

Comparative neuroimaging of sex differences in human and mouse brain anatomy

Reviewed Preprint

Published from the original preprint after peer review and assessment by eLife.

About eLife's process

Reviewed preprint version 1

January 5, 2024 (this version)

Sent for peer review

September 20, 2023

Posted to preprint server

August 24, 2023

Elisa Guma , Antoine Beauchamp, Siyuan Liu, Elizabeth Levitis, Jacob Ellegood, Linh Pham, Rogier B Mars, Armin Raznahan , Jason P Lerch 

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA • Mouse Imaging Centre, Toronto, Ontario, Canada • The Hospital for Sick Children, Toronto, Ontario, Canada • Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada • Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom • Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands

 https://en.wikipedia.org/wiki/Open_access

 Copyright information

Abstract

In vivo neuroimaging studies have established several reproducible volumetric sex differences in the human brain, but the causes of such differences are hard to parse. While mouse models are useful for understanding the cellular and mechanistic bases of sex-biased brain development in mammals, there have been no attempts to formally compare mouse and human sex differences across the whole brain to ascertain how well they translate. Addressing this question would shed critical light on use of the mouse as a translational model for sex differences in the human brain and provide insights into the degree to which sex differences in brain volume are conserved across mammals. Here, we use cross-species structural magnetic resonance imaging to carry out the first comparative neuroimaging study of sex-biased neuroanatomical organization of the human and mouse brain. In line with previous findings, we observe that in humans, males have significantly larger and more variable total brain volume; these sex differences are not mirrored in mice. After controlling for total brain volume, we observe modest cross-species congruence in the volumetric effect size of sex across 60 homologous brain regions ($r=0.30$; e.g.: M>F amygdala, hippocampus, bed nucleus of the stria terminalis, and hypothalamus and F>M anterior cingulate, somatosensory, and primary auditory cortices). This cross-species congruence is greater in the cortex ($r=0.33$) than non-cortex ($r=0.16$). By incorporating regional measures of gene expression in both species, we reveal that cortical regions with greater cross-species congruence in volumetric sex differences also show greater cross-species congruence in the expression profile of 2835 homologous genes. This phenomenon differentiates primary sensory regions with high congruence of sex effects and gene expression from limbic cortices where congruence in both these features was weaker between species. These findings help identify aspects of sex-biased brain anatomy present in mice that are retained, lost, or inverted in humans. More broadly, our work provides an empirical basis for targeting mechanistic studies of sex-biased brain development in mice to brain regions that best echo sex-biased brain development in humans.

eLife assessment

In this **important** study, Guma and colleagues describe the use of structural neuroimaging to assess the cross-species convergence of sex differences in global and regional brain volumes in humans and mice. The goal of the work is to inform to what extent mouse studies of these aforementioned sex differences have relevance to humans. The authors suggest which aspects of brain anatomy (as measured by volume) are conserved or not, across species, which has theoretical and practical implications beyond a single sub-field. The evidence to support the findings is **solid**, it uses methods and data analysis that are appropriate and validated.

1. Introduction

Humans show numerous sex differences in the prevalence, age of onset, and presentation of brain-related conditions (Bao and Swaab, 2010). Early onset neurodevelopmental conditions, such as autism spectrum disorder, attention deficit/hyperactivity disorder, Tourette syndrome, and language impairments tend to disproportionately affect males. Adolescent and adult-onset conditions such as depression, anxiety, eating disorders, and Alzheimer's disease tend to disproportionately affect females (Bölte et al., 2023). There is also evidence from multiple large-scale studies for sex differences in certain cognitive and behavioural traits such as in language and face processing (Herlitz and Lovén, 2013; Olderbak et al., 2019), spatial rotation (Lippa et al., 2010), and aggression (Archer, 2004). These observations may reflect sex differences in brain organization arising from a complex mix of genetic and environmental influences. To date, the largest studies testing for sex differences in human brain organization have focused on anatomical measures extracted from *in vivo* structural magnetic resonance images (sMRI). While there is considerable heterogeneity in the findings of this literature (Eliot et al., 2021), owing potentially to variation in the methods used (Zhou et al., 2022), there are several large scale studies that recover highly reproducible sex differences in regional human brain volume above and beyond sex differences in total brain size (DeCasien et al., 2022). These include larger limbic, and temporal regional volumes in males, and larger cingulate and prefrontal regional volumes in females (Liu et al., 2020; Lotze et al., 2019; Ruigrok et al., 2014; Williams et al., 2021).

Gaining a deeper understanding of the causes and consequences of sex differences in the human brain is challenging due to its relative inaccessibility, inability to perform invasive experiments, and potential environmental confounds. Significant advances in our understanding of sex differences in regional volume of the mammalian brain have come from rodent studies. This literature provides important context for thinking about volumetric sex differences in the harder to study human brain. Highly robust sex differences in regional volume of the rodent brain have been historically identified using classical histology (Gorski et al., 1978; Hines et al., 1992; Kim et al., 2017). These differences have also been recovered using sMRI methods, analogous to those used to study regional sex differences in human brain volume (Qiu et al., 2018; Spring et al., 2007). These histologically- and sMRI-resolvable sex differences in regional volume of the rodent brain include a male-bias in the bed nucleus of the stria terminalis (BNST), the medial amygdala (MeA), and the medial preoptic nucleus (MPON). In addition to these canonical sex differences, sMRI has uncovered several other sex differences in regional brain volume (Qiu et al., 2018; Spring et al., 2007; Wilson et al., 2022) including larger anterior cingulate cortex, hippocampus, and olfactory bulb volume in males and larger cerebellum, midbrain, caudoputamen, thalamus, and cortex volume in females. Modern tools for brain-wide histology in mice have established that foci of volumetric sex-bias from sMRI are also salient foci of sex

differences in cellular composition (Kim et al., 2017 [↗](#)). Further, they are concentrated within circuits subserving sex-biased reproductive and social behaviors in mice. Third, beyond allowing paired description of sex differences in gross volume (using sMRI) and cellular composition (using histology), mice also enable mechanistic dissection of regional sex differences through genetic and environmental manipulations. For example, the four core genotype (FCG) model, in which the complement of sex chromosomes (XX vs XY) is made independent of gonadal sex (testes vs ovaries), has allowed researchers to appreciate the differential effects of gonadal sex (presence of testes or ovaries independent of chromosome complement) from sex chromosome complement (XX vs XY mice of either gonadal sex) (Arnold and Chen, 2009 [↗](#); McCarthy and Arnold, 2011 [↗](#)).

The above considerations drive a pressing need for systematic comparison of volumetric sex differences between the human and mouse brain. Such a comparison would provide two critical outputs. First, it would advance understanding of brain evolution by formally testing for conservation of sex-biased brain organization between two distantly related mammals. Second, any homologous brain regions that show congruent volumetric sex differences in humans and mice would represent high-priority targets for translational research - leveraging research opportunities in mice to scaffold studies on the causes and consequences of sex differences in the human brain.

Here, we characterize sex differences in global and regional brain volume in a large young adult human cohort from the Human Connectome Project (Van Essen et al., 2012 [↗](#)) and young adult mouse cohort (Ellegood et al., 2015 [↗](#)). In addition to mean differences, we also assess sex differences in the variance of brain volume measures. We assess the cross-species correspondence of sex-biased brain volume changes in a subset of homologous brain regions based on the directionality and magnitude of volume changes. Furthermore, we build on these anatomical comparisons by assessing whether a brain region's cross-species similarity for sex-biased neuroanatomy is related to its cross-species similarity in expression levels of homologous genes. These quantitative comparisons of neuroanatomical sex differences between humans and mice provide an important reference frame for future studies that seek to use the mouse as a translation model to study sex differences in the human brain. Defining those brain regions with volumetric sex differences that are highly conserved between humans and mice may shed light on evolutionary constraints shaping sex-biased brain development in mammals and highlights high-priority targets for future translational research.

1. Results

2.1 Males have larger brains than females in humans but not in mice

We first examined the effects of sex on total tissue volume (TTV) in humans (597 females/496 males) and mice (213 females/216 males) using sMRI data from healthy young adults in both species. Replicating a well-established sex differences in prior studies (Liu et al., 2020 [↗](#); Lotze et al., 2019 [↗](#); Ruigrok et al., 2014 [↗](#); Williams et al., 2021 [↗](#)), we observed in humans that males had significantly larger mean TTV than females (13.5% larger in males; $\beta=1.28$, $t=26.60$, $p<2e-16$; **Fig 1A** [↗](#)). In contrast, we did not observe a statistically significant sex difference in TTV for mice (0.3% larger in males; $\beta=0.091$, $t=0.706$, $p=0.481$; **Fig 1B** [↗](#)). Sex differences in total gray and white matter were also observed, with opposite patterns in humans (larger gray matter in males and white matter in females) and mice (larger grey matter in females and white matter in males; **Supplement 2.1 & Supplementary Figure 1**).

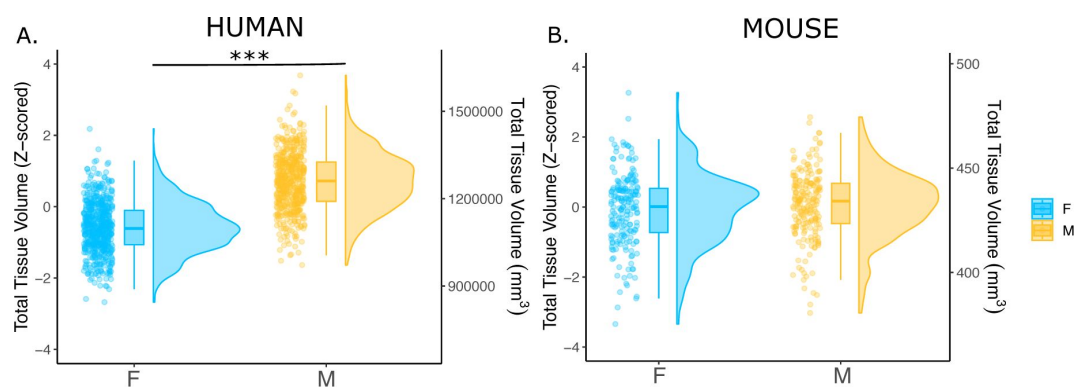


Figure 1.

Effects of sex on total tissue volume (TTV) in humans and mice.

Distributions of TTV are shown for the effects of sex in humans (A) and mice (B). Data are represented using individual points, boxplot, and half-violin plot. *** $p < 0.0001$. M= male, F=female.

