Greater male than female variability in regional brain structure across the lifespan

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Abstract

For many traits, males show greater variability than females, with possible implications for understanding sex differences in health and disease. Here, the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Consortium presents the largest-ever mega-analysis of sex differences in variability of brain structure, based on international data spanning nine decades of life. Subcortical volumes, cortical surface area and cortical thickness were assessed in MRI data of 16,683 healthy individuals 1-90 years old (47% females). We observed patterns of greater male than female between-subject variance for all brain measures. This pattern was stable across the lifespan for 50% of the subcortical structures, 70% of the regional area measures, and nearly all regions for thickness. Our findings that these sex differences are present in childhood implicate early life genetic or gene-environment interaction mechanisms. The findings highlight the importance of individual differences within the sexes, that may underpin sex-specific vulnerability to disorders.

Introduction

For a diverse set of human traits and behaviors, males are often reported to show greater variability than females (Hyde, 2014). This sex difference has been noted for aspects of personality[1], cognitive abilities[2-4], and school achievement[5,6]. A fundamental question is to what degree these sex differences are related to genetic mechanisms or social factors, or their interactions. Lehre et al. (2009) found compelling evidence for an early genetic or in utero contribution, reporting greater male variability in anthropometric traits (e.g. body weight and height, blood parameters) already detectable at birth. Recent studies suggest greater male variability also in brain structure and its development[7-10], but studies with larger samples that cover both early childhood and old age are critically needed. Specifically, we do not know when sex differences in variability in brain structure emerge and whether they change with development and throughout life. Yet, data on this could inform us on the origins and factors that influence this phenomenon. For this reason, we set out to analyze magnetic resonance imaging (MRI) data from a large sample of individuals across a very wide age range (n = 16,683, age 0-90) to robustly characterize sex differences in variability of brain structure and test how these differences interact with age.

Many prior studies report sex differences in brain structure, but the specificity, regional pattern and functional relevance of such effects are not clear[11-15]. One reason could be that most studies have examined mean differences between the sexes, while sex differences in variability remain understudied[16,17]. As mean and variance measure two different aspects of the distribution (center and spread), knowledge on variance effects may provide important insights into sex differences in the brain. Recent studies observed greater male variance for subcortical volumes and for cortical surface area to a larger extent than for cortical thickness[7-9]. However, further studies are needed to explore regional patterns of variance differences, and, critically, to test how sex differences in variability in the brain unfold across the lifespan.

An important question pertains to the mechanisms involved in sex differences in variability. It is hypothesized that the lack of two parental X-chromosomal copies in human males may directly relate to greater variability and vulnerability to developmental disorders in males compared to females[18]. All cells in males express an X-linked variant, while female brain tissues show two variants. Consequently, one could expect that in addition to greater variability across the population, interregional anatomical correlations may be stronger in male relative to female brains. This was indeed observed for a number of regional brain volumes in children and adolescents, showing greater within-subject homogeneity across regions in males than females[8]. These results remain to be replicated in larger samples as they may provide clues about mechanisms and risk factors in neurodevelopmental disorders (e.g. attention-deficit/hyperactivity disorder and autism spectrum disorder) that show sex differences in prevalence[19], age of onset, heritability rates[20], or severity of symptoms and course[21].

In the present study, we performed mega-analyses on data from the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Lifespan working group[22-24]. A mega-analysis allows for analyses of data from multiple sites with a single statistical model that fits all data and simultaneously accounting for the effect of site. Successfully pooling lifespan data was recently shown in a study combining 18 datasets to derive age trends of brain structure[25]. This contrasts with meta-analysis where summary statistics are combined and weighted from data that is analyzed at each site[26]. MRI data from a large sample (n = 16,683) of participants aged 1 to 90 years was included. We investigated subcortical volumes and regional cortical surface area and thickness. Our first aim was to replicate previous findings of greater male variability in brain structure in a substantially larger sample. Based on prior studies[7-10] and reports of somewhat greater genetic effect on surface area than thickness[27,28], we hypothesized that greater male variance would be more pronounced for subcortical volumes and cortical surface area than for cortical thickness, and that greater male variance would be observed at both upper and lower ends of the distribution. Our second aim was to test whether observed sex differences in variability of brain structure are stable across the lifespan from birth until 90 years of age, or e.g. increase with the accumulation of experiences[29]. Third, in line with the single X-chromosome hypothesis, we aimed to replicate whether males show greater interregional anatomical correlations (i.e. within-subject homogeneity) across brain regions that show greater male compared to female variance[9].

Results

Sex Differences in Mean and Variance

All brain measures were adjusted for cohort, field strength, FreeSurfer version and (non-linear) age. As a background analysis, we first assessed whether brain structural measures showed mean differences between males and females to align our findings to previous reports (Figure 1, Table 1A-C). All subcortical volumes were significantly larger in males, with effect sizes (Cohen's *d*-values) ranging from 0.41 (left accumbens) to 0.92 (right thalamus), and an average effect size of 0.7. In follow-up analyses with total brain volume as an additional covariate we found a similar pattern, although effect sizes were smaller (Supplementary Table S2A). Also for cortical surface area, all regions showed significantly larger values in males than females, with effect sizes ranging from 0.42 (left caudal anterior cingulate area) to 0.97 (left superior temporal area), on average 0.71. When total surface area was included as an additional covariate, a similar pattern was observed, although effect sizes were smaller (Supplementary Table S2B). Cortical thickness showed significant mean sex differences in 43 (out of 68) regions, of which 38 regions showed larger thickness values in females than males. These were mostly frontal and parietal regions. The largest effect size, however, was only 0.12 (right caudal anterior cingulate cortex). When total average cortical thickness was included as an additional covariate, nine regions showed a male advantage that was not observed in the raw data analysis, and six of the 38 regions showing female advantage did not reach significance (Supplementary Table S2C).

We then tested for sex differences in variance of brain structure, adjusted for cohort, field strength, FreeSurfer version and age (Figure 2, Tables 1A-C). All subcortical volumes had significantly greater variance in males than females. Log transformed variance ratios ranged from 0.12 (right accumbens) to 0.36 (right pallidum), indicating greater variance in males than females. Similar results were also observed when total brain volume was taken into account (Supplementary Table S2A). Cortical surface area also showed significantly greater variance in males for all regions: variance ratios ranged from 0.13 (left caudal anterior cingulate cortex) to 0.36 (right parahippocampal cortex). This pattern was also observed when total surface area was included in the model (Supplementary Table S2B). Cortical thickness showed significantly greater male variance in 41 out of 68 regions, with the greatest variance ratio being 0.11 (left precentral cortex). Notably, 37 of these 41 regions did not show significantly larger mean thickness values in males. When additionally accounting for total average thickness, we found greater male variance in 39 regions and greater females variance in 5 regions. Also here, significant variance ratios were present in the absence of mean sex differences (Supplementary Table S2C).

Next, we directly tested whether the regions showing larger variance effects were also those showing larger mean differences, by correlating the variance ratios with the vector of *d*-values (Supplementary Figure 1). There was a significant association for subcortical volumes (r (12) = 0.7, *P*-value = 0.005), but no significant relation for regional cortical surface area (r (66) = 0.18, *P*-value = 0.14), or thickness (r (66) = -0.21, *P*-value = 0.09).

Greater Variance in Males at Upper and Lower Tails

In order to characterise how the distributions of males and females differ, quantiles were compared using a shift function[30]. As in the previous models, brain measures were adjusted for cohort, field strength, FreeSurfer version and age. In addition, the distribution means were aligned. Results showed greater male variance at both upper and lower tails for regions that showed significant variance differences between males and females. The top three variance ratio effects for subcortical volume, cortical surface area and cortical thickness are shown in Figure 3.

Variance Difference Between Sexes Across Age

We next tested whether the sex differences in variance interacted with age (Figure 4). In this set of analyses, brain measures were adjusted for cohort, field strength, and FreeSurfer version. For 50% of the subcortical volume measures there was a significant interaction, specifically for the bilateral thalami, bilateral putamen, bilateral pallidum and the left hippocampus (Table 2A, Figure 5). Cortical surface area showed significant interaction effects in 30% of the cortical regions (Table 2C, Figure 5). In both cases, younger individuals tended to show greater sex differences in variance than older individuals. For cortical thickness, an interaction with age was detected only in the left insula (Table 2B, Figure 5). This region showed greater male than female variance in the younger age group, whereas greater female variance was observed in older individuals.

Next, these analyses were repeated using a quadratic age model (Supplementary Tables 3A-C). None of the subcortical or cortical surface area measures showed quadratic age by sex interaction effects in variance. Cortical thickness showed significant quadratic age by sex effects in two regions; left superior frontal cortex and right lateral orbitofrontal cortex.

Sex Differences in Anatomical Correlations

Finally, we tested whether females showed greater diversity than males in anatomical correlations by comparing inter-regional anatomical associations between males and females. Using permutation testing (B = 10000), the significance of correlation differences between males and females was assessed.

Of the 91 subcortical-subcortical correlation coefficients, 2% showed significantly stronger correlations in males, while, unexpectedly, 19% showed stronger correlations in females (tested two-sided) (Figure 6A). For surface area, significantly stronger male homogeneity was observed in 4% of the 2,278 unique anatomical correlations, while significantly stronger female correlations were also observed in 4% of the correlations (Figure 6B). For thickness, stronger male than female homogeneity was observed in 21% of the correlations, while stronger female correlations were observed in <1% of the correlations (Figure 6C).

Discussion

In this study, we analyzed a large lifespan sample of neuroimaging data from 16,683 participants spanning nine decades of life starting at birth. Results confirmed the hypothesis of greater male variability in brain structure[7-10]. Variance differences were more pronounced for subcortical volumes and regional cortical surface area than for regional cortical thickness. We also corroborated prior findings of greater male brain structural variance at both upper and lower tails of brain measures[8]. These variance effects seem to describe a unique aspect of sex differences in the brain that does not follow the regional pattern of mean sex differences. A novel finding was that sex differences in variance appear stable across the lifespan for around 50% of subcortical volumes, 70% of cortical surface area measures and almost all cortical thickness measures. Unexpectedly, regions with significant change in variance effects across the age range showed decreasing variance differences between the sexes with increasing age. Finally, we observed greater male inter-regional homogeneity for cortical thickness, but not for surface area or subcortical volumes, partly replicating prior results of greater within-subject homogeneity in the male brain[8].

Greater male variance was most pronounced in brain regions involved in planning, regulation and inhibition of motor movements (pallidum, right inferior parietal cortex and paracentral region), episodic memory (hippocampus), and multimodal sensory integration (thalamus)[31-33]. In addition, the early presence of sex differences in brain structural variability may be indicative of genetic effects, in line with findings in a pediatric sample[8]. We also observed that sex differences in structural variation are either stable or may reduce in old age. Longitudinal designs are, however, needed to address the mechanisms underlying this observation.

The expression of greater male variability in both upper and lower tails of the distribution may be related to architectural and geometric constraints that are critical for a delicate balance for effective local-global communication. For example, neurons only partly regulate their size, and the number of neural connections does not vary strongly with neocortical size across species[34]. Although axon size and myelin can compensate firing rates in larger brains by speeding up conduction time, there is a limited energy budget to optimize both volume and conduction time[35]. As such, extreme brain structure (in both directions) may come at a cost. This is in line with recent findings that show that extreme neural activity patterns may induce suboptimal expressions of mental states[36]. Interestingly, it has been found that individuals with autism spectrum disorder show atypical patterns of brain structure and development in both the upper and lower range[37], suggesting a possible link between greater male variability and vulnerability for developmental disorders (see also [38]). Together with our findings, this opens up new approaches to understanding sex biased developmental disorders, beyond group-level mean differences.

Factors underlying or influencing sex differences in the brain may include sex chromosomes, sex steroids, and the neural embedding of social influences during the life span[39]. Although we could not directly test these mechanisms, our findings of greater male variance and greater male inter-regional homogeneity for cortical thickness are in line with the single X-chromosome expression in males compared to the mosaic pattern of X-inactivation in females[18]. Whereas female brain tissue shows two variants of X-linked genes, males only show one. This mechanism may lead to increased male vulnerability, as is also seen for a number of rare X-linked genetic mutations[40-44].

