

The Brain's Gendered Architecture: An MRI Study of Cortical and Subcortical Volume Differences

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ABSTRACT

OBJECTIVE For the advancement of neuroscience and therapeutic applications, it is crucial to understand how cerebral and subcortical volumes change across sexes. This study utilized magnetic resonance imaging (MRI) to investigate volumetric variations in various brain areas across different sexes.

METHODS A cross-sectional study was conducted on 200 healthy participants (100 males and 100 females). High-resolution MRI scans were acquired using a 1.5T General Electric Signa scanner, and cortical segmentation was performed using a standardized semi-automated method. Statistical analyses were conducted using IBM SPSS, with independent sample t-tests employed to compare volumetric differences between sexes. Effect sizes were computed using Cohen's d, and multiple comparisons were adjusted via the Bonferroni method.

RESULTS There were considerably greater volumes of total cerebral white matter ($p < 0.001$, $d = -1.1$), total cortex ($p < 0.001$, $d = -0.635$), and total cerebrum ($p < 0.001$, $d = -1.352$) in males. Males also had considerably bigger ventricular structures, such as the lateral ($p < 0.001$, $d = -0.71$) and third ($p < 0.001$, $d = -1.229$) ventricles, although there was no significant difference in the fourth ventricle ($p = 0.171$). Males had substantially greater volumes in the inferior temporal gyrus ($p < 0.001$, $d = -0.58$), middle temporal gyrus ($p < 0.001$, $d = -0.55$), and superior temporal gyrus ($p < 0.001$, $d = -0.73$) among cortical areas with low-density sex hormone receptors. Significant differences were seen in the occipital pole ($p < 0.001$, $d = -1.342$), thalamus ($p < 0.001$, $d = -1.282$), and postcentral gyrus ($p < 0.001$, $d = -1.536$) in areas with high-density sex hormone receptors.

CONCLUSIONS This study confirms significant sex-based differences in brain volume, particularly in cortical and subcortical structures. These findings highlight the role of sex hormones in shaping neuroanatomy and provide insights for future research on sex-specific neurological and psychiatric conditions.

KEYWORDS sex differences, cortical and subcortical volumes, MRI, brain morphometry, neuroanatomy

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INTRODUCTION

Many studies have examined sex-based differences in brain morphology, especially with regard to volumetric variances in various brain areas (1, 2). Examining neurodevelopmental patterns, cognitive processes, and possible ramifications in neurological and psychiatric illnesses requires an understanding of these distinctions. The goal of the current study is to thoroughly examine the volumetric differences between males and females in a variety of brain regions, such as the whole cerebrum, cortical structures, ventricular gaps, and areas with different densities of androgen and estrogen receptors (3). This study sheds light on anatomical differences that might be responsible for sex-specific behavioral patterns, neurological susceptibilities, and cognitive capacities (4).

Using a variety of neuroimaging methods, recent research has investigated sex-based variations in brain shape. Males often have bigger regional and overall brain sizes (5, 6), while there are fewer noticeable sex variations in cortical thickness (7). Fronto-parietal, subcortical, and cerebellar areas have been found to have sex-specific differences in gray matter volume. Regional volumetric differences have been observed, with some areas showing higher volumes in males and others in females (7). These differences persist throughout the lifespan and are not solely attributable to body size variations (8). Sex chromosomes and hormones may have contributed to the creation of these disparities, which last throughout life (6). Multivariate sex disparities in gray matter volume, however, diminish when total cerebral volume is taken into account. Crucially, Sanchis-Segura et al. point out that these variations do not create unique “male/female brain” characteristics (9). It has been suggested that sex-specific brain templates be created in order to enhance neuroimaging investigations and more accurately depict population-specific neuroanatomy (5).