2.2 Sex differences in regional brain volume exist in both humans and mice

After correction for TTV and adjusting for multiple comparisons, we found that 65.8% of human regions showed statistically significant sex differences in volume, of which 63.8% were female-biased and 36.3% were male-biased. In mice, 58.6% of all regions showed statistically significant sex differences in volume, of which 53.0% were female-biased and 47.0% were male-biased. In humans, the median effect size (i.e., standardized beta coefficients) for female-biased regions was -0.09 ± 0.09 standard deviation (SD) (range= -8.90×10^{-16} to -0.44), while it was slightly larger, 0.15 ± 0.19 SD (range= 0.0008 to 0.84), for male-biased regions (**Fig2A** [↗](#)). In mice, the median effect size across female-biased regions was -0.19 ± 0.13 SD (-0.003 to -0.6), similar to that of male-biased regions 0.20 ± 0.20 SD (range=0.004 to 1.04) (**Fig2B** [↗](#)). Next, we ensured that in humans, the observed sex effects were not biased by inclusion of twin or sibling pairs (**Supplementary Figure 2; Supplement 1.3 & 2.1**). Furthermore, we repeated the regional analyses without co-varying for TTV and found that all human volumes were male-biased, due to overall larger brain size. In mice, however, the patterns of sex-bias remained largely unchanged, likely due to the similarity of total brain size between the sexes (**Supplementary Figure 3; Supplement 2.3**).

In humans, we observed statistically significantly larger regional volume in females than males in the frontal, cingulate, orbital, somatosensory, motor, parietal, parahippocampal, and precuneus cortex, as well as the nucleus accumbens. Males had statistically significantly larger volume in the visual, parieto-occipital, piriform, insula, retrosplenial, medial prefrontal cortex, fusiform face complex, as well as the cerebellum, brainstem, hippocampus, amygdala (including the MeA), the BNST, and hypothalamus (including the MPON) (FDR threshold: $t=2.23$, $q<0.05$) (**Figure 2C** [↗](#)). In mice, females had significantly larger regional volume of the auditory, orbital, entorhinal, anterior cingulate, somatosensory, motor, frontal, and insular cortex, as well as in the caudoputamen and cerebellum. Males had significantly larger regional volume of the olfactory bulb, hippocampus, subiculum, brainstem, amygdala (including MeA), BNST, and hypothalamus (including the MPON) ($t=2.23$, $q<0.05$) (**Figure 2D** [↗](#)). For the full list of regional sex differences in human or mouse brain volume, consult **Supplementary Tables 5 & 6**, respectively. Notable cross-species congruences in regional volumetric sex differences included female-biased frontal, cingulate, orbital, somatosensory, motor, and auditory cortex and male-biased hypothalamus (including MPON), BNST, amygdala (including MeA), hippocampus, subiculum, brainstem, and cerebellum. Notable opposing sex differences between species included the nucleus accumbens, cerebellum, and frontal cortex (male-biased in humans and female-biased in mice) (**Figure 2** [↗](#)). Of note, there are several regions showing a sex-bias in mice for which we do not have a parcellation/segmentation in the human brain (either due to resolution or lack of available atlases), so we cannot conclude that they are mouse specific.

2.3 Human males have greater variance in brain volume than females, while mice show no sex differences in variance

Next, we evaluated sex differences in the variance of global and regional brain volumes in each species using Levene's test for equality of variances. Variance in TTV was significantly greater in males than females for humans (Levene's test: $F=10.19$, $p=0.0014$), whereas mice showed no sex difference in TTV variance (Levene's test: $F=0.765$, $p=0.382$) (**Supplementary Figure 4AB**). In humans, several regional brain volumes (residualized for TTV, age, and Euler number) showed greater variance in males than females after correction for multiple comparisons ($q<0.05$, e.g., parieto-occipital cortex, posterior cingulate cortex, and left amygdala). In mice, no brain regions (residualized for TTV, age, and background strain) showed sex differences in variance following multiple comparisons correction, however, at a relaxed threshold of $p<0.05$ mice showed sex differences in regional volumetric variance for the olfactory bulbs and culmen (male>female) and

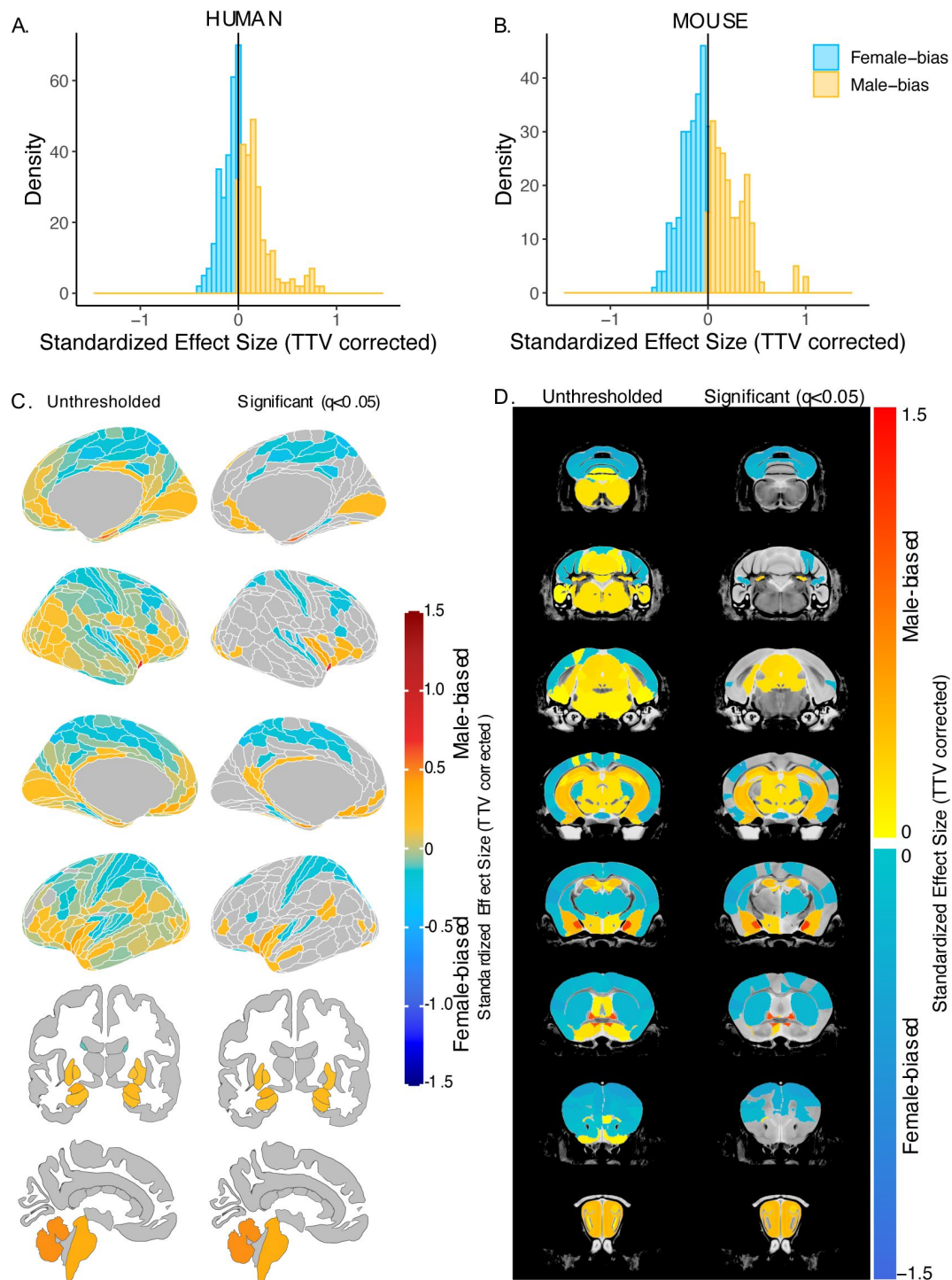


Figure 2.

Effect of sex on regional brain volume in humans and mice.

A, B. Distribution of sex-biased standardized effect sizes across anatomical regions for humans (**A**) and mice (**B**). **C, D.** Unthresholded (left) and significant ($q < 0.05$; right) standardized effect sizes for the effect of sex displayed on the human (**C**) and mouse (**D**) brains. Regions in yellow-red are male-biased and regions in blue are female-biased.

visual, sensorimotor cortex, and CA1 (female>male) (*Supplement 2.3; Supplementary Figure 4*). These findings remained unchanged after repeating analyses of regional volumetric variance without residualizing for TTV (*Supplement 2.3; Supplementary Figure 5*).

2.4 Sex differences in the size of homologous brain regions is similar across species

We next focused on a set of predefined homologous brain regions ($n=60$, 28 bilateral and 4 midline) with well-established homology based on comparative studies (Balsters et al., 2020 [DOI](#); Beauchamp et al., 2022 [DOI](#); Glasser et al., 2016 [DOI](#); Gogolla, 2017 [DOI](#); Swanson and Hof, 2019 [DOI](#); Vogt and Paxinos, 2014 [DOI](#)) to achieve a formal quantitative cross-species comparison of regional sex differences in brain volume. The robust correlation (less sensitive to outliers (Tabatabai et al., 2021 [DOI](#)), computed using the *pbcor* R library) of effect size for sex across all homologous brain regions was significant at $r=0.30$ ($p=0.013$) (*Figure 3A* [DOI](#)), with a stronger correlation for cortex ($r=0.33$, $p=0.10$) than non-cortex ($r=0.16$, $p=0.35$) - although neither of these compartments showed a statistically significant correlation between species in isolation from each other (*Figure 3B* [DOI](#), but note the reduction in sample size in these intra-compartment analyses).

