Are sex differences in human brain structure associated with sex differences in behaviour?

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Abstract

On average, men and women differ in brain structure and behaviour, raising the possibility of a link between sex differences in brain and behaviour. But women and men are also subject to different societal and cultural norms. We navigated this challenge by investigating variability of sex-differentiated brain structure within each sex. Using data from the Queensland Twin IMaging study (N=1,040) and Human Connectome Project (N=1,113), we obtained data-driven measures of individual differences along a male-female dimension for brain and behaviour based on average sex differences in brain structure and behaviour, respectively. We found a weak association between these brain and behavioural differences, driven by brain size. These brain and behavioural differences were moderately heritable. Our findings suggest that behavioural sex differences are to some extent related to sex differences in brain structure, but that this is mainly driven by differences in brain size, and causality should be interpreted cautiously.

Keywords: masculinization, brain structure, neuroimaging, MRI, twin modelling

Statement of Relevance

Females and males differ on average in brain structure and in behaviour. A long-standing question is the extent to which these sex differences are related. The question is difficult to address because men and women are subject to different societal and cultural norms. In this research, to navigate this challenge, we examined individual differences in brain structure along the male-female dimension separately for each gender group. We then determined whether the differences were associated with physical and behavioural measures such as endurance, body mass index, cognition, and personality traits. We found that brain differences on the male-female dimension were weakly associated with behaviour, but this association was driven by differences in brain size. Importantly, the associations were small, suggesting that brain structure is only one of many factors explaining behavioural sex differences.

Are sex differences in human brain structure associated with sex differences in behaviour?

Females and males differ, on average, in many ways. Obvious physical differences in measures such as height and strength are generally accepted to have a biological and evolutionary basis. But the basis of average differences in male and female behaviour – for example, specific cognitive abilities (Gur & Gur, 2016) and personality traits (Archer, 2019) – is not well understood and is subject to controversy. On one hand, there is little doubt that historically and culturally ingrained social expectations and gender roles contribute to observed sex differences in behaviour. On the other hand, there is strong resistance in some quarters to the idea that evolved predispositions – stemming from different selection pressures on our female and male ancestors – may also contribute to the observed behavioural sex differences (Eagly & Wood, 2013). Indeed, because many behavioural sex differences appear to fit with predictions from both evolutionary biology and social role theory, it is difficult to determine whether behavioural sex differences reflect evolved dispositions at all.

One clue is the observation of structural differences, on average, between female and male brains. In adulthood, male brains are on average 10-15% larger than female brains (Ruigrok et al., 2014), even after adjusting for body height (Ritchie et al., 2018). Also, several regional sex differences remain after adjusting for overall brain size: for instance, the largest single-sample study to-date (N=5,216) (Ritchie et al., 2018) showed that after adjusting for brain size, female UK Biobank participants had smaller volumes than males in the amygdala, pallidum, and putamen, while males had smaller nucleus accumbens. A recent large voxel-wise study (N=2,838) (Lotze et al., 2019) also found sex differences in subcortical and cortical grey matter in adults. Other studies (Bruner, de la Cuétara, Colom, & Martin-Loeches, 2012; Kim et al., 2012) have reported sex differences in the shape of regional brain structures. Moreover, several studies have succeeded in predicting an

individual's biological sex based on brain structure differences, showing an accuracy between 69 to 93% (Anderson et al., 2019; Chekroud, Ward, Rosenberg, & Holmes, 2016; Del Giudice et al., 2016; Joel et al., 2018; Tunç et al., 2016; Xin, Zhang, Tang, & Yang, 2019), even after correction for height (Chekroud et al., 2016) or brain size (grey matter volume) (Anderson et al., 2019) – despite the substantial overlap on brain structure measures between males and females (Ritchie et al., 2018). However, although these studies adjusted for global brain size, the findings may still be driven by differences in brain size as brain regions scale differently with brain size (de Jong et al., 2017).

Importantly, the well-established existence of sex differences in brain structure does not necessarily mean that these differences relate to behavioural sex differences. Indeed, some researchers propose that sex differences in brain structure may instead promote similarity in women and men's behaviour, by compensating for scaling differences due to the sex difference in body and brain size (De Vries, 2004). A key obstacle to examining the association between sex differences in brain structure and behaviour is that men and women, as well as having brains that differ on average, are also, on average, subject to different societal and cultural norms and expectations that might lead to behavioural sex differences. One way to eliminate sex-differentiated socialization as a confound is to examine brain differences among individuals of the same sex. Individuals vary in genetic predispositions as well as exposure and sensitivity to gonadal hormones: some men will develop a more female-like brain, while other men an exaggeratedly male-like brain (and conversely, for women).

Such an approach has recently been applied successfully by predicting sex based on differences in the structural connectome, i.e. how the brain is wired. Using a large imaging dataset of the Philadelphia Neurodevelopmental Cohort (N=900) (Tunç et al., 2016), a weak but significant association was found between sex predictor scores based on the structural connectome and those based on motor and cognitive test performance. Using the same

dataset, Philips et al. (2019) constructed a ‘sex differentiation score’ from several other brain structure measures – surface area, volume, thickness, and diffusion measures, which correlated in the expected direction with externalizing symptoms within males but not within females; predicted correlations with internalizing symptoms were not significant in either sex. However, the question remains whether such association between brain and behavioural sex predictor scores exist once we control for brain size on a regional level – that is, to take into account that different brain regions scale differently with brain size.

In this paper, we obtained a measure of brain differences along a male-female dimension based on sex differences in brain shape and structure, while adjusting for brain size on a regional level. Next, we derived a composite measure of behavioural differences along a male-female dimension from sex differences in behaviour, and tested whether individual differences along a male-female dimension for brain and behaviour were correlated (within sex). Lastly, we used the classical twin design to estimate the extent to which these individual differences in brain and behaviour can be explained by genetic and environmental influences.

Methods

Participants

We analysed two large independent imaging datasets to obtain a measure of brain differences along a male-female dimension, and to test the relationship between individual differences along a male-female dimension for brain and behaviour.. Both datasets were drawn from the general population. The first consisted of 1,040 individuals from 616 families as part of the Queensland Twin IMaging (QTIM) study (ages 15 to 30 years, mean age of 22.42 ± 3.33, 64.81% female), including 157 identical (monozygotic; MZ) twin pairs, 261 nonidentical (dizygotic; DZ) twin pairs and their siblings. Behavioural measures were

collected as part of the Brisbane Longitudinal Twin Study (Gillespie et al., 2013), also known as the Brisbane Adolescent Twin Study (Wright & Martin, 2004). In addition, a sub-sample of 40 individuals (mean age = 23.36 ± 2.27, 55% female) was scanned a second time within three months. Diffusion tensor imaging scans were available for 460 individuals (ages 16.85 to 29.16 years, mean age of 22.20 ± 2.71, 63.10% female) after excluding 36 individuals, including 26 due to incidental findings of potential clinical relevance and 10 due to poor scan quality. Individuals with developmental, neurological, or psychiatric disorders, impaired intellectual functioning, or head trauma were excluded. Only right-handed twins were recruited in the study. All individuals gave written informed consent. Ethics approval for the study was given by the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute, University of Queensland, and UnitingCare Health.

The second dataset was provided as part of the Human Connectome Project (HCP) (Van Essen et al., 2012), and comprised 1,113 (left and right-handed) individuals (ages 22 to 37 years, mean age of 28.80 ± 3.70, 54.40% female) from 428 families, including 129 MZ, 72 DZ twin pairs, and their siblings. In addition, 46 individuals were scanned a second time (mean age of 30.29 ± 3.34, 68.89% female). Diffusion tensor imaging scans were available for 972 individuals (ages 22 to 37 years, mean age of 28.73 ± 3.70, 53.60% female). Test-retest diffusion scans were available for 41 individuals (mean age of 30.46 ± 3.15, 70.73% female). Individuals with severe neurodevelopmental disorders, documented neuropsychiatric disorders, neurologic disorders, diabetes, high blood pressure, or those born premature were excluded. All individuals gave written informed consent. Ethics approval was given by the institutional review board.

Image acquisition

For the QTIM dataset, structural MRI scans were obtained at 4-Tesla (Siemens Bruker), acquiring a 3D structural T1-weighted image (T1/TR/TE = 700/1500/3.35 ms; flip angle = 8°, voxel size = 0.9375 × 0.9375 × 0.9 mm^3). 81% with a coronal acquisition, 19% with a sagittal acquisition. The test-retest sample included only participants scanned with a coronal acquisition on both occasions. Diffusion-weighted images were also collected (TR/TE= 6090/91.7 ms, number of slices= 55, voxel size = 1.79 x 1.79 x 2 mm^3, 94 directions with b = 1159 s/mm^2 and 11 b = 0 images).

For the HCP dataset, structural MRI scans were obtained at 3-Tesla (Siemens Connectome Skyra), acquiring a 3D structural T1-weighted image (T1/TR/TE = 1000/2400/2.14 ms; flip angle = 8°, slice thickness = 0.7 mm, voxel size = 0.70 x 0.70 x 0.70 mm^3). Diffusion-weighted images were also collected (TR/TE= 5520/89.5 ms, number of slices = 111, voxel size = 1.25 x 1.25 x 1.25 mm^3, 90 directions with b = 1000/2000/3000 s/mm^2 and 6 b=0 images).

Image preprocessing

All structural scans were preprocessed to remove signal inhomogeneity using the Statistical Parametric Mapping (SPM) (Friston et al., 1995) version 12 software package in Matlab version R2018a. Scans were not registered to common template space to avoid distortions in the shape of the brain structures. Using the FMRIB Software Library (FSL) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) software package, diffusion-weighted images were corrected for eddy current distortions, a brain mask was applied, and the images were registered to the structural scan. For more details, see Jahanshad et al. (2011) for the QTIM dataset, and Glasser et al. (2013) for the HCP dataset.

Obtaining a measure of brain differences along a male-female dimension

Using two different approaches, we obtained a measure of individual differences along a male-female dimension based on sex differences in brain shape (using the landmark-approach) or structure (using the vertex-wise approach).

The landmark approach: A measure derived from brain shape

For the landmark approach, we developed and placed subcortical landmarks, and placed existing cortical landmarks (called Dense Individualized and Common Connectivity-based Cortical Landmarks; DICCCOLs (Zhu et al., 2013)) (**Fig. 1**). The initial landmark approach included landmarks placed in both subcortical and cortical regions using the T1-weighted scan only. Landmarks were placed on a mask on the standard template (MNI152 1mm) in FSL's FSLVIEW (Jenkinson et al., 2012) to serve as an example for automatic placement. Automatic placement to each individual scan was done using SPM's function 'normalize'. While visually inspecting the landmarks, the placement of landmarks in cortical regions showed too much error using the method described above, so all cortical landmarks were excluded.

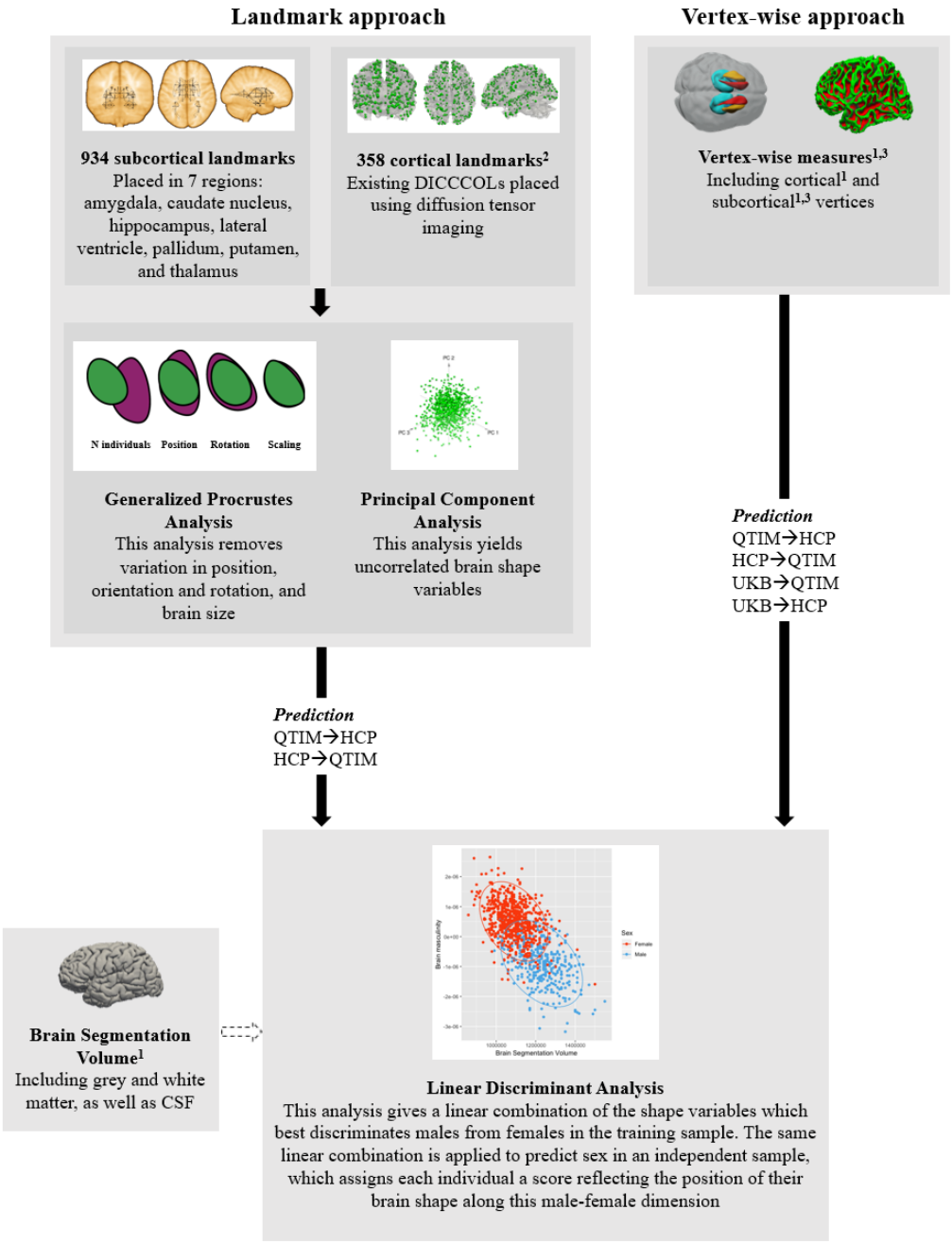

Fig. 1.

The different stages to obtain a measure of brain differences along a male-female dimension, either derived from the landmark or vertex-wise approach; brain size was used as a crude proxy for comparison.

[1] From FreeSurfer; [2] From Ou et al. (2015); [3] From the ENIGMA Shape protocol; Abbreviations: DICCCOLs=Dense Individualized and Common Connectivity-based Cortical Landmarks; CSF=CerebroSpinal Fluid; UKB= UK Biobank; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project.

This process resulted in 467 subcortical landmarks per hemisphere (934 in total) placed in seven subcortical regions: amygdala, caudate nucleus, hippocampus, lateral ventricle, pallidum, putamen, and thalamus (Supplementary Fig. 1). We visually inspected the placement of the 934 landmarks for ten individuals each to confirm the accuracy of the placement method. Next, the 3D coordinates of the landmarks were extracted for each landmark. On a rare occasion, landmarks were not transformed to native space, which led to missing data. Missing data (0.035% of the data points) was imputed with the R statistics package 'Geomorph' TPG option.

In addition, we included 358 existing cortical landmarks (DICCCOLs) based on diffusion-weighted images (Zhu et al., 2013). These data-driven cortical landmarks are placed by using consistent white-matter fiber connection patterns derived from diffusion tensor imaging data. Fibers were extracted using the software package medInria for the QTIM dataset and MRtrix for the HCP dataset, using an FA threshold of 0.2 and a minimum length of 20. We then placed the cortical landmarks by using the DICCCOL toolbox[1], and we extracted the 3D coordinates for each landmark.