The findings reveal significant sex-based differences in total brain volume, with males exhibiting larger total cerebrum and cortical volumes compared to females. Specifically, males demonstrated significantly greater total cerebral white matter and lateral and third ventricle volumes, with large effect sizes (10). However, no significant

sex-based difference was observed in the fourth ventricle volume, indicating that not all ventricular structures follow the same pattern of volumetric variation (2). Further analysis of brain regions with low Estrogen and Androgen receptor densities indicated that males generally had larger volumes across multiple structures, including the superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, and subcallosal cortex (1). However, some regions, such as the superior occipital lateral gyri and temporal pole, did not exhibit significant sex-based differences, suggesting that receptor density alone does not fully account for volumetric variations (3).

In contrast, analysis of regions with high-density estrogen and androgen receptors revealed a more complex pattern of volumetric differences. Males had significantly larger volumes in key structures, including the postcentral gyrus, occipital pole, hippocampus, insula, and thalamus (4). Additionally, males exhibited larger volumes in the anterior cingulate gyrus, paracingulate cortex, and middle frontal gyrus, which are regions implicated in cognitive control and emotional regulation (10).

Interestingly, the fronto-orbital cortex was significantly larger in females, suggesting potential functional and structural distinctions in this region, which may relate to differences in social cognition and affective processing (2). These results align with existing literature highlighting sex-based variations in brain morphology and emphasizing the importance of considering biological sex in neuroimaging studies. The observed differences may be attributed to a combination of genetic, hormonal, and environmental factors that influence brain development and function (3). Future research should explore the functional implications of these volumetric differences, particularly in relation to cognitive performance, susceptibility to neuropsychiatric disorders, and brain plasticity across the lifespan (4). A deeper understanding of these structural distinctions will enhance our knowledge of sex-specific neurobiological processes and their relevance to health and disease. Hence, this study utilizes magnetic resonance imaging (MRI) to comprehensively analyze sex-based variations in the volumetric measurements of both cortical and subcortical brain regions, aiming to enhance our

understanding of neuroanatomical differences influenced by biological sex.

METHODS

Study design and participants

This study utilized a cross-sectional design to investigate sex differences in cerebral cortical volumes using MRI. A total of 200 healthy participants (100 males and 100 females) were included in the study. Ethical approval (Approval/Reference Number: [MMC/IEC/2022/2945/03/2025, approve April 4, 2025]) was obtained from the institutional review board Mamata Medical College, and informed consent was secured from all participants prior to data collection.

MRI Acquisition parameters and segmentation procedures

MRI scans were obtained at the Department of Radiology, Mamata Medical College, using a 1.5 T General Electric Signa scanner. Coronal spoiled-gradient echo images of the entire brain were acquired with a slice thickness of 3.1 mm, using the following parameters: repetition time (TR) = 40 ms, echo time (TE) = 8 ms, flip angle = 50°, the field of view = 30 cm, matrix resolution = 256 × 256, and one average per scan. The images were subsequently processed and analyzed in the Department of Radiology, Mamata Medical College Khammam, Telangana.

To ensure consistency in spatial orientation across subjects, each MRI scan was standardized using a three-dimensional coordinate system. This was achieved by aligning the scans based on anatomical landmarks, specifically the midpoints of the decussations of the anterior and posterior commissures and the midsagittal plane at the level of the posterior commissure, following the methodology described by Filipek et al. and Caviness et al. (11, 12). This positional normalization technique minimizes discrepancies arising from variations in head positioning during scanning. After alignment, the scans were resliced into 3.1 mm coronal sections.

Segmentation of the T1-weighted, positionally normalized coronal images involved differentiating gray matter, white matter, and ventricular structures. A semi-automated intensity contour mapping algorithm, in conjunction with signal intensity histogram distributions, was employed

to delineate these structures (11–13). This method partitions the brain into distinct compartments, including the neocortex, subcortical gray nuclei, white matter, and ventricular system subdivisions, which correspond to the natural variations in signal intensity observed in T1-weighted images.