Homologous brain regions that were statistically significantly female-biased ($q<0.05$) in both species include the bilateral primary somatosensory cortex (human $|\beta|>0.22$, mouse $|\beta|>0.24$), primary auditory cortex (right in humans [$|\beta|>0.16$] and bilateral in mice [$|\beta|>0.20$]), and anterior cingulate cortex (bilateral in humans [$|\beta|>0.10$] and right in mice, $|\beta|>0.20$). The right posterior parietal association area was female-biased in both species but significant ($q<0.05$) only in humans (human $|\beta|>0.25$, mouse $|\beta|>0.02$), while the bilateral primary motor areas and left thalamus were female-biased in both species but only significant ($q<0.05$) in mice. Finally, the left thalamus and left ventral orbital area were female-biased but not significant in either species. Homologous regions that were statistically significantly male-biased in both species ($q<0.05$) include the bilateral amygdala (human $|\beta|>0.20$, mouse $|\beta|>0.15$) (bulk and MeA), bilateral globus pallidus (human $|\beta|>0.14$, mouse $|\beta|>0.11$), hippocampus (human $|\beta|>0.12$, mouse $|\beta|>0.35$; bilateral bulk and CA1, right in humans and bilateral in mice), BNST (human $|\beta|>0.36$, mouse $|\beta|>0.92$), hypothalamus (human $|\beta|>0.62$, mouse $|\beta|>0.11$; bulk and MPON), and brainstem (human $|\beta|>0.35$, mouse $|\beta|>0.20$; medulla and midbrain). Additionally, the left primary visual area, right retrosplenial area, and pons were male-biased in both species but only significant in humans, while CA3 was male-biased in both but only significant in mice (*Table 3* [DOI](#)). Regions that showed an incongruent direction of volumetric sex differences between species (with a significant difference in at least one of the species at $q<0.05$) were the bilateral agranular insula and cerebellar cortex (female-biased in mice, but male-biased in humans) (*Table 3* [DOI](#); *Figure 4* [DOI](#)). As expected, given the robust sex differences for TTV in humans but not mice, we observed a weaker robust correlation for sex differences in the volume of homologous brain regions when repeating the above analyses without controlling for TTV, $r=0.15$ ($p=0.25$) for the effect of sex across homologous regions (*Supplementary Figure 6 & Supplementary Table 4*).

2.5 Regions that are more congruent between species in their volumetric sex differences tend to be more congruent in their gene expression signatures

Next, we explored whether regions that are more similar between species in their volumetric sex differences are also more similar in their gene expression profile. To derive a region-level measure of between-species congruence in anatomical sex differences (henceforth “anatomical sex effect similarity score”) we multiplied the human and mouse sex effect sizes for each of the 60 homologous brain regions. To derive a region-level measure of cross-species transcriptional similarity, we leveraged gene expression data from the Allen Human and Allen Mouse Brain Atlases (Hawrylycz et al., 2012 [DOI](#); Lein et al., 2007 [DOI](#)) within the subset of homologous regions

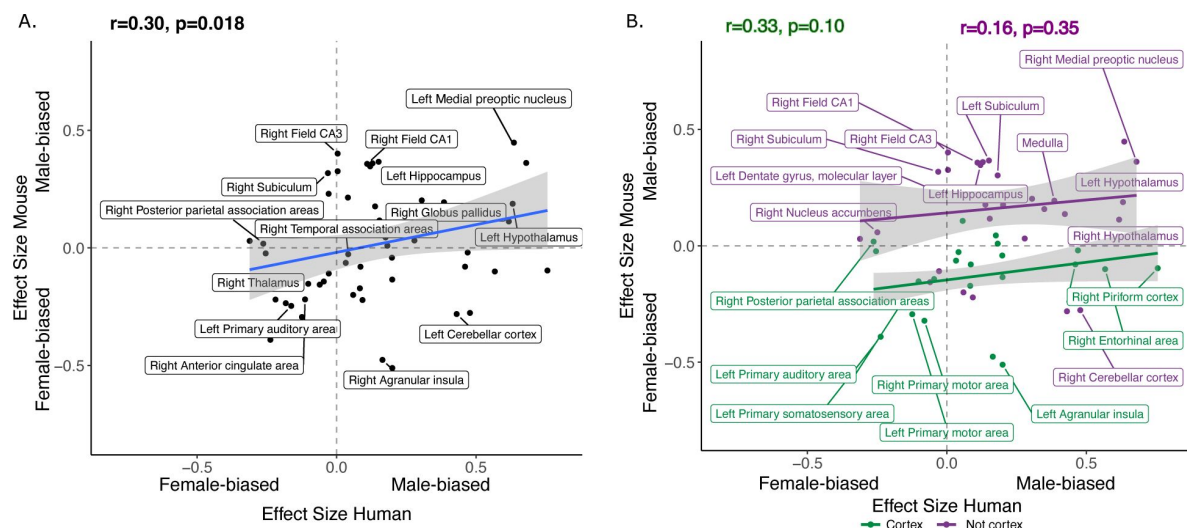


Figure 3.

Correlation of sex effects on regional volume in homologous regions of the human and mouse brain.

A. Standardized effect size correlation for the effect of sex in humans (x-axis) and mice (y-axis) (robust correlation coefficient, $r=0.30$). **B.** Correlation of standardized effect sizes for the effect of sex across species for cortical regions (green, $r=0.31$), and non-cortical regions (purple, $r=0.16$).

Label	Glasser/Freesurfer# names	Mouse atlas	Hemisphere	Human effect size (β)	Mouse effect size (β)
Agranular insula	AVI, AAIC, MI	Agranular insular area	L	0.200 *	-0.558 *
			R	0.164 *	-0.522 *
Amygdala	Amygdala#	Cortical subplate	L	0.305 *	0.163 *
			R	0.201 *	0.151 *
Anterior cingulate area	A24pr, a24, p24pr, p24, 24dd, 24dv, p32pr, d32, a32pr, p32, s32	Anterior cingulate area	L	-0.102 *	-0.198
			R	-0.113 *	-0.267 *
Bed nucleus of stria terminalis	Bed nucleus of stria terminalis	Bed nucleus of stria terminalis	L	0.466 *	0.918 *
			R	0.360 *	0.971 *
Caudoputamen	Caudate#, Putamen#	Caudoputamen	L	0.093	-0.224 *
			R	0.059	-0.188 *
Cerebellar cortex	Cerebellar cortex#	Cerebellar cortex	L	0.430 *	-0.268 *
			R	0.478 *	-0.250 *
Dentate gyrus, molecular layer	Dentate gyrus, molecular layer	Dentate gyrus, molecular layer	L	-0.029	0.247 *
			R	0.041	0.232 *
CA1	CA1	CA1	L	0.151 *	0.385 *
			R	0.109	0.377 *
Brain stem (midline)	Brainstem#	Midbrain, Hindbrain	M	0.349 *	0.200 *
Medulla (midline)	Medulla	Medulla	M	0.385 *	0.204 *
Midbrain (midline)	Midbrain	Midbrain	M	0.423 *	0.191 *
Pons (midline)	Pons	Pons	M	0.279 *	0.065

Table 3.

Species-specific effect sizes for volumetric sex differences for 60 homologous brain regions.

Effect sizes are color coded (blue: male-biased / yellow: female-biased) and asterisk/bold text denotes statistical significance. All results are from analyses covarying for TTV.

	Female-biased in Human	Male-biased in Human
Male-biased in Mouse	Posterior Parietal Association Cortex Nucleus Accumbens (R) Dentate Gyrus (L) Subiculum (R)	Amygdala * (medial amygdala *) Hypothalamus* (MPON *) Hippocampus * (R DG, CA1 *, CA3) Globus Pallidus *, BNST * Brainstem* (Pons, Midbrain *, Medulla *) Retrosplenial Cortex Subiculum (L) Temporal Association Cortex (L)
Female-biased in Mouse	Anterior cingulate cortex * Primary Auditory Cortex * Primary Somatosensory Cortex * Primary Motor Cortex Thalamus Nucleus Accumbens (L) Posterior Parietal Association Cortex (L) Ventral Orbital Cortex (R)	Agranular Insula * Cerebellar Cortex * Caudoputamen Entorhinal Cortex Perirhinal Cortex Piriform Cortex Primary Visual Cortex Temporal Association Cortex (R) Ventral Orbital Cortex (L)

Figure 4.

Homologous brain regions showing either congruent or divergent sex bias across species.

There are no regions that are larger in human females and mouse males (top left quadrant, light green). Several regions show male-bias (top right quadrant in yellow) and female-bias (bottom left quadrant in blue) across species. A subset of regions show male-bias in humans but female bias in mice (bottom right quadrant in green). * Denotes significant sex effect in both species. Ordering of quadrants matches quadrants of the scatter plots in [Figures 3](#) and [5](#).

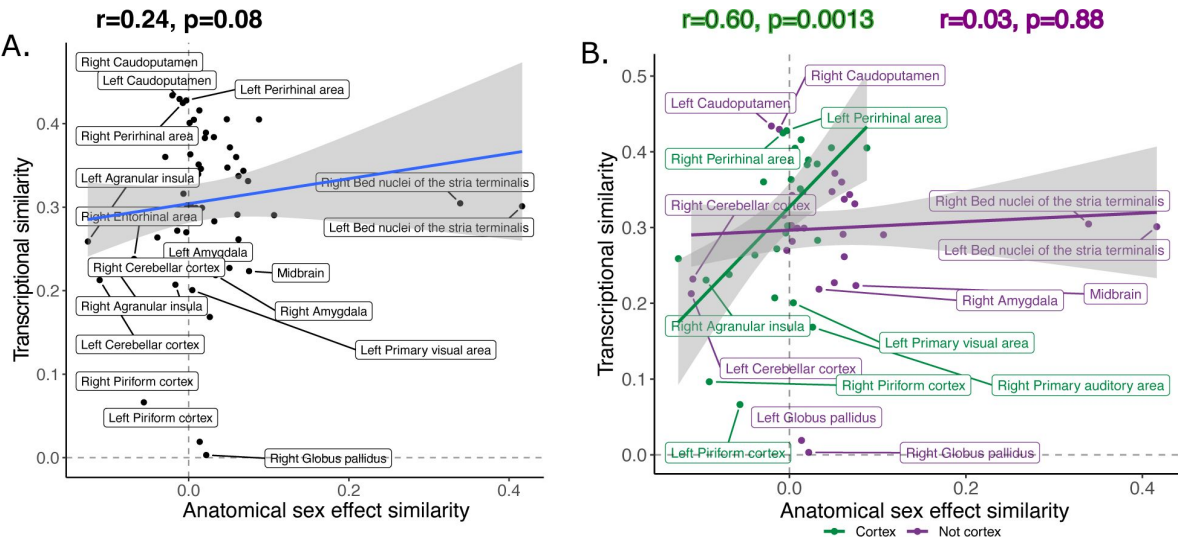


Figure 5.

Inter-species anatomical sex congruence and gene expression shows modest correlation across homologous brain regions.

Correlation between similarity in volumetric sex differences and similarity in transcriptional profile using all homologous genes across all homologous regions modest (**A**). There was a stronger correlation across cortical (green) compared to non-cortical (purple) regions (**B**).

defined above. We filtered the gene sets to only human-mouse homologous genes (Beauchamp et al., 2022; NCBI Resource Coordinators, 2018) and correlated the regional expression of the homologous genes to derive a measure of transcriptional similarity across species per brain region. These analyses considered the set of 56 homologous brain regions (4 of the original 60 did not have transcriptomic data: bilateral MeA and MPON) and 2835 homologous genes - with supplementary tests based on a priori defined subsets of brain regions and genes (**Methods 4.5.2**). The steps outlined above yielded two measures for each of 56 homologous brain regions: an anatomical sex effect similarity score and a transcriptional similarity score.