This paper has several strengths including its sample size, the age range spanning nine decades, the inclusion of different structural measures (subcortical volumes and cortical surface area and thickness) and the investigation of variance effects. These points are important, as most observed mean sex differences in the brain are modest in size[45]. We were able to analyze data from a far larger sample than those included in recent meta-analyses of mean sex differences[13-15], and a very wide age range covering childhood, adolescence, adulthood and senescence. The results of this study may have important implications for studies on mean sex differences in brain structure, as analyses in such studies typically assume that group variances are equal, which the present study shows might not be tenable. This can be particularly problematic for studies with small sample sizes[30].

The current study has some limitations. First, the multi-site sample was heterogeneous and specific samples were recruited in different ways, not always representative of the entire population. Furthermore, although structural measures may be quite stable across different scanners, the large number of sites may increase the variance in observed MRI measures, but this would be unlikely to be systematically biased with respect to age or sex. In addition, variance effects may change in non-linear ways across the age-range. This may be particularly apparent for surface area and subcortical volume measures, as these showed pronounced non-linear developmental patterns through childhood and adolescence[46,47]. Also, the imbalanced number of subjects across the age range may have diminished variability effects in the older part of the age range. As such, future studies including longitudinal data are warranted to further explore the lifespan dynamics of sex differences in variability in the brain.

Conclusions

The present study included a large lifespan sample and robustly confirmed previous findings of greater male variance in brain structure in humans. We found greater male variance in all brain measures, including subcortical volumes and regional cortical surface area and thickness, at both the upper and the lower end of the distributions. The results have important implications for the interpretation of studies on (mean) sex differences in brain structure. Furthermore, the results of decreasing sex differences in variance across age opens a new direction for research focusing on lifespan changes in variability within sexes. Our findings of sex differences in regional brain structure being present already in childhood may suggest early genetic or gene-environment interaction mechanisms. Further insights into the ontogeny and causes of variability differences in the brain may provide clues for understanding male biased neurodevelopmental disorders.

Methods

Participants

The datasets analyzed in the present study were from the Lifespan working group within the ENIGMA Consortium[22]. There were 78 independent samples with MRI data, in total including 16,683 (7,966 males) healthy participants aged 1-90 years from diverse ethnic backgrounds (see detailed descriptions at the cohort level in Table 3). Samples were drawn from the general population or were healthy controls in clinical studies. Screening procedures and the eligibility criteria (e.g. head trauma, neurological history) may be found in Supplementary Table 1. Participants in each cohort gave written informed consent at the local sites. Furthermore, at each site local research ethics committees or Institutional Review Boards gave approval for the data collection, and all local institutional review boards permitted the use of extracted measures of the completely anonymized data that were used in the present study.

Imaging Data Acquisition and Processing

For definition of all brain measures, whole-brain T1-weighted anatomical scan were included. Detailed information on scanner model and image acquisition parameters for each site can be found in Supplementary Table 1. T1 weighted scans were processed at the cohort level, where subcortical segmentation and cortical parcellation were performed by running the T1-weighted images in FreeSurfer using versions 4.1, 5.1, 5.3 or 6.0 (see Supplementary Table 1 for specifications per site). This software suite is well validated and widely used, and documented and freely available online (surfer.nmr.mgh.harvard.edu). The technical details of the automated reconstruction scheme are described elsewhere[48-50]. The outcome variables included volumes of seven subcortical structures: accumbens, caudate, pallidum, putamen, amygdala, hippocampus, and thalamus[48], and cortical surface area and thickness measures[49,50] of 68 regions of the cerebral cortex (Desikan-Killiany atlas)[51]. Quality control was also implemented at the cohort level following detailed protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols). The statistical analyses included 13,696 participants for subcortical volumes, 11,338 for surface area measures, and 12,533 participants for cortical thickness analysis.

Statistical Analysis

Statistical analyses were performed using R Statistical Software. The complete scripts are available in the Supplementary materials in the SI Appendix. In brief, we first adjusted all brain structure variables for cohort, field strength and FreeSurfer version effects. As age ranges differed for each cohort this was done in two steps: initially, a linear model was used to account for cohort effects and non-linear age effects, using a third-degree polynomial function. Next, random forest regression modelling[52] was used to additionally account for field strength and FreeSurfer version. See Supplementary Figure 3 for adjusted values. This was implemented in the R package *randomForest*, which can accommodate models with interactions and non-linear effects.

Mean differences

Mean sex differences in brain structure variables were tested using t-tests (FDR corrected, see[53]) and effect sizes were estimated using Cohen's d-value. A negative effect size indicates that the mean was higher in females, and a positive effect size indicates it was higher in males. The brain structure variables were adjusted for age and covariates described above. Graphs were created with R package ggseg[54].

Variance ratio

Variance differences between males and females were examined, after accounting for age and other covariates as described above. Fisher's variance ratio (VR) was estimated by dividing variance measures for males and females. VR was log transformed to account for VR bias[6,55]. 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 residual variance Var_{males} and $Var_{females}$ were computed separately for males and females, and used to form the test statistic

$$T = Var_{males} / Var_{females}$$

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 β permutations, the p-value for the k-th outcome measure was computed as

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

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. FDR corrected values are reported as significant.

Shift Function

To assess the nature of the variability difference between males and females, shift functions were estimated for each brain measure that showed significant variance differences between males and females using quantile regression forests[30,56], implemented in the R package quantregForest (see [8] for a similar approach). First, as described above, brain measures were accounted for site, age, field strength and FreeSurfer version. Next, quantile distribution functions were estimated for males and females separately after aligning the distribution means. Let q be a probability between 0 and 1. The quantile function specifies the values at which the volume of a brain measure will be at or below any given q. The quantile function for males is given as $Q(q|males)$ and for females as $Q(q|females)$. The quantile distance function is then defined as:

$$D(q) = Q(q|males) - Q(q|females)$$

A bootstrap method was used to estimate the standard error of the quantile difference functions, which was used to form approximate 95% confidence intervals. If the quantile distance function is a straight-line parallel to the *x* axis, this indicates a stable difference between the sexes across the distribution and thus no detectable difference in variability. A positive slope indicates greater male variance. More specifically, this would indicate that the males with the largest values have relatively larger values than females with the largest values, and males with the smallest values are relatively smaller values than the females with the smallest values. A negative slope of the quantile distance function would indicate larger variability in females at both ends of the distribution.

Variance change with age

To study whether the sex differences in variance are stable across the age range we used the residuals of the predicted outcome measure and each individual i:

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

The absolute value of r_i was then used in a regression model. It was next explored whether there was a significant (FDR corrected) age by sex interaction effect using a linear model 1 and quadratic model 2:

$$y_i = Age_i * sex_i + error_i \quad (model\ 1)$$

$$y_i = Age_i^2 * sex_i + error_i \quad (model\ 2)$$

Anatomical correlation analysis

Inter-regional anatomical associations were assessed by defining the correlation between two brain structures, after accounting for age and other covariates as described above. Anatomical correlation matrices were estimated as previously applied in several structural MRI studies for males and females separately (see e.g. [57,58]). Next, the anatomical correlation matrix for females was subtracted from the anatomical correlation matrix for males, yielding a difference matrix.

Thus, the Pearson correlation coefficient between any two regions i and j was assessed for males and females separately. This produced two group correlation matrices M_{ij} and F_{ij} where $i, j, = 1, 2, \ldots, N$, where N is the number of brain regions.

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 computed using permutations.

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Figure legends

Figure 1. Sex differences in volumetric measures of subcortical volumes (left), cortical surface area (center), and cortical thickness (right). Shown are effect sizes (Cohen's d-value) of FDR corrected mean sex differences. Greater mean values for males are displayed in blue, greater mean values for females are displayed in red. Darker colors indicate larger effect sizes.

Figure 2. Sex differences in variance ratio for subcortical volumes (Left), cortical surface area (center), and cortical thickness (right). Shown are log transformed variance ratios, where significant larger variance ratio for males than females is displayed in blue ranging from 0 to 1. Darker colors indicate a larger variance ratio.

Figure 3. Jittered marginal distribution scatterplots (A) are displayed together with their shift function (B) for the top three variance ratio effects of subcortical volumes (top), cortical surface area (middle) and cortical thickness (right). The central, darkest line on each distribution is the median, note that main sex effects are removed. The other lines mark the deciles of each distribution. The shift values are included, which refer to the number of units that the male (upper) distribution would have to be shifted to match the female (lower) distribution. Confidence intervals are included for each of these shift values.

Figure 4. Regions where sex differences in variability of brain structure interacted with age displayed for subcortical volumes (left), cortical surface area (center), and cortical thickness (right).

Figure 5. Sex differences in variability interacted with age in 50% of the subcortical volumes, 30% of the surface area measures, and only one thickness measure. Three representative results are shown: right thalamus volume (top left), surface area of the right parahippocampal gyrus (top right) and thickness of the left insula (bottom center). Absolute residual values are modeled across

the age range. Effects showed larger male than female variance in the younger age group, this effect attenuated with increasing age.

Figure 6 A-C. Stronger anatomical correlations for males than females are indicated in blue (larger homogeneity in males than females), while stronger correlations for females are displayed in red (larger homogeneity in females than males). The bottom left half shows the significant variance ratio's only, using two sided permutation testing. Results are displayed for subcortical volumes (A), surface area (B) and cortical thickness (C). Cortical regions are ordered by lobe and hemisphere (left frontal, left occipital, left parietal, left temporal, right frontal, right occipital, right parietal, right temporal).

Supplementary Figure 1. Correlation between variance ratio and vector of d-values for each region. Results show a significant association for subcortical volumes (left), but no significant relation for regional cortical surface area (middle), or thickness (right).

Supplementary Figure 2A. Sex differences in variability interacted with age in 50% of the subcortical volumes. Absolute residual values are modeled across the age range. Effects showed larger male than female variance in the younger age group, and a general trend of decreasing sex differences in variance with increasing age.

Supplementary Figure 2B. Sex differences in variability interacted with age in 30% of cortical surface area measures. Absolute residual values are modeled across the age range. Effects showed larger male than female variance in the younger age group, and a general trend of decreasing sex differences in variance with increasing age.

Supplementary Figure 3. Boxplot visualization of comparison of right hippocampal volume, and parahippocampal surface area and thickness before and after adjustment. As age ranges differed for each cohort adjustments were performed in two steps: initially, a linear model was used to account for cohort and non-linear age effects. Next, random forest regression modelling was used to additionally account for field strength and FreeSurfer version. In the left panel, volumes were not adjusted, this displays the raw data for each cohort. In the right panel, volumes were adjusted.

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Author contributions

LMW developed the theoretical framework and prepared the manuscript with support from GED, PMT, EAC, SF, and CKT. LMW designed the models and scripts, GED and SF analyzed the data. All sites processed the imaging data and conducted quality control. GD, DD, and SF brought together and organized the datasets. *Cohort PI/ENIGMA core*: DD, IA, OAA, PA, TB, AB, DIB, SB, DB, HB, GFB, DMC, XC, TMCA, CRKC, VPC, PJC, AC, DvE, SEF, BF, ADG, DCG, IHG, HJG, OG, PG, REG, RCG, LdH, BJH, PJH, OAvdH, FMH, HEHP, CH, NJ, JAJ, AJK, JK, LL, ISL, CL, NGM, DM-C, BM, BCM, CMcD, AMM, KLM, JMM, LN, JO, PP, EP-C, MJP, JR, JLR, PGPR, MDS, PSS, TDS, AJS, KS, AS, JWS, IES, CS-M, AJS, DJS, SIT, JNT, DJV, HW, YW, BW, LTW, HCW, SCRW, MJW, MVZ, GIdZ, YW, PMT, EAC, SF. *Image data collection*: IA, TNA, AA-E, KIA, PA, SB, RB-S, AB, AB, SB, JB, AdB, AB, VDC, XC, FXC, TMCA, VPC, AC, FC, CGD, DvE, PF-C, EJCdG, ADG, DCG, IHG, HJG, PG, REG, LdH, BH, BJH, SNH, IBH, OAvdH, IBB, CAH, DJH, SH, AJH, MH, NH, FMH, CH, ACJ, EGJ, AJK, KKK, JL, LL, LdH, ISL, CL, MWJM, BM, BCM, YW, CMcD, AMM, GM, JN, YP, PP, GP, EP-C, JR, SS, AR, GR, JLR, PSS, RS, SS, TDS, AJS, MHS, KS, AS, LTS, PRS, AST, JNT, AU, N, HV, LW, YW, BW, WW, JDW, LTW, SCRW, DHW, YNY, MVZ, GCZ, EAC. *Image data processing/quality control*: GED, MA, TNA, AA-E, DA, KIA, AA, NB, SB, SE, AB, JB, AdB, RMB, VDC, EJC-R, XC, FXC, CRKC, AC, CGD, EWD, SE, DvE, JPF, PF-C, ADG, DCG, IHG, PG, TPG, BJH, SNH, OAvdH, AJH, MH, CH, ACJ, JJ, LK, BK, JL, ISL, PHL, MWJM, SM, IM-Z, BM, BCM, YW, GM, DvdM, JN, RS, EJC-R, YP, JR, GR, MDS, RS, TDS, KS, AS, LTS, PRS, SIT, AST, AU, IMV, LW, YW, WW, JDW, SCRW, KW, DHW, YNY, CKT. Manuscript revision: GED, IA, MA, AA-E, PA, AB, HB, RMB, JKB, VDC, EJC-R, XC, AC, CGD, DD, SE, PF-C, EJCdG, ADG, DCG, IHG, HJG, REG, RCG, TPG, BH, BJH, CAH, OAvdH, AJH, NH, FMH, ACJ, EGJ, JAJ, MK, JL, PHL, CL, DM-C, BM, BCM, AMM, DvdM, YP, GP, EP-C, MJP, JR, GR, PSS, RS, AJS, KS, AS, DJS, HST, AST, JNT, AU, N, HV, BW, LTW, KW, DHW.

