex, pallidum, putamen and cerebral cortex. **=$p<0.05$; *=$p<0.01$; n.s. = non significant.

Figure 3. Greater brain volume variability for males than females in both upper and lower extremities of distributions for volumes adjusted for age, scan site and mean sex difference for cerebral white matter, hippocampus, pallidum, cerebellar cortex, putamen and cerebral cortex. A) panels shows spread difference in volume (in mm^3, x-axis) distributions of females (yellow) and males (green) are illustrated using jittered scatterplots. The vertical lines mark the deciles for each sex with the median indicated by the thicker middle line. Because of the difference in spread the first decile of each volume is lower for males than females (indicated with a yellow line) while the nineth decile is larger for males than females (indicated with a green line). The values of the differences (adjusted

volumes) for deciles one and nine are indicated in the superimposed labels. Panels B focus on the proportion of the A panels marked by the grey shaded box. Shift functions (95% bootstrap CI) x-axis values match male volumes for each decile in panel A. The y-axis shows the difference compared to females for each decile. The superimposed labels indicate how much each decile should be shifted for females to match males. Dotted lines indicate difference between the medians of males and females (distance at quantile .5). All curves show greater male variability at both extremities as indicated by the positive values on the right and negative values on the left.

Figure 4. Overall stronger anatomical correlation between brain regions in males than females. Anatomical correlation sex difference matrix between all pairs of brain regions (*i* and *j*). Blue colors indicate stronger covariance in males (Mij), and yellow colors indicate stronger covariance in females (Fij). Deeper colors indicate stronger differences in covariance between sexes (up to $r = \pm .15$). Post hoc analysis revealed that 10 brain region pairs showed significant differences between the sexes (10,000 permutations). These are displayed on the left lower side of the matrix.