The transcriptional similarity score ranged between 0.003 and 0.43 with a mean/median correlation of 0.30, (0.10, interquartile range: 0.25-0.36; **Supplementary Figure 7**). Across homologous brain regions, interregional variation in this transcriptional similarity was positively correlated with anatomical sex effect similarity, $r=0.24$ ($p=0.08$) (**Figure 5A**). Stratification by brain compartment showed that this relationship was stronger, and statistically significant, for cortical regions, $r=0.60$ ($p=0.0013$), than non-cortical regions, $r=0.03$ ($p=0.88$) (**Figure 5B**). Visualizing these relationships indicated that cortical regions showing higher anatomical sex effect similarity scores (mainly primary sensory cortices) tended to show above average transcriptional similarity with each other (i.e., $r>0.3$), whereas cortical regions with lower anatomical sex effect similarity scores (mainly limbic cortex) showed below average transcriptional similarity. Subcortical regions failed to show a correspondence between anatomical sex effect similarity and transcriptional similarity - but we noted that this could be driven the influences of the BNST as an outlier region (Cook's d: left BNST=0.20, right BNST=0.13). However, the correlation between anatomical sex effect similarity and transcriptional similarity remained low for subcortical regions after exclusion of the BNST from analysis ($r=0.02$, $p=0.92$) (**Supplementary Figure 8AB**).

Finally, we asked if the observed correlations between anatomical sex effect similarity and transcriptional similarity would be significantly modified by recomputing correlations using biologically informed subsets of homologous genes: (i) X-linked genes ($n=91$) or (ii) sex hormone genes ($n=34$). Across these sensitivity analyses we observed a similar correlation when using X-linked genes ($r=0.25$, $p=0.07$) compared to the full gene set with stronger correlations in cortical ($r=0.62$, $p=0.0007$) vs. non-cortical ($r=0.30$, $p=0.11$) regions (**Supplementary Figure 8CD**). Interestingly, we observed an exception to this pattern for the subset of sex hormone genes involved in androgen vs. estrogen and progesterone pathways. Transcriptional similarity scores based on androgen pathways were weakly correlated with anatomical sex effect similarity score in the cortex ($r=0.05$, $p=0.81$), but were strongly correlated with anatomical sex effect similarity in the non-cortical regions ($r=0.46$, $p=0.01$). In contrast, the correlation between anatomical sex effect similarity and transcriptional similarity based on estrogen/progesterone pathways was positive in the cortex ($r=0.29$, $p=0.15$) but negative in the non-cortex ($r=-0.27$, $p=0.15$) (**Supplementary Figures 8G-J & 9**). For combined sex hormone analysis see (**Supplement 2.6 & Supplementary Figure 8EF**).

2. Discussion

This study provides the first cross-species comparison of the effects of sex on human and mouse brain anatomy. Our findings suggest that sex differences in overall brain volume are not conserved across species, but that there is a meaningful degree of cross-species concordance for sex differences in regional volumes. Furthermore, regions with more similar sex effects between species also tended to show more similar transcriptional profiles - particularly amongst cortical brain regions. This work has consequences for understanding sex differences in the mammalian brain, use of mice as translational models for human sex differences, and the broader topic of comparative structural neuroimaging between humans and mice.

First, in line with many previous observations (Liu et al., 2020 [↗](#); Lotze et al., 2019 [↗](#); Ruigrok et al., 2014 [↗](#); Williams et al., 2021 [↗](#)), we find that in humans, males have larger mean total brain volume than females. In contrast, we observe no sex differences in total brain size in mice, in line with a recent study reporting no sex differences in total brain volume, cell density, and total cell number (Elkind et al., 2023 [↗](#)). In previous studies, only subtle sex differences in total brain size have been reported in C57BL6/J mice (2.5% larger male brain). However, this subtle difference in brain size is lost when accounting for sex differences in body weight (Spring et al., 2007 [↗](#)), which is not the case in humans where the sex difference in brain size is dampened but not lost when accounting for body size (Dekaban, 1978 [↗](#); Williams et al., 2021 [↗](#)).

As seen for sex differences in total brain volume, humans and mice also showed a striking contrast for sex differences in anatomical variance. In humans, males showed more variance for both total and regional brain volume measures, in line with previous findings (Forde et al., 2020 [↗](#)). In mice, no sex differences in anatomical variance were observed. While variance in brain anatomy has not been previously studied in mice, greater male variability has been observed for morphological traits, while greater female variability has been observed for immunological and metabolic traits (Zajitschek et al., 2020 [↗](#)). The observation of greater neuroanatomical variance in human, but not mouse males questions the theory that males are more variable because they are heterogametic (have XY chromosomes) (Reinhold and Engqvist, 2013 [↗](#)), since male mice are also heterogametic. Gaining understanding of the causes of sex differences in variability of brain structures may provide clues for understanding sex differences in brain development and in neurodevelopmental disorders (Wierenga et al., 2022 [↗](#)).

After accounting for global brain size differences, we identified several sex-biased regions in the human and mouse brain, several of which showed consistent sex-bias across species. For these regions, available mechanistic information in mice can be used to refine mechanistic hypotheses in humans. We find that males of both species have larger amygdala (including the MeA), hippocampus, BNST, hypothalamus (including the MPON) volumes in line with a previous human (Lotze et al., 2019 [↗](#); Neudorfer et al., 2020 [↗](#); Ruigrok et al., 2014 [↗](#)) and mouse neuroimaging studies (Qiu et al., 2018 [↗](#)). Rodent studies have shown that the emergence of sMRI defined volume differences aligns with the developmental timing of sex differences in apoptosis in the BNST and MPON, (Chung et al., 2000 [↗](#)), and sex differences in synaptic organization in the MeA (Cooke and Woolley, 2005 [↗](#); Nishizuka and Arai, 1981 [↗](#)); these male-biased regions also tend to show greater density than female-biased brain regions (Elkind et al., 2023 [↗](#)). To further support the organizational role of hormones, masculinized female mice display male-biased sex difference in the BNST and MeA (and behaviour) (McCarthy, 2020 [↗](#); Wu and Shah, 2011 [↗](#)). Additionally, neuroimaging studies of FCG mice identified independent effects of sex hormones from sex chromosome dosage on brain anatomy. For example, the MeA is larger in mice with testes than mice with ovaries, but is smaller in XY than XX mice, which further points to the importance of sex hormones in sculpting this specific brain region (Corre et al., 2016 [↗](#); Vousden et al., 2018 [↗](#)). While we do not have causal mechanistic data in humans, neuroimaging studies have shown that male-biased regional volume differences emerge in early development, and may be sensitive to the amount of fetal testosterone exposure (Knickmeyer et al., 2014 [↗](#); Lombardo et al., 2012 [↗](#)). In females, we show that both species have a larger anterior cingulate, somatosensory, and primary auditory cortex in line with human (Lotze et al., 2019 [↗](#); Neudorfer et al., 2020 [↗](#); Ruigrok et al., 2014 [↗](#)) and mouse studies (Qiu et al., 2018 [↗](#)). While the mechanisms driving female-bias in regional brain volume are not as well understood, neuroimaging studies in both species find that female-biased regions tend to emerge during puberty (Knickmeyer et al., 2014 [↗](#); Qiu et al., 2018 [↗](#)), which may point to an important role of pubertal hormones in shaping brain structure. Regions showing congruent sex bias across species, such as the primary somatosensory cortex, may be high priority targets for conducting mechanistic studies in the mouse brain that have relevance to the human.

We also observe regions where there is a significant sex difference in volume in one species that is absent or inverted in the other, including the agranular insula and cerebellar cortex (male-biased in humans and female-biased in mice). This incongruence may be due to species differences in the composition of these regions. For example, a recent study comparing the cerebellum of humans, macaques, and mice identified a group of progenitor cells present in the human brain but not in the mouse or macaque (Haldipur et al., 2019 [↗](#)). Furthermore, comparison of cell populations in the middle temporal gyrus of humans and mice found that in humans, there is greater interaction between neurons and non-neuronal cells as well as greater diversity and density of glia, which may in turn lead to cross-species differences in brain size (Fang et al., 2022 [↗](#)). The divergence in sex effects may be due to a divergence in gene expression patterns. This idea is supported by our analyses that incorporate information on bulk regional gene expression, which is heavily shaped by cellular composition (Yao et al., 2021 [↗](#)). Brain regions with more similar gene expression profiles between species (and likely more similar cellular compositions) also tend to show more similar volumetric sex differences across species. Finally, the lack of congruence in the cross-species sex effects may also be due to species differences in the function of the brain regions.

Our comparison of homologous brain regions based on the similarity of anatomical sex differences and of homologous gene expression revealed good cross-species alignment between those metrics. This relationship was much stronger in the cortical areas than in non-cortical areas. Within cortical regions, the primary sensory areas showed stronger transcriptional and anatomical sex congruence, while limbic structures showed lower congruence. In non-cortical regions the transcriptional similarity was consistent across regions, independent of anatomical sex congruence. Limiting the homologous gene set of X-linked genes did not alter the congruence between the anatomical effects and transcriptional similarity, however, limiting the genes to include sex hormone genes did. The transcriptional similarity based on androgen genes was weakly correlated with cortical sex effects but strongly correlated with non-cortical sex differences, while the transcriptional similarity based on estrogen and progesterone genes was positively correlated with cortical but negatively correlated with non-cortical sex effects. This interesting observation may point to a differential role for sex hormone classes in patterning either cortical or non-cortical sex differences in the brain, which warrants further investigation.