Then, we brought the landmark coordinates from each individual into standard space by applying a Generalized Procrustes Analysis, which removes variation in size, position, orientation, and rotation of the brains (Supplementary Fig. 2). During this process a Principal Component Analysis was also performed (**Fig. 1)**, rotating the data into uncorrelated components, using the R statistics package 'Shapes'. We ran this analysis separately for the cortical and subcortical landmarks, because the cortical landmarks were extracted from diffusion space while the subcortical landmarks were extracted in native (individual) T1-space. These analyses were performed while scaling for brain size in the Procrustes Analysis, to obtain a measure of brain shape independent of brain size.

[1] https://www.nitrc.org/projects/dicccol_0_1

Next, the first 52 principal components, with an eigenvalue larger than or equal to one, from both Procrustes Analyses were used as predictors for the variable 'sex'. We used the package 'MASS' in R statistics version 3.4.4 (R Core Team, 2018) to perform a linear discriminant analysis (LDA) (**Fig. 1**), which gives a linear combination of the shape variables that best discriminates males from females, and assigns each individual a score reflecting the position of their brain shape along this male-female dimension.

The vertex-wise approach: A measure derived from brain structure

For the QTIM dataset, the program FreeSurfer version 5.3 (Fischl, 2012) was used to segment the brain from the structural T1-weighted scan, and to extract the vertex-wise measures for thickness and surface area (**Fig. 1**). For the HCP dataset, the processed images were downloaded. This segmentation also yielded a measure of brain size, i.e. Brain Segmentation Volume (BSV), which includes grey and white matter and cerebrospinal fluid[2]. For processing in FreeSurfer, all individuals' brain images were transformed to the FreeSurfer template. Then, the ENIGMA Shape pipeline[3] was run to extract vertex-wise measures for deep grey matter volume as well (**Fig. 1**). For both the FreeSurfer and shape segmentation, we performed a detailed post-processing quality check in line with procedures used by the ENIGMA consortium[4]. Next, FreeSurfer's cortical and subcortical vertex-wise measures were included to predict sex to obtain a measure of brain differences along a male-female dimension derived from brain structure (**Fig. 1**).

Using the software package OSCA[5] (a tool for omic-data-based complex trait analysis) (Zhang et al., 2019), we predicted the participants' sex using Best Linear Unbiased Prediction (BLUP) scores, which allow handling the large number of vertex-wise

[2] https://surfer.nmr.mgh.harvard.edu/fswiki/MorphometryStats
[3] http://enigma.ini.usc.edu/ongoing/enigma-shape-analysis/
[4] http://enigma.ini.usc.edu/protocols/imaging-protocols/
[5] http://cnsgenomics.com/software/osca/#Overview

measurements. BLUP scores are powerful and efficient predictors, which do not require hyper-parameter estimation (Robinson, 1991), unlike other machine learning algorithms (e.g. SVM or penalised regression). In practice, BLUP scores constrain the weights given to the vertices to follow a normal distribution (Robinson, 1991). To improve the prediction accuracy, our BLUP scores were trained on the first 9,888 participants of the UK Biobank who underwent MRI imaging (Miller et al., 2016) and had usable cortical and subcortical data from processed T1-weighted and T2-FLAIR MRI images (Couvy-Duchesne et al., 2019). The UK Biobank participants were aged between 44.6 and 79.6 (mean age of 62.60, SD=7.5), and 52.40% of the sample were female (Couvy-Duchesne et al., 2019).

For the vertex-wise measure, we included three different approaches to obtain a measure of brain differences along a male-female dimension. Most importantly, as brain regions scale differently with brain size, we used an allometric scaling approach, adjusting the vertex-wise measures for brain size on a regional (vertex by vertex) level. For this we applied a log-log regression – regressing out brain size (brain segmentation volume; BSV) for each vertex by using the logs for brain size and the respective vertex, and using the residuals of the vertices in the next analyses. For comparison, we regressed out brain size from the uncorrected prediction scores (instead of for each vertex as in the allometric approach). As another alternative, we only regressed out brain size differences associated with sex from the vertex-wise measures before predicting sex, to ensure sex differences in brain size were not driving the prediction accuracy.

Obtaining a measure of behavioural differences along a male-female dimension

In a similar way to the derivation of our brain measures, we derived a measure of individual differences in behaviour along a male-female dimension by using the behavioural variables to predict sex in an LDA. Behavioural data comprised of a variety of measures

including physical measures (e.g. body mass index, blood pressure), measures of intelligence (e.g. total, verbal and performance intelligence), neurocognitive subtests (e.g. vocabulary, working memory, and visuospatial skills), and other measures (e.g. personality traits, anxiety and depression symptoms).

Unlike the brain imaging data, the behavioural variables were different in the QTIM and HCP samples (Supplementary Table 4) – therefore, we divided each sample and trained the prediction in one half before predicting in the other half. For this we used the package 'MASS' in R statistics version 3.4.4 (R Core Team, 2018). Note that this approach excluded data for several behavioural measures and individuals to deal with missing values: We removed behavioural variables with scores for less than 75% of the individuals, resulting in 12 of 27 variables for QTIM and 26 of 26 measures for HCP retained in the prediction. Participants with missing values on one of the behavioural variables could not receive a prediction score (QTIM=324; HCP=69), resulting in including 1760 of the 2153 individuals in the analyses.

Genetic analyses

For our genetic analysis, up to two siblings per family were included and half siblings were excluded. We used a saturated univariate ACE model in the R package OpenMx (Boker et al., 2011) to examine how much of the variation in brain size, as well as the individual differences along a male-female dimension for brain and behaviour can be explained by genetic (A), common environmental (C), and residual effects including idiosyncratic environmental factors and measurement error (E), adjusting for sex and age. This model relies on the principle that MZ twins are genetically identical, while DZ twins share approximately half of their segregating genes. Non-twin siblings were added to the classical twin design to improve statistical power.

We also tested the assumptions for twin modelling. These include 1) testing a mean and variance difference between the first and second twin; 2) testing a mean and variance difference between MZ and DZ (same-sex) twin pairs within females and within males; 3) testing a mean and variance difference between male MZ and DZ groups and female MZ and DZ groups; 4) testing a mean and variance difference between females and males. We also examined whether we could identify sex-limitation (which would indicate that the magnitude of the genetic effect differs between the sexes, or that different genes in males and females affect the expression of the phenotype), while including sex and age as covariates in the model. All twin modelling assumptions were met, and no significant sex-limitation (i.e. different influences on males and females) was found (except for brain size, for which variances were greater in males than females). Therefore, only one mean and one variance were estimated in the ACE-model (and two variances were estimated for brain size) as well as two covariances (MZ versus DZ twins), while a sex effect was modelled to account for differences in means. We performed the above analyses for all measures of brain differences along a male-female dimension, as well as brain size and the measure of behavioural differences along a male-female dimension.

Next, using a bivariate Cholesky decomposition model (including sex and age as covariates), we examined the influence of genetic and environmental influences on the covariance between individual differences along a male-female dimension for brain and behaviour as well as brain size and behavioural differences along a male-female dimension. As we found robust associations between brain differences along a male-female dimension with both brain size and height, we also examined these variables for a common genetic and environmental factor. Due to the excellent prediction of sex when using the vertex-wise measure, the moderate-to-strong correlation between the brain measures with one another, and the similar heritability results for the different brain measures, only the brain measure

derived from the vertex-wise approach (trained on the UK Biobank dataset) was used for this analysis.

Results

Obtaining a measure of brain differences along a male-female dimension

Using data from either the landmark or the vertex-wise approaches, we trained the algorithm to predict sex based on brain shape or structure, and predicted sex in an independent imaging sample, to derive a score for each individual reflecting the position of their brain shape or structure along a male-female dimension (**Fig. 1**). Both the landmark and vertex-wise approaches yielded scores that differed substantially (though with considerable overlap) between the sexes, as expected (Supplementary Figure 3, Panel B-H). Brain size also showed a comparable difference in female and male distributions (Supplementary Figure 3, Panel A). Although the landmark-approach already scaled the brains to the same size, it is possible that brain shape covaries with brain size. If this were the case, then the brain measures based only on shape (i.e. brain size-controlled) may still contain brain size information. To derive a brain measure that is independent of brain size, we also used an allometric scaling approach to adjust for brain size (BSV) on a regional (vertex-wise) level. Specifically, we regressed out brain size for each vertex within each sex and used the residuals of the vertices in the prediction. This adjustment for brain size yielded a brain measure that showed more overlap between males and females than the vertex-wise measure where only brain size differences associated with sex were removed (Supplementary Figure 3, Panel H), but the measure could still accurately discriminate between the sexes (d =1.01 (0.88; 1.14); red lines in **Fig.2**). We found similar results when regressing out brain size from the uncorrected prediction scores (orange lines in **Fig.2;** Supplementary Figure 3, Panel G).

Validity and reliability of the brain measures

Brain measures based on both approaches showed good-to-excellent test-retest reliability (Supplementary Table 1), defined as the correlation between the brain scores from both time points. The validity (i.e. to what extent the measure could predict sex in an independent sample) was measured with the Area Under the Curve (AUC) – defined by the true positive rate against the false positive rate – using the 'pROC' package. The AUC is, unlike accuracy, insensitive to class imbalance. Both approaches predicted sex well (**Fig. 2**; Supplementary Table 1) – as reflected in the "good-to-excellent" AUC – and the prediction was often better when brain size was not filtered out (Supplementary Table 1).

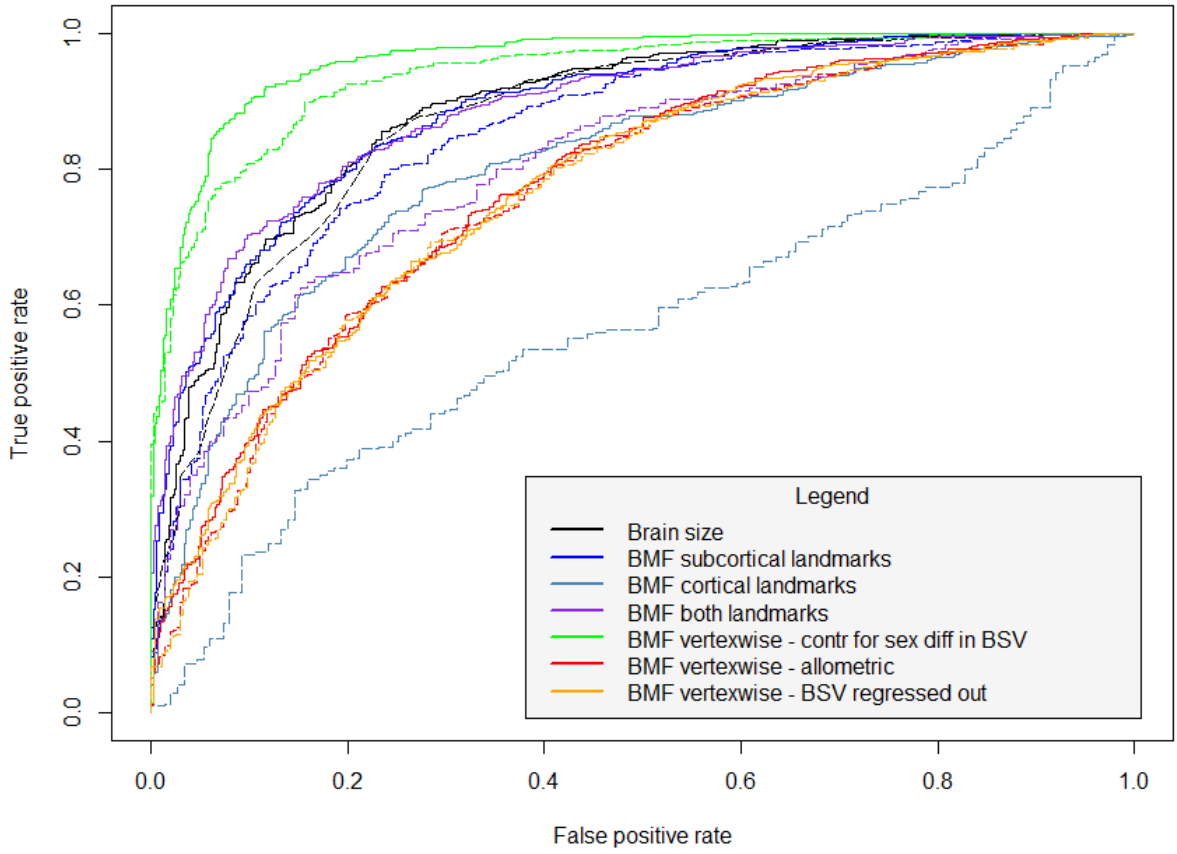

Fig. 2.

Predicting sex based on the brain data, using two approaches (landmark and vertex-wise), as well as brain size as a crude proxy for comparison. The landmark approach includes the subcortical, cortical, and both subcortical and cortical landmarks. The vertex-wise approach includes scores controlled for brain size (BSV) by 1) regressing out brain size differences associated with sex, 2) applying allometric scaling, or 3) regressing out brain size from the uncorrected scores. Predictions of sex in the QTIM sample are displayed with a dashed line, and predictions for HCP are displayed with a solid line. BSV=Brain Segmentation Volume (measure of brain size). BMF=Brain differences along a male-female dimension; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; UKB=UK Biobank.

Comparing the two approaches, the landmark approach (including the subcortical, or both subcortical and cortical landmarks) resulted in a more accurate prediction than the vertex-wise approach once controlling for brain size (Supplementary Table 1 B2 and B4 versus B5), until we trained the vertex-wise model on the large UK Biobank dataset (N=9,888), which improved the prediction markedly (green lines in **Fig. 2**; Supplementary Table 1 A2). However, in both datasets, once we applied an allometric scaling approach to adjust for brain size (red lines in **Fig. 2**; Supplementary Table 1 A3), the prediction worsened and was no longer better than when using the landmark approach - results were similar when we regressed out brain size from the uncorrected vertex-wise scores (orange lines in **Fig. 2**).

Further, the prediction based only on cortical landmarks was not significantly better than chance when predicting from the QTIM (N=1,040) to the HCP (N=1,113) dataset, and *vice versa* (**Fig. 2**; Supplementary Table 1 B3), or when dividing the QTIM dataset in two halves (Supplementary Table 1 C3). In contrast, when dividing the HCP dataset in two halves, the cortical landmarks were predictive of sex (Supplementary Table 1 D3). Due to the poor predictive power of the QTIM cortical landmarks in comparison to the HCP cortical landmarks, only the prediction scores derived from cortical landmarks for the HCP dataset were included for further analysis. The poor performance of the QTIM cortical landmarks prediction may be explained by the poorer resolution and lower signal-to-noise ratio of the diffusion scans of the QTIM dataset compared to the HCP dataset, which may have led to more error in landmark placement. For all further analyses, outliers (z-scores ± 3.29) were winsorized within each sex.

Correlations among brain measures

Brain measures derived from the landmark and vertex-wise approaches were associated with one another (**Table 1**), after adjusting for sex, age, and scanning acquisition

in the total sample. The vertex-wise scores for which brain size is regressed out of the uncorrected prediction scores showed high overlap with the allometric scores ($r = 0.999$, $p \leq 0.001$), and were therefore excluded from further analyses. As expected, brain measures were associated with brain size across samples ($p \leq 0.001$) (**Table 1**), even after adjusting the brain measures for brain size (by scaling brains to the same size, or by regressing out BSV). This association raised the question of whether sex differences in brain size may still be confounding the brain measures, i.e. the prediction of sex. To further examine this possibility, we used two subsamples where female and male brains were matched for brain size (maximum of 10 ml difference in BSV) (QTIM, N=262; HCP, N=372) (for more details see van Eijk et al., 2020). The association between brain measures and brain size remained in both subsamples where males and females are matched for brain size (Supplementary Table 2). This finding shows that our prediction of sex (and resulting brain measures) are not driven by potential confounding sex differences in brain size, and provides additional evidence for the scaling relationship between brain differences along a male-female dimension and brain size.

Table 1.

Correlation matrix for the measures of brain differences along a male-female dimension (BMF) controlled for covariates (sex, age, and scan acquisition), displaying correlations for the QTIM dataset in the lower triangle (grey), and for the HCP dataset in the upper triangle. Measures were derived from the landmark (subcortical, cortical, and both landmarks) and vertex-wise (controlled for sex differences in brain size (BSV), and allometric brain size-corrected) approaches, as well as from brain size as a crude proxy for comparison.