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Collaborators

Members of the Karolinska Schizophrenia Project (KaSP) consortium: Farde L [1], Flyckt L [1], Engberg G [2], Erhardt S [2], Fatouros-Bergman H [1], Cervenka S[1], Schwieler L [2], Piehl F [3], Agartz I [1,4,5], Collste K [1], Sellgren CM [2], Victorsson P [1], Malmqvist A [2], Hedberg M [2], Orhan F [2]. [1] Centre for

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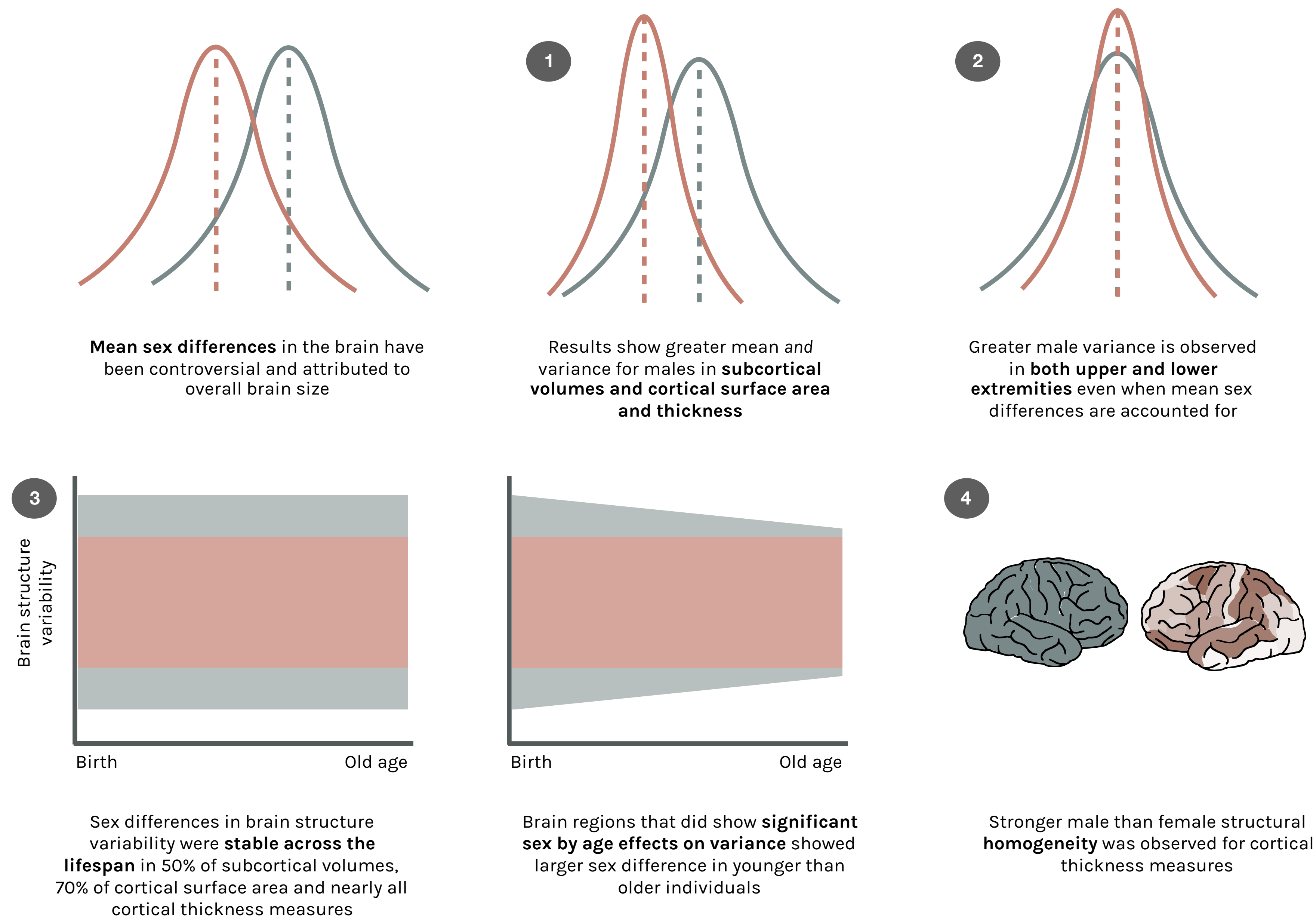
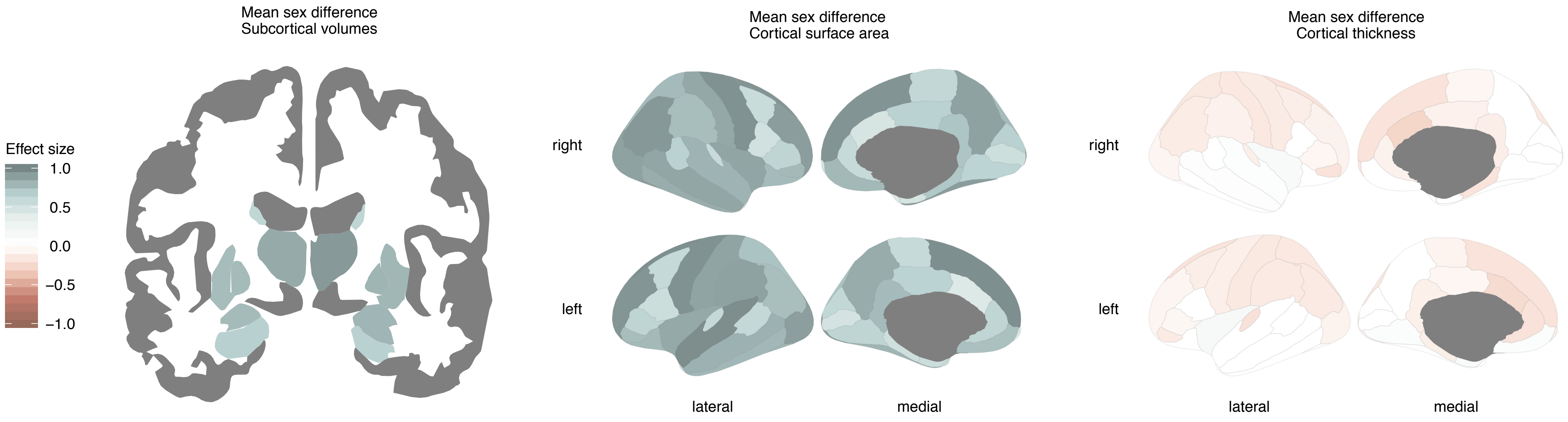
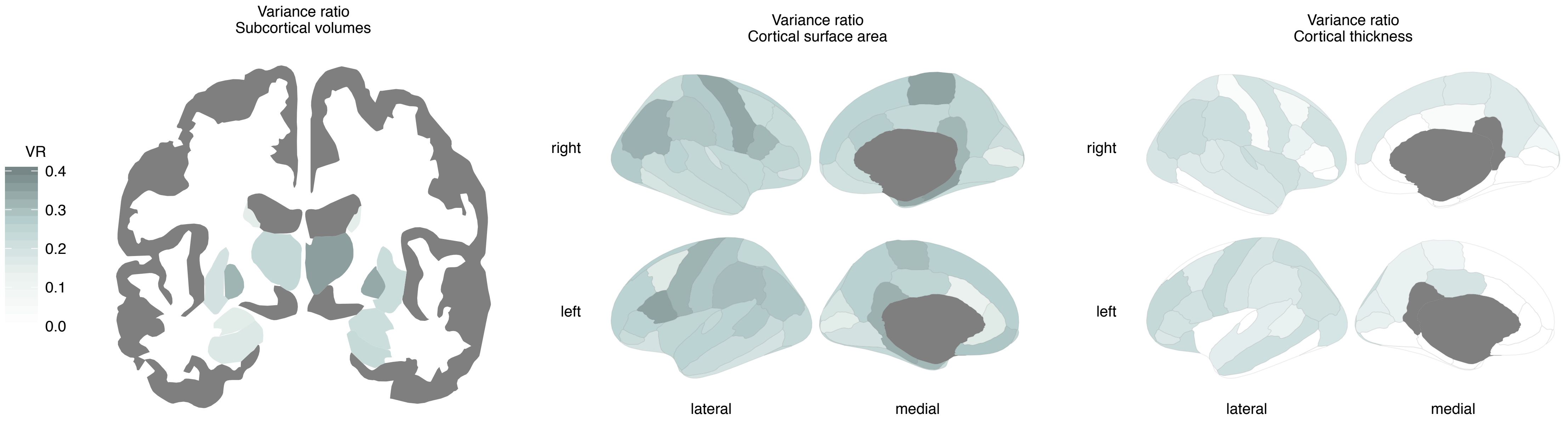

1
2
Mean sex differences in the brain have been controversial and attributed to overall brain size
Results show greater mean and variance for males in subcortical volumes and cortical surface area and thickness
Greater male variance is observed in both upper and lower extremities even when mean sex differences are accounted for
3
Brain structure variability
Birth
Old age
Birth
Old age
4
Sex differences in brain structure variability were stable across the lifespan in 50% of subcortical volumes, 70% of cortical surface area and nearly all cortical thickness measures
Brain regions that did show significant sex by age effects on variance showed larger sex difference in younger than older individuals
Stronger male than female structural homogeneity was observed for cortical thickness measures



Effect size
1.0
0.5
0.0
−0.5
−1.0
Mean sex difference
Subcortical volumes
Mean sex difference
Cortical surface area
right
left
lateral
medial
Mean sex difference
Cortical thickness
right
left
lateral
medial



Variance ratio
Subcortical volumes
Variance ratio
Cortical surface area
Variance ratio
Cortical thickness
VR
0.4
0.3
0.2
0.1
0.0
right
left
right
left
lateral
medial
lateral
medial