The findings presented here indicate that there is modest cross-species alignment for regional sex differences, but that humans and mice show very different effects of sex on overall brain size. Interpretation of this cross-species difference is challenged by our limited causal understanding of the mechanisms driving sex differences in overall brain size within humans. It has been theorized that a potential evolutionary driver for sex differences in body size (and the contributions of this to brain size) is sexual selection for larger body size in species where there is higher competition for mates (Plavcan, 2012 [↗](#)). However, evolutionary causes for inter-species variation in the sex effects on total brain volume are hard to test empirically. In contrast, there is empirical evidence for the role of sex hormones and sex chromosomes in shaping sex differences in brain size, therefore, species differences in the modulation of these biological processes may contribute to species differences in brain size (McCarthy and Arnold, 2011 [↗](#)). Large-scale neuroimaging studies in humans suggest that sex differences in total brain volume are already apparent in toddlerhood (Bethlehem et al., 2022 [↗](#)), at birth (Dean et al., 2018 [↗](#); Gilmore et al., 2007 [↗](#)), and even prenatally (Conte et al., 2018 [↗](#); Griffiths et al., 2023 [↗](#)). These differences are therefore likely to reflect pre- and perinatal influences of sex differences in circulating sex steroids and/or sex chromosome dosage on the human brain, where males are exposed to a perinatal testosterone surge and females are not (McCarthy, 2020 [↗](#)). While sex differences in the total brain size of mice have not been well characterized in prenatal and early postnatal life, there is some experimental in vitro evidence of differential gonadal steroid effects on early neurogenesis in humans vs. mice. In human brain organoids (both XX and XY) in vitro androgen exposure (as a model for the perinatal “mini-puberty” seen in humans (Kelava et al., 2022 [↗](#))) has been associated with an increased proliferation of excitatory cortical progenitors and radial glia, increasing the neurogenic niche (Kelava et al., 2022 [↗](#)). In contrast, in mouse brain organoids, estradiol, but not testosterone

exposure leads to an increase in progenitor cell proliferation (Kelava et al., 2022 [↗](#)). This species difference aligns with evidence that gonadal steroids masculinize the mouse brain via activation of the estrogen E2 receptor by aromatized testosterone, whereas the masculinizing effects of gonadal steroids on the primate brain are more dependent on direct activation of the androgen receptor by testosterone (Schwarz and McCarthy, 2008 [↗](#); Zuloaga et al., 2008 [↗](#)). There is also some evidence that sex chromosome dosage may be differentially related to brain size in humans vs. mice. In humans with sex chromosome aneuploidy, increased Y-chromosomes dosage is associated with increased total brain size, while increased X-chromosome dosage is associated with decreased total brain size (Guma et al., 2023 [↗](#); Raznahan et al., 2016 [↗](#)). Importantly, these global differences are not recapitulated in the mouse brain, where extra X- or Y-chromosome dosage is not associated with any differences in brain size (Guma et al., 2023 [↗](#)). This may be, in part, explained by species differences in the size and gene content of the Y-chromosome; mice have an expanded proportion of ampliconic genes compared to primates (Soh et al., 2014 [↗](#)), as well as in the process of XCI, where more genes escape inactivation in humans (12-15%) than mice (2-5%) (Deng et al., 2014 [↗](#)).

The work presented here should be considered in light of some caveats and limitations. First, while we used detailed segmentation to characterize sex differences in the human and mouse brain, several canonically sex-biased nuclei in mice are difficult to detect with human MRI. Second, as with our previous study (Guma et al., 2023 [↗](#)), we employ a parcellation-based approach which is limited to anatomically defined brain structures for which one-to-one mapping across species may not always be accurate (Mars et al., 2018 [↗](#)). Third, we focus on the comparison of brain anatomy in young adulthood, but extending across different spatial and temporal scales would be critical to our understanding of the emergence and evolution of sex differences across species. Fourth, our incorporation of gene expression data relied on available atlases that are largely (humans) or exclusively (mice) derived from male brains. Fifth, while comparison of humans and mice provides an important first step in comparative analyses of sex-biased brain development in mammals, formal phylogenetic analysis will require incorporation of data from other animals including non-human primates. Lastly, although we carefully characterize sex differences in brain anatomy, it is important to stress that such differences provide no information regarding brain function or behavior (DeCasien et al., 2022 [↗](#)). Moreover, sex differences in human brain development are likely to be uniquely shaped by the closely related but distinct construct of gender, which is typically considered to be absent in all non-human animals including mice.

Notwithstanding these limitations and caveats, we show that sex differences in global brain size are not well conserved across species, but that sex differences in regional brain volume do show some congruence between humans and mice. Furthermore, we find that human-mouse congruence in volumetric sex differences is stronger for cortical as compared to non-cortical structures, and - especially in the cortex - echoed by cross-species similarities in regional gene expression. In conclusion, this quantitative comparison of sex-biased neuroanatomy across humans and mice may inform future translational studies aimed at using mice to better understand sex differences in the human brain.

3. Methods

4.1 Human participants and neuroimaging data

4.1.1 Data acquisition

The human sample included 3T T1-weighted 0.7mm³ sMRIs from healthy young adults (597 females/496 males aged 22-35 years) from the Human Connectome Project (HCP) 1200 release. Recruitment procedures are detailed in the original publication as are scan acquisition parameters (T1-MPRAGE: TR=2400ms; TE=2.14ms; TI=1000ms; Flip angle=8 deg; FoV=224×224mm) (Van Essen et al., 2012 [↗](#)). Participant characteristics are detailed in **Supplementary Table 1**.

4.1.2 Data processing

Cortical morphometry

T1-weighted sMRI data were preprocessed using the PreFreeSurfer pipeline, described in detail here (Glasser et al., 2013 [↗](#)). Next, we used FreeSurfer's (version 7.1.0) (Fischl, 2012 [↗](#)) *recon-all* with the *highres* flag to reconstruct and parcellate the cortex of all individuals at the original resolution of the data (Zaretskaya et al., 2018 [↗](#)). This pipeline is freely available for download, documented (<http://surfer.nmr.mgh.harvard.edu/> [↗](#)), and well described in previous publications (Dale et al., 1999 [↗](#); Dale and Sereno, 1993 [↗](#); Desikan et al., 2006 [↗](#); Fischl et al., 2004a [↗](#), 2004b [↗](#), 2002 [↗](#), 2001 [↗](#), 1999 [↗](#), 1998 [↗](#); Fischl and Dale, 2000 [↗](#); Han et al., 2006 [↗](#); Jovicich et al., 2006 [↗](#); Kuperberg et al., 2003 [↗](#); Reuter et al., 2010 [↗](#)). The *mri_anatomical_stats* utility was used to extract several features including cortical volume from the cortical surfaces. These vertex-level measures were averaged across 360 regions from the multimodally informed Glasser Human Connectome Project atlas (Glasser et al., 2016 [↗](#)).

Subcortical morphometry

For subcortical segmentation, each voxel is assigned one of 43 labels using FreeSurfer “aseg” feature (version 7.1.0; see (Fischl et al., 2004b [↗](#), 2002 [↗](#)) for full details). Of the 40 labels, 20 were included in analyses as they segmented grey matter structures. We aimed to build upon the standard segmentations above to include more nuclei previously shown to be different between sexes. We used FreeSurfer's joint segmentation of hippocampal subfields (Iglesias et al., 2015a [↗](#)), sub-nuclei of the amygdala (Saygin et al., 2017 [↗](#)), and brainstem (Iglesias et al., 2015b [↗](#)). Since the hypothalamus and related nuclei including the BNST are not available through FreeSurfer, we used a different published atlas (Neudorfer et al., 2020 [↗](#)) (available for download here: <https://zenodo.org/record/3942115> [↗](#)). Segmentation was performed by registering the atlas labels to our study specific average (using deformation based morphometry processing with ANTs based tools https://github.com/CoBrALab/optimized_antsMultivariateTemplateConstruction [↗](#); **Supplement 1.2**). Voxel-wise volume differences were summed within the regions of interest of the hypothalamic atlas to generate structure volumes. Finally, each segmentation (cortical and subcortical) was visually quality controlled to ensure region boundaries matched anatomy, and excluded if there was a segmentation fault. Additionally, participants with a Euler number (extracted from each individual's cortical reconstruction) less than -200 were excluded from statistical analyses based on previous reports (Rosen et al., 2018 [↗](#)).

4.2 Mouse subjects and neuroimaging data

4.2.1 Data acquisition

Mice included in this study were all wild-type controls from a large collection of autism mouse models made up of separate cohorts from diverse labs, sent to the Mouse Imaging Centre in Toronto for neuroimaging (Ellegood et al., 2015). To model normative sex differences in the young adult mouse brain, we included wild-type mice from lab cohorts that had a minimum of 5 males and 5 females (to allow for appropriate covariation of potential background genotype and strain effects) on a C57BL6 (J or N) background strain. This yielded $n=216$ males (mean age = postnatal day [PND] 62.7 $\pm$ 8.5; range = PND 56-90) and $n=213$ females (mean age = PND 62.0 $\pm$ 7.5; range = PND 56-90). We harmonized neuroimaging measures between cohorts within background strain (134F/141M C57BL6J mice from 12 cohorts, 79F/75M C57BL6J mice from 6 cohorts, **Supplementary Table 2 & 3**) using ComBat from the *sva* library in R. This method is a popular adjustment method initially developed for genomics data (Johnson et al., 2007), but adapted to neuroimaging to harmonize measurements across scanners (Fortin et al., 2018, 2017).

Young adult mice were transcardially perfused following a standard protocol which was consistent across mouse cohorts (Cahill et al., 2012). Fixed brains (kept in skull to avoid distortions) were scanned at the Mouse Imaging Centre on a multichannel 7.0-T scanner with a 40-cm diameter bore magnet (Varian Inc., Palo Alto, CA). A T2-weighted fast spin echo sequence was used with the following scan parameters: T2W 3D FSE cylindrical *k*-space acquisition sequence, TR/TE/ETL = 350 ms/12 ms/6, two averages, FOV/matrix-size = $20 \times 20 \times 25$ mm/ $504 \times 504 \times 630$, total-imaging-time = 14 h (Spencer Noakes et al., 2017). All procedures were approved by the animal care committees of the originating labs.

4.2.2 Data processing

sMRIs were registered using an unbiased deformation-based morphometry registration pipeline (Avants et al., 2009; Collins et al., 1994; Friedel et al., 2014). This results in an average brain, from which log-transformed Jacobian determinants can be calculated (Chung et al., 2001); these encode voxel-wise volume differences between each individual mouse brain and the average brain. sMRIs were also segmented into 355 unique brain regions using previously published atlases (Dorr et al., 2008; Richards et al., 2011; Steadman et al., 2014; Ullmann et al., 2013) with the MAGeT brain algorithm (Chakravarty et al., 2013; Pipitone et al., 2014). Visual quality control was performed to evaluate accuracy of registrations and segmentations.

2.3 Gene expression data

4.3.1 Human gene expression data

Human gene expression data were obtained from the Allen Human Brain Atlas (Hawrylycz et al., 2012), downloaded from the Allen Institute's API (<http://api.brain-map.org>), and preprocessed using *abagen* package in Python (<https://abagen.readthedocs.io/en/stable/>) (Arnatkeviciute et al., 2019; Hawrylycz et al., 2012; Markello et al., 2021) as previously described by (Beauchamp et al., 2022). Data from all six donors was preprocessed as described in (Beauchamp et al., 2022) yielding a gene-by-sample expression matrix with 15,627 genes and 3702 samples across all donors.