	BMF (subcortical)	**BMF (cortical)**	**BMF (subc+ cort)**	**BMF (vertex-wise contr for sex diff in BSV)**	**BMF (vertex-wise allometric)**	**Brain size**
BMF (subcortical landmarks)		0.242**	0.686**	0.227**	0.116**	0.110**
BMF (cortical landmarks)	0.114*		0.278**	0.208**	-0.097*	0.322**
BMF (subc+cort landmarks)	0.535**	0.271**		0.210**	0.045	0.178**
BMF (vertex-wise contr for sex diff in BSV)	0.222**	0.041	0.084		0.531**	0.491**
BMF (vertex-wise allometric)	0.072*	-0.062	0.039	0.664**		-0.452**
Brain size	0.173**	0.149**	0.065	0.370**	-0.389**	

Brain Segmentation Volume is used as a measure of brain size. As the prediction of sex using brain measures derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis. BMF=Brain differences along a male-female dimension; subc=subcortical; cort=cortical; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project.
* $p \leq 0.05$. ** $p \leq 0.001$

Association between sex differences in brain and behaviour

We tested for a link between sex differences in brain and behaviour by computing a composite score of brain differences along a male-female dimension and testing its

association with a score of behavioural differences along a male-female dimension. This follows a similar approach to that of Tunç et al. (2016). Further, we examined the associations between the brain scores with specific behavioural measures.

Association between brain and behavioural scores

Prediction of individuals' sex based on behavioural measures (Supplementary Table 3) yielded a good AUC (74.94-78.89%). After combining both samples and adjusting for sex, age, and a dummy variable for study (QTIM/HCP), the resulting behavioural score correlated significantly with the brain scores derived from the landmark and vertex-wise approaches (with the exception of the measure based only on cortical landmarks) (**Table 2**). We also tested the same correlations within each sex – these tests have lower power (due to the split sample), but would reveal if the brain-behaviour association was markedly different in each sex (**Table 2**). Statistical significance was inconsistent across methods, but the point estimates were small and positive. For the vertex-wise measure we found a significant correlation within both sexes, with effect sizes similar to those found by Tunç et al. (2016) (within females: $r = 0.129$ (95% CI: 0.068; 0.188), $p \leq 0.001$; within males: $r = 0.137$ (95% CI: 0.065; 0.207), $p \leq 0.001$). Note that brain size itself showed a stronger association with the behavioural score than any of the shape-based brain scores ($r = 0.162$ (95% CI: 0.116; 0.207), $p \leq 0.001$). After controlling for brain size the association between brain and behavioural scores was no longer significant (**Table 2**), while the association remained significant when adjusting for body size (height) instead of brain size, in the total sample and within males (though the effect became smaller) (r = 0.066 (95% CI: 0.018; 0.114), p = 0.007; females r=0.034 (95% CI: -0.029; 0.096), p =0.294; males r= 0.105 (95% CI: 0.031; 0.178), p =0.006).

Association between the brain scores with behavioural measures

Next, we aimed to gain more insight into whether and how the brain scores are associated with specific physical and behavioural measures. We also examined associations within each sex, under the hypothesis that we would find a similar correlation within each sex. As we found an association between the brain scores with brain size (**Table 1**), brain size may possibly confound the correlations between the brain scores with behavioural traits, which is why we adjusted correlations for brain size, as well as sex and age.

The brain scores showed only very weak associations with physical and behavioural measures regardless of the approach used (Supplementary Table 6-14), and not always in the direction of the sex effect found for these measures (Supplementary Table 5). One association that remained across samples and across the different brain measures (except the allometric approach) was the association between the brain scores with height (r = 0.064 to 0.203) (Supplementary Table 6-14). However, no association showed a trend ($p \leq 0.05$) in both the total sample and within-sex analyses and was consistent across the different brain measures (Supplementary Table 6-14). As a comparison, brain size showed more and stronger associations with behavioural measures (r = 0.059 to 0.243, $p \leq 0.05$; Supplementary Table 17-18) than did any of the brain scores (r = 0.059 to -0.207, $p \leq 0.05$; Supplementary Table 6-14). After adjusting the brain scores for body size (height) instead of brain size (Supplementary Table 12-13 right panel), several associations remained for the brain measures with physical and behavioural measures (Supplementary Table 15-16) –suggesting that the associations are driven by brain size more so than body size.

Table 2.

Association between measures of brain and behavioural differences along a male-female dimension – adjusted for sex, age, and study (first panel), or sex, age, study, and brain size (BSV) (second panel).

Brain measures derived from:	**total**					**within females**					**within males**				
	r	*CI*	*t*	*dfs*	*p*	*r*	*CI*	*t*	*dfs*	*p*	*r*	*CI*	*t*	*dfs*	*p*
Brain size	0.162	0.116; 0.207	6.869	1758	<0.001	0.145	0.085; 0.204	4.718	1033	<0.001	0.181	0.109; 0.250	4.943	723	<0.001
Subcortical landmarks	0.060	0.013; 0.106	2.510	1758	0.012	0.014	-0.047; 0.075	0.453	1033	0.651	0.119	0.046; 0.190	3.218	723	0.001
Cortical landmarks[1]	0.044	-0.019; 0.107	1.361	953	0.174	0.017	-0.070; 0.104	0.383	506	0.702	0.077	-0.016; 0.168	1.6020	445	0.106
Both subcortical and cortical landmarks[1]	0.073	0.009; 0.135	2.247	953	0.025	0.044	-0.043; 0.131	0.993	506	0.321	0.108	0.016; 0.199	2.300	445	0.022
Vertex-wise controlled for sex differences in BSV	0.132	0.090; 0.178	5.580	1758	<0.001	0.129	0.068; 0.188	4.165	1033	<0.001	0.137	0.065; 0.207	3.711	723	<0.001
Adjusted for brain size															
Subcortical landmarks[r]	0.040	-0.007; 0.086	1.652	1758	0.100	-0.005	-0.066; 0.056	-0.159	1033	0.873	0.097	0.024; 0.169	2.618	723	0.009
Cortical landmarks[1,r]	-0.017	-0.081; 0.046	-0.549	953	0.583	-0.027	-0.114; 0.060	-0.605	506	0.545	-0.001	-0.094; 0.092	-0.020	445	0.984
Both subcortical and cortical landmarks[1,r]	0.037	-0.026; 0.1000	1.144	953	0.253	0.022	-0.065; 0.109	0.500	506	0.618	0.057	-0.036; 0.149	1.200	445	0.231
Vertex-wise allometric[a]	-0.004	-0.051; 0.043	-0.165	1736	0.869	0.009	-0.052; 0.070	0.288	1023	0.773	-0.020	-0.094; 0.053	-0.544	711	0.586

[1] Based on HCP cohort only, including 972 of 1113 individuals of the HCP cohort due to diffusion data not being available for 89 subjects with a behavioural score.
r=Pearson correlation; CI=95% confidence interval; *t*=*t*-statistic; *dfs*= degrees of freedom; *p*=*p*-value; Brain Segmentation Volume (BSV) is used as a measure of brain size.
[r] BSV was regressed out of the brain scores before testing the correlation with the behavioural score, [a] BSV was regressed out of the brain data before deriving a brain score on a (vertex) regional level using an allometric scaling approach.

Genetic analyses

In both datasets and all brain measures, intra-class correlation in MZ twin pairs was greater than in DZ twin pairs or non-twin siblings, which suggests the influence of genetic effects (Supplementary Table 19-21). Consistent with previous work (Rentería et al., 2014), brain size was highly heritable (Supplementary Table 22): 86-92% of the variation in brain size could be explained by genetic influences (A), 0-7% by shared environmental influences (C), and 7-8% by residual effects (E), which include idiosyncratic environmental factors and measurement error. In contrast, the brain measures showed more modest heritability: depending on the measure used, 33-50% of the variance could be explained by genetic influences, 0-10% by shared environmental influences, and 40-67% by residual effects (Supplementary Table 22). The behavioural measure was also moderately heritable: 32-51% of the variation in the behavioural measure could be explained by genetic influences, 0-6% by shared environmental influences, and 43-68% by residual effects (Supplementary Table 22). Results were similar when excluding opposite-sex twin or sibling pairs (Supplementary Table 23).

Next, we examined the extent to which common genetic, shared environmental, or residual factors underlie the association of brain and behavioural differences along a male-female dimension, brain size, and height, and of brain size with height. As there was no evidence for shared environmental influence, we used a bivariate model with an AE-model. To improve the power of our analyses, we combined the two samples. Our analyses showed a genetic correlation between brain and behavioural measures (combined r_g = .296; within females r_g = .220; within males r_g = .409) when deriving the brain measure from the vertex-wise scores (for which brain size differences associated with sex were removed). However, this correlation was no longer significant when using the vertex-wise allometric scores, suggesting brain size may be driving this correlation. In line with this possibility, we found a

similar genetic correlation between brain size and the behavioural measure (combined r_g = .261; within females r_g = .208; within males r_g = .333), and we found a genetic correlation between brain size and the brain measure (combined r_g = .566; within females r_g = .526; within males r_g = .602) when deriving the brain score from the vertex-wise scores (for which brain size differences associated with sex were removed), and also when using the allometric approach (removing all brain size differences) though the association became negative (combined r_g = -.571; within females r_g = -.640; within males r_g = -.455).

Further, we found a genetic correlation between the brain measures with height (combined r_g = .162; within females r_g = .128; within males r_g = .145), but only for the vertex-wise scores (for which brain size differences associated with sex were removed) and not for the vertex-wise allometric scores. In comparison, brain size showed a similar genetic correlation with height (combined r_g = .195; within females r_g = .147; within males r_g = .205).

Discussion

We investigated whether sex differences in brain structure are associated with sex differences in behaviour within sex, thereby circumventing the confound of different socialization of females and males. We obtained a data-driven measure of brain differences along a male-female dimension (derived from sex differences in brain shape and structure) and behavioural differences along a male-female dimension (derived from sex differences in behaviour), while adjusting brain measures for brain size using an allometric scaling approach. Our key finding is that there is a small positive association between sex differences in brain and behaviour, but that association disappears when we take into account differences in brain size.

Previous research (Phillips et al., 2019; Tunç et al., 2016) showed some (mixed) evidence of an association between brain and behavioural differences along a male-female

dimension, but ours uses two independent samples (total sample size more than double as Tunç (2016) and Phillips (2019)) and two different methods for deriving the brain measures, and carefully considers whether brain size may drive the brain-behaviour association. It is possible brain size could drive the association between brain and behaviour found previously, as the previous two studies (Phillips et al., 2019; Tunç et al., 2016) did not adjust (all) brain measures for brain size, and did not apply an allometric approach to consider that different brain regions scale differently to brain size. As a consequence, their brain data could still contain shape differences that are associated with the original size differences, and their score reflecting brain differences along a male-female dimension could be driven by these size differences.

Our findings are consistent with this possibility. First, we showed that the brain measures were substantially correlated with brain size in the total sample and within each sex, even though all brains were scaled to the same size from the start. This is consistent with the concept of allometry, i.e. that a structure's shape is not independent of its size. Larger brains tend to have a different shape from those of smaller brains, for example showing more folding on average. Second, we found an association between individual differences in brain and behaviour similar to that previously reported by Tunç (2016), but once we applied an allometric approach, adjusting for brain size on a regional (vertex-by-vertex) level, the correlation between brain and behaviour disappeared. Our results suggest that any previous findings of a relationship between sex differences in brain structure and behaviour may have been driven by brain size.

The brain measures were associated with both physical and behavioural variables (although possibly driven by brain size differences), which implies that brain and behavioural sex differences may be subject to the same underlying processes of masculinization without being directly causally related. This possibility is strengthened by the correlation of the brain

measures with height, as there is no obvious reason to suspect that brain differences along a male-female dimension and height are causally related. Further, although it is well established that brain size is functionally relevant – for example, it is correlated at around 0.24-0.33 with IQ after adjusting for differences in body size (Goriounova & Mansvelder, 2019) – its relation to the nexus of brain and behavioural sex differences is less clear. Van der Linden et al. (2017) found that brain size partially mediated the small sex difference in IQ in the HPC sample (which also forms part of our sample) – but many studies find a negligible sex difference in IQ, and when van der Linden et al. (2017) used male and female samples matched on IQ, males still had larger brains. This finding raises the possibility that there are sex differences in brain structure that compensate for size differences between the sexes. On the one hand, it could be that some sex differences in brain structure are compensatory and make female and male behaviour more similar despite different average brain sizes. On the other hand, other sex differences in brain structure may result in adaptive behavioural sex differences and, due to joint hormonal mediation, also covary with brain size. We are not able to resolve these complexities here. Also, the weakness of the associations suggests that sex differences in brain structure are among many other factors related to sex differences in behaviour.

We also estimated the heritability of brain and behavioural differences along a male-female dimension. Using twin modelling, we estimated that variance in the brain and behavioural measures can be attributed in roughly similar proportions to genetic (32-50%) and unshared environmental (40-68%) influences. Phillips et al. (2019) estimated the heritability of sex-differentiated brain structure at 0-1.5% using single nucleotide polymorphism (SNP) data. SNP heritability estimates are extremely imprecise in samples of that size (N=900), and in any case SNPs typically do not capture most of the total heritability of complex traits (Wainschtein et al., 2019). Twin studies like ours estimate a trait's total

heritability. As for behaviour, our heritability estimates were in line with those of a previous twin study using a different method with different data (Verweij, Mosing, Ullen, & Madison, 2016).

This project has some limitations. Most importantly, our research does not imply that no association could exist between behaviour and sex differences in regional (as opposed to global) brain structure, microstructure, or brain function, all of which our study is silent on. Second, the range of sexually dimorphic behaviours we analysed was limited by the measures that happened to have been collected in the QTIM and HCP studies, and they may not be the most sensitive to detect sex differences in behaviour compared to more sexually differentiated behavioural traits. However, our prediction performance was similar to that previously reported by Tunç (2016). In addition, several behavioural measures in the QTIM dataset were obtained at a different time to when the imaging scans were acquired. Further, it is unclear to what degree the sex differences from which our measures are derived are influenced by genetic factors (e.g. number of X chromosomes, the presence of a Y chromosome, and mitochondrial DNA inheritance (Pearse & Young-Pearse, 2019)) as well as sex hormone levels. In addition, despite our efforts to remove the confound of socialisation between females and males by looking at within-sex differences, our measures may capture environmental differences among females and among males beyond those based on biology.

Future research with even larger samples and richer brain and behavioural measures, and a longitudinal study design, will further elucidate the biological and social influences on brain and behavioural sex differences. Such an approach will help to answer questions such as at what stage(s) across the lifespan sex hormones play the most prominent role in influencing brain and behaviour, and whether specific sex hormones have distinct influences on brain and behaviour. It will also provide insights into the directionality of the association

between sex differences in brain and behaviour, and shed light on the distinction between biological sex and gender differences.

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Conflicts of interest

None. Paul M. Thompson received grant funding from Biogen, Inc. (Boston, USA) for research unrelated to this manuscript.

Data Availability

The QTIM dataset used in this manuscript is available through the following link: https://doi.org/10.14264/38dde15. Access to the HCP dataset needs to be requested through the Human Connectome Project team.