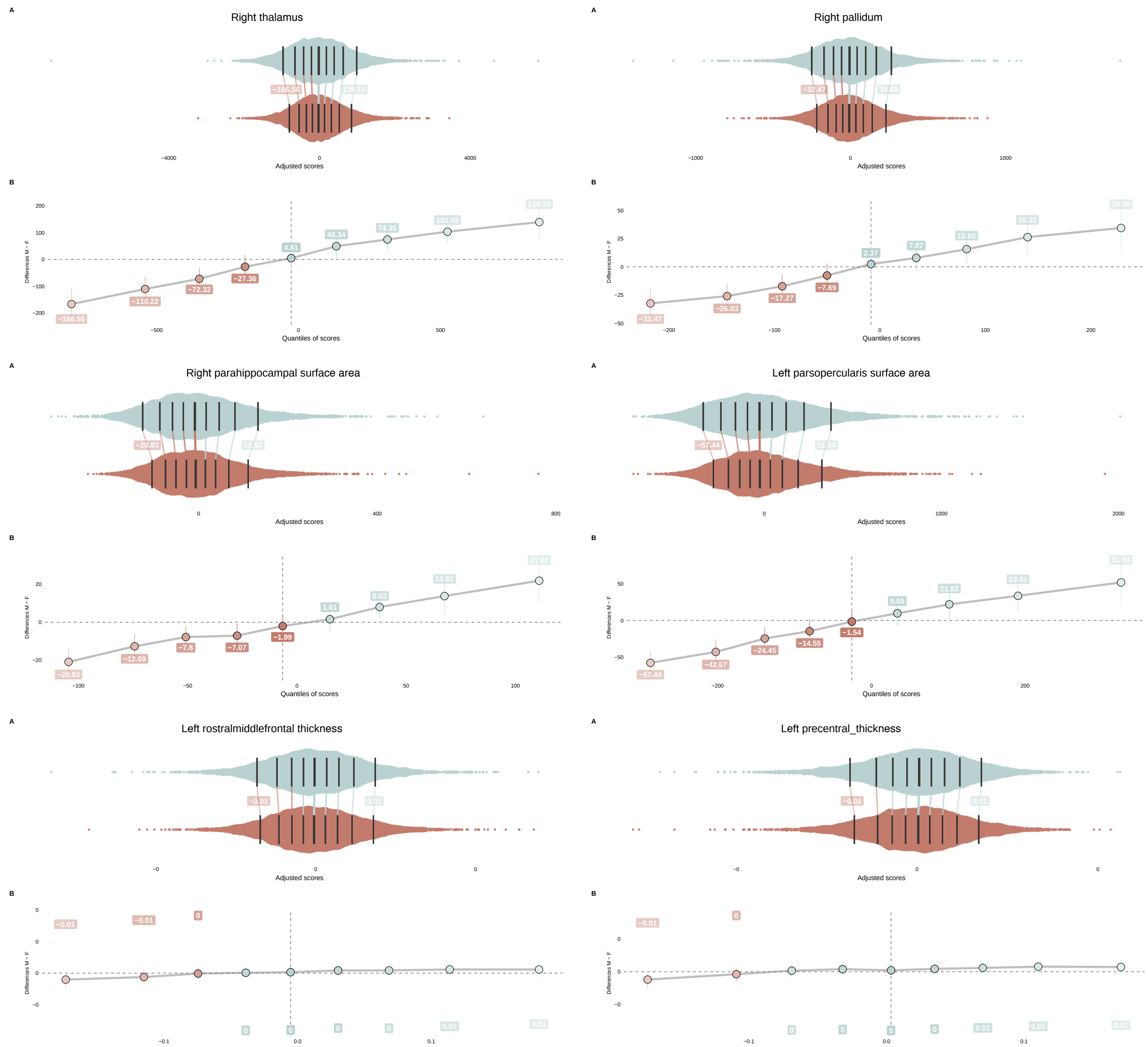
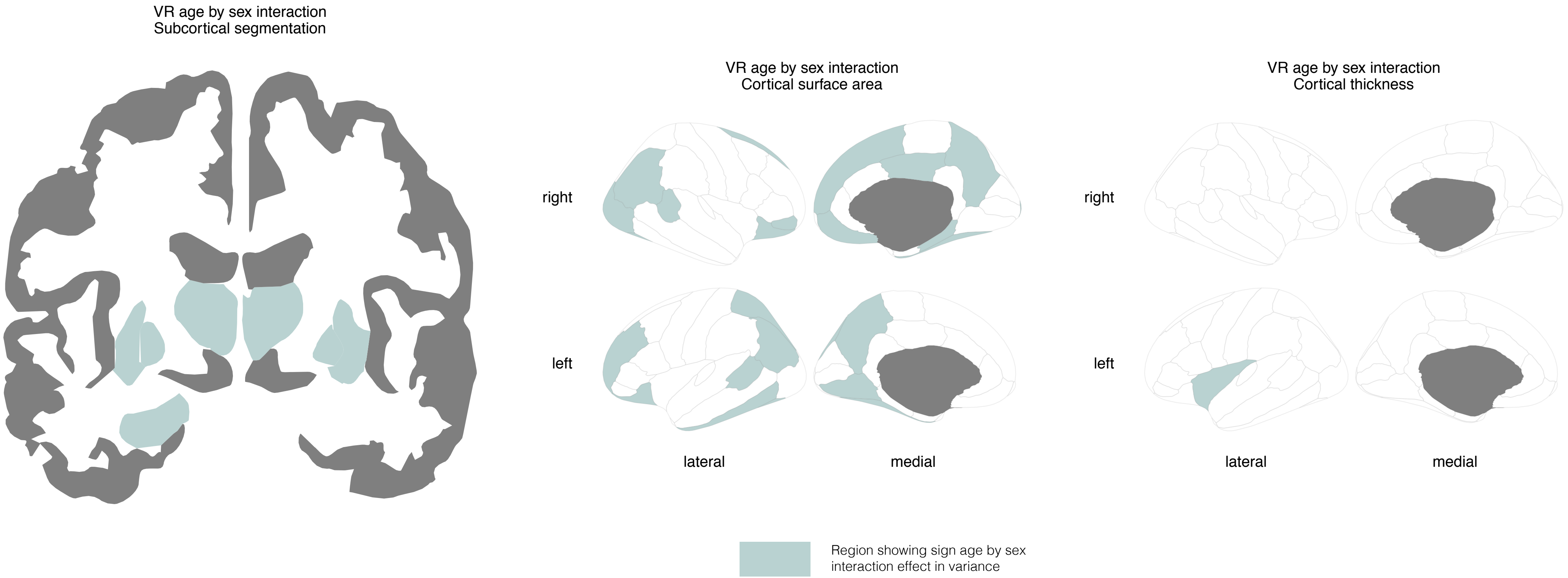


Figure 3. Jittered marginal distribution scatterplots (A) are displayed together with their shift function (B) for the top two variance ratio effects of subcortical volumes (left), cortical surface area (middle) and thickness measures (right). The central, darkest line on each distribution is the median, note that main sex effects are removed. The other lines mark the deciles of each distribution. The shift values are included, which refer to the number of units that the male (upper) distribution would have to be shifted to match the female (lower) distribution. Confidence intervals are included for each of these shift values.



VR age by sex interaction
Subcortical segmentation
VR age by sex interaction
Cortical surface area
VR age by sex interaction
Cortical thickness
right
left
lateral
medial
right
left
lateral
medial
Region showing sign age by sex
interaction effect in variance

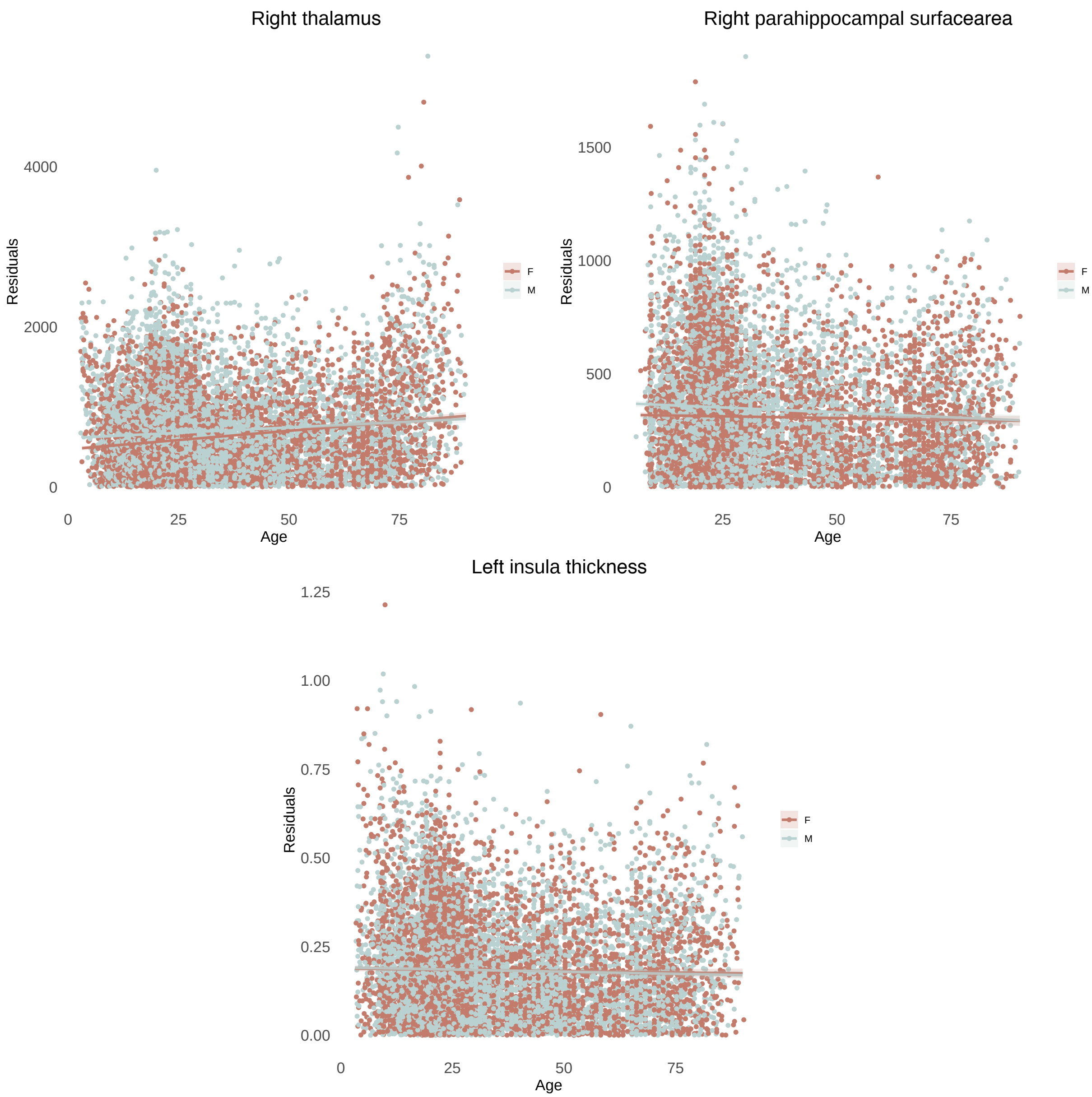
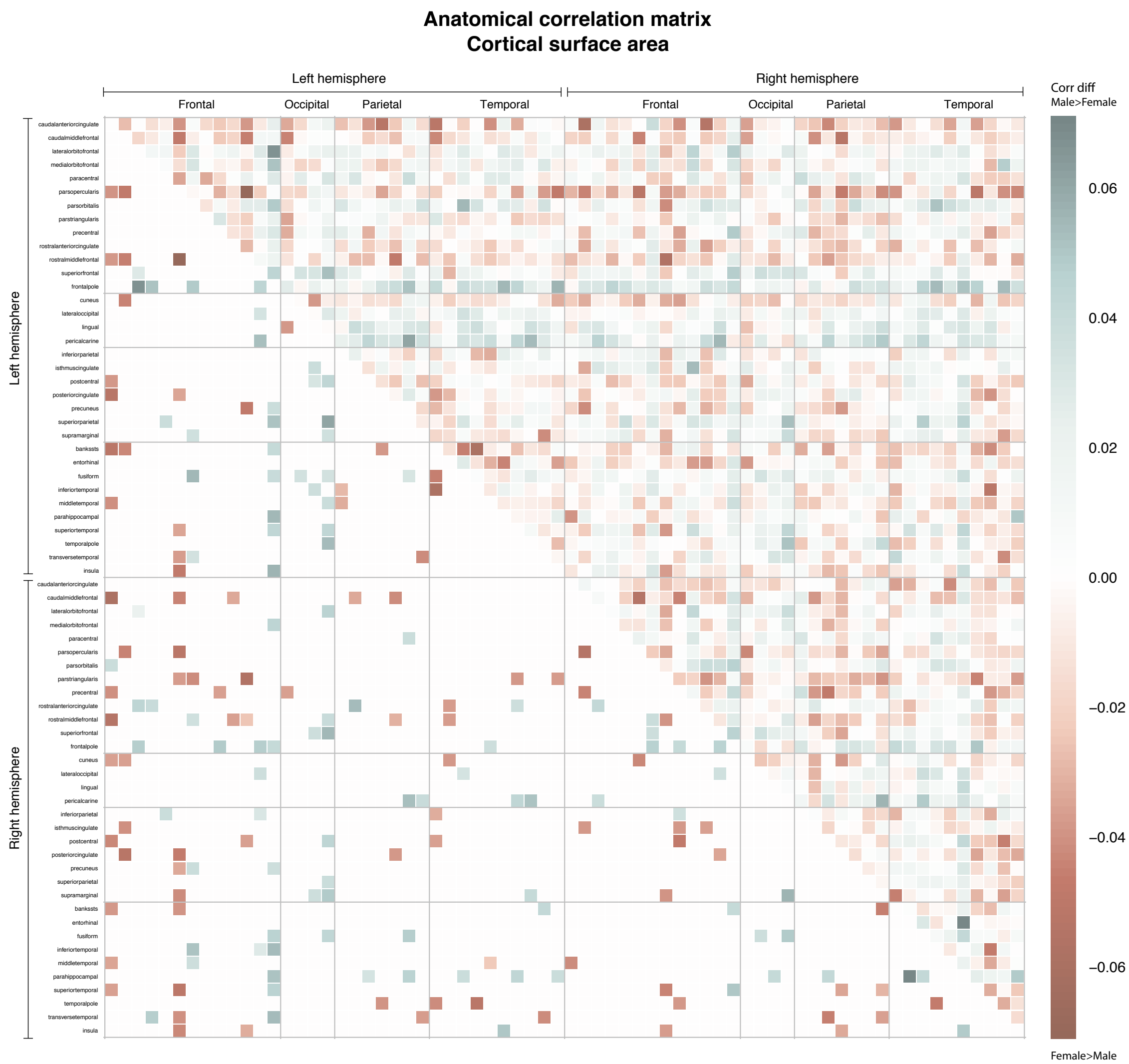