4.3.2 Mouse gene expression data

Mouse gene expression data were obtained from the Allen Mouse Brain Atlas (Lein et al., 2007). Briefly, the whole-brain in-situ hybridization expression data were downloaded using Allen Institute's API (<http://help.brain-map.org/display/api/Downloading+3-D+Expression+Grid+Data>)

coronal in-situ hybridization experiments and reshaped into 3D images in the Medical Image NetCDF (MINC) format and preprocessed as previously described by (Beauchamp et al., 2022 [↗](#)). The result of this pre-processing pipeline was a gene-by-voxel expression matrix with 3958 genes and 61,315 voxels.

4.3.3 Expression matrices for homologous genes within homologous regions

To obtain gene expression data for each homologous brain region described above, the human atlases used to perform the segmentations were registered into MNI ICBM 152 2009c non-linear symmetric space (Fonov et al., 2011 [↗](#), 2009 [↗](#)) and each human sample was annotated with one of the labels from either the FreeSurfer (Glasser, subcortical, hippocampus subfield, amygdala subnuclei, brainstem) or hypothalamus atlases. Next, we created a gene-by-region expression matrix. For the human, we weighted the average of gene expression data based on the volume of the region of interest; this was particularly important since we combined several regions within the human atlases to obtain our 60 homologous regions (28 bilateral and 4 midline). Several regions were missing expression data from the human right hemisphere, including the right hypothalamus, BNST, DG, and CA3, so we reflected the left hemisphere data to the right to increase our sample for subsequent analyses. Furthermore, the MeA and MPON were missing transcriptomic data and were excluded from these analyses, yielding a total of 56 homologous brain regions. Similarly, the mouse atlas was registered into the Allen Mouse Brain Common Coordinate Framework (CCFv3) space (Wang et al., 2020 [↗](#)) and each voxel was annotated with one of the 60 homologous brain region labels. To create a gene-by-region expression matrix for the human and mouse, we averaged voxel-level gene expression data within regions of interest. To obtain homologous genes, each species' full gene set was intersected with a list of 3331 homologous genes obtained from NCBI HomoloGene database (NCBI Resource Coordinators, 2018 [↗](#)), yielding 2835 homologous genes present in both species' expression matrices, as described by (Beauchamp et al., 2022 [↗](#)). Each matrix was z-scored across brain regions to normalize gene expression measures.

4.4 Statistical analysis

4.4.1 Sex differences in mean total and regional brain volume

Human

All statistical analyses were performed in R version 3.4.2. A linear model was used to test for the effect of sex (β_1 : male vs female) on z-scored total or regional brain volumes, with mean-centered age (β_2), TTV (β_3), and Euler number (β_4) as covariates (ϵ : error term). The beta-value for the effect of sex (β_1) is referred to as a standardized effect size as it was computed on standardized (z-scored) volumes. The false discovery rate (FDR) correction (Benjamini and Hochberg, 1995 [↗](#); Benjamini and Yekutieli, 2001 [↗](#)) was applied to control for multiple comparisons with the expected proportion of false positives(q) set to 0.05. The formula, using ROI_volume as the example region:

$$\text{ROI_volume} \sim \text{intercept} + \beta_1(\text{Sex: male vs female}) + \beta_2(\text{age} - \text{mean age}) + \beta_3(\text{TTV}) + \beta_4(\text{Euler number}) + \epsilon$$

To ensure that the effects we observed were not driven by inclusion of twin or sibling pairs, we re-ran the same linear model on a subset of the data that included only one of the two twin pairs. Additionally, we ran a linear-mixed effects model on the full data set with family ID as a random intercept. We correlated the standardized effect size for sex from both of these models to the ones generated from our main model to ensure that the effects were equivalent (**Supplement 1.3**).

Mouse

The analysis performed in humans was replicated in mice by using a linear model to test for the effect of sex (β_1 : male vs female) on z-scored total or regional brain volume. Mean-centered age (β_2), TTV (β_3), and background strain (β_4) were also included as covariates (ϵ : error term). Again, the beta-value for sex (β_1) is referred to as a standardized effect size.

$$\text{ROI_volume} \sim \text{intercept} + \beta_1(\text{Sex: male vs female}) + \beta_2(\text{age} - \text{mean age}) + \beta_3(\text{TTV}) + \beta_4(\text{Background Strain}) + \epsilon$$

In both species we repeated the regional analyses described above without covarying for TTV. Finally, we used a Levene's test to assess sex differences in variance of global and regional brain volume in each species (**Supplement 1.4**).

4.5 Cross-species comparison

4.5.1 Sex-biased brain anatomy

To test for the convergence between sex effects in humans and mice, we considered a subset of 60 brain regions for which there is well established homology based on comparative structural and functional studies (Balsters et al., 2020 [DOI](#); Beauchamp et al., 2022 [DOI](#); Glasser et al., 2016 [DOI](#); Gogolla, 2017 [DOI](#); Swanson and Hof, 2019 [DOI](#); Vogt and Paxinos, 2014 [DOI](#)). We also leveraged previous work which maps brain regions between humans and mice using 6 cytoarchitectonic and MRI-derived human atlases, and 3 cytoarchitectonic mouse atlases (as well as 2 rat atlases) in order to narrow down regions with cross-species homologs (Swanson and Hof, 2019 [DOI](#)). We computed the standardized effect sizes of sex on volume of each of these regions as described in the section above for humans and mice. We used a robust correlation to determine the similarity of sex differences in regional brain volume across species by correlating the effect size for sex between species across regions. We also repeated this analysis using effect size estimates derived in each species without covarying for TTV.

4.5.2 Testing if cross-species congruence for sex differences is related to cross-species similarity in gene expression

To derive a regional measure for the cross-species concordance of sex differences in volume we multiplied the effect size of sex for each species. This product (i.e., “anatomical sex effect similarity score”) is positive for regions showing congruent sex differences between species (i.e., larger in males for both or larger in females for both), and negative for regions showing incongruent sex effects (e.g., larger in males for females for humans but larger in males for mice). Next, to derive a regional measure of cross-species transcriptional similarity, we computed the Pearson correlation between scaled expression values for all homologous genes in humans and mice per brain region. These steps created two measures per brain region - one for the cross-species similarity of volumetric sex differences (anatomical sex effect similarity score) and another for the cross-species similarity in gene expression - which we could then correlate across brain regions to test if regions with more conserved sex differences show more conserved gene expression. We estimated this correlation using a robust correlation - once using measures from all brain regions and all genes and again using subsets of brain regions and genes. Specifically, we compared the correlation between conserved sex effects and conserved expression for cortical vs. subcortical regions and also recomputed these correlations using the following subsets of homologous genes: (i) X-linked genes (n=91) or (ii) sex hormone signaling genes (n=34). Next, we split the sex hormone genes into either (i) androgen-signaling related genes (n=11), or (ii) estrogen or progesterone signaling related genes (n=23). The sex hormone signaling genes were identified based on Gene Ontology data for biological process modules from the Bader Lab (University of Toronto, <http://>

baderlab.org/GeneSets [↗](#)). For each analysis using subsets of genes, we generated a null distribution of correlations based on 10,000 randomly sampled gene sets of the same size (i.e., 91 to match X-chromosome genes), and compared the observed correlations with these null distributions using the ‘get_p_valu’ function in R’s infer package (**Supplement 2.4**).

Acknowledgements

This study was supported by the intramural research program of the National Institute of Mental Health (project funding: 1ZIAMH002949-03), the National Institute of Child Health and Disease (R01HD100298), as well as Canadian Institutes of Health Research, BrainCanada, and the Ontario Brain Institute. EG also receives salary support from the Fonds de Recherche du Québec en Santé. This research was enabled in part by support provided by Compute Canada (www.computecanada.ca [↗](#))

Author contributions

Conceptualization, writing - original draft, EG, AR, JPL; supervision, AR, JPL; project administration, EG, AR, JPL; methodology, software, and formal analysis, EG, AB, SL, EL, LP, AR, JPL; visualization, EG, AB; mouse data collection, JE; funding acquisition, AR, JPL, EG; writing - review & editing, all authors.

Resource Availability

Further information and requests for resources should be directed to and will be fulfilled by the lead contacts, Dr. Armin Raznahan (raznahan@mail.nih.gov) and Dr. Jason Lerch (jason.lerch@ndcn.ox.ac.uk). Input regional volume measures for humans and mice, as well as original code for statistical analyses have been deposited to GitHub and are publicly available here: <https://github.com/elisaguma/Normative-Sex-Differences> [↗](#), while code for gene expression processing is available here: <https://github.com/abeaucha/NormativeSexDifferences> [↗](#).

References

- Archer J. (2004) **Sex Differences in Aggression in Real-World Settings: A Meta-Analytic Review** *Rev Gen Psychol* **8**:291–322
- Arnatkeviciute A, Fulcher BD, Fornito A. (2019) **A practical guide to linking brain-wide gene expression and neuroimaging data** *Neuroimage* **189**:353–367
- Arnold AP, Chen X. (2009) **What does the “four core genotypes” mouse model tell us about sex differences in the brain and other tissues?** *Front Neuroendocrinol* **30**:1–9
- Avants BB, Tustison N, Song G (2009) **Advanced normalization tools (ANTs)** *Insight J* **2**:1–35
- Balsters JH, Zerbi V, Sallet J, Wenderoth N, Mars RB. (2020) **Primate homologs of mouse cortico-striatal circuits** *eLife* <https://doi.org/10.7554/elife.53680>
- Bao A-M, Swaab DF. (2010) **Sex differences in the brain, behavior, and neuropsychiatric disorders** *Neuroscientist* **16**:550–565
- Beauchamp A, Yee Y, Darwin B, Raznahan A, Mars RB, Lerch JP. (2022) **Whole-brain comparison of rodent and human brains using spatial transcriptomics** *eLife* <https://doi.org/10.7554/eLife.79418>
- Benjamini Y, Hochberg Y. (1995) **Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing** *Journal of the Royal Statistical Society: Series B (Methodological)* <https://doi.org/10.1111/j.2517-6161.1995.tb02031.x>
- Benjamini Y, Yekutieli D. (2001) **The Control of the False Discovery Rate in Multiple Testing under Dependency** *Ann Stat* **29**:1165–1188
- Bethlehem RAI *et al.* (2022) **3R-BRAIN, AIBL, Alzheimer’s Disease Neuroimaging Initiative, Alzheimer’s Disease Repository Without Borders Investigators, CALM Team, Cam-CAN, CCNP, COBRE, cVEDA, ENIGMA Developmental Brain Age Working Group, Developing Human Connectome Project, FinnBrain, Harvard Aging Brain Study, IMAGEN, KNE96, Mayo Clinic Study of Aging, NSPN, POND, PREVENT-AD Research Group, VETSA, Bullmore ET, Alexander-Bloch AF** *Brain charts for the human lifespan. Nature* **604**:525–533
- Bölte S, Neufeld J, Marschik PB, Williams ZJ, Gallagher L, Lai M-C. (2023) **Sex and gender in neurodevelopmental conditions** *Nat Rev Neurol* **19**:136–159
- Cahill LS, Laliberté CL, Ellegood J, Spring S, Gleave JA, van Eede MC, Lerch JP, Henkelman RM. (2012) **Preparation of fixed mouse brains for MRI** *Neuroimage* **60**:933–939
- Chakravarty MM, Steadman P, van Eede MC, Calcott RD, Gu V, Shaw P, Raznahan A, Collins DL, Lerch JP. (2013) **Performing label-fusion-based segmentation using multiple automatically generated templates** *Hum Brain Mapp* **34**:2635–2654
- Chung MK, Worsley KJ, Paus T, Cherif C, Collins DL, Giedd JN, Rapoport JL, Evans AC. (2001) **A unified statistical approach to deformation-based morphometry** *Neuroimage* **14**:595–606