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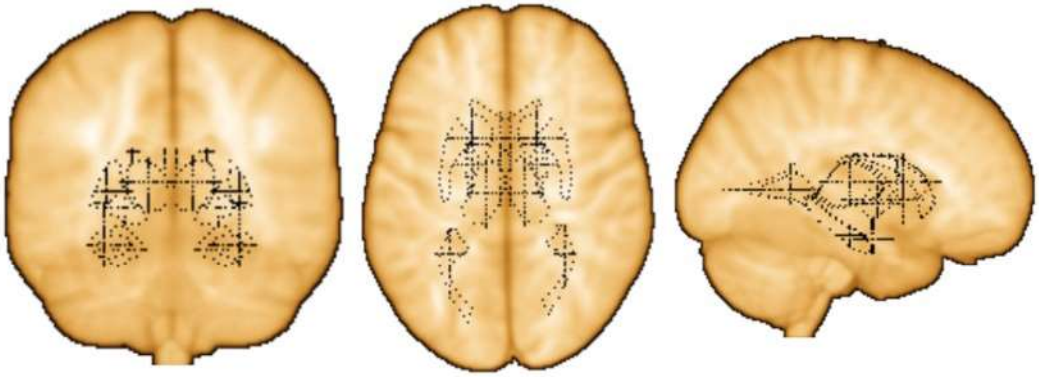
Supplementary Information for:

Psychological Science

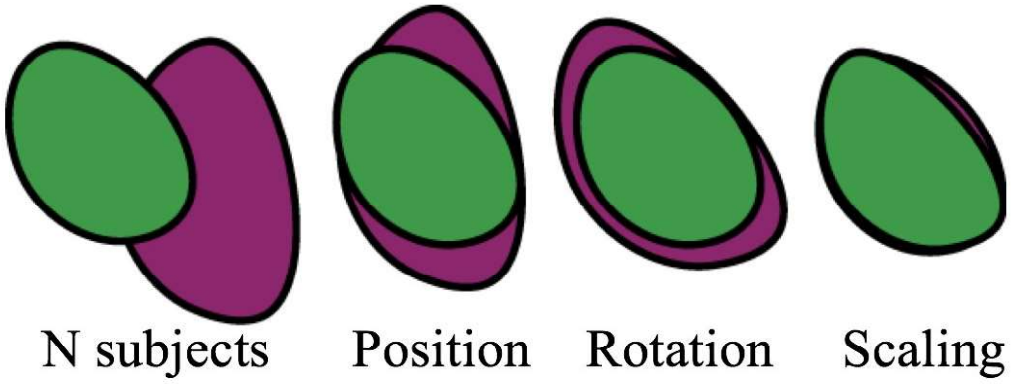
Are sex differences in human brain structure associated with sex differences in behaviour?

Contents:

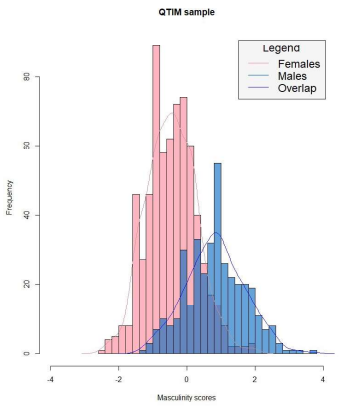
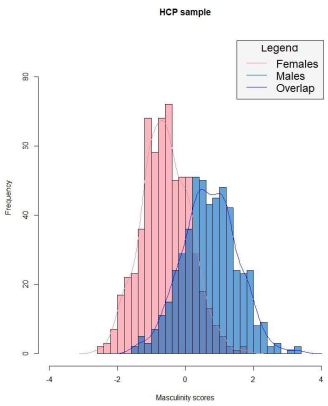
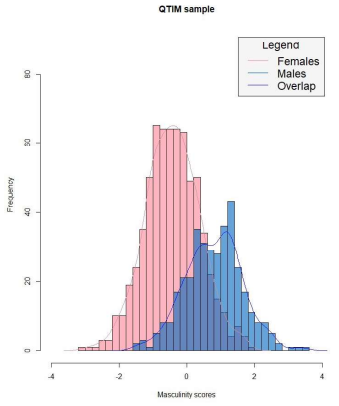
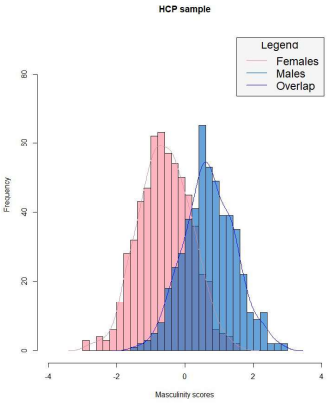
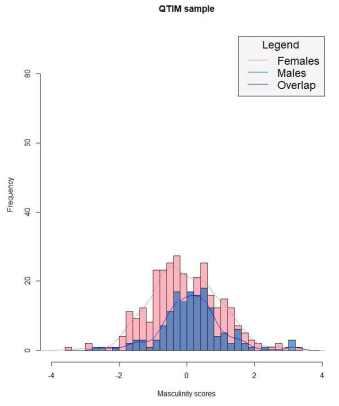
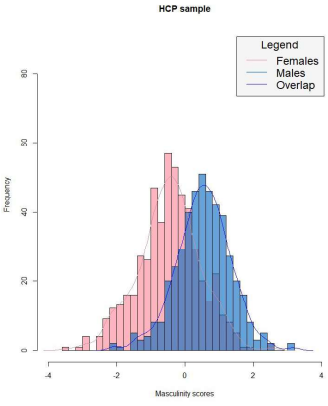
Supplementary Figures

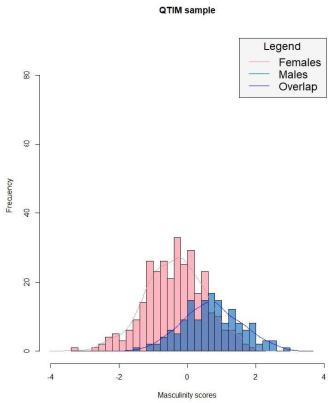
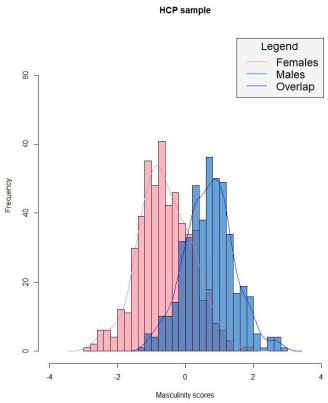
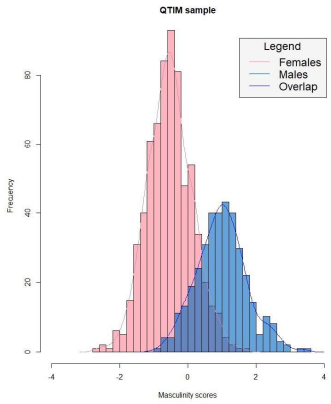
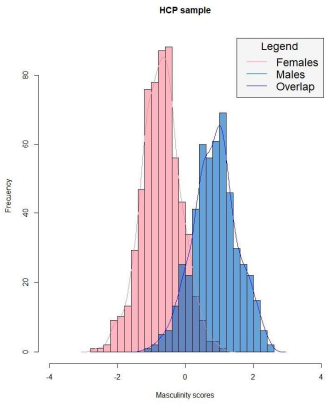
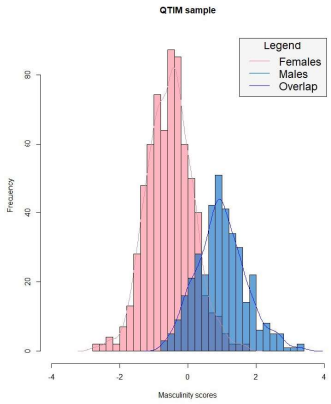
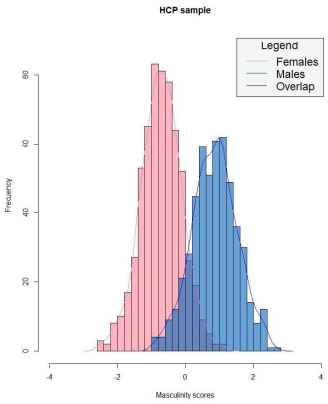


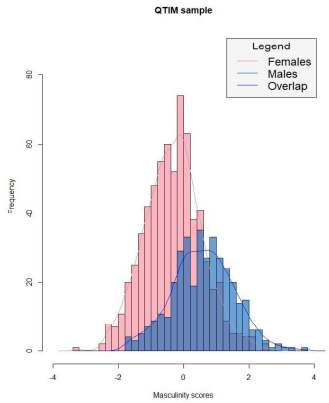
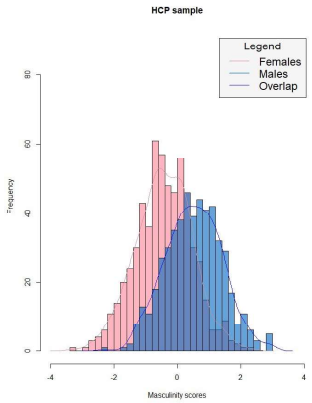
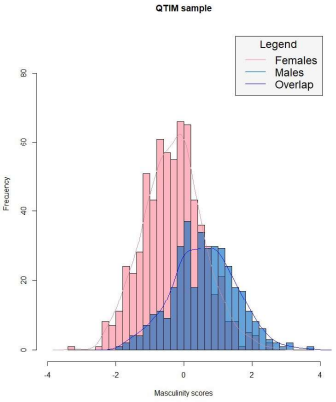
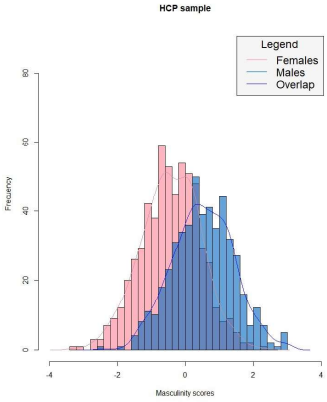
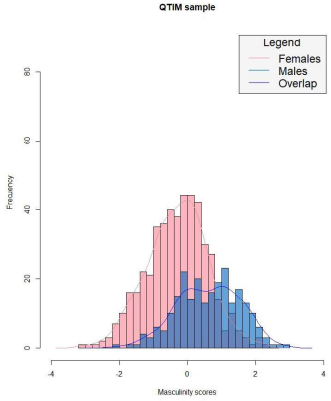
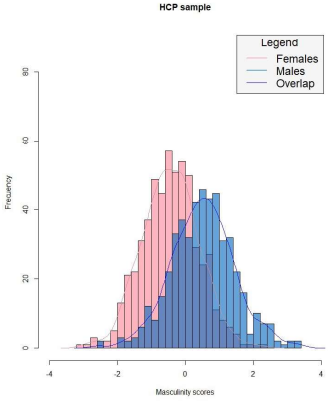
Supplementary Fig. 1.
Subcortical landmarks placed on the standard template (MNI152) brain. 467 subcortical landmarks per hemisphere were placed in seven subcortical regions: amygdala, caudate nucleus, hippocampus, lateral ventricle, pallidum, putamen, and thalamus



Supplementary Fig. 2.
Generalized Procrustes Analysis, removing variation in position, orientation and rotation, and brain size

	QTIM	HCP
A) Brain size[1]		
	d = 1.64 (1.50; 1.79)	*d* = 1.71 (1.57; 1.84)
B) Subcortical landmarks[1]		
	d = 1.49 (1.35; 1.63)	*d* = 1.70 (1.56; 1.84)
C) Cortical landmarks[1]		
	d = 0.21 (0.01; 0.40)	*d* = 1.16 (1.02; 1.29)

D) Both subcortical and cortical landmarks[1]		
	d = 1.20 (0.99; 1.41)	*d* = 1.71 (1.56; 1.86)
E) Brain structure (Uncorrected Vertex-wise)[2]		
	d = 2.23 (2.07; 2.39)	*d* = 2.59 (2.43; 2.75)
F) Brain structure (Vertex-wise controlled for sex differences in BSV)[2]		
	d = 2.18 (2.02; 2.34)	*d* = 2.51 (2.36; 2.67)

G) Brain structure (Vertex-wise BSV regressed out)[2]		
	d = 1.00 (0.87; 1.14)	*d* = 1.06 (0.93; 1.18)
H) Brain structure (Vertex-wise allometric scaling)[2,3]		
	d = 1.01 (0.88; 1.14)	*d* = 1.07 (0.94; 1.20)
I) Behaviour		
	d = 1.01 (0.85; 1.18)	*d* = 1.08 (0.95; 1.22)

Supplementary Fig. 3.
Distribution of the scores for males and females, derived from brain size, brain differences along a male-female dimension (derived from subcortical landmarks, cortical landmarks, subcortical and cortical landmarks, vertex-wise measures, or vertex-wise measures with allometric scaling applied), as well as behavioural differences along a male-female dimension.
Females are displayed in pink, males are displayed in light blue. Overlap is displayed in blue. *d* corresponds to Cohen's *d* measuring the standardized differences between male and female means. [1]Deriving from the QTIM dataset and predicting in the HCP dataset, or vice versa, deriving from HCP and predicting in QTIM. . [2]For the FS measures, we derived the function from the UK Biobank dataset while predicting in the QTIM and HCP datasets [3]We regionally corrected for brain size (brain segmentation volume) by using an allometric scaling approach. QTIM= Queensland Twin IMaging; HCP= Human Connectome Project.

Supplementary Tables

Supplementary Table 1.
Reliability and validity of the measure: Results of the prediction of sex based on brain size, shape and/or structure, and the test-retest reliability for the different brain measures.

Brain measure based on:	Test-retest reliability[1]		Prediction[2]		Prediction filtering out brain size[2]	
	QTIM	***HCP***	***UKBio***[5] ↓ ***QTIM***	***UKBio***[5] ↓ ***HCP***	***UKBio***[5] ↓ ***QTIM***	***UKBio***[5] ↓ ***HCP***
A1) Brain size	0.992**	0.998**	87.34% (85.11-89.57)	88.46% (86.51-90.41)	NA	NA
A2) Brain structure (Vertex-wise)	0.933**	0.998**	94.06% (92.67-95.45)	96.46% (95.50-97.42)	93.91% (92.52-95.30)	96.13% (95.12-97.13)
A3) Brain structure (Vertex-wise allometric scaling)	0.849**	0.882**	NA	NA	76.30% (73.26-79.34)	77.41% (74.66-80.16)
	QTIM	***HCP***	***QTIM***[3] ↓ ***HCP***	***HCP***[3] ↓ ***QTIM***	***QTIM***[3] ↓ ***HCP***	***HCP***[3] ↓ ***QTIM***
B1) Brain size	0.992**	0.998**	88.46% (86.51-90.41)	87.34% (85.11-89.57)	NA	NA
B2) Brain shape (Subcortical landmarks)	0.955**	1.000**	95.30% (94.15-96.46)	94.81% (93.55-96.07)	87.01% (84.95-89.06)	85.69% (83.33-88.05)
B3) Brain shape (Cortical landmarks)	No TRT	1.000**	49.28% (45.37-53.19)	53.16% (44.81-61.52)	50.81% (46.91-54.71)	51.93% (43.56-60.30)
B4) Brain shape (Subcortical and Cortical landmarks)	(combo)	(combo)	93.89% (92.27-95.52)	72.26% (67.43-77.08)	83.79% (81.26-86.33)	61.71% (56.28-67.13)
B5) Brain structure (Vertex-wise)	0.933**	0.998**	94.99% (93.80-96.17)	94.23% (92.86-95.59)	70.00% (66.96-73.05)	67.87% (64.46-71.27)

	split-half within sample (both directions)			
	QTIM[4] ↓ ***QTIM***	***QTIM***[4] ↓ ***QTIM***	***QTIM***[4] ↓ ***QTIM***	***QTIM***[4] ↓ ***QTIM***
C1) Brain size	87.06% (83.85-90.28)	87.69% (84.62-90.77)	NA	NA
C2) Brain shape (Subcortical landmarks)	94.00% (92.00-96.00)	94.71% (92.95-96.47)	85.44% (82.02-88.85)	86.30% (83.20-89.41)
C3) Brain shape (Cortical landmarks)	56.18% (47.88-64.40)	58.04% (50.67-65.42)	56.01% (47.69-64.33)	56.63% (49.21-64.04)
C4) Brain shape (Subcortical and Cortical landmarks)	86.59% (81.51-91.67)	87.71% (83.46-91.96)	79.58% (73.14-86.02)	75.85% (69.68-82.03)
	HCP[4] ↓ ***HCP***	***HCP***[4] ↓ ***HCP***	***HCP***[4] ↓ ***HCP***	***HCP***[4] ↓ ***HCP***
D1) Brain size	87.05% (84.10-90.00)	89.89% (87.35-92.43)	NA	NA
D2) Brain shape (Subcortical landmarks)	95.26% (93.59-96.93)	97.33% (96.30-98.35)	88.38% (85.65-91.10)	89.39% (86.84-91.93)
D3) Brain shape (Cortical landmarks)	76.15% (71.91-80.39)	74.41% (70.05-78.76)	75.46% (71.17-79.74)	73.94% (69.54-78.34)
D4) Brain shape (Subcortical and Cortical landmarks)	95.12% (93.38-96.87)	96.50% (95.15-97.85)	88.75% (85.88-91.63)	89.05% (86.26-91.83)

[1]The reliability for the measure was investigated in a test-retest subset, using a Pearson correlation between the brain scores from both time points.[2]Prediction displayed as the Area Under the Curve (AUC) (95% confidence interval). Sex was predicted based on deriving the function from one sample while predicting in another independent sample. [3]Deriving from the QTIM dataset and predicting in the HCP dataset, or vice versa, deriving from HCP and predicting in QTIM. [4]Deriving from the first half of the HCP dataset and predicting in the second half or vice versa. [5]For the FS measures, we also derived the function from the UK Biobank dataset while predicting in the QTIM and HCP datasets, in addition, we regionally corrected for brain size (BSV) by using an allometric scaling approach. TRT=test-retest diffusion sample; combo=combination; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; BSV=Brain Segmentation Volume

***p<.001.*

Supplementary Table 2.
Correlation matrix for the measures of brain differences along a male-female dimension (BMF) controlled for covariates (sex, age, and scan acquisition) in the matched subsamples where males and females are matched on brain size, displaying correlations for the QTIM subsample (N=262) in the lower triangle (grey), and for the HCP subsample (N=372) in the upper triangle.
Measures were derived from the landmark (subcortical, cortical, and both landmarks) and vertex-wise (controlled for sex differences in BSV, and allometric BSV-corrected) approaches, as well as from brain size as a crude proxy for comparison.