100
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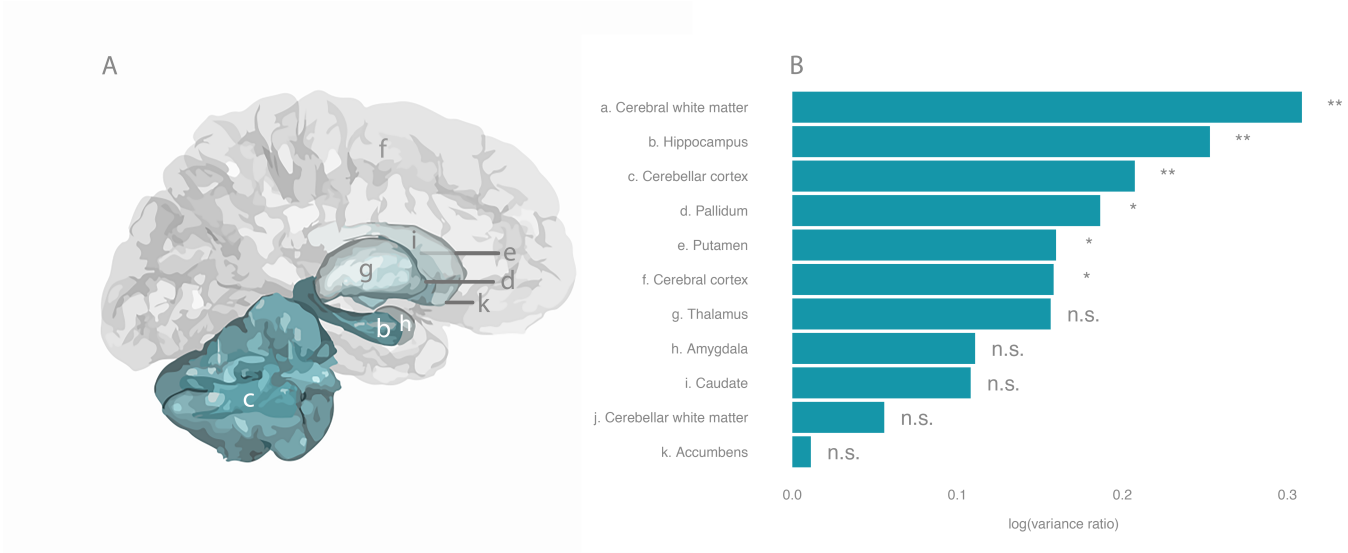
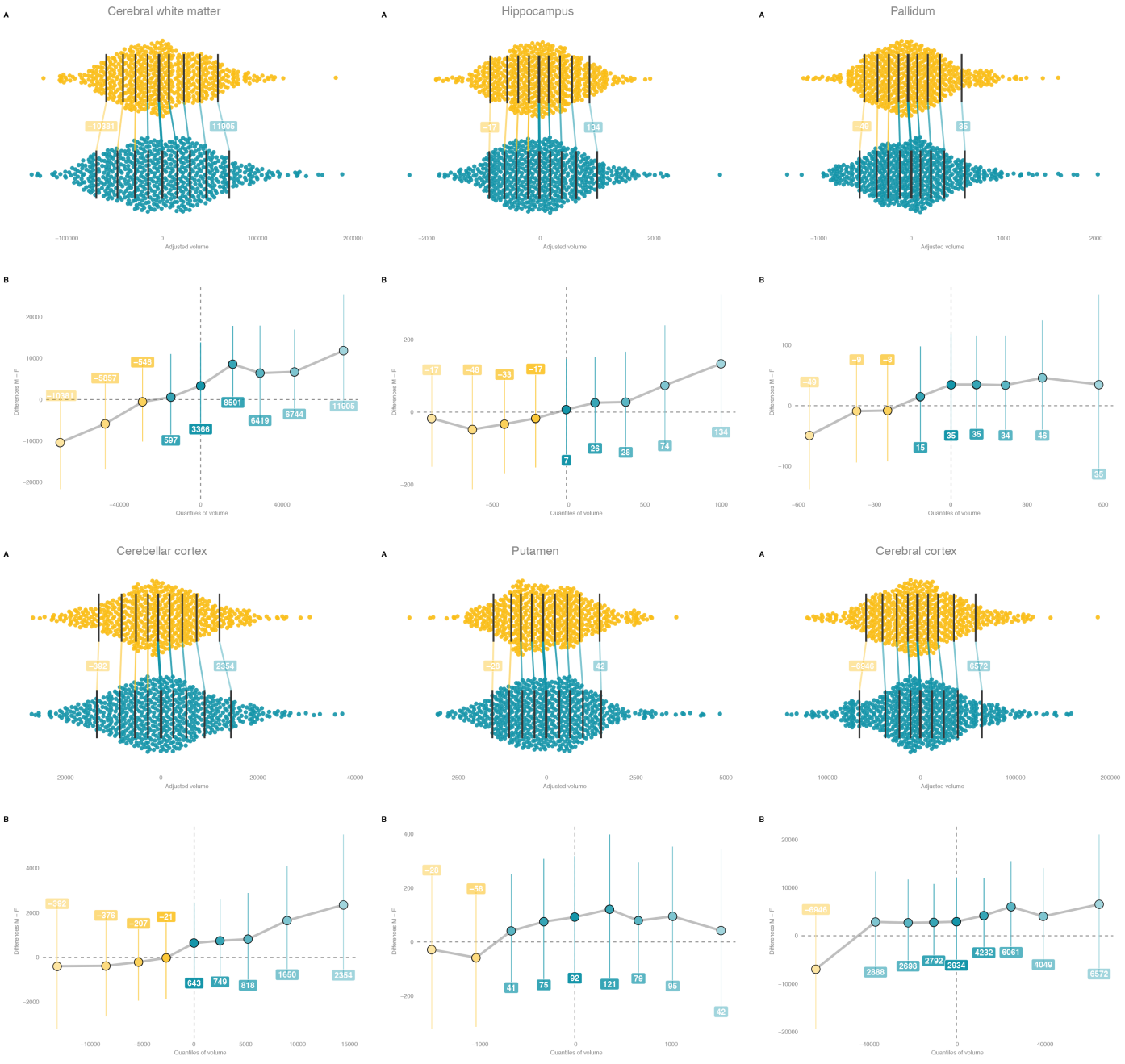

A
f
i
e
g
d
k
b
h
c
B
a. Cerebral white matter
b. Hippocampus
c. Cerebellar cortex
d. Pallidum
e. Putamen
f. Cerebral cortex
g. Thalamus
h. Amygdala
i. Caudate
j. Cerebellar white matter
k. Accumbens
**
**
**
*
*
*
n.s.
n.s.
n.s.
n.s.
0.0
0.1
0.2
0.3
log(variance ratio)