- Chung WC, Swaab DF, De Vries GJ. (2000) **Apoptosis during sexual differentiation of the bed nucleus of the stria terminalis in the rat brain** *J Neurobiol* **43**:234–243
- Collins DL, Neelin P, Peters TM, Evans AC. (1994) **Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space** *J Comput Assist Tomogr* **18**:192–205
- Conte G *et al.* (2018) **Prenatal Brain MR Imaging: Reference Linear Biometric Centiles between 20 and 24 Gestational Weeks** *AJNR Am J Neuroradiol* **39**:963–967
- Cooke BM, Woolley CS. (2005) **Sexually dimorphic synaptic organization of the medial amygdala** *J Neurosci* **25**:10759–10767
- Corre C, Friedel M, Vousden DA, Metcalf A, Spring S, Qiu LR, Lerch JP, Palmert MR. (2016) **Separate effects of sex hormones and sex chromosomes on brain structure and function revealed by high-resolution magnetic resonance imaging and spatial navigation assessment of the Four Core Genotype mouse model** *Brain Struct Funct* **221**:997–1016
- Dale AM, Fischl B, Sereno MI. (1999) **Cortical Surface-Based Analysis** *NeuroImage* <https://doi.org/10.1006/nimg.1998.0395>
- Dale AM, Sereno MI. (1993) **Improved Localizadon of Cortical Activity by Combining EEG and MEG with MRI Cortical Surface Reconstruction: A Linear Approach** *J Cogn Neurosci* **5**:162–176
- Dean DC, Planalp EM, Wooten W, Schmidt CK, Kecskemeti SR, Frye C, Schmidt NL, Goldsmith HH, Alexander AL, Davidson RJ. (2018) **Investigation of brain structure in the 1-month infant** *Brain Struct Funct* **223**:1953–1970
- DeCasien AR, Guma E, Liu S, Raznahan A. (2022) **Sex differences in the human brain: a roadmap for more careful analysis and interpretation of a biological reality** *Biol Sex Differ* **13**
- Dekaban AS. (1978) **Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights** *Ann Neurol* **4**:345–356
- Deng X, Berletch JB, Nguyen DK, Disteché CM. (2014) **X chromosome regulation: diverse patterns in development, tissues and disease** *Nat Rev Genet* **15**:367–378
- Desikan RS *et al.* (2006) **An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest** *Neuroimage* **31**:968–980
- Dorr AE, Lerch JP, Spring S, Kabani N, Henkelman RM. (2008) **High resolution three-dimensional brain atlas using an average magnetic resonance image of 40 adult C57Bl/6J mice** *Neuroimage* **42**:60–69
- Eliot L, Ahmed A, Khan H, Patel J. (2021) **Dump the “dimorphism”: Comprehensive synthesis of human brain studies reveals few male-female differences beyond size** *Neurosci Biobehav Rev* **125**:667–697
- Elkind D, Hochgerner H, Aloni E, Shental N, Zeisel A. (2023) **Sex, strain, and lateral differences in brain cytoarchitecture across a large mouse population** *Elife* **12** <https://doi.org/10.7554/eLife.82376>

Ellegood J *et al.* (2015) **Clustering autism: using neuroanatomical differences in 26 mouse models to gain insight into the heterogeneity** *Mol Psychiatry* **20**:118–125

Fang R *et al.* (2022) **Conservation and divergence of cortical cell organization in human and mouse revealed by MERFISH** *Science* **377**:56–62

Fischl B. (2012) **FreeSurfer** *Neuroimage* **62**:774–781

Fischl B, Dale AM. (2000) **Measuring the thickness of the human cerebral cortex from magnetic resonance images** *Proc Natl Acad Sci U S A* **97**:11050–11055

Fischl B, Dale AM, Sereno MI, Tootell RBH, Rosen BR. (1998) **A Coordinate System for the Cortical Surface** *NeuroImage* [https://doi.org/10.1016/s1053-8119\(18\)31573-8](https://doi.org/10.1016/s1053-8119(18)31573-8)

Fischl B, Liu A, Dale AM. (2001) **Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex** *IEEE Trans Med Imaging* **20**:70–80

Fischl B *et al.* (2002) **Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain** *Neuron* **33**:341–355

Fischl B, Salat DH, van der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM. (2004) **Sequence-independent segmentation of magnetic resonance images** *Neuroimage* **23**:S69–84

Fischl B, Sereno MI, Tootell RB, Dale AM. (1999) **High-resolution intersubject averaging and a coordinate system for the cortical surface** *Hum Brain Mapp* **8**:272–284

Fischl B *et al.* (2004) **Automatically parcellating the human cerebral cortex** *Cereb Cortex* **14**:11–22

Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL, Brain Development Cooperative Group (2011) **Unbiased average age-appropriate atlases for pediatric studies** *Neuroimage* **54**:313–327

Fonov VS, Evans AC, McKinstry RC, Almli CR, Collins DL. (2009) **Unbiased nonlinear average age-appropriate brain templates from birth to adulthood** *Neuroimage* **47**

Forde NJ, Jeyachandra J, Joseph M, Jacobs GR, Dickie E, Satterthwaite TD, Shinohara RT, Ameis SH, Voineskos AN. (2020) **Sex Differences in Variability of Brain Structure Across the Lifespan** *Cereb Cortex* **30**:5420–5430

Fortin J-P *et al.* (2018) **Harmonization of cortical thickness measurements across scanners and sites** *NeuroImage* <https://doi.org/10.1016/j.neuroimage.2017.11.024>

Fortin J-P *et al.* (2017) **Harmonization of multi-site diffusion tensor imaging data** *NeuroImage* <https://doi.org/10.1016/j.neuroimage.2017.08.047>

Friedel M, van Eede MC, Pipitone J, Chakravarty MM, Lerch JP. (2014) **Pydipiper: a flexible toolkit for constructing novel registration pipelines** *Front Neuroinform* **8**

Gilmore JH *et al.* (2007) **Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain** *J Neurosci* **27**:1255–1260

- Glasser MF *et al.* (2016) **A multi-modal parcellation of human cerebral cortex** *Nature* **536**:171–178
- Glasser MF *et al.* (2013) **The minimal preprocessing pipelines for the Human Connectome Project** *Neuroimage* **80**:105–124
- Gogolla N. (2017) **The insular cortex** *Curr Biol* **27**:R580–R586
- Gorski RA, Gordon JH, Shryne JE, Southam AM. (1978) **Evidence for a morphological sex difference within the medial preoptic area of the rat brain** *Brain Res* **148**:333–346
- Griffiths PD, Jarvis D, Mooney C, Campbell MJ. (2023) **Sex differences in fetal intracranial volumes assessed by in utero MR imaging** *Biol Sex Differ* **14**
- Guma E *et al.* (2023) **A cross-species neuroimaging study of sex chromosome dosage effects on human and mouse brain anatomy** *J Neurosci* <https://doi.org/10.1523/JNEUROSCI.1761-22.2022>
- Haldipur P *et al.* (2019) **Spatiotemporal expansion of primary progenitor zones in the developing human cerebellum** *Science* **366**:454–460
- Han X *et al.* (2006) **Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer** *NeuroImage* <https://doi.org/10.1016/j.neuroimage.2006.02.051>
- Hawrylycz MJ *et al.* (2012) **An anatomically comprehensive atlas of the adult human brain transcriptome** *Nature* **489**:391–399
- Herlitz A, Lovén J. (2013) **Sex differences and the own-gender bias in face recognition: A meta-analytic review** *Vis cogn* **21**:1306–1336
- Hines M, Allen LS, Gorski RA. (1992) **Sex differences in subregions of the medial nucleus of the amygdala and the bed nucleus of the stria terminalis of the rat** *Brain Res* **579**:321–326
- Iglesias JE *et al.* (2015) **A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI** *Neuroimage* **115**:117–137
- Iglesias JE, Van Leemput K, Bhatt P, Casillas C, Dutt S, Schuff N, Truran-Sacrey D, Boxer A, Fischl B, Alzheimer's Disease Neuroimaging Initiative (2015) **Bayesian segmentation of brainstem structures in MRI** *Neuroimage* **113**:184–195
- Johnson WE, Li C, Rabinovic A. (2007) **Adjusting batch effects in microarray expression data using empirical Bayes methods** *Biostatistics* **8**:118–127
- Jovicich J *et al.* (2006) **Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data** *Neuroimage* **30**:436–443
- Kelava I, Chiaradia I, Pellegrini L, Kalinka AT, Lancaster MA. (2022) **Androgens increase excitatory neurogenic potential in human brain organoids** *Nature* **602**:112–116
- Kim Y *et al.* (2017) **Brain-wide Maps Reveal Stereotyped Cell-Type-Based Cortical Architecture and Subcortical Sexual Dimorphism** *Cell* **171**:456–469