	BM (subcortical)	**BM (cortical)**	**BM (subc+ cort)**	**BM (vertex-wise contr for sex diff in BSV)**	**BM (vertex-wise allometric)**	**Brain size**
BM (subcortical landmarks)		0.227**	0.715**	0.209**	0.124**	0.137*
BM (cortical landmarks)	0.142		0.287**	0.151*	-0.042	0.277**
BM (subc+cort landmarks)	0.472**	0.291**		0.095	0.136*	0.095
BM (vertex-wise contr for sex diff in BSV)	0.197**	0.003	0.026		0.701**	0.370**
BM (vertex-wise allometric)	0.032	0.010	0.100	0.775**		-0.354**
Brain size	0.158*	-0.020	-0.159	0.213**	-0.376**	

Brain Segmentation Volume is used as a measure of brain size. As the prediction of sex using the brain measure derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis. BMF=Brain differences along a male-female dimension; subc=subcortical; cort=cortical; QTIM=Queensland Twin Imaging; HCP=Human Connectome Project.
* $p<.05$. ** $p<.001$

Supplementary Table 3.
Behavioural prediction: Prediction of biological sex derived from behavioural measures, displaying the Area Under the Curve with its 95% confidence interval.

	First half of sample	*Second half of sample*
QTIM sample	77.56% (72.33-82.79)	74.94% (69.55-80.33)
HCP sample	78.89% (74.99-82.78)	77.51% (73.53-81.49)

QTIM=Queensland Twin Imaging; HCP=Human Connectome Project.
Note: In order for the prediction to work, behavioural measures with data for less than 75% of the participants were removed from training the prediction model (resulting in 12 measures for QTIM and 26 measures for HCP to be included in the prediction), and participants with missing values on one of the measures could not receive a prediction score (QTIM NA=324; HCP NA=69).

Supplementary Table 4.
Overview of physical and behavioural measures: Physical and behavioural measures of interest in the QTIM and HCP dataset.

QTIM	*HCP*
Physical	
Brain size (Brain Segmentation Volume)	Brain size (Brain Segmentation Volume)
Body Height	Body Height
Body Mass Index	Body Mass Index
Blood Pressure Diastolic	Blood Pressure Diastolic
Blood Pressure Systolic	Blood Pressure Systolic
Dexterity	Grip Strength
	Endurance
	Gait Speed
	Dexterity
Intelligence Quotient (IQ)	
Verbal IQ (Multidimensional Aptitude Battery II)	Crystallized IQ (NIH Toolbox)
Performance IQ (Multidimensional Aptitude Battery II)	Fluid IQ (NIH Toolbox)
Full IQ (Multidimensional Aptitude Battery II)	Total Cognition (NIH Toolbox)
Neurocognition	
Verbal Fluency	
Vocabulary (Multidimensional Aptitude Battery II) Schonell Graded Word Reading Test National Australian Reading Test (NART)	Picture Vocabulary (NIHT) Reading English (NIHT)
Matrix Reasoning (WAIS)	Penn Matrix Test (PMAT24)
Arithmetic (Multidimensional Aptitude Battery II)	Math task during fMRI language task
Object Assembly (Multidimensional Aptitude Battery II)	
Spatial Rotation (Multidimensional Aptitude Battery II)	Spatial Orientation (Variable Short Penn Line Orientation Test)
Information (Multidimensional Aptitude Battery II)	Verbal Episodic Memory (Penn Word Memory Test) Episodic Memory (Picture Sequence Memory)
Digit Span backwards (WAIS) Letter Number Sequencing (WAIS)	Working Memory (List sorting) Executive Function/Cognitive Flexibility (Dimensional Change Card Sort)
Processing Speed (Digit Symbols)/Digit span forwards	Processing Speed (NIH Pattern Comparison Processing Speed Test)
	Emotion Recognition (Penn Emotion Recognition Test)
	Social Task (Perc rated as Theory of Mind) (fMRI)
Other	
Personality Traits (NEO Five Factor Inventory)	Personality Traits (NEO Five Factor Inventory)
Anxiety Symptoms (N1 ‘Anxiety’ of the NEO Five Factor Inventory)	Anxiety Symptoms (Achenbach Adult Self Report; DSM-Oriented Scale)
Physical Aggression (N2 ‘Angry Hostility’ of the NEO Five Factor Inventory)	Anger-Hostility (NIHT) Anger-Aggression (NIHT)
Depression Symptoms (SPHERE-34; N3 ‘Depression’ of the NEO Five Factor Inventory)	Depression Symptoms (DSM-Oriented Scale)
	Perceived Stress (NIH Perceived Stress

	Survey)
Autism Spectrum Traits (Autism Spectrum Quotient)	

QTIM=Queensland Twin Imaging; HCP=Human Connectome Project; NART=National Australian Reading Test; DSM=Diagnostic and Statistical Manual of mental disorders; NIH=National Institute of Health; WAIS=Wechsler Adult Intelligence Scale; PMAT24=Penn Matrix Test; IQ=intelligence quotient; fMRI=functional magnetic resonance imaging.

Supplementary Table 5.
Sex effect for physical and behavioural measures for the QTIM dataset, adjusted for age.

Variable	*Sex effect larger in*	*d*	*t*	*p*	R^2	*N*
Brain size (BSV)	M	1.677	-25.825	<.001	0.385	1040
Height	M	2.024	-29.076	<.001	0.481	915
Body Mass Index	M	0.343	-4.928	<.001	0.025	911
Diastolic blood pressure	N	0.143	NONE	NS	0.004	285
Systolic blood pressure	M	0.529	-4.084	<.001	0.055	285
Dexterity	N	-0.212	NONE	NS	0.011	166
Verbal IQ (MAB)	M	0.488	-7.405	<.001	0.052	1011
Performance IQ (MAB)	M	0.290	-4.398	<.001	0.019	1011
Full-scale IQ (MAB)	M	0.430	-6.522	<.001	0.041	1010
Verbal fluency	F	-0.275	2.314	0.021	0.016	331
Vocabulary (MAB)	M	0.176	-2.666	0.008	0.007	1011
National Adult Reading Test	M	0.204	-2.907	0.004	0.009	893
Schonell Reading Test	M	0.196	-2.805	0.005	0.009	894
Matrix Reasoning (WAIS)	N	0.163	NONE	NS	0.006	331
Arithmetic (MAB)	M	0.454	-6.886	<.001	0.045	1011
Object assembly (MAB)	M	0.178	-2.704	0.007	0.007	1011
Spatial (MAB)	M	0.296	-4.496	<.001	0.020	1012
Information (MAB)	M	0.473	-7.181	<.001	0.049	1011
Digit span forwards (WAIS)	N	0.007	NONE	NS	<0.001	331
Digit span backwards (WAIS)	N	0.151	NONE	NS	0.005	331
Letter-number sequencing (WAIS)	M	0.367	-3.090	0.002	0.028	331
Digit symbol (WAIS)	F	-0.718	10.762	<.001	0.102	990
Neuroticism	F	-0.739	5.684	<.001	0.109	268
Extraversion	F	-0.494	3.805	<.001	0.052	268
Openness	F	-0.665	5.120	<.001	0.090	268
Conscientiousness	N	-0.239	NONE	NS	0.013	268
Agreeableness	F	-0.619	4.764	<.001	0.079	268
Neuroticism scale 1 (Anxiety)	F	-0.878	6.760	<.001	0.147	268
Neuroticism scale 2 (Anger hostility)	F	-0.383	2.947	0.003	0.032	268
Neuroticism scale 3 (Depression)	F	-0.296	2.276	0.024	0.019	268
SPHERE (anxiety depression-score)	F	-0.298	4.068	<.001	0.020	834
Autism spectrum quotient	N	0.102	NONE	NS	0.002	249

QTIM=Queensland Twin Imaging; F=Females; M=Males; N=None; NS= not significant (p>0.05); BSV=Brain Segmentation Volume; IQ=Intelligent Quotient; MAB=Multidimensional Aptitude Battery; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; d=Cohen's *d*; *t*=*t*-statistic; *p*=*p*-value; R^2=proportion of the variance in the physical or behavioural measure that can be explained by the variable sex; N=number of individuals.

Supplementary Table 6.
Sex effect for physical and behavioural measures for the HCP dataset, adjusted for age.

Variable	*Sex effect larger in*	*d*	*t*	*p*	R^2	*N*
Brain size (BSV)	M	1.581	-27.387	<.001	0.412	1113
Height	M	1.892	-32.998	<.001	0.514	1112
Body Mass Index	M	0.147	-2.511	0.012	0.006	1112
Diastolic blood pressure	M	0.356	-6.035	<.001	0.034	1099
Systolic blood pressure	M	0.623	-10.568	<.001	0.097	1099
Grip strength	M	2.093	-36.708	<.001	0.572	1112
Endurance	M	0.626	-10.682	<.001	0.098	1111
Gait speed	N	-0.023	NONE	NS	<0.001	1113
Dexterity	F	-0.452	7.716	<.001	0.054	1113
Crystallized IQ (NIHT)	M	0.246	-4.191	<.001	0.016	1110
Fluid IQ (NIHT)	N	0.084	NONE	NS	0.002	1110
Total Cognition (Full-scale IQ) (NIHT)	M	0.171	-2.908	0.004	0.008	1110
Picture Vocabulary (NIHT)	M	0.238	-4.054	<.001	0.015	1113
Reading English (NIHT)	M	0.211	-3.598	<.001	0.012	1113
Penn Matrix Test	M	0.207	-3.517	<.001	0.012	1104
Math accuracy	M	0.344	-5.711	<.001	0.032	1054
Spatial orientation (VSPLOT)	M	0.404	-6.873	<.001	0.043	1105
Penn Word Memory	F	-0.209	3.559	<.001	0.012	1105
Picture sequence memory (NIHT)	F	-0.277	4.722	<.001	0.021	1112
List sorting (NIHT)	M	0.154	-2.629	0.009	0.006	1113
Card sorting (NIHT)	M	0.126	-2.140	0.033	0.004	1111
Processing speed (NIHT)	N	0.013	NONE	NS	<0.001	1113
Penn Emotion recognition	F	-0.120	2.038	0.042	0.004	1105
Social task	M	0.265	-4.389	<.001	0.019	1054
Neuroticism	F	-0.234	3.978	<.001	0.015	1106
Extraversion	N	-0.014	NONE	NS	<0.001	1106
Openness	M	0.138	-2.349	0.019	0.005	1106
Conscientiousness	F	-0.198	3.366	0.001	0.011	1106
Agreeableness	F	-0.391	6.655	<.001	0.040	1106
Anger-Hostility (NIHT)	N	0.059	NONE	NS	0.001	1112
Anger-Aggression (NIHT)	M	0.463	-7.901	<.001	0.055	1112
DSM Depression	N	-0.089	NONE	NS	0.002	1105
ASR Anxiety	N	-0.096	NONE	NS	0.003	1105
DSM Anxiety	F	-0.272	4.617	<.001	0.020	1105
Perceived stress	N	-0.111	NONE	NS	0.003	1112

HCP=Human Connectome Project; F=Females; M=Males; N=None; NS= not significant (p>0.05); ASR=Achenbach Adult Self-Report; BSV=Brain Segmentation Volume; DSM=Diagnostic and Statistical Manual of mental disorders; NIHT=National Institute of Health Toolbox; VSPLOT=visuospatial line orientation test; IQ=intelligence quotient; d=Cohen's *d*; *t*=*t*-statistic; *p*=*p*-value; R^2=proportion of the variance in the physical or behavioural measure that can be explained by the variable sex; N=number of individuals.

Supplementary Table 7.
Correlation between brain differences along a male-female dimension (based on subcortical landmarks) and physical and behavioural measures for the QTIM dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.175**√	0.171**√	0.176**√	1040	NA	NA	NA
Height	0.110**√	0.104*√	0.122*√	915	0.074*√	0.071√	0.081√
Body Mass Index	-0.011X	0.001√	-0.035X	911	-0.012X	-0.006X	-0.027X
Diastolic blood pressure	-0.026	-0.019	-0.040	285	-0.027	-0.037	-0.019
Systolic blood pressure	-0.010X	-0.064X	0.103√	285	-0.015X	-0.085X	0.121√
Dexterity	0.095	0.074	0.113	166	0.096	0.084	0.106
Verbal IQ (MAB)	0.094*√	0.047√	0.164*√	1011	0.064*√	0.018√	0.136*√
Performanc e IQ (MAB)	0.011√	-0.008X	0.037√	1011	-0.021X	-0.038X	0.005√
Full-scale IQ (MAB)	0.054√	0.017√	0.110*√	1010	0.020√	-0.016X	0.077√
Verbal fluency	0.095X	0.097X	0.089X	331	0.056X	0.038X	0.106X
Vocabulary (MAB)	0.056√	-0.005X	0.154*√	1011	0.035√	-0.018X	0.123*√
National Adult Reading Test	0.047√	-0.008X	0.136*√	893	0.026√	-0.022X	0.109√
Schonell Reading Test	0.057√	0.015√	0.142*√	894	0.038√	0.001√	0.118*√
Matrix Reasoning (WAIS)	0.040	0.044	0.026	331	0.036	0.020	0.068
Arithmetic (MAB)	0.056√	0.031√	0.090√	1011	0.030√	0.005√	0.066√
Object assembly (MAB)	0.028√	0.028√	0.026√	1011	-0.003X	<0.001	-0.009X
Spatial (MAB)	-0.008X	-0.045X	0.050√	1012	-0.034X	-0.071X	0.025√
Information (MAB)	0.087*√	0.053√	0.138*√	1011	0.062*√	0.025√	0.120*√
Digit span forwards (WAIS)	-0.035	0.054	-0.208*	331	-0.025	0.062	-0.198*
Digit span	0.055	0.141*	-0.075	331	0.040	0.133*	-0.097

backwards (WAIS)							
Letter-number sequencing (WAIS)	0.003√	0.093√	-0.153X	331	-0.011X	0.074√	-0.156X
Digit symbol (WAIS)	-0.029√	-0.040√	-0.013√	990	-0.046√	-0.056√	-0.030√
Neuroticism	0.026X	0.067X	-0.045√	268	0.025X	0.057X	-0.051√
Extraversion	0.029X	0.047X	-0.001√	268	0.039X	0.062X	-0.009√
Openness	-0.002√	0.045X	-0.084√	268	0.001X	0.048X	-0.089√
Conscientiousness	-0.067	-0.090	-0.032	268	-0.064	-0.088	-0.038
Agreeableness	-0.090√	-0.116√	-0.051√	268	-0.083√	-0.107√	-0.059√
Neuroticism scale 1 (Anxiety)	0.029X	0.095X	-0.096√	268	0.028X	0.090X	-0.097√
Neuroticism scale 2 (Anger hostility)	0.026X	-0.011√	0.115X	268	0.024X	-0.025√	0.110X
Neuroticism scale 3 (Depression)	0.070X	0.141X	-0.078√	268	0.070X	0.136X	-0.083√
SPHERE (anxiety depression-score)	0.012X	0.028X	-0.021√	834	0.011X	0.031X	-0.027√
Autism spectrum quotient	0.042	-0.028	0.169	249	0.057	0.001	0.164