Figure 5. Sex differences in variablity interacted with age in 50% of the subcortical volumes, 30% of the surface area measures, and only one thickness measure. Three representative results are shown: right thalamus volume (left top), surface area of the right parahippocampal gyrus (right top) and thickness of the left insula (bottom venter). Absolute residual values are modeled across the age range. Effects showed larger male than female variance in the younger age group, this effect attenuated with increasing age.


Anatomical correlation matrix
Subcortical volumes
Left hemisphere
Right hemisphere
Corr diff
Male>Female
Female>Male
Accumbens
Amygdala
Caudate
Hippocampus
Pallidum
Putamen
Thalamus
0.06
0.04
0.02
0.00
−0.02
−0.04
−0.06


Anatomical correlation matrix
Cortical surface area
Left hemisphere
Right hemisphere
Frontal
Occipital
Parietal
Temporal
Corr diff
Male>Female
Female>Male
0.06
0.04
0.02
0.00
−0.02
−0.04
−0.06

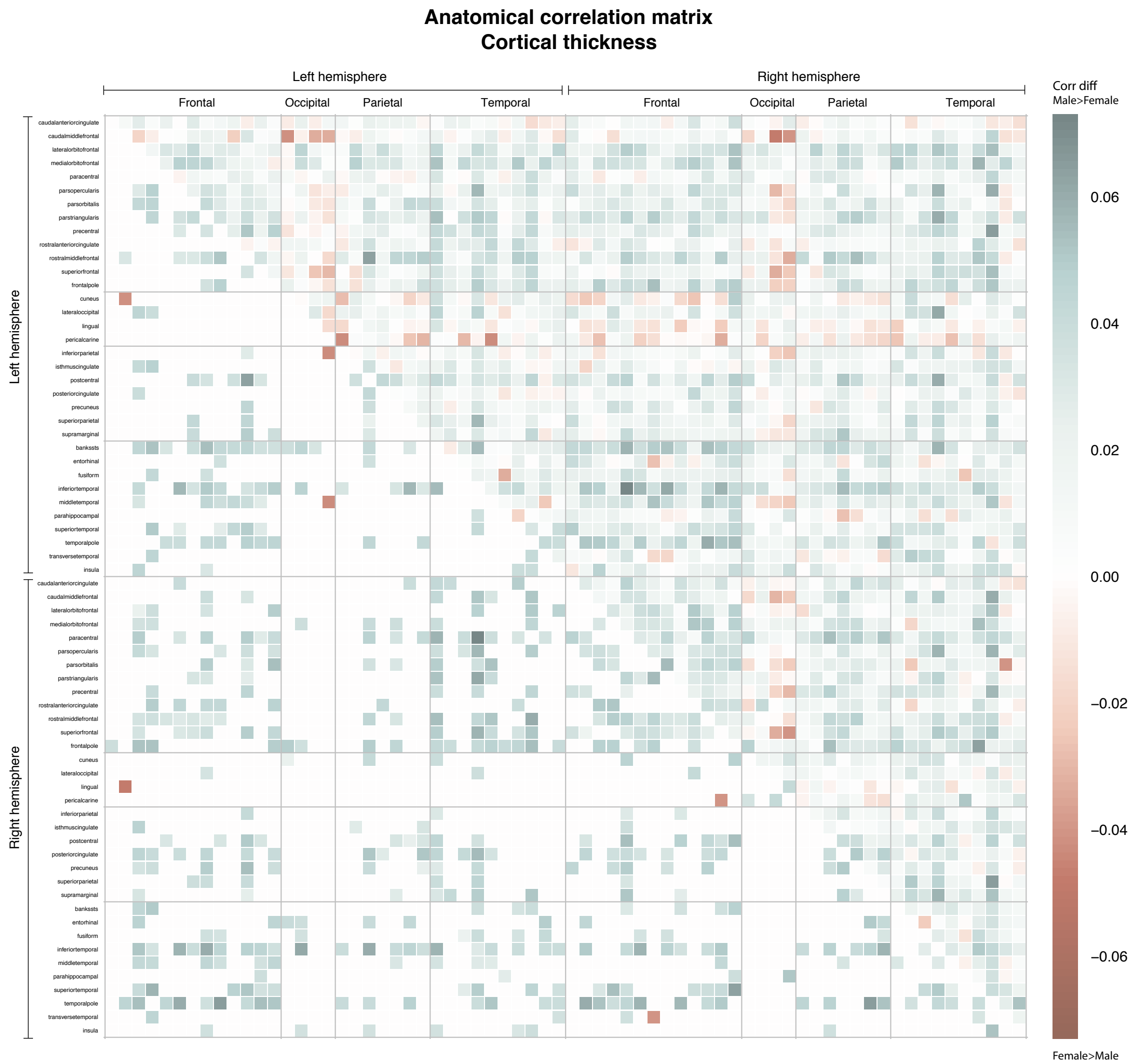


Figure 6. Stronger anatomical correlations for males than females are indicated in blue (larger homogeneity in males than females), while stronger correlations for females are displayed in red (larger homogeneity in females than males). Results are displayed for subcortical volumes (top), surface area (middle) and cortical thickness (bottom). Cortical regions are orderd by lobe and hemisphere (left frontal, left occipital, left parietal, left temporal, right frontal, right occipital, right parietal, right temporal).

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Table 1A

Subcortical volume	Female (n=7141)	Male (n=6555)	Mean difference test		Variance Ratio test	
	M	M	P	Cohen's D	VR	P
left thal	-328.287	357.024	**	0.840	0.237	**
right thal	-317.358	345.963	**	0.918	0.357	**
left caud	-139.573	152.488	**	0.609	0.150	**
right caud	-147.366	160.706	**	0.625	0.147	**
left put	-237.405	257.178	**	0.757	0.197	**
right put	-233.415	252.623	**	0.786	0.220	**
left pal	-86.166	93.761	**	0.768	0.317	**
right pal	-74.910	81.507	**	0.793	0.339	**
left hippo	-137.976	149.409	**	0.673	0.173	**
right hippo	-134.745	145.724	**	0.669	0.232	**
left amyg	-73.754	80.305	**	0.765	0.154	**
right amyg	-80.242	87.372	**	0.790	0.216	**
left accumb	-22.255	24.369	**	0.414	0.168	**
right accumb	-22.755	24.685	**	0.454	0.119	**

Table 1B

Surface area	Female (n=6243)	Male (n=5092)	Mean difference test		Variance Ratio test	
	M	M	P	Cohen's D	VR	P
left bankssts	-45.976	56.715	**	0.596	0.282	**
left caudalanteriorcingulate	-25.875	31.956	**	0.420	0.131	**
left caudalmiddlefrontal	-100.326	123.509	**	0.589	0.163	**
left cuneus	-55.069	67.958	**	0.605	0.188	**
left entorhinal	-19.379	23.824	**	0.540	0.310	**
left fusiform	-142.081	174.977	**	0.794	0.240	**
left inferiorparietal	-203.760	250.694	**	0.751	0.288	**
left inferiortemporal	-158.709	195.821	**	0.778	0.193	**
left isthmuscingulate	-54.544	67.228	**	0.765	0.326	**
left lateraloccipital	-229.910	284.223	**	0.893	0.240	**
left lateralorbitofrontal	-93.815	115.782	**	0.771	0.194	**
left lingual	-114.132	141.130	**	0.630	0.197	**
left medialorbitofrontal	-76.336	94.318	**	0.741	0.288	**
left middletemporal	-139.909	172.666	**	0.808	0.227	**
left parahippocampal	-24.273	30.139	**	0.522	0.330	**
left paracentral	-46.588	57.790	**	0.578	0.303	**
left parsopercularis	-63.862	78.461	**	0.536	0.350	**
left parsorbitalis	-27.703	34.060	**	0.755	0.223	**
left parstriangularis	-55.836	68.926	**	0.633	0.262	**
left pericalcarine	-48.359	58.895	**	0.485	0.151	**
left postcentral	-176.934	217.762	**	0.867	0.286	**
left posteriorcingulate	-50.597	62.161	**	0.651	0.253	**
left precentral	-207.652	255.826	**	0.949	0.319	**
left precuneus	-163.276	200.728	**	0.834	0.266	**
left rostralanteriorcingulate	-40.967	50.637	**	0.619	0.160	**
left rostralmiddlefrontal	-297.267	365.653	**	0.934	0.261	**
left superiorfrontal	-330.564	406.757	**	0.962	0.269	**
left superiorparietal	-202.642	249.403	**	0.730	0.241	**
left superiortemporal	-177.562	218.916	**	0.970	0.262	**
left supramarginal	-205.547	254.230	**	0.877	0.304	**
left frontalpole	-6.671	8.241	**	0.439	0.249	**
left temporalpole	-15.185	18.664	**	0.557	0.224	**
left transversetemporal	-19.898	24.463	**	0.585	0.239	**
left insula	-84.765	104.782	**	0.847	0.250	**
right bankssts	-42.654	52.655	**	0.662	0.261	**
right caudalanteriorcingulate	-31.929	39.489	**	0.465	0.275	**
right caudalmiddlefrontal	-95.924	117.705	**	0.563	0.225	**
right cuneus	-61.606	75.541	**	0.668	0.213	**
right entorhinal	-16.941	20.615	**	0.467	0.339	**
right fusiform	-155.696	191.647	**	0.900	0.225	**
right inferiorparietal	-278.411	342.870	**	0.920	0.325	**
right inferiortemporal	-157.460	193.922	**	0.827	0.187	**
right isthmuscingulate	-47.046	57.740	**	0.723	0.314	**
right lateraloccipital	-227.765	282.023	**	0.876	0.279	**
right lateralorbitofrontal	-99.594	122.823	**	0.765	0.234	**
right lingual	-110.640	136.478	**	0.644	0.225	**
right medialorbitofrontal	-70.180	86.695	**	0.777	0.203	**
right middletemporal	-155.924	192.222	**	0.857	0.224	**
right parahippocampal	-30.721	37.810	**	0.708	0.357	**
right paracentral	-57.941	71.375	**	0.609	0.349	**
right parsopercularis	-53.895	65.892	**	0.506	0.312	**
right parsorbitalis	-35.086	43.159	**	0.771	0.197	**
right parstriangularis	-69.557	85.138	**	0.634	0.252	**
right pericalcarine	-56.327	68.894	**	0.528	0.145	**
right postcentral	-168.595	208.307	**	0.851	0.278	**
right posteriorcingulate	-52.836	65.327	**	0.662	0.237	**
right precentral	-216.995	267.894	**	0.950	0.341	**
right precuneus	-184.909	228.043	**	0.878	0.248	**
right rostralanteriorcingulate	-33.179	41.005	**	0.576	0.221	**
right rostralmiddlefrontal	-294.685	363.055	**	0.898	0.228	**
right superiorfrontal	-325.198	400.002	**	0.939	0.258	**
right superiorparietal	-205.624	252.962	**	0.765	0.216	**
right superiortemporal	-132.506	163.787	**	0.800	0.243	**
right supramarginal	-168.426	207.920	**	0.754	0.285	**
right frontalpole	-9.712	11.996	**	0.481	0.194	**
right temporalpole	-11.097	13.725	**	0.422	0.228	**
right transversetemporal	-14.315	17.6[illegible]6	**	0.564	0.194	**
right insula	-95.695	117.482	**	0.863	0.238	**