- Knickmeyer RC, Wang J, Zhu H, Geng X, Woolson S, Hamer RM, Konneker T, Styner M, Gilmore JH. (2014) **Impact of sex and gonadal steroids on neonatal brain structure** *Cereb Cortex* **24**:2721–2731
- Kuperberg GR *et al.* (2003) **Regionally Localized Thinning of the Cerebral Cortex in Schizophrenia** *Archives of General Psychiatry* <https://doi.org/10.1001/archpsyc.60.9.878>
- Lein ES *et al.* (2007) **Genome-wide atlas of gene expression in the adult mouse brain** *Nature* **445**:168–176
- Lippa RA, Collaer ML, Peters M. (2010) **Sex differences in mental rotation and line angle judgments are positively associated with gender equality and economic development across 53 nations** *Arch Sex Behav* **39**:990–997
- Liu S, Seidlitz J, Blumenthal JD, Clasen LS, Raznahan A. (2020) **Integrative structural, functional, and transcriptomic analyses of sex-biased brain organization in humans** *Proc Natl Acad Sci U S A* **117**:18788–18798
- Lombardo MV, Ashwin E, Auyeung B, Chakrabarti B, Taylor K, Hackett G, Bullmore ET, Baron-Cohen S. (2012) **Fetal testosterone influences sexually dimorphic gray matter in the human brain** *J Neurosci* **32**:674–680
- Lotze M, Domin M, Gerlach FH, Gaser C, Lueders E, Schmidt CO, Neumann N. (2019) **Novel findings from 2,838 Adult Brains on Sex Differences in Gray Matter Brain Volume** *Sci Rep* **9**
- Markello RD, Arnatkevičiūtė A, Poline J-B, Fulcher BD, Fornito A, Misic B. (2021) **Standardizing workflows in imaging transcriptomics with the abagen toolbox** *bioRxiv* <https://doi.org/10.1101/2021.07.08.451635>
- Mars RB, Sotiropoulos SN, Passingham RE, Sallet J, Verhagen L, Khrapitchev AA, Sibson N, Jbabdi S. (2018) **Whole brain comparative anatomy using connectivity blueprints** *Elife* **7** <https://doi.org/10.7554/eLife.35237>
- McCarthy MM. (2020) **A new view of sexual differentiation of mammalian brain** *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* **206**:369–378
- McCarthy MM, Arnold AP. (2011) **Reframing sexual differentiation of the brain** *Nat Neurosci* **14**:677–683
- Resource Coordinators NCBI (2018) **Database resources of the National Center for Biotechnology Information** *Nucleic Acids Res* **46**:D8–D13
- Neudorfer C, Germann J, Elias GJB, Gramer R, Boutet A, Lozano AM. (2020) **A high-resolution in vivo magnetic resonance imaging atlas of the human hypothalamic region** *Sci Data* **7**
- Nishizuka M, Arai Y. (1981) **Sexual dimorphism in synaptic organization in the amygdala and its dependence on neonatal hormone environment** *Brain Res* **212**:31–38
- Olderbak S, Wilhelm O, Hildebrandt A, Quoidbach J. (2019) **Sex differences in facial emotion perception ability across the lifespan** *Cognition and Emotion* <https://doi.org/10.1080/02699931.2018.1454403>

Pipitone J, Park MTM, Winterburn J, Lett TA, Lerch JP, Pruessner JC, Lepage M, Voineskos AN, Chakravarty MM, Alzheimer's Disease Neuroimaging Initiative (2014) **Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates** *Neuroimage* **101**:494–512

Plavcan JM. (2012) **Sexual size dimorphism, canine dimorphism, and male-male competition in primates: where do humans fit in?** *Hum Nat* **23**:45–67

Qiu LR, Fernandes DJ, Szulc-Lerch KU, Dazai J, Nieman BJ, Turnbull DH, Foster JA, Palmert MR, Lerch JP. (2018) **Mouse MRI shows brain areas relatively larger in males emerge before those larger in females** *Nat Commun* **9**

Raznahan A, Lee NR, Greenstein D, Wallace GL, Blumenthal JD, Clasen LS, Giedd JN. (2016) **Globally Divergent but Locally Convergent X- and Y-Chromosome Influences on Cortical Development** *Cereb Cortex* **26**:70–79

Reinhold K, Engqvist L. (2013) **The variability is in the sex chromosomes** *Evolution* **67**:3662–3668

Reuter M, Rosas HD, Fischl B. (2010) **Highly accurate inverse consistent registration: a robust approach** *Neuroimage* **53**:1181–1196

Richards K *et al.* (2011) **Segmentation of the mouse hippocampal formation in magnetic resonance images** *Neuroimage* **58**:732–740

Rosen AFG *et al.* (2018) **Quantitative assessment of structural image quality** *Neuroimage* **169**:407–418

Ruigrok ANV, Salimi-Khorshidi G, Lai M-C, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J. (2014) **A meta-analysis of sex differences in human brain structure** *Neurosci Biobehav Rev* **39**:34–50

Saygin ZM *et al.* (2017) **High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas** *Neuroimage* **155**:370–382

Schwarz JM, McCarthy MM. (2008) **Cellular mechanisms of estradiol-mediated masculinization of the brain** *J Steroid Biochem Mol Biol* **109**:300–306

Soh YQS *et al.* (2014) **Sequencing the mouse Y chromosome reveals convergent gene acquisition and amplification on both sex chromosomes** *Cell* **159**:800–813

Noakes TL, Spencer, Henkelman RM, Nieman BJ. (2017) **Partitioning k-space for cylindrical three-dimensional rapid acquisition with relaxation enhancement imaging in the mouse brain** *NMR Biomed* **30**

Spring S, Lerch JP, Henkelman RM. (2007) **Sexual dimorphism revealed in the structure of the mouse brain using three-dimensional magnetic resonance imaging** *Neuroimage* **35**:1424–1433

Steadman PE, Ellegood J, Szulc KU, Turnbull DH, Joyner AL, Henkelman RM, Lerch JP. (2014) **Genetic effects on cerebellar structure across mouse models of autism using a magnetic resonance imaging atlas** *Autism Res* **7**:124–137

- Swanson LW, Hof PR. (2019) **A model for mapping between the human and rodent cerebral cortex** *J Comp Neurol* **527**:2925–2927
- Tabatabai M, Bailey S, Bursac Z, Tabatabai H, Wilus D, Singh KP. (2021) **An introduction to new robust linear and monotonic correlation coefficients** *BMC Bioinformatics* **22**
- Ullmann JFP, Watson C, Janke AL, Kurniawan ND, Reutens DC. (2013) **A segmentation protocol and MRI atlas of the C57BL/6J mouse neocortex** *Neuroimage* **78**:196–203
- Van Essen DC *et al.* (2012) **The Human Connectome Project: A data acquisition perspective** *NeuroImage* <https://doi.org/10.1016/j.neuroimage.2012.02.018>
- Vogt BA, Paxinos G. (2014) **Cytoarchitecture of mouse and rat cingulate cortex with human homologies** *Brain Struct Funct* **219**:185–192
- Vousden DA, Corre C, Spring S, Qiu LR, Metcalf A, Cox E, Lerch JP, Palmert MR. (2018) **Impact of X/Y genes and sex hormones on mouse neuroanatomy** *Neuroimage* **173**:551–563
- Wang Q *et al.* (2020) **The Allen Mouse Brain Common Coordinate Framework: A 3D Reference Atlas** *Cell* **181**:936–953
- Wierenga LM *et al.* (2022) **Greater male than female variability in regional brain structure across the lifespan** *Hum Brain Mapp* **43**:470–499
- Williams CM, Peyre H, Toro R, Ramus F. (2021) **Sex differences in the brain are not reduced to differences in body size** *Neurosci Biobehav Rev* **130**:509–511
- Wilson LAB, Zajitschek SRK, Lagisz M, Mason J, Haselimashhadi H, Nakagawa S. (2022) **Sex differences in allometry for phenotypic traits in mice indicate that females are not scaled males** *Nat Commun* **13**
- Wu MV, Shah NM. (2011) **Control of masculinization of the brain and behavior** *Curr Opin Neurobiol* **21**:116–123
- Yao Z *et al.* (2021) **A taxonomy of transcriptomic cell types across the isocortex and hippocampal formation** *Cell* **184**:3222–3241
- Zajitschek SR *et al.* (2020) **Sexual dimorphism in trait variability and its eco-evolutionary and statistical implications** *Elife* **9** <https://doi.org/10.7554/eLife.63170>
- Zaretskaya N, Fischl B, Reuter M, Renvall V, Polimeni JR. (2018) **Advantages of cortical surface reconstruction using submillimeter 7 T MEMPRAGE** *Neuroimage* **165**:11–26
- Zhou X *et al.* (2022) **Choice of Voxel-based Morphometry processing pipeline drives variability in the location of neuroanatomical brain markers** *Commun Biol* **5**
- Zuloaga DG, Puts DA, Jordan CL, Breedlove SM. (2008) **The role of androgen receptors in the masculinization of brain and behavior: what we've learned from the testicular feminization mutation** *Horm Behav* **53**:613–626

Article and author information

Elisa Guma

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA

For correspondence: elisa.guma@nih.gov

ORCID iD: [0000-0003-4651-8529](https://orcid.org/0000-0003-4651-8529)

Antoine Beauchamp

Mouse Imaging Centre, Toronto, Ontario, Canada, The Hospital for Sick Children, Toronto, Ontario, Canada, Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

Siyuan Liu

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA

Elizabeth Levitis

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA

Jacob Ellegood

Mouse Imaging Centre, Toronto, Ontario, Canada, The Hospital for Sick Children, Toronto, Ontario, Canada

Linh Pham

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA, Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

ORCID iD: [0000-0001-6664-726X](https://orcid.org/0000-0001-6664-726X)

Rogier B Mars

Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands

Armin Raznahan

Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA

For correspondence: raznahana@mail.nih.gov

Jason P Lerch

Mouse Imaging Centre, Toronto, Ontario, Canada, The Hospital for Sick Children, Toronto, Ontario, Canada, Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada, Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

For correspondence: jason.lerch@ndcn.ox.ac.uk

Copyright

© 2024, Guma et al.

This article is distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use and redistribution provided that the original author and source are credited.

Editors

Reviewing Editor

Floris de Lange

Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands

Senior Editor

Floris de Lange

Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands

Joint Public Review:

Summary:

Guma and colleagues set out to compare to what extent differences in total and regional brain volumes, as measured by structural magnetic resonance imaging (MRI) are conserved or not, between humans and mice. The rationale for this work is to inform the best use of the mouse as a model system to carry out mechanistic studies of how sex differences arise in brain volumes, based on convergence to humans. This has practical implications for multiple fields in neuroscience. The authors find a modest convergence on these measures highlighting important areas for further mechanistic study.

Strengths:

The main strengths of the study lie in the use of a cross-species technology, i.e. structural MRI, using tools and methods that have been extensively validated.

Weaknesses:

Limitations of the study include, as acknowledged by the authors, the focus on a specific age range in mice and humans (which may not be congruent) and the lack of information regarding sex differences earlier or later in life. This has relevance with regard to the ages of onset for psychiatric and neurological disorders for example, which show apparent sex differences in prevalence. The paper also does provide data for an intermediate phylogenetic level of analysis, such as data from primates. Lastly, these data do not provide any evidence as to the mechanisms underlying sex differences, when they arise, and to what extent they impact behavior.

- <https://doi.org/10.7554/eLife.92200.1.sa0>