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. QTIM=Queensland Twin IMaging; BSV=Brain Segmentation Volume; MAB=Multidimensional Aptitude Battery II; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; IQ=intelligence quotient; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 8.
Correlation between brain differences along a male-female dimension (based on subcortical landmarks) and physical and behavioural measures for the HCP dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.113**√	0.090*√	0.136*√	1113	NA	NA	NA
Height	0.131**√	0.097*√	0.170**√	1112	0.107**√	0.082*√	0.135*√
Body Mass Index	0.002√	0.040√	-0.058X	1112	0.005√	0.048√	-0.066X
Diastolic blood pressure	0.023√	0.014√	0.034√	1099	0.036√	0.029√	0.044√
Systolic blood pressure	0.021√	0.037√	0.003√	1099	0.028√	0.045√	0.008√
Grip strength	0.035√	0.046√	0.025√	1112	0.023√	0.044√	0.002√
Endurance	-0.040X	-0.040X	-0.039X	1111	-0.055X	-0.052X	-0.058X
Gait speed	0.001	0.031	-0.034	1113	-0.005	0.027	-0.043
Dexterity	-0.058√	-0.005√	-0.125*√	1113	-0.066*√	-0.010√	-0.136*√
Crystallized IQ (NIHT)	-0.005X	-0.065X	0.061√	1110	-0.034X	-0.090*X	0.030√
Fluid IQ (NIHT)	0.099**	0.059	0.143*	1110	0.081*	0.043	0.124*
Total Cognition (Full-scale IQ) (NIHT)	0.073*√	0.017√	0.137*√	1110	0.048√	-0.006X	0.110*√
Picture Vocabulary (NIHT)	-0.014X	-0.064X	0.043√	1113	-0.041X	-0.086*X	0.012√
Reading English (NIHT)	0.001√	-0.055X	0.062√	1113	-0.025X	-0.079X	0.035√
Penn Matrix Test	0.039√	0.036√	0.043√	1104	0.012√	0.017√	0.005√
Math accuracy	-0.008X	-0.018X	0.002√	1054	-0.038X	-0.041X	-0.035X
Spatial orientation (VSPLOT)	0.044√	0.014√	0.079√	1105	0.022√	-0.001X	0.051√
Penn Word Memory	-0.048√	-0.063√	-0.031√	1105	-0.056√	-0.071√	-0.037√
Picture sequence memory (NIHT)	0.072*X	0.067X	0.078X	1112	0.062*X	0.060X	0.065X
List sorting	0.095*√	0.082*√	0.108*√	1113	0.079*√	0.070√	0.089*√

(NIHT)							
Card sorting (NIHT)	0.063*√	0.035√	0.094*√	1111	0.051√	0.025√	0.083√
Processing speed (NIHT)	0.045	-0.020	0.117*	1113	0.036	-0.029	0.109*
Penn Emotion recognition	0.032X	0.023X	0.041X	1105	0.024X	0.014X	0.035X
Social task	0.005√	-0.042X	0.059√	1054	0.001√	-0.041X	0.050√
Neuroticism	-0.033√	0.003X	-0.073√	1106	-0.030√	0.004X	-0.066√
Extraversion	-0.021	-0.061	0.027	1106	-0.025	-0.067	0.025
Openness	-0.025X	-0.040X	-0.010X	1106	-0.033X	-0.046X	-0.020X
Conscientiousness	-0.021√	-0.015√	-0.028√	1106	-0.013√	-0.011√	-0.014√
Agreeableness	-0.004√	-0.008√	0.002X	1106	-0.006√	-0.015√	0.005X
Anger-Hostility (NIHT)	-0.051	-0.039	-0.067	1112	-0.048	-0.037	-0.062
Anger-Aggression (NIHT)	-0.019X	-0.041X	0.004√	1112	-0.016X	-0.040X	0.010√
DSM Depression	0.011	0.040	-0.024	1105	0.011	0.036	-0.018
ASR Anxiety	-0.020	-0.005	-0.038	1105	-0.021	-0.009	-0.033
DSM Anxiety	-0.043√	-0.034√	-0.056√	1105	-0.038√	-0.030√	-0.049√
Perceived stress	-0.065*	-0.039	-0.096*	1112	-0.059	-0.038	-0.082

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 9.
Correlation between brain differences along a male-female dimension (based on cortical landmarks) and physical and behavioural measures for the HCP dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.314**√	0.322**√	0.310**√	972	NA	NA	NA
Height	0.064*√	0.036√	0.100*√	971	-0.011X	-0.021X	0.008√
Body Mass Index	-0.017X	-0.015X	-0.019X	971	-0.011X	0.011√	-0.039X
Diastolic blood pressure	-0.075*X	-0.053X	-0.105*X	960	-0.048X	-0.011X	-0.092X
Systolic blood pressure	-0.081*X	-0.040X	-0.135*X	960	-0.069*X	-0.026X	-0.126*X
Grip strength	-0.025X	-0.085X	0.024√	971	-0.068*X	-0.099*X	-0.038X
Endurance	0.002√	0.034√	-0.029X	971	-0.037X	-0.003X	-0.072X
Gait speed	0.095*	0.099*	0.091	972	0.083*	0.085	0.079
Dexterity	0.101*X	0.139*X	0.048X	972	0.085*X	0.120*X	0.035X
Crystallized IQ (NIHT)	0.128**√	0.152**√	0.095*√	969	0.066*√	0.084√	0.038√
Fluid IQ (NIHT)	0.095*	0.102*	0.085	969	0.052	0.046	0.056
Total Cognition (Full-scale IQ) (NIHT)	0.128**√	0.143*√	0.107*√	969	0.069*√	0.072√	0.060√
Picture Vocabulary (NIHT)	0.128**√	0.151**√	0.094*√	972	0.071*√	0.093*√	0.038√
Reading English (NIHT)	0.112**√	0.124*√	0.094*√	972	0.054√	0.058√	0.045√
Penn Matrix Test	0.128**√	0.130*√	0.127*√	969	0.061√	0.065√	0.054√
Math accuracy	0.067*√	0.040√	0.104*√	963	-0.008X	-0.028X	0.021√
Spatial orientation (VSPLOT)	0.044√	0.044√	0.042√	970	-0.013X	-0.009X	-0.020X
Penn Word Memory	-0.024√	-0.018√	-0.031√	970	-0.047√	-0.047√	-0.050√
Picture sequence memory (NIHT)	0.072*X	0.087*X	0.055X	971	0.052X	0.065X	0.036X
List sorting (NIHT)	0.088*√	0.055√	0.128*√	972	0.045√	0.009√	0.091√

Card sorting (NIHT)	0.030	0.022	0.040	970	0.005	-0.018	0.030
Processing speed (NIHT)	0.053	0.089*	0.012	972	0.035	0.062	-0.001
Penn Emotion recognition	0.055X	0.094*X	0.004X	970	0.035X	0.066X	-0.006√
Social task	0.047√	0.026√	0.074√	964	0.042√	0.035√	0.055√
Neuroticism	-0.039√	-0.028√	-0.053√	971	-0.025√	-0.026√	-0.029√
Extraversion	-0.038	-0.054	-0.015	971	-0.052	-0.079	-0.020
Openness	0.026√	-0.013X	0.075√	971	0.003√	-0.029X	0.047√
Conscientiousness	-0.035√	-0.039√	-0.029√	971	-0.018√	-0.037√	0.003X
Agreeableness	0.002X	-0.020√	0.032X	971	-0.003√	-0.044√	0.044X
Anger-Hostility (NIHT)	-0.003	0.022	-0.037	971	0.003	0.026	-0.030
Anger-Aggression (NIHT)	-0.026X	0.003√	-0.060X	971	-0.028X	-0.002X	-0.062X
DSM Depression	0.014	-0.005	0.036	970	0.007	-0.021	0.040
ASR Anxiety	-0.009	-0.025	0.011	970	-0.017	-0.046	0.015
DSM Anxiety	-0.048√	-0.061√	-0.030√	970	-0.038√	-0.052√	-0.019√
Perceived stress	-0.017	0.023	-0.071	971	-0.003	0.021	-0.040

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 10.
Correlation between brain differences along a male-female dimension (based on all landmarks) and physical and behavioural measures for the HCP dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.187**√	0.167**√	0.215**√	972	NA	NA	NA
Height	0.112**√	0.049√	0.182**√	971	0.070*√	0.021√	0.125*√
Body Mass Index	-0.013X	0.059√	-0.130*X	971	-0.009X	0.074√	-0.146*X
Diastolic blood pressure	0.001√	0.025√	-0.028X	960	0.019√	0.048√	-0.016X
Systolic blood pressure	-0.017X	0.026√	-0.074X	960	-0.008X	0.035√	-0.065X
Grip strength	0.013√	0.019√	0.012√	971	-0.011X	0.015√	-0.030X
Endurance	0.008√	<0.001	0.012√	971	-0.015X	-0.019X	-0.016X
Gait speed	0.018	0.021	0.014	972	0.008	0.012	0.003
Dexterity	-0.015√	<0.001	-0.032√	972	-0.027√	-0.013√	-0.044√
Crystallized IQ (NIHT)	0.027√	0.009√	0.057√	969	-0.014X	-0.031X	0.016√
Fluid IQ (NIHT)	0.054	0.054	0.056	969	0.027	0.024	0.034
Total Cognition (Full-scale IQ) (NIHT)	0.053√	0.045√	0.068√	969	0.015√	0.005√	0.034√
Picture Vocabulary (NIHT)	<0.001	-0.024X	0.037√	972	-0.038X	-0.06X	-0.003X
Reading English (NIHT)	0.045√	0.041√	0.055√	972	0.008√	0.005√	0.020√
Penn Matrix Test	0.068*√	0.081√	0.051√	969	0.026√	0.048√	-0.003X
Math accuracy	0.057√	0.066√	0.048√	963	0.013√	0.032√	-0.010X
Spatial orientation (VSPLOT)	0.076*√	0.026√	0.146*√	970	0.045√	<0.001	0.108*√
Penn Word Memory	-0.028√	-0.073√	0.026X	970	-0.041√	-0.087*√	0.015X
Picture sequence memory (NIHT)	0.040X	0.053X	0.023X	971	0.027X	0.041X	0.008X
List sorting (NIHT)	0.103*√	0.125*√	0.083√	972	0.078*√	0.103*√	0.055√

Card sorting (NIHT)	0.018	0.008	0.032	970	0.003	-0.012	0.025
Processing speed (NIHT)	<0.001	-0.034	0.036	972	-0.013	-0.050	0.028
Penn Emotion recognition	0.051X	0.082X	0.021X	970	0.039X	0.067X	0.014X
Social task	-0.035X	-0.054X	-0.010X	964	-0.040X	-0.051X	-0.025X
Neuroticism	-0.029√	-0.032√	-0.025√	971	-0.021√	-0.031√	-0.008√
Extraversion	-0.008	-0.025	0.009	971	-0.015	-0.036	0.006
Openness	0.007√	-0.027X	0.050√	971	-0.007X	-0.035X	0.029√
Conscientiousness	-0.039√	-0.019√	-0.065√	971	-0.029√	-0.017√	-0.044√
Agreeableness	-0.022√	-0.031√	-0.016√	971	-0.026√	-0.043√	-0.010√
Anger-Hostility (NIHT)	-0.046	-0.053	-0.035	971	-0.044	-0.052	-0.030
Anger-Aggression (NIHT)	-0.002X	-0.028X	0.026√	971	-0.003X	-0.031X	0.028√
DSM Depression	0.016	-0.001	0.040	970	0.012	-0.009	0.043
ASR Anxiety	-0.008	-0.025	0.013	970	-0.013	-0.034	0.015
DSM Anxiety	-0.030√	-0.061√	0.013X	970	-0.024√	-0.056√	0.023X
Perceived stress	-0.014	-0.029	0.007	971	-0.005	-0.031	0.031

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 11.
Correlation brain between differences along a male-female dimension (based on vertex-wise measures) and physical and behavioural measures for the QTIM dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.398**√	0.385**√	0.416**√	1040	NA	NA	NA
Height	0.176**√	0.198**√	0.140*√	915	0.100*√	0.132*√	0.048√
Body Mass Index	-0.019X	-0.005X	-0.045X	911	-0.024X	-0.023X	-0.027X
Diastolic blood pressure	0.040	0.056	0.011	285	0.043	0.035	0.045
Systolic blood pressure	0.081√	0.085√	0.080√	285	0.081√	0.065√	0.108√
Dexterity	-0.005	-0.064	0.105	166	-0.005	-0.041	0.085
Verbal IQ (MAB)	0.107**√	0.092*√	0.130*√	1011	0.043√	0.032√	0.062√
Performanc e IQ (MAB)	0.051√	0.027√	0.089√	1011	-0.019X	-0.039X	0.016√
Full-scale IQ (MAB)	0.085*√	0.061√	0.122*√	1010	0.008√	-0.011X	0.041√
Verbal fluency	0.072X	0.096X	0.037X	331	0.006X	<0.001	0.060X
Vocabulary (MAB)	0.072*√	0.022√	0.151*√	1011	0.027√	-0.005X	0.077√
National Adult Reading Test	0.045√	0.013√	0.097√	893	-0.009X	-0.019X	0.011√
Schonell Reading Test	0.065√	0.040√	0.114*√	894	0.020√	0.010√	0.041√
Matrix Reasoning (WAIS)	0.056	0.088	0.017	331	0.053	0.053	0.084
Arithmetic (MAB)	0.081*√	0.060√	0.109*√	1011	0.025√	0.004√	0.057√
Object assembly (MAB)	0.047√	0.009√	0.109*√	1011	-0.023X	-0.055X	0.031√
Spatial (MAB)	0.052√	0.037√	0.076√	1012	-0.003X	-0.016X	0.020√
Information (MAB)	0.105**√	0.108*√	0.101√	1011	0.053√	0.051√	0.059√
Digit span forwards (WAIS)	-0.025	0.026	-0.109	331	-0.009	0.039	-0.088
Digit span	0.034	0.085	-0.059	331	0.009	0.071	-0.095

backwards (WAIS)							
Letter-number sequencing (WAIS)	-0.003X	0.050√	-0.089X	331	-0.027X	0.018√	-0.092X
Digit symbol (WAIS)	0.006X	0.009X	-0.003√	990	-0.034√	-0.025√	-0.050√
Neuroticism	-0.030√	-0.039√	-0.005√	268	-0.039√	-0.077√	0.046X
Extraversion	-0.090√	-0.031√	-0.202√	268	-0.041√	0.015X	-0.146√
Openness	-0.207**√	-0.204*√	-0.217*√	268	-0.198*√	-0.205*√	-0.189√
Conscientiousness	-0.049	0.009	-0.155	268	-0.028	0.015	-0.111
Agreeableness	-0.155*√	-0.149*√	-0.170√	268	-0.118√	-0.125√	-0.111√
Neuroticism scale 1 (Anxiety)	-0.029√	-0.020√	-0.040√	268	-0.041√	-0.039√	-0.032√
Neuroticism scale 2 (Anger hostility)	0.040X	0.052X	0.029X	268	0.030X	0.010X	0.088X
Neuroticism scale 3 (Depression)	-0.036√	-0.037√	-0.028√	268	-0.038√	-0.058√	0.011X
SPHERE (anxiety depression-score)	<0.001	0.017X	-0.030√	834	-0.004√	0.023X	-0.049√
Autism spectrum quotient	0.078	0.009	0.158	249	0.106	0.055	0.154

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. QTIM=Queensland Twin IMaging; BSV=Brain Segmentation Volume; MAB=Multidimensional Aptitude Battery II; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; IQ=intelligence quotient; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 12.
Correlation between brain differences along a male-female dimension (based on vertex-wise measures) and physical and behavioural measures for the HCP dataset – adjusted for sex and age, or sex, age, and brain size (Brain Segmentation Volume).