Table 16

Thickness	Female (n=6620)	Male (n=5913)	Mean difference test		Variance Ratio test	
	M	M	P	Cohen's D	VR	P
left bankssts	0.001	-0.001	n.s.	0.011	0.039	**
left caudalanteriorcingulate	0.026	-0.028	**	0.213	-0.042	n.s.
left caudalmiddlefrontal	0.008	-0.008	**	0.103	0.061	*
left cuneus	0.000	0.000	n.s.	0.001	0.050	*
left entorhinal	-0.013	0.015	**	0.084	0.023	n.s.
left fusiform	0.001	-0.001	n.s.	0.016	0.022	n.s.
left inferiorparietal	0.009	-0.009	**	0.128	0.092	**
left inferiortemporal	-0.002	0.003	n.s.	0.027	0.004	n.s.
left isthmuscingulate	0.009	-0.009	**	0.088	-0.007	**
left lateraloccipital	0.005	-0.005	**	0.074	0.079	**
left lateralorbitofrontal	-0.002	0.003	n.s.	0.036	0.101	**
left lingual	-0.003	0.004	**	0.058	0.040	n.s.
left medialorbitofrontal	-0.004	0.006	**	0.058	0.027	n.s.
left middletemporal	-0.003	0.004	n.s.	0.037	0.093	*
left parahippocampal	0.015	-0.016	**	0.098	0.016	n.s.
left paracentral	0.006	-0.005	**	0.067	0.030	**
left parsopercularis	-0.002	0.003	n.s.	0.027	0.087	**
left parsorbitalis	0.013	-0.014	**	0.120	0.071	**
left parstriangularis	0.004	-0.004	*	0.049	0.084	**
left pericalcarine	0.000	0.001	n.s.	0.006	0.043	**
left postcentral	0.008	-0.009	**	0.133	0.078	**
left posteriorcingulate	0.004	-0.004	**	0.052	0.080	**
left precentral	0.007	-0.007	**	0.097	0.112	**
left precuneus	0.000	0.000	n.s.	0.002	0.041	**
left rostralanteriorcingulate	0.020	-0.021	**	0.170	-0.046	n.s.
left rostralmiddlefrontal	0.005	-0.004	**	0.061	0.112	**
left superiorfrontal	0.013	-0.014	**	0.168	0.048	n.s.
left superiorparietal	0.009	-0.009	**	0.136	0.098	**
left superiortemporal	-0.001	0.001	n.s.	0.014	0.052	**
left supramarginal	0.009	-0.009	**	0.126	0.064	**
left frontalpole	0.015	-0.016	**	0.100	0.036	n.s.
left temporalpole	0.004	-0.004	n.s.	0.023	0.027	n.s.
left transversetemporal	0.020	-0.021	**	0.177	0.018	n.s.
left insula	-0.009	0.011	**	0.121	0.049	n.s.
right bankssts	-0.001	0.002	n.s.	0.016	0.064	**
right caudalanteriorcingulate	0.027	-0.030	**	0.242	-0.029	n.s.
right caudalmiddlefrontal	0.008	-0.009	**	0.109	0.019	**
right cuneus	0.003	-0.002	n.s.	0.034	0.027	*
right entorhinal	0.005	-0.005	n.s.	0.028	0.026	n.s.
right fusiform	0.001	0.000	n.s.	0.008	0.029	n.s.
right inferiorparietal	0.008	-0.008	**	0.110	0.103	**
right inferiortemporal	0.000	0.001	n.s.	0.003	0.032	n.s.
right isthmuscingulate	0.010	-0.010	**	0.099	-0.038	**
right lateraloccipital	0.004	-0.004	**	0.057	0.078	**
right lateralorbitofrontal	0.003	-0.003	n.s.	0.036	0.074	**
right lingual	-0.002	0.003	n.s.	0.036	0.036	n.s.
right medialorbitofrontal	0.003	-0.003	n.s.	0.033	0.056	n.s.
right middletemporal	-0.003	0.004	*	0.047	0.065	**
right parahippocampal	0.021	-0.023	**	0.162	0.028	n.s.
right paracentral	0.004	-0.004	**	0.055	0.065	**
right parsopercularis	0.000	0.000	n.s.	0.001	0.037	**
right parsorbitalis	0.018	-0.019	**	0.164	0.026	n.s.
right parstriangularis	0.004	-0.004	**	0.053	0.008	**
right pericalcarine	0.001	-0.001	n.s.	0.017	0.020	n.s.
right postcentral	0.009	-0.009	**	0.135	0.009	**
right posteriorcingulate	0.007	-0.007	**	0.082	0.013	**
right precentral	0.008	-0.009	**	0.119	0.084	**
right precuneus	-0.001	0.002	n.s.	0.018	0.063	**
right rostralanteriorcingulate	0.009	-0.010	**	0.080	0.055	n.s.
right rostralmiddlefrontal	0.006	-0.006	**	0.078	0.085	**
right superiorfrontal	0.013	-0.013	**	0.165	0.065	*
right superiorparietal	0.008	-0.009	**	0.132	0.065	**
right superiortemporal	-0.003	0.004	*	0.042	0.073	**
right supramarginal	0.006	-0.007	**	0.086	0.096	**
right frontalpole	0.021	-0.022	**	0.140	0.012	n.s.
right temporalpole	-0.006	0.007	*	0.038	0.023	n.s.
right transversetemporal	0.011	-0.011	**	0.095	0.101	*
right insula	-0.008	0.010	**	0.107	0.092	**

Table 2A

Subcortical	Intercept	(s.e.)	P	Age	(s.e.)	P	Sex	(s.e.)	P	Sex by age	(s.e.)	P
left thal	587.987	6.178	**	9398.523	652.185	**	60.310	9.199	**	-3107.885	979.201	**
right thal	515.416	5.524	**	6424.232	583.119	**	82.380	8.225	**	-3102.267	875.503	**
left caud	361.790	3.729	**	879.545	393.693	*	28.152	5.553	**	270.769	591.096	n.s.
right caud	371.773	3.785	**	1290.352	399.567	**	31.395	5.636	**	-561.719	599.915	n.s.
left put	495.399	5.150	**	4435.730	543.701	**	54.586	7.669	**	-2966.533	816.321	**
right put	460.842	4.887	**	5622.177	515.939	**	51.687	7.277	**	-3853.454	774.638	**
left pal	165.039	1.816	**	837.030	191.768	**	26.852	2.705	**	-784.363	287.923	*
right pal	140.799	1.598	**	910.463	168.695	**	26.247	2.379	**	-850.994	253.281	**
left hippo	309.722	3.308	**	2755.892	349.231	**	31.626	4.926	**	-1375.500	524.341	*
right hippo	305.607	3.264	**	2615.969	344.571	**	35.732	4.860	**	-890.970	517.345	n.s.
left amyg	148.932	1.598	**	1378.267	168.734	**	13.800	2.380	**	-233.236	253.340	n.s.
right amyg	154.218	1.645	**	1621.298	173.675	**	16.477	2.450	**	-540.141	260.758	n.s.
left accumb	82.473	0.875	**	442.922	92.410	**	7.382	1.303	**	-136.472	138.746	n.s.
right accumb	78.541	0.823	**	539.975	86.850	**	7.412	1.225	**	-106.522	130.398	n.s.