A
Cerebral white matter
−10381
11905
−100000
0
100000
200000
Adjusted volume
B
Differences M − F
20000
10000
0
−10000
−20000
−10381
−5857
−546
597
3366
8591
6419
6744
11905
−40000
0
40000
Quantiles of volume
A
Hippocampus
−17
134
−2000
0
2000
Adjusted volume
B
Differences M − F
200
0
−200
−17
−48
−33
−17
7
26
28
74
134
−500
0
500
1000
Quantiles of volume
A
Pallidum
−49
35
−1000
0
1000
2000
Adjusted volume
B
Differences M − F
100
0
−100
−46
−9
−8
15
35
35
34
46
35
−600
−300
0
300
600
Quantiles of volume
A
Cerebellar cortex
−392
2354
−20000
0
20000
40000
Adjusted volume
B
Differences M − F
4000
2000
0
−2000
−392
−376
−207
−21
643
749
818
1650
2354
−10000
−5000
0
5000
10000
15000
Quantiles of volume
A
Putamen
−28
42
−2500
0
2500
5000
Adjusted volume
B
Differences M − F
400
200
0
−200
−28
−58
41
75
92
121
79
95
42
−1000
0
1000
Quantiles of volume
A
Cerebral cortex
−8946
6572
−100000
0
100000
200000
Adjusted volume
B
Differences M − F
20000
10000
0
−10000
−20000
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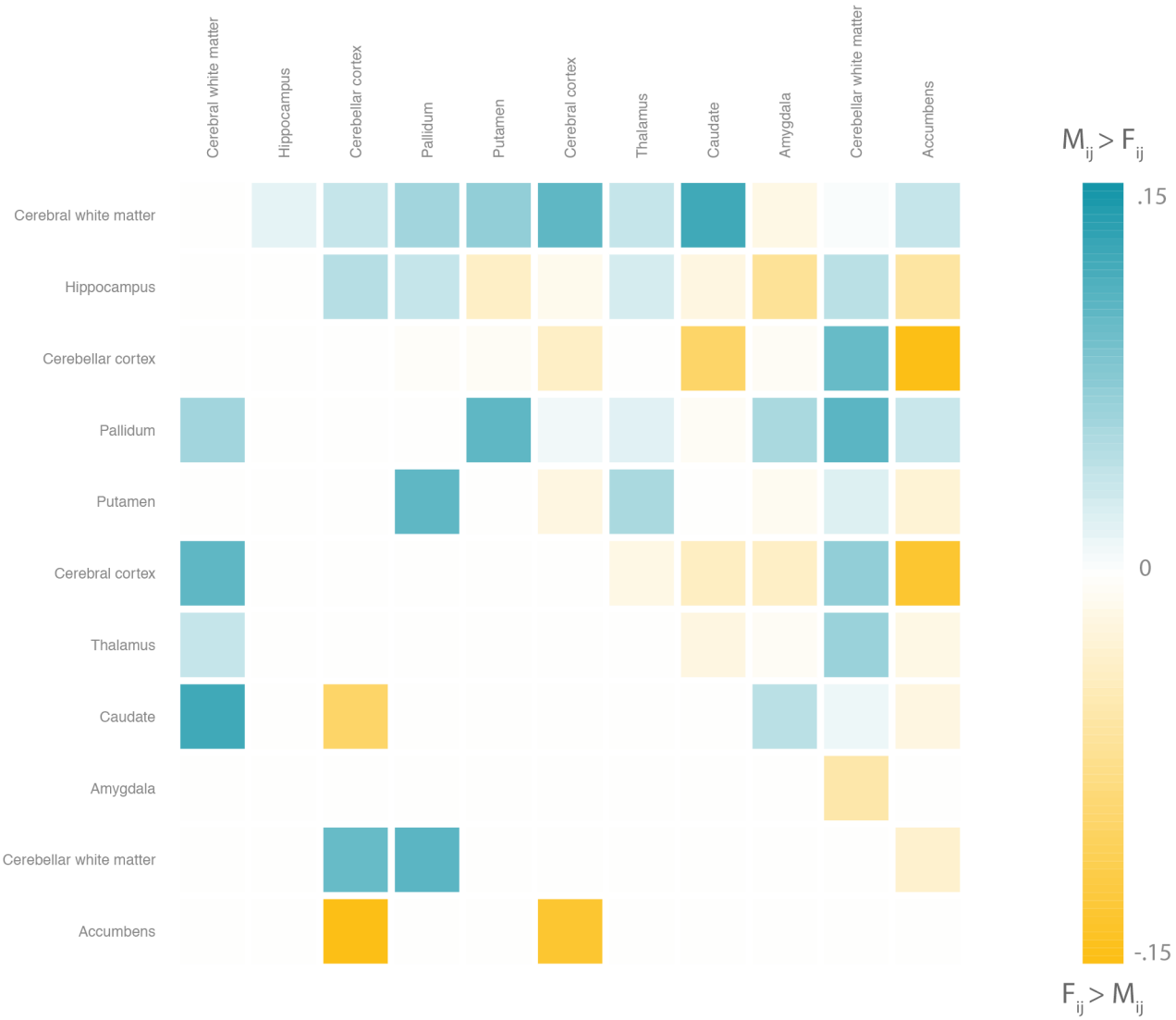
2888
2698
2792
2934
4232
6061
4049
6572
−40000
0
40000
Quantiles of volume


Cerebral white matter
Hippocampus
Cerebellar cortex
Pallidum
Putamen
Cerebral cortex
Thalamus
Caudate
Amygdala
Cerebellar white matter
Accumbens
Cerebral white matter
Hippocampus
Cerebellar cortex
Pallidum
Putamen
Cerebral cortex
Thalamus
Caudate
Amygdala
Cerebellar white matter
Accumbens
$M_{ij} > F_{ij}$
.15
0
-.15
$F_{ij} > M_{ij}$