	Adjusted for sex and age				***Adjusted for sex, age, and brain size***		
Variable	*Total*	*Females*	*Males*	*N*	*Total*	*Females*	*Males*
Brain size (BSV)	0.510**√	0.466**√	0.550**√	1113	NA	NA	NA
Height	0.203**√	0.179**√	0.226**√	1112	0.093*√	0.111*√	0.070√
Body Mass Index	0.006√	-0.031X	0.058√	1112	0.022√	0.010√	0.034√
Diastolic blood pressure	-0.065*X	-0.09*X	-0.038X	1099	-0.010X	-0.021X	-0.002X
Systolic blood pressure	-0.064*X	-0.039X	-0.090*X	1099	-0.038X	<0.001	-0.083X
Grip strength	0.043√	0.013√	0.063√	1112	-0.015X	0.006√	-0.040X
Endurance	0.102**√	0.097*√	0.110*√	1111	0.044√	0.043√	0.046√
Gait speed	0.088*	0.064	0.113*	1113	0.067*	0.044	0.094*
Dexterity	0.058X	0.043X	0.074X	1113	0.031X	0.022X	0.041X
Crystallized IQ (NIHT)	0.158**√	0.142**√	0.170**√	1110	0.040√	0.033√	0.050√
Fluid IQ (NIHT)	0.153**	0.160**	0.145*	1110	0.075*	0.083*	0.067
Total Cognition (Full-scale IQ) (NIHT)	0.184**√	0.183**√	0.183**√	1110	0.075*√	0.078√	0.074√
Picture Vocabulary (NIHT)	0.129**√	0.112*√	0.145*√	1113	0.017√	0.012√	0.023√
Reading English (NIHT)	0.164**√	0.150**√	0.174**√	1113	0.061*√	0.049√	0.076√
Penn Matrix Test	0.149**√	0.109*√	0.192**√	1104	0.030√	0.012√	0.049√
Math accuracy	0.139**√	0.130*√	0.149**√	1054	0.015√	0.028√	0.001√
Spatial orientation (VSPLOT)	0.117**√	0.103*√	0.132*√	1105	0.023√	0.030√	0.013√
Penn Word Memory	0.023X	0.074X	-0.028√	1105	-0.010√	0.040X	-0.061√
Picture sequence memory (NIHT)	0.054X	0.021X	0.088*X	1112	0.009X	-0.019√	0.038X
List sorting (NIHT)	0.147**√	0.161**√	0.131*√	1113	0.080*√	0.105*√	0.052√

Card sorting (NIHT)	0.093*√	0.125*√	0.059√	1111	0.044√	0.078√	0.009√
Processing speed (NIHT)	0.096*	0.063	0.130*	1113	0.063*	0.021	0.107*
Penn Emotion recognition	-0.002√	0.038X	-0.043√	1105	-0.045√	-0.009√	-0.079√
Social task	0.025√	0.023√	0.026√	1054	0.011√	0.033√	-0.017X
Neuroticism	-0.027√	<0.001	-0.054√	1106	-0.012√	0.005X	-0.026√
Extraversion	0.033	0.028	0.041	1106	0.018	-0.001	0.042
Openness	0.057√	0.054√	0.059√	1106	0.027√	0.030√	0.023√
Conscientiousness	-0.019√	-0.003√	-0.034√	1106	0.021X	0.015X	0.030X
Agreeableness	0.007X	-0.001√	0.016X	1106	-0.004√	-0.039√	0.037X
Anger-Hostility (NIHT)	-0.039	-0.008	-0.074	1112	-0.028	0.003	-0.062
Anger-Aggression (NIHT)	-0.019X	0.005√	-0.041X	1112	-0.003X	0.013√	-0.017X
DSM Depression	0.018	0.057	-0.025	1105	0.020	0.043	-0.001
ASR Anxiety	0.013	0.066	-0.040	1105	0.012	0.047	-0.021
DSM Anxiety	-0.006√	0.031X	-0.049√	1105	0.022X	0.056X	-0.020√
Perceived stress	-0.058	0.015	-0.134*	1112	-0.033	0.022	-0.087*

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 13.
Correlation between brain differences along a male-female dimension (based on vertex-wise measures regionally adjusted for brain size with an allometric scaling approach) and physical and behavioural measures for the QTIM dataset – adjusted for sex and age.

Variable	*Total*	*Females*	*Males*	*N*
Brain size (BSV)	-0.382**X	-0.411**X	-0.337**X	1040
Height	0.008√	0.036√	-0.039X	915
Body Mass Index	-0.022X	-0.032X	-0.002X	911
Diastolic blood pressure	0.034	0.001	0.086	285
Systolic blood pressure	0.066√	0.035√	0.127√	285
Dexterity	0.012	0.011	0.040	166
Verbal IQ (MAB)	-0.027X	-0.040X	-0.002X	1011
Performance IQ (MAB)	-0.081*X	-0.102*X	-0.042X	1011
Full-scale IQ (MAB)	-0.066*X	-0.086*X	-0.030X	1010
Verbal fluency	-0.050√	-0.098√	0.063X	331
Vocabulary (MAB)	-0.019X	-0.033X	0.006√	1011
National Adult Reading Test	-0.058X	-0.051X	-0.066X	893
Schonell Reading Test	-0.029X	-0.029X	-0.027X	894
Matrix Reasoning (WAIS)	0.036	0.007	0.095	331
Arithmetic (MAB)	-0.034X	-0.059X	0.008√	1011
Object assembly (MAB)	-0.085*X	-0.114*X	-0.034X	1011
Spatial (MAB)	-0.053X	-0.068X	-0.025X	1012
Information (MAB)	-0.007X	-0.017X	0.013√	1011
Digit span forwards (WAIS)	-0.004	0.035	-0.076	331
Digit span backwards (WAIS)	-0.013	0.041	-0.105	331
Letter-number sequencing (WAIS)	-0.049X	-0.027X	-0.089X	331
Digit symbol (WAIS)	-0.067*√	-0.059√	-0.082√	990
Neuroticism	-0.043√	-0.111√	0.100X	268
Extraversion	0.032X	0.073X	-0.044√	268
Openness	-0.150*√	-0.165*√	-0.127√	268
Conscientiousness	0.000	0.018	-0.037	268
Agreeableness	-0.048√	-0.064√	-0.024√	268
Neuroticism scale 1 (Anxiety)	-0.044√	-0.052√	-0.020√	268
Neuroticism scale 2 (Anger hostility)	0.007X	-0.054√	0.147X	268
Neuroticism scale 3 (Depression)	-0.034√	-0.071√	0.054X	268
SPHERE (anxiety depression-score)	-0.008√	0.026X	-0.068√	834
Autism spectrum quotient	0.119	0.096	0.137	249

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. QTIM=Queensland Twin IMaging; BSV=Brain Segmentation Volume; MAB=Multidimensional Aptitude Battery II; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; IQ=intelligence quotient; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 14.
Correlation between brain differences along a male-female dimension (based on vertex-wise measures regionally adjusted for brain size with an allometric scaling approach) and physical and behavioural measures for the HCP dataset – adjusted for sex and age.

Variable	*Total*	*Females*	*Males*	*N*
Brain size (BSV)	-0.449**X	-0.484**X	-0.413**X	1089
Height	-0.032X	0.004√	-0.070X	1088
Body Mass Index	0.037√	0.056√	0.008√	1088
Diastolic blood pressure	0.042√	0.047√	0.036√	1075
Systolic blood pressure	-0.006X	0.036√	-0.057X	1075
Grip strength	-0.064*X	-0.006X	-0.111*X	1088
Endurance	-0.020X	-0.032X	-0.011X	1087
Gait speed	0.028	-0.002	0.062	1089
Dexterity	0.003X	-0.003√	0.010X	1089
Crystallized IQ (NIHT)	-0.068*X	-0.080X	-0.052X	1086
Fluid IQ (NIHT)	-0.014	-0.019	-0.008	1086
Total Cognition (Full-scale IQ) (NIHT)	-0.039X	-0.049X	-0.026X	1086
Picture Vocabulary (NIHT)	-0.081*X	-0.084*X	-0.075X	1089
Reading English (NIHT)	-0.039X	-0.060X	-0.013X	1089
Penn Matrix Test	-0.076*X	-0.084*X	-0.067X	1080
Math accuracy	-0.091*X	-0.083X	-0.100*X	1032
Spatial orientation (VSPLOT)	-0.061*X	-0.050X	-0.074X	1081
Penn Word Memory	-0.041√	-0.010√	-0.076√	1081
Picture sequence memory (NIHT)	-0.038√	-0.063√	-0.010√	1088
List sorting (NIHT)	-0.003X	0.015√	-0.021X	1089
Card sorting (NIHT)	-0.012X	0.009√	-0.034X	1087
Processing speed (NIHT)	0.020	-0.030	0.073	1089
Penn Emotion recognition	-0.069*√	-0.040√	-0.098*√	1081
Social task	0.005√	0.049√	-0.046X	1032
Neuroticism	-0.010√	-0.003√	-0.016√	1082
Extraversion	0.013	-0.020	0.048	1082
Openness	-0.008X	-0.003X	-0.012X	1082
Conscientiousness	0.048X	0.027X	0.072X	1082
Agreeableness	-0.009√	-0.066√	0.051X	1082
Anger-Hostility (NIHT)	-0.017	0.009	-0.044	1088
Anger-Aggression (NIHT)	0.010√	0.018√	0.003√	1088
DSM Depression	0.010	0.016	0.006	1081
ASR Anxiety	-0.005	0.002	-0.013	1081
DSM Anxiety	0.028X	0.051X	0.001X	1081
Perceived stress	-0.008	0.022	-0.039	1088

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 15.
Correlation between brain differences along a male-female dimension (based on vertex-wise measures not adjusted for brain size) and physical and behavioural measures for the QTIM dataset – adjusted for sex, age and body size (height).

Variable	*Total*	*Females*	*Males*	*N*
Brain size (BSV)	0.375**√	0.365**√	0.391**√	915
Body Mass Index	-0.016X	0.001√	-0.046X	911
Diastolic blood pressure	0.016	0.039	-0.052	270
Systolic blood pressure	0.048√	0.061√	-0.002X	270
Dexterity	-0.008	-0.044	0.054	166
Verbal IQ (MAB)	0.076*√	0.063√	0.093√	887
Performance IQ (MAB)	0.038√	0.005√	0.089√	886
Full-scale IQ (MAB)	0.060√	0.032√	0.103√	886
Verbal fluency	0.053X	0.083X	0.000	289
Vocabulary (MAB)	0.045√	-0.005X	0.125*√	887
National Adult Reading Test	0.037√	0.001√	0.089√	781
Schonell Reading Test	0.061√	0.033√	0.115√	782
Matrix Reasoning (WAIS)	0.012	0.062	-0.060	289
Arithmetic (MAB)	0.046√	0.028√	0.069√	887
Object assembly (MAB)	0.033√	0.002√	0.085√	886
Spatial (MAB)	0.042√	0.008√	0.094√	887
Information (MAB)	0.094*√	0.103*√	0.078√	887
Digit span forwards (WAIS)	-0.058	0.004	-0.158	289
Digit span backwards (WAIS)	-0.016	0.063	-0.146	289
Letter-number sequencing (WAIS)	-0.058X	0.011√	-0.162X	289
Digit symbol (WAIS)	-0.001√	0.019X	-0.039√	874
Neuroticism	-0.071√	-0.076√	-0.058√	220
Extraversion	-0.115√	-0.011√	-0.299*√	220
Openness	-0.212*√	-0.150√	-0.313*√	220
Conscientiousness	-0.082√	0.019X	-0.246*√	220
Agreeableness	-0.199*√	-0.165*√	-0.249*√	220
Neuroticism scale 1 (Anxiety)	-0.061√	-0.063√	-0.051√	220
Neuroticism scale 2 (Anger hostility)	0.024X	0.045X	-0.010√	220
Neuroticism scale 3 (Depression)	-0.024√	0.007X	-0.093√	220
SPHERE (anxiety depression-score)	0.018X	0.019X	0.016X	742
Autism spectrum quotient	0.101	0.0470	0.152	207

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. QTIM=Queensland Twin IMaging; BSV=Brain Segmentation Volume; MAB=Multidimensional Aptitude Battery II; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; IQ=intelligence quotient; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 16.
Correlation between brain differences along a male-female dimension (based on vertex-wise measures not adjusted for brain size) and physical and behavioural measures for the HCP dataset – adjusted for sex, age and body size (height).

Variable	*Total*	*Females*	*Males*	*N*
Brain size (BSV)	0.486**√	0.449**√	0.519**√	1112
Body Mass Index	0.014√	-0.019X	0.058√	1112
Diastolic blood pressure	-0.073*X	-0.101*X	-0.042X	1098
Systolic blood pressure	-0.077*X	-0.053X	-0.101*X	1098
Grip strength	-0.016X	-0.048X	0.002√	1111
Endurance	0.083*√	0.079√	0.091*√	1110
Gait speed	0.073*	0.052	0.095*	1112
Dexterity	0.081*X	0.056X	0.112*X	1112
Crystallized IQ (NIHT)	0.147**√	0.143**√	0.143*√	1109
Fluid IQ (NIHT)	0.135**	0.144**	0.125*	1109
Total Cognition (Full-scale IQ) (NIHT)	0.166**√	0.171**√	0.158**√	1109
Picture Vocabulary (NIHT)	0.120**√	0.113*√	0.120*√	1112
Reading English (NIHT)	0.155**√	0.151**√	0.153**√	1112
Penn Matrix Test	0.136**√	0.095*√	0.183**√	1103
Math accuracy	0.119**√	0.113*√	0.125*√	1053
Spatial orientation (VSPLOT)	0.110**√	0.098*√	0.122*√	1104
Penn Word Memory	0.016X	0.077X	-0.048√	1104
Picture sequence memory (NIHT)	0.051X	0.030X	0.070X	1111
List sorting (NIHT)	0.131**√	0.147**√	0.111*√	1112
Card sorting (NIHT)	0.076*√	0.104*√	0.048√	1110
Processing speed (NIHT)	0.084*	0.048	0.123*	1112
Penn Emotion recognition	-0.005√	0.035X	-0.047√	1104
Social task	0.026√	0.028√	0.021√	1053
Neuroticism	-0.026√	0.005X	-0.059√	1105
Extraversion	0.028	0.024	0.035	1105
Openness	0.071*√	0.081*√	0.056√	1105
Conscientiousness	-0.019√	-0.011√	-0.024√	1105
Agreeableness	0.004X	-0.010√	0.023X	1105
Anger-Hostility (NIHT)	-0.044	-0.010	-0.082	1111
Anger-Aggression (NIHT)	-0.019X	0.002√	-0.037X	1111
DSM Depression	0.024	0.067	-0.026	1104
ASR Anxiety	0.019	0.073	-0.038	1104
DSM Anxiety	0.002X	0.043X	-0.049√	1104
Perceived stress	-0.045	0.024	-0.117*	1111

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 17.
Correlation brain size (Brain Segmentation Volume) with physical and behavioural measures for the QTIM dataset – adjusted for sex and age.