Table 2B

Surface area	Intercept	(s.e.)	P	Age	(s.e.)	P	Sex	(s.e.)	P	Sex by age	(s.e.)	P
left bankssts	127.133	1.376	**	-437.616	142.554	**	16.563	2.056	**	-574.105	219.785	*
left caudalanteriorcingulate	104.209	1.113	**	-302.669	115.254	**	4.299	1.663	**	-277.614	177.695	n.s.
left caudalmiddlefrontal	293.750	2.943	**	-1359.284	304.791	**	21.272	4.397	**	-660.300	469.918	n.s.
left cuneus	154.129	1.607	**	-360.698	166.430	*	13.158	2.401	**	-330.457	256.596	n.s.
left entorhinal	57.126	0.651	**	-458.398	67.397	**	9.241	0.972	**	1.893	103.911	n.s.
left fusiform	305.090	3.105	**	250.591	321.575	n.s.	35.738	4.639	**	-2446.584	495.794	**
left inferiorparietal	454.916	4.708	**	-614.521	487.682	n.s.	63.459	7.035	**	-2243.805	751.894	*
left inferiortemporal	352.394	3.540	**	-353.703	366.628	n.s.	31.482	5.289	**	-1652.239	565.256	*
left isthmuscingulate	116.771	1.249	**	-32.188	129.411	n.s.	19.544	1.867	**	-204.545	199.522	n.s.
left lateraloccipital	438.089	4.474	**	-1416.631	463.377	**	50.571	6.685	**	-813.654	714.421	n.s.
left lateralorbitofrontal	208.173	2.120	**	204.108	219.597	n.s.	20.633	3.168	**	-1428.745	338.567	**
left lingual	310.573	3.141	**	-234.334	325.364	n.s.	29.898	4.694	**	-1268.288	501.636	*
left medialorbitofrontal	172.506	1.795	**	3.188	185.938	n.s.	23.450	2.682	**	-213.946	286.673	n.s.
left middletemporal	296.794	2.997	**	-421.492	310.480	n.s.	31.627	4.479	**	-1014.822	478.689	n.s.
left parahippocampal	72.669	0.887	**	-211.577	91.839	*	10.825	1.325	**	-241.097	141.595	n.s.
left paracentral	133.446	1.419	**	-195.857	147.019	n.s.	19.139	2.121	**	-171.708	226.670	n.s.
left parsopercularis	193.582	2.113	**	-540.023	218.880	*	31.583	3.158	**	-459.911	337.462	n.s.
left parsorbitalis	61.886	0.643	**	-172.940	66.566	**	7.120	0.960	**	-131.612	102.629	n.s.
left parstriangularis	148.566	1.524	**	-644.966	157.820	**	19.173	2.277	**	-546.829	243.322	n.s.
left pericalcarine	171.607	1.690	**	-245.127	175.004	n.s.	13.803	2.525	**	-283.583	269.815	n.s.
left postcentral	340.927	3.572	**	-1033.492	370.007	**	46.097	5.338	**	-1240.366	570.466	n.s.
left posteriorcingulate	130.459	1.363	**	-176.189	141.217	n.s.	13.905	2.037	**	-400.954	217.724	n.s.
left precentral	360.893	3.926	**	-1088.967	406.693	**	47.580	5.867	**	-876.707	627.028	n.s.
left precuneus	329.439	3.386	**	-444.670	350.720	n.s.	44.718	5.060	**	-1691.713	540.730	*
left rostralanteriorcingulate	113.700	1.156	**	-6.807	119.754	n.s.	7.691	1.728	**	-80.447	184.632	n.s.
left rostralmiddlefrontal	541.319	5.553	**	-1574.677	575.208	**	63.888	8.298	**	-2391.074	886.838	*
left superiorfrontal	577.465	6.015	**	-1306.494	623.063	*	75.007	8.988	**	-2320.740	960.620	n.s.
left superiorparietal	471.735	4.793	**	-1198.240	496.487	*	57.076	7.162	**	-2051.708	765.468	*
left superiortemporal	308.552	3.215	**	-864.236	333.037	**	40.486	4.804	**	-1222.034	513.467	n.s.
left supramarginal	392.296	4.082	**	-1937.799	422.787	**	58.041	6.099	**	-775.470	651.841	n.s.
left frontalpole	25.431	0.265	**	-114.432	27.425	**	3.212	0.396	**	-7.992	42.283	n.s.
left temporalpole	45.410	0.478	**	-173.235	49.555	**	5.115	0.715	**	-59.323	76.403	n.s.
left transversetemporal	56.992	0.594	**	-201.824	61.535	**	6.690	0.888	**	-81.655	94.872	n.s.
left insula	164.339	1.842	**	-460.767	190.830	*	17.215	2.753	**	6.824	294.215	n.s.
right bankssts	107.290	1.139	**	-392.600	117.986	**	13.575	1.702	**	-493.453	181.908	*
right caudalanteriorcingulate	114.549	1.199	**	-266.524	124.192	*	14.948	1.792	**	-8.218	191.475	n.s.
right caudalmiddlefrontal	288.671	2.929	**	-1415.348	303.395	**	30.576	4.377	**	-360.883	467.765	n.s.
right cuneus	152.647	1.656	**	-146.322	171.565	n.s.	16.151	2.475	**	-436.462	264.513	n.s.
right entorhinal	57.865	0.641	**	-455.979	66.351	**	10.302	0.957	**	-50.231	102.298	n.s.
right fusiform	295.259	3.000	**	43.695	310.723	n.s.	32.408	4.483	**	-1812.528	479.064	**
right inferiorparietal	504.767	5.239	**	-577.142	542.646	n.s.	82.015	7.828	**	-2767.949	836.635	**
right inferiortemporal	327.236	3.331	**	-482.481	345.043	n.s.	28.512	4.978	**	-1116.568	531.977	n.s.
right isthmuscingulate	105.700	1.157	**	-228.263	119.818	n.s.	16.311	1.729	**	-192.830	184.732	n.s.
right lateraloccipital	436.925	4.537	**	-1283.916	469.975	**	58.726	6.780	**	-1927.057	724.593	*
right lateralorbitofrontal	220.527	2.284	**	236.472	236.616	n.s.	24.442	3.413	**	-1470.759	364.808	**
right lingual	289.568	3.001	**	-299.806	310.855	n.s.	34.596	4.484	**	-1128.138	479.266	n.s.
right medialorbitofrontal	154.743	1.568	**	74.312	162.424	n.s.	15.452	2.343	**	-964.430	250.420	**
right middletemporal	309.733	3.171	**	-517.078	328.408	n.s.	34.194	4.738	**	-1188.068	506.329	n.s.
right parahippocampal	70.171	0.781	**	-155.100	80.940	n.s.	11.822	1.168	**	-420.498	124.790	**
right paracentral	156.024	1.669	**	-273.907	172.868	n.s.	25.570	2.494	**	-271.297	266.523	n.s.
right parsopercularis	174.570	1.866	**	-1036.595	193.296	**	25.454	2.789	**	-231.029	298.018	n.s.
right parsorbitalis	77.607	0.794	**	-103.424	82.287	n.s.	7.160	1.187	**	-311.879	126.867	*
right parstriangularis	184.989	1.887	**	-925.697	195.494	**	21.344	2.820	**	-662.628	301.407	n.s.
right pericalcarine	184.490	1.818	**	-314.748	188.350	n.s.	13.276	2.717	**	-264.356	290.392	n.s.
right postcentral	330.886	3.494	**	-1175.639	361.875	**	44.061	5.220	**	-907.204	557.928	n.s.
right posteriorcingulate	133.953	1.413	**	42.583	146.371	n.s.	14.739	2.112	**	-695.150	225.670	*
right precentral	374.619	4.131	**	-1039.063	427.849	*	53.576	6.172	**	-579.997	659.645	n.s.
right precuneus	355.783	3.685	**	-894.373	381.705	*	42.292	5.507	**	-1788.652	588.501	*
right rostralanteriorcingulate	97.009	1.005	**	198.486	104.078	n.s.	10.668	1.501	**	-140.756	160.464	n.s.
right rostralmiddlefrontal	560.924	5.691	**	-2015.333	589.514	**	60.682	8.504	**	-1467.830	908.895	n.s.
right superiorfrontal	586.059	6.054	**	-748.583	627.121	n.s.	72.274	9.047	**	-3613.685	966.876	**
right superiorparietal	453.081	4.716	**	-1983.725	488.528	**	49.530	7.048	**	42.170	753.197	n.s.
right superiortemporal	281.023	2.898	**	-481.481	300.133	n.s.	31.844	4.330	**	-1005.995	462.736	n.s.
right supramarginal	376.538	3.839	**	-1315.029	397.627	**	51.001	5.736	**	-1362.209	613.049	n.s.
right frontalpole	34.322	0.352	**	-93.541	36.451	*	2.974	0.526	**	-112.046	56.199	n.s.
right temporalpole	44.173	0.457	**	-144.791	47.330	**	5.067	0.683	**	-32.370	72.972	n.s.
right transversetemporal	43.342	0.436	**	-122.601	45.112	**	4.348	0.651	**	-76.872	69.553	n.s.
right insula	185.386	1.947	**	167.564	201.684	n.s.	22.970	2.910	**	-270.419	310.950	n.s.

Table 26

Thickness	Intercept	(s.e.)	P	Age	(s.e.)	P	Sex	(s.e.)	P	Sex by age	(s.e.)	P
left bankssts	0.138	0.001	**	0.012	0.150	n.s.	0.002	0.002	n.s.	0.345	0.217	n.s.
left caudalanteriorcingulate	0.204	0.002	**	1.405	0.217	**	-0.005	0.003	n.s.	0.207	0.314	n.s.
left caudalmiddlefrontal	0.119	0.001	**	0.375	0.131	**	0.002	0.002	n.s.	-0.108	0.190	n.s.
left cuneus	0.108	0.001	**	-0.194	0.118	n.s.	0.003	0.002	n.s.	-0.386	0.171	n.s.
left entorhinal	0.263	0.003	**	0.348	0.288	n.s.	0.001	0.004	n.s.	-0.414	0.417	n.s.
left fusiform	0.114	0.001	**	0.484	0.125	**	0.000	0.002	n.s.	-0.340	0.181	n.s.
left inferiorparietal	0.109	0.001	**	0.329	0.122	**	0.005	0.002	**	0.023	0.176	n.s.
left inferiortemporal	0.128	0.001	**	0.515	0.138	**	0.000	0.002	n.s.	-0.327	0.199	n.s.
left isthmuscingulate	0.165	0.002	**	0.491	0.175	**	-0.003	0.002	n.s.	-0.076	0.254	n.s.
left lateraloccipital	0.096	0.001	**	0.132	0.106	n.s.	0.004	0.001	**	0.057	0.154	n.s.
left lateralorbitofrontal	0.124	0.001	**	0.212	0.138	n.s.	0.006	0.002	**	-0.438	0.201	n.s.
left lingual	0.099	0.001	**	0.343	0.109	**	0.001	0.001	n.s.	-0.308	0.157	n.s.
left medialorbitofrontal	0.135	0.001	**	0.067	0.150	n.s.	0.004	0.002	n.s.	-0.425	0.217	n.s.
left middletemporal	0.129	0.001	**	0.493	0.140	**	0.004	0.002	*	-0.012	0.203	n.s.
left parahippocampal	0.248	0.002	**	0.441	0.254	n.s.	0.002	0.003	n.s.	-0.372	0.368	n.s.
left paracentral	0.126	0.001	**	0.321	0.138	*	0.003	0.002	n.s.	-0.017	0.199	n.s.
left parsopercularis	0.123	0.001	**	0.497	0.134	**	0.005	0.002	**	-0.358	0.194	n.s.
left parsorbitalis	0.178	0.002	**	-0.413	0.192	*	0.004	0.003	n.s.	0.266	0.278	n.s.
left parstriangularis	0.134	0.001	**	0.145	0.144	n.s.	0.004	0.002	*	-0.073	0.209	n.s.
left pericalcarine	0.101	0.001	**	0.202	0.114	n.s.	0.001	0.002	n.s.	-0.325	0.165	n.s.
left postcentral	0.097	0.001	**	0.340	0.106	**	0.004	0.001	**	0.222	0.154	n.s.
left posteriorcingulate	0.131	0.001	**	0.308	0.142	*	0.005	0.002	**	-0.236	0.205	n.s.
left precentral	0.110	0.001	**	1.223	0.122	**	0.004	0.002	*	0.181	0.177	n.s.
left precuneus	0.111	0.001	**	0.521	0.121	**	0.003	0.002	n.s.	-0.056	0.176	n.s.
left rostralanteriorcingulate	0.193	0.002	**	0.470	0.205	*	-0.005	0.003	n.s.	-0.378	0.298	n.s.
left rostralmiddlefrontal	0.109	0.001	**	0.153	0.122	n.s.	0.005	0.002	**	0.039	0.177	n.s.
left superiorfrontal	0.124	0.001	**	0.505	0.137	**	0.002	0.002	n.s.	0.083	0.198	n.s.
left superiorparietal	0.099	0.001	**	0.158	0.109	n.s.	0.004	0.001	**	0.224	0.158	n.s.
left superiortemporal	0.129	0.001	**	0.832	0.139	**	0.004	0.002	*	-0.123	0.201	n.s.
left supramarginal	0.114	0.001	**	0.396	0.122	**	0.005	0.002	**	0.063	0.177	n.s.
left frontalpole	0.241	0.002	**	-1.236	0.266	**	0.004	0.004	n.s.	0.112	0.386	n.s.
left temporalpole	0.268	0.003	**	-2.010	0.301	**	0.006	0.004	n.s.	-0.518	0.436	n.s.
left transversetemporal	0.182	0.002	**	0.027	0.194	n.s.	-0.001	0.003	n.s.	-0.168	0.281	n.s.
left insula	0.125	0.001	**	1.184	0.135	**	0.002	0.002	n.s.	-0.700	0.195	*
right bankssts	0.146	0.001	**	-0.094	0.157	n.s.	0.003	0.002	n.s.	0.217	0.228	n.s.
right caudalanteriorcingulate	0.186	0.002	**	0.936	0.198	**	-0.008	0.003	**	-0.105	0.288	n.s.
right caudalmiddlefrontal	0.120	0.001	**	0.226	0.130	n.s.	0.002	0.002	n.s.	0.179	0.189	n.s.
right cuneus	0.110	0.001	**	0.037	0.118	n.s.	0.001	0.002	n.s.	-0.334	0.170	n.s.
right entorhinal	0.288	0.003	**	0.122	0.310	n.s.	0.004	0.004	n.s.	-0.746	0.449	n.s.
right fusiform	0.114	0.001	**	0.657	0.125	**	0.001	0.002	n.s.	-0.171	0.181	n.s.
right inferiorparietal	0.109	0.001	**	0.390	0.120	**	0.005	0.002	**	0.233	0.174	n.s.
right inferiortemporal	0.124	0.001	**	0.539	0.135	**	0.003	0.002	n.s.	-0.132	0.196	n.s.
right isthmuscingulate	0.162	0.002	**	0.401	0.172	*	-0.002	0.002	n.s.	0.223	0.249	n.s.
right lateraloccipital	0.101	0.001	**	0.280	0.110	*	0.005	0.001	**	0.023	0.159	n.s.
right lateralorbitofrontal	0.129	0.001	**	-0.174	0.144	n.s.	0.004	0.002	*	-0.110	0.208	n.s.
right lingual	0.102	0.001	**	0.172	0.111	n.s.	0.000	0.002	n.s.	-0.201	0.161	n.s.
right medialorbitofrontal	0.142	0.001	**	-0.424	0.156	**	0.003	0.002	n.s.	-0.201	0.227	n.s.
right middletemporal	0.123	0.001	**	0.067	0.137	n.s.	0.006	0.002	**	0.400	0.198	n.s.
right parahippocampal	0.207	0.002	**	0.554	0.224	*	0.005	0.003	n.s.	-0.115	0.325	n.s.
right paracentral	0.124	0.001	**	0.492	0.134	**	0.002	0.002	n.s.	-0.050	0.194	n.s.
right parsopercularis	0.131	0.001	**	0.330	0.139	*	0.001	0.002	n.s.	-0.056	0.201	n.s.
right parsorbitalis	0.175	0.002	**	-0.470	0.188	*	0.002	0.003	n.s.	0.159	0.273	n.s.
right parstriangularis	0.131	0.001	**	-0.016	0.141	n.s.	0.002	0.002	n.s.	0.052	0.204	n.s.
right pericalcarine	0.102	0.001	**	0.199	0.112	n.s.	0.002	0.002	n.s.	-0.336	0.163	n.s.
right postcentral	0.102	0.001	**	0.121	0.111	n.s.	0.002	0.002	n.s.	0.251	0.161	n.s.
right posteriorcingulate	0.129	0.001	**	0.442	0.139	**	0.000	0.002	n.s.	-0.014	0.202	n.s.
right precentral	0.110	0.001	**	0.992	0.124	**	0.005	0.002	**	0.411	0.179	n.s.
right precuneus	0.110	0.001	**	0.473	0.121	**	0.004	0.002	*	-0.148	0.176	n.s.
right rostralanteriorcingulate	0.185	0.002	**	0.390	0.205	n.s.	0.009	0.003	**	-0.713	0.298	n.s.
right rostralmiddlefrontal	0.108	0.001	**	0.084	0.120	n.s.	0.003	0.002	n.s.	-0.162	0.174	n.s.
right superiorfrontal	0.120	0.001	**	0.499	0.131	**	0.003	0.002	n.s.	-0.189	0.190	n.s.
right superiorparietal	0.099	0.001	**	0.231	0.110	*	0.003	0.002	*	0.154	0.160	n.s.
right superiortemporal	0.127	0.001	**	0.738	0.138	**	0.005	0.002	*	0.153	0.201	n.s.
right supramarginal	0.117	0.001	**	0.723	0.127	**	0.004	0.002	*	-0.037	0.184	n.s.
right frontalpole	0.236	0.002	**	-0.642	0.255	*	0.002	0.003	n.s.	-0.248	0.369	n.s.
right temporalpole	0.274	0.003	**	-2.088	0.317	**	0.007	0.004	n.s.	0.219	0.459	n.s.
right transversetemporal	0.181	0.002	**	0.511	0.198	*	0.010	0.003	**	-0.175	0.287	n.s.
right insula	0.130	0.001	**	1.079	0.146	**	0.005	0.002	*	-0.468	0.211	n.s.

Table 3. Sex distributions and age of subjects by sample

Sample	Total N	Sex	N	Age Mean	SD	Range
EDINBURGH	55	Male	20	23.9	2.5	18.5 - 28.4
		Female	35	23.7	3.1	18.6 - 30.6
UNIBA	131	Male	67	30.3	10.0	18.0 - 63.0
		Female	64	24.3	6.8	18.0 - 52.0
Tuebingen	50	Male	22	38.4	11.1	26.0 - 61.0
		Female	28	42.2	12.5	24.0 - 61.0
GSP	2009	Male	894	27.8	16.8	18.0 - 90.0
		Female	1115	26.7	16.2	18.0 - 89.0
Melbourne	102	Male	54	19.5	2.9	15.0 - 25.0
		Female	48	19.6	3.1	15.0 - 26.0
HMS	55	Male	21	41.3	11.2	24.0 - 59.0
		Female	34	38.5	12.8	19.0 - 64.0
ENIGMA-OCD (1)	66	Male	30	30.6	8.9	19.0 - 56.0
		Female	36	35.1	10.9	18.0 - 61.0
NUIG	93	Male	54	34.1	11.6	18.0 - 57.0
		Female	39	39.0	11.0	18.0 - 58.0
NeuroIMAGE	383	Male	177	16.8	3.6	7.7 - 28.5
		Female	206	17.0	3.8	7.8 - 28.6
CAMH	141	Male	72	43.2	18.9	18.0 - 86.0
		Female	69	44.1	19.8	18.0 - 82.0
Basel	44	Male	17	25.7	4.5	19.0 - 35.0
		Female	27	25.3	4.2	19.0 - 39.0
Bordeaux	452	Male	220	26.9	7.8	18.0 - 57.0
		Female	232	26.6	7.7	18.0 - 56.0
FBIRN	174	Male	124	37.6	11.3	19.0 - 60.0
		Female	50	37.4	11.3	19.0 - 58.0
KaSP	32	Male	15	27.4	5.5	21.0 - 43.0
		Female	17	27.6	5.9	20.0 - 37.0
CODE	72	Male	31	43.7	12.4	25.0 - 64.0
		Female	41	36.6	13.4	20.0 - 63.0
Indiana (1)	49	Male	9	71.9	6.6	63.0 - 80.0
		Female	40	60.4	11.6	37.0 - 84.0
COMPULS/TS EUROTRAIN	53	Male	36	10.8	1.0	8.7 - 12.9
		Female	17	11.0	1.1	9.2 - 12.9
FIDMAG	123	Male	54	36.4	8.5	19.0 - 63.0
		Female	69	38.4	11.2	19.0 - 64.0
NU	79	Male	46	31.6	14.5	14.6 - 66.3
		Female	33	34.4	15.3	14.2 - 67.9
SHIP-2	818	Male	467	50.5	14.4	22.0 - 81.0
		Female	351	49.6	14.0	21.0 - 81.0
SHIP-TREND	373	Male	207	55.6	12.8	31.0 - 84.0
		Female	166	54.4	12.0	32.0 - 88.0
QTIM	340	Male	111	22.5	3.3	16.0 - 29.3
		Female	229	22.7	3.4	16.1 - 30.0
Betula	287	Male	136	61.6	12.5	25.5 - 81.3
		Female	151	64.1	13.1	25.7 - 80.9
TOP	303	Male	159	34.5	8.8	18.3 - 56.2
		Female	144	36.3	10.9	19.3 - 73.4
HUBIN	102	Male	69	42.1	9.0	19.4 - 54.9
		Female	33	41.7	8.5	19.9 - 56.2
StrokeMRI	52	Male	19	47.9	20.8	20.0 - 77.0
		Female	33	43.6	23.0	18.0 - 78.0
AMC	99	Male	65	22.5	3.4	17.0 - 32.0
		Female	34	23.6	3.3	18.0 - 29.0
NESDA	65	Male	23	40.7	9.7	23.0 - 56.0
		Female	42	40.1	9.9	21.0 - 54.0
Barcelona (1)	30	Male	14	15.1	1.5	13.0 - 17.0
		Female	16	14.9	2.1	11.0 - 17.0
Barcelona (2)	44	Male	24	14.4	1.8	11.0 - 17.0
		Female	20	14.8	2.4	11.0 - 17.0
Stages-Dep	32	Male	9	46.6	8.4	37.0 - 58.0
		Female	23	45.8	8.2	27.0 - 58.0
IMpACT	144	Male	57	34.2	11.0	19.0 - 62.0
		Female	87	37.2	12.6	19.0 - 63.0
BIG	1319	Male	657	29.8	15.4	17.0 - 82.0
		Female	662	26.9	12.9	13.0 - 79.0
IMH	56	Male	22	36.0	10.5	20.4 - 60.5
Stanford	34	Female	34	37.5	10.8	18.9 - 56.3
MCIC (1) + (2)	93	Male	63	32.8	12.2	18.0 - 58.0
		Female	30	32.5	11.9	19.0 - 60.0
OLIN	599	Male	237	36.3	13.3	22.0 - 86.5
		Female	362	35.9	12.8	21.0 - 74.0
Neuroventure	137	Male	62	13.7	0.6	12.4 - 14.9
		Female	75	13.6	0.7	12.3 - 14.9
CIAM	30	Male	16	27.1	5.9	19.0 - 40.0
		Female	14	26.1	3.8	20.0 - 33.0
ENIGMA-HIV	31	Male	16	25.6	4.7	19.0 - 33.0
		Female	15	23.9	4.1	20.0 - 32.0
Meth-CT	62	Female	13	26.1	4.1	19.0 - 34.0
		Males	49	27.0	7.9	18.0 - 53.0
ENIGMA-OCD	26	Male	10	34.6	13.6	19.0 - 56.0
		Female	16	28.8	7.8	20.0 - 46.0
Oxford	38	Male	18	16.5	1.6	14.1 - 18.9
		Female	20	15.9	1.1	13.7 - 17.7
Yale	23	Male	12	14.4	2.4	10.3 - 17.5
		Female	11	14.0	2.0	9.9 - 16.5
Sao Paulo-1	69	Male	45	27.1	5.6	18.0 - 42.0
		Female	24	27.5	6.4	17.0 - 43.0
Sao Paulo-3	85	Male	45	28.2	7.3	18.0 - 43.0
		Female	40	32.7	8.8	18.0 - 50.0
ENIGMA-OCD (2)	49	Male	19	32.1	7.8	24.0 - 53.0
		Female	30	31.3	7.7	21.0 - 50.0
ENIGMA-OCD (3)	35	Male	16	42.9	12.9	22.5 - 64.0
		Female	19	36.0	8.8	21.5 - 49.3
ENIGMA-OCD (4)	23	Male	9	13.1	2.9	8.8 - 15.9
		Female	14	13.8	2.4	8.7 - 16.8
ENIGMA-OCD (5)	33	Male	12	30.7	8.8	21.0 - 53.0
		Female	21	39.2	11.5	24.0 - 63.0
SYDNEY	157	Male	65	42.0	22.4	12.0 - 84.0
		Female	92	37.1	21.7	13.0 - 78.0
IMH	79	Male	50	30.7	8.3	23.0 - 53.9
		Female	29	34.2	12.4	20.4 - 59.0
UPENN	187	Male	86	35.7	12.9	18.0 - 71.0
		Female	101	35.8	14.7	16.0 - 85.0
ADHD-NF	13	Male	7	13.3	1.2	11.9 - 14.8
		Female	6	13.4	0.8	12.1 - 14.2
Indiana (2)	66	Male	26	40.2	15.3	19.0 - 65.0
		Female	40	39.4	14.1	20.0 - 65.0
Sydney MAS	523	Male	236	78.3	4.6	70.3 - 89.8
		Female	287	78.5	4.7	70.5 - 90.1
OADS (1)	118	Male	39	73.8	5.5	65.0 - 84.0
		Female	79	70.4	5.6	65.0 - 84.0
Cardiff	318	Male	89	28.1	7.8	19.0 - 57.0
		Female	229	24.2	7.0	18.0 - 58.0
CEG	32	Male	32	15.6	1.7	13.0 - 19.0
NYU	51	Male	31	30.2	7.7	18.8 - 46.0
		Female	20	31.4	10.3	19.8 - 51.9
CLiNG	321	Male	131	25.5	5.4	19.0 - 58.0
		Female	190	24.9	5.1	18.0 - 57.0
NTR (1)	112	Male	42	28.5	8.0	19.0 - 56.0
		Female	70	37.0	10.5	19.0 - 57.0
NTR (2)	30	Male	11	28.4	3.6	22.0 - 33.0
		Female	19	28.6	9.8	1.0 - 42.0
NTR (3)	37	Male	14	15.1	1.5	12.0 - 17.0
		Female	23	14.5	1.4	11.0 - 18.0
Indiana (2) + (3)	201	Male	97	21.6	14.4	6.0 - 79.0
		Female	104	33.0	22.8	7.0 - 87.0
BIG	1291	Male	553	25.1	9.3	18.0 - 71.0
		Female	738	23.3	6.9	18.0 - 66.0
OADS (2)	35	Male	15	70.1	5.7	65.0 - 81.0
		Female	20	67.4	3.8	65.0 - 78.0
OADS (3)	153	Male	59	70.3	4.2	65.0 - 81.0
		Female	94	69.7	4.6	65.0 - 81.0
OADS (4)	108	Male	30	69.8	4.5	65.0 - 85.0
		Female	78	70.1	4.9	65.0 - 89.0
MHRC	52	Male	52	22.3	2.9	16.1 - 27.6
BRAINSCALE	277	Male	146	10.1	1.5	9.0 - 15.0
		Female	131	9.9	1.2	9.0 - 14.1
Leiden	611	Male	299	16.2	4.7	8.3 - 28.1
		Female	312	16.9	4.9	8.4 - 28.9
IMAGEN	1964	Male	952	14.5	0.4	13.2 - 15.7
		Female	1012	14.5	0.4	13.3 - 16.0
ENIGMA-HIV	175	Male	175	38.8	6.5	29.0 - 50.0
UMCU	172	Male	84	40.2	16.5	18.0 - 80.0
		Female	88	39.2	17.9	18.0 - 84.0