Variable	*Total*	*Females*	*Males*	*N*
Height	0.216**√	0.202**√	0.238**√	915
Body Mass Index	0.007√	0.040√	-0.050X	911
Diastolic blood pressure	0.001	0.060	-0.102	285
Systolic blood pressure	0.017√	0.064√	-0.072X	285
Dexterity	-0.001	-0.073	0.078	166
Verbal IQ (MAB)	0.168**√	0.161**√	0.173*√	1011
Performance IQ (MAB)	0.167**√	0.159**√	0.175**√	1011
Full-scale IQ (MAB)	0.191**√	0.180**√	0.201**√	1010
Verbal fluency	0.145*X	0.224**X	-0.030√	331
Vocabulary (MAB)	0.119**√	0.066√	0.193**√	1011
National Adult Reading Test	0.133**√	0.078√	0.215**√	893
Schonell Reading Test	0.118**√	0.081√	0.190**√	894
Matrix Reasoning (WAIS)	0.019	0.092	-0.110	331
Arithmetic (MAB)	0.143**√	0.144**√	0.136*√	1011
Object assembly (MAB)	0.167**√	0.152**√	0.189**√	1011
Spatial (MAB)	0.134**√	0.130**√	0.136*√	1012
Information (MAB)	0.141**√	0.157**√	0.112*√	1011
Digit span forwards (WAIS)	-0.037	-0.022	-0.066	331
Digit span backwards (WAIS)	0.057	0.051	0.046	331
Letter-number sequencing (WAIS)	0.047√	0.080√	-0.018X	331
Digit symbol (WAIS)	0.088*X	0.082*X	0.097X	990
Neuroticism	0.021X	0.110X	-0.144√	268
Extraversion	-0.165*√	-0.147*√	-0.202√	268
Openness	-0.063√	-0.030√	-0.119√	268
Conscientiousness	-0.071	-0.018	-0.156	268
Agreeableness	-0.137*√	-0.098√	-0.200√	268
Neuroticism scale 1 (Anxiety)	0.029X	0.057X	-0.029√	268
Neuroticism scale 2 (Anger hostility)	0.035X	0.135X	-0.160√	268
Neuroticism scale 3 (Depression)	0.002X	0.057X	-0.114√	268
SPHERE (anxiety depression-score)	0.008X	-0.012√	0.043X	834
Autism spectrum quotient	-0.049	-0.103	0.041	249

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. QTIM=Queensland Twin IMaging; BSV=Brain Segmentation Volume; MAB=Multidimensional Aptitude Battery II; WAIS=Wechsler Adult Intelligence Scale; SPHERE=Somatic and Psychological Health Report; IQ=intelligence quotient; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 18.
Correlation brain size (Brain Segmentation Volume) with physical and behavioural measures for the HCP dataset – adjusted for sex and age.

Variable	*Total*	*Females*	*Males*	*N*
Height	0.245**√	0.177**√	0.311**√	1112
Body Mass Index	-0.026X	-0.085*X	0.054√	1112
Diastolic blood pressure	-0.111**X	-0.155**X	-0.066X	1099
Systolic blood pressure	-0.063*X	-0.083*X	-0.038X	1099
Grip strength	0.110**√	0.018√	0.174**√	1112
Endurance	0.127**√	0.128*√	0.132*√	1111
Gait speed	0.059*	0.055	0.064	1113
Dexterity	0.061*X	0.052X	0.072X	1113
Crystallized IQ (NIHT)	0.243**√	0.246**√	0.235**√	1110
Fluid IQ (NIHT)	0.176**	0.188**	0.163**	1110
Total Cognition (Full-scale IQ) (NIHT)	0.238**√	0.249**√	0.223**√	1110
Picture Vocabulary (NIHT)	0.226**√	0.217**√	0.229**√	1113
Reading English (NIHT)	0.221**√	0.232**√	0.204**√	1113
Penn Matrix Test	0.243**√	0.211**√	0.278**√	1104
Math accuracy	0.243**√	0.223**√	0.265**√	1054
Spatial orientation (VSPLOT)	0.192**√	0.164**√	0.220**√	1105
Penn Word Memory	0.063*X	0.084*X	0.041X	1105
Picture sequence memory (NIHT)	0.091*X	0.082*X	0.103*X	1112
List sorting (NIHT)	0.156**√	0.148**√	0.160**√	1113
Card sorting (NIHT)	0.107**√	0.120*√	0.092*√	1111
Processing speed (NIHT)	0.082*	0.095*	0.073	1113
Penn Emotion recognition	0.072*X	0.100*X	0.041X	1105
Social task	0.030√	-0.014X	0.072√	1054
Neuroticism	-0.033√	-0.008√	-0.058√	1106
Extraversion	0.035	0.063	0.011	1106
Openness	0.067*√	0.060√	0.072√	1106
Conscientiousness	-0.072*√	-0.036√	-0.107*√	1106
Agreeableness	0.019X	0.071X	-0.026√	1106
Anger-Hostility (NIHT)	-0.029	-0.023	-0.041	1112
Anger-Aggression (NIHT)	-0.033X	-0.015X	-0.049X	1112
DSM Depression	0.001	0.042	-0.044	1105
ASR Anxiety	0.006	0.051	-0.041	1105
DSM Anxiety	-0.048√	-0.041√	-0.059√	1105
Perceived stress	-0.058	-0.009	-0.112*	1112

X represent an effect in the opposite direction as the sex effect found, while √ represents an effect in the same direction as the sex effect found. HCP=Human Connectome Project; BSV= Brain Segmentation Volume; NIHT=National Institute of Health Toolbox; IQ=intelligence quotient; VSPLOT=Variable Short Penn Line Orientation Test; ASR=Achenbach adult self-report questionnaire; DSM=Diagnostic and Statistical Manual of mental disorders; N=number of individuals.
*$p \leq 0.05$; ** $p \leq 0.001$.

Supplementary Table 19.
Genetic analyses: Intra-Twin Correlations for identical (MZ) and non-identical (DZ) twins for each measure of brain and behavioural differences along a male-female dimension (including DZ opposite sex twins and siblings) – adjusted for sex and age.

Measure derived from:	*Sample*	*MZ*	*DZ*
Brain Size (BSV)	QTIM	0.92 (0.89, 0.94)	0.41 (0.24, 0.55)
Brain Size (BSV)	HCP	0.93 (0.90, 0.94)	0.47 (0.31, 0.60)
Subcortical landmarks	QTIM	0.55 (0.43, 0.64)	0.38 (0.21, 0.52)
Subcortical landmarks	HCP	0.60 (0.50, 0.68)	0.45 (0.27, 0.59)
Cortical landmarks	QTIM	-	-
Cortical landmarks	HCP	0.38 (0.23, 0.51)	0.08 (-0.12, 0.27)
Both type of landmarks	QTIM	-	-
Both type of landmarks	HCP	0.42 (0.27, 0.54)	0.18 (-0.08, 0.39)
Vertex-wise	QTIM	0.47 (0.35, 0.57)	0.23 (0.04, 0.38)
Vertex-wise	HCP	0.48 (0.35, 0.59)	0.29 (0.09, 0.46)
Vertex-wise allometric	QTIM	0.41 (0.27, 0.53)	0.27 (0.10, 0.42)
Vertex-wise allometric	HCP	0.53 (0.41, 0.63)	0.13 (-0.07, 0.31)
Behaviour	QTIM	0.57 (0.44, 0.67)	0.30 (0.09, 0.47)
Behaviour	HCP	0.40 (0.23, 0.54)	0.00 (-0.22, 0.23)

As the prediction derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis – represented with an '-'. MZ=monozygotic; DZ=dizygotic; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; BSV=Brain Segmentation Volume.

Supplementary Table 20.
Genetic analyses: Intra-Twin Correlations for identical (MZ) and non-identical (DZ) twins for each measure of brain and behavioural differences along a male-female dimension (excluding DZ opposite sex twins and siblings) – adjusted for sex and age.

Measure derived from:	*Sample*	*MZ*	*DZ*
Brain Size (BSV)	QTIM	0.92 (0.89, 0.93)	0.40 (0.23, 0.54)
Brain Size (BSV)	HCP	0.93 (0.90, 0.94)	0.48 (0.32, 0.61)
Subcortical landmarks	QTIM	0.53 (0.41, 0.63)	0.37 (0.20, 0.51)
Subcortical landmarks	HCP	0.59 (0.49, 0.67)	0.44 (0.26, 0.58)
Cortical landmarks	QTIM	-	-
Cortical landmarks	HCP	0.40 (0.23, 0.53)	0.08 (-0.13, 0.28)
Both type of landmarks	QTIM	-	-
Both type of landmarks	HCP	0.42 (0.27, 0.54)	0.18 (-0.07, 0.39)
Vertex-wise	QTIM	0.47 (0.35, 0.57)	0.23 (0.04, 0.39)
Vertex-wise	HCP	0.48 (0.35, 0.59)	0.30 (0.09, 0.47)
Vertex-wise allometric	QTIM	0.41 (0.27, 0.53)	0.27 (0.09, 0.42)
Vertex-wise allometric	HCP	0.53 (0.41, 0.63)	0.14 (-0.06, 0.32)
Behaviour	QTIM	0.57 (0.44, 0.68)	0.30 (0.08, 0.48)
Behaviour	HCP	0.39 (0.22, 0.52)	-0.00 (-0.22, 0.22)

As the prediction derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis – represented with an '-'. MZ=monozygotic; DZ=dizygotic; QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; BSV=Brain Segmentation Volume.

Supplementary Table 21.
Genetic analyses: Intra-Twin Correlations across the different zygosity groups for each measure of brain and behavioural differences along a male-female dimension – adjusted for sex and age.

Measure derived from:	*Sample*	*MZ F*	*MZ M*	*DZ F*	*DZ M*	*DZ OS*
Brain Size (BSV)	QTIM	0.92 (0.88, 0.94)	0.94 (0.90, 0.96)	0.47 (0.26, 0.61)	0.32 (0.01, 0.56)	0.51 (0.32, 0.64)
Brain Size (BSV)	HCP	0.92 (0.89, 0.94)	0.95 (0.92, 0.96)	0.40 (0.18, 0.58)	0.54 (0.32, 0.70)	0.52 (0.40, 0.62)
Subcortical landmarks	QTIM	0.54 (0.39, 0.65)	0.53 (0.31, 0.68)	0.37 (0.16, 0.54)	0.40 (0.10, 0.61)	0.28 (0.08, 0.44)
Subcortical landmarks	HCP	0.61 (0.49, 0.70)	0.60 (0.41, 0.72)	0.47 (0.19, 0.64)	0.45 (0.18, 0.63)	0.44 (0.30, 0.56)
Cortical landmarks	QTIM	-	-	-	-	-
Cortical landmarks	HCP	0.35 (0.17, 0.50)	0.47 (0.16, 0.65)	0.08 (-0.17, 0.32)	0.09 (-0.21, 0.37)	-0.10 (-0.32, 0.14)
Both type of landmarks	QTIM	-	-	-	-	-
Both type of landmarks	HCP	0.37 (0.18, 0.52)	0.50 (0.25, 0.66)	0.16 (-0.16, 0.43)	0.20 (-0.16, 0.49)	0.24 (0.03, 0.42)
Vertex-wise	QTIM	0.49 (0.35, 0.60)	0.41 (0.20, 0.57)	0.25 (0.04, 0.44)	0.17 (-0.13, 0.43)	0.27 (0.03, 0.46)
Vertex-wise	HCP	0.36 (0.17, 0.52)	0.60 (0.44, 0.71)	0.39 (0.13, 0.57)	0.18 (-0.10, 0.43)	0.26 (0.10, 0.41)
Vertex-wise allometric	QTIM	0.39 (0.20, 0.53)	0.44 (0.23, 0.60)	0.29 (0.07, 0.47)	0.23 (-0.05, 0.46)	0.23 (0.02, 0.42)
Vertex-wise allometric	HCP	0.50 (0.33, 0.62)	0.61 (0.43, 0.73)	0.26 (-0.00, 0.47)	-0.07 (-0.36, 0.25)	0.20 (0.03, 0.35)
Behaviour	QTIM	0.50 (0.32, 0.63)	0.77 (0.59, 0.86)	0.28 (0.04, 0.47)	0.42 (NA, 0.68)	0.32 (0.05, 0.53)
Behaviour	HCP	0.25 (-0.02, 0.46)	0.53 (0.31, 0.67)	0.01 (-0.34, 0.36)	0.01 (-0.25, 0.27)	0.18 (0.03, 0.33)

As the prediction derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis – represented with an '-'. QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; MZ=monozygotic; DZ=dizygotic; OS=Opposite-sex; M=Male; F=Female; BSV=Brain Segmentation Volume.

Supplementary Table 22.
Genetic analyses: ACE-model for each measure of brain and behavioural differences along a male-female dimension – adjusted for sex and age, including both twins and siblings in the model.

Measure derived from	*Sample*	*A*	*C*	*E*
Brain Size (BSV)	QTIM	0.92 (0.78, 0.94)	0.00 (0.00, 0.14)	0.08 (0.06, 0.10)
Brain Size (BSV)	HCP	0.86 (0.74, 0.95)	0.07 (0.00, 0.20)	0.07 (0.05, 0.09)
Subcortical landmarks	QTIM	0.48 (0.18, 0.64)	0.07 (0.00, 0.29)	0.45 (0.36, 0.57)
Subcortical landmarks	HCP	0.50 (0.29, 0.67)	0.10 (0.00, 0.26)	0.40 (0.32, 0.49)
Subcortical landmarks	QTIM	-	-	-
Cortical landmarks	HCP	0.33 (0.10, 0.45)	0.00 (0.00, 0.14)	0.67 (0.55, 0.80)
Cortical landmarks	QTIM	-	-	-
Both type of landmarks	HCP	0.41 (0.08, 0.53)	0.01 (0.00, 0.23)	0.58 (0.47, 0.73)
Vertex-wise	QTIM	0.39 (0.08, 0.57)	0.07 (0.00, 0.31)	0.53 (0.43, 0.65)
Vertex-wise	HCP	0.42 (0.15, 0.59)	0.06 (0.00, 0.23)	0.52 (0.41, 0.65)
Vertex-wise allometric	QTIM	0.33 (0.00, 0.53)	0.08 (0.00, 0.33)	0.59 (0.47, 0.73)
Vertex-wise allometric	HCP	0.46 (0.32, 0.57)	0.00 (0.00, 0.00)	0.54 (0.43, 0.65)
Behaviour	QTIM	0.51 (0.15, 0.67)	0.06 (0.00, 0.34)	0.43 (0.33, 0.56)
Behaviour	HCP	0.32 (0.10, 0.45)	0.00 (0.00, 0.12)	0.68 (0.55, 0.81)

As the prediction derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis – represented with an '-'. QTIM=Queensland Twin IMaging; HCP=Human Connectome Project; A=additive genetic influences; C=common environmental influences; E=non-shared environmental influences; BSV=Brain Segmentation Volume.

Supplementary Table 23.
Genetic analyses: ACE-model for each measure of brain and behavioural differences along a male-female dimension– adjusted for sex and age, excluding opposite-sex twin and sibling pairs from the model.

Measure derived from	*Sample*	*A*	*C*	*E*
Brain Size (BSV)	QTIM	0.92 (0.78, 0.94)	0.00 (0.00, 0.14)	0.08 (0.06, 0.10)
Brain Size (BSV)	HCP	0.83 (0.68, 0.94)	0.11 (0.00, 0.26)	0.07 (0.05, 0.09)
Subcortical landmarks	QTIM	0.39 (0.07, 0.63)	0.15 (0.00, 0.40)	0.47 (0.37, 0.59)
Subcortical landmarks	HCP	0.55 (0.32, 0.67)	0.04 (0.00, 0.23)	0.41 (0.33, 0.51)
Subcortical landmarks	QTIM	-	-	-
Cortical landmarks	HCP	0.36 (0.10, 0.49)	0.00 (0.00, 0.17)	0.64 (0.51, 0.78)
Cortical landmarks	QTIM	-	-	-
Both type of landmarks	HCP	0.36 (0.03, 0.54)	0.05 (0.00, 0.28)	0.58 (0.46, 0.73)
Vertex-wise	QTIM	0.45 (0.10, 0.57)	0.03 (0.00, 0.30)	0.53 (0.43, 0.65)
Vertex-wise	HCP	0.41 (0.13, 0.59)	0.08 (0.00, 0.27)	0.51 (0.41, 0.64)
Vertex-wise allometric	QTIM	0.32 (0.00, 0.53)	0.09 (0.00, 0.37)	0.59 (0.47, 0.73)
Vertex-wise allometric	HCP	0.49 (0.33, 0.60)	0.00 (0.00, 0.00)	0.51 (0.40, 0.62)
Behaviour	QTIM	0.54 (0.14, 0.68)	0.03 (0.00, 0.37)	0.43 (0.32, 0.56)
Behaviour	HCP	0.29 (0.09, 0.43)	0.00 (0.00, 0.11)	0.71 (0.57, 0.85)

As the prediction derived from cortical landmarks in the QTIM dataset was no better than chance, these prediction scores were excluded from further analysis – represented with an '-'. A=additive genetic influences; C=common environmental influences; E=non-shared environmental influences; BSV=Brain Segmentation Volume.