The neocortex, as defined by the gray–white matter segmentation approach, was further subdivided into bilateral regions using the parcellation framework originally established by Caviness et al. and subsequently applied by Goldstein et al. This comprehensive system facilitates the division of the neocortex into anatomically and functionally relevant subdivisions based on well-defined topographical landmarks. Detailed anatomical definitions of these parcellation units can be found in prior studies (12, 13).

MRI segmentation and cortical parcellation were conducted by extensively trained MR technicians with a background in Neuroanatomy or Behavioral Neuroscience. These technicians were supervised continuously by an experienced neuroanatomist (N.M.) to ensure accuracy and reliability. In addition, a blinded specialist radiologist at Mamata Medical College independently reviewed and validated the segmentation and volumetric analysis, ensuring objectivity in the measurement process. Importantly, both the technicians and the radiologist were blinded to all socio-demographic and clinical information of the participants, including sex.

The reliability of these segmentation and parcellation procedures has been established in multiple previous studies, including those focusing on the dataset used in this study (12, 14, 15). Brain region volumes, measured in cubic centimeters (cm³), were computed by multiplying the area of each region on a given slice by the slice thickness and summing the values across all slices in which the region was present. This method ensures precise volume estimation and has been widely used in neuroimaging research.

Statistical methods

All statistical analyses were conducted using IBM SPSS Statistics (version 27.0). The volumetric measurements of different brain regions were compared between males and females using independent sample *t*-tests. The normality of the data was assessed using the Shapiro-Wilk test,

and the homogeneity of variance was evaluated with Levene's test. For each brain region, mean volume ($\pm$ standard deviation) was calculated separately for males and females. Independent *t*-tests were applied to determine whether there were statistically significant differences in regional brain volumes between the two sexes. The *t*-values, degrees of freedom, and *p*-values were reported for each comparison. Effect sizes were computed using Cohen's *d* to assess the magnitude of differences. Effect size interpretation followed the conventional guidelines: small ($d = 0.2$), moderate ($d = 0.5$), and large ($d \geq 0.8$). A *p*-value of < 0.05 was considered statistically significant, and multiple comparisons were corrected using the Bonferroni method to minimize type I errors. The brain regions were categorized based on their developmental sensitivity to sex hormones, distinguishing between regions with low-density and high-density estrogen and androgen receptors. Statistical comparisons were made separately for each category to evaluate sex-related volumetric differences.

RESULTS

Total cerebrum and cortex volume

Males exhibited significantly larger total cerebrum volume compared to females ($t(198) = -9.56$, $p < 0.001$, $d = -1.352$), indicating a large effect size. Similarly, the total cortex volume was greater in males than in females ($t(198) = -4.487$, $p < 0.001$, $d = -0.635$), with a moderate effect size (Figure 1A).

Total cerebral white matter

A significant difference was observed in total cerebral white matter volume, with males having larger volumes than females ($t(198) = -7.781$, $p < 0.001$, $d = -1.1$), suggesting a strong effect size (Figure 1A).

Comparison of brain region volumes between males and females

Ventricular volumes

The lateral ventricles were significantly larger in males than in females ($t(198) = -5.022$, $p < 0.001$, $d = -0.71$), representing a moderate effect. The third ventricle volume also showed a significant sex-based difference, with males having larger volumes than females ($t(198) = -8.689$, $p < 0.001$, $d = -1.229$), indicating a large effect size. However, the fourth ventricle did not show a statistically significant difference between sexes ($t(198) = -1.374$, $p = 0.171$, $d = -0.194$), suggesting minimal variation (Figure 1B). Overall, the findings indicate that males have significantly larger volumes in most brain regions, with the most pronounced differences observed in total cerebrum, total cerebral white matter, and third ventricle volumes. The observed effect sizes highlight substantial sex-based variations in brain morphology.

Comparison of brain region volumes in developmentally low estrogen and androgen receptor regions

Occipital lobe regions

The superior occipital lateral gyri did not show a significant difference between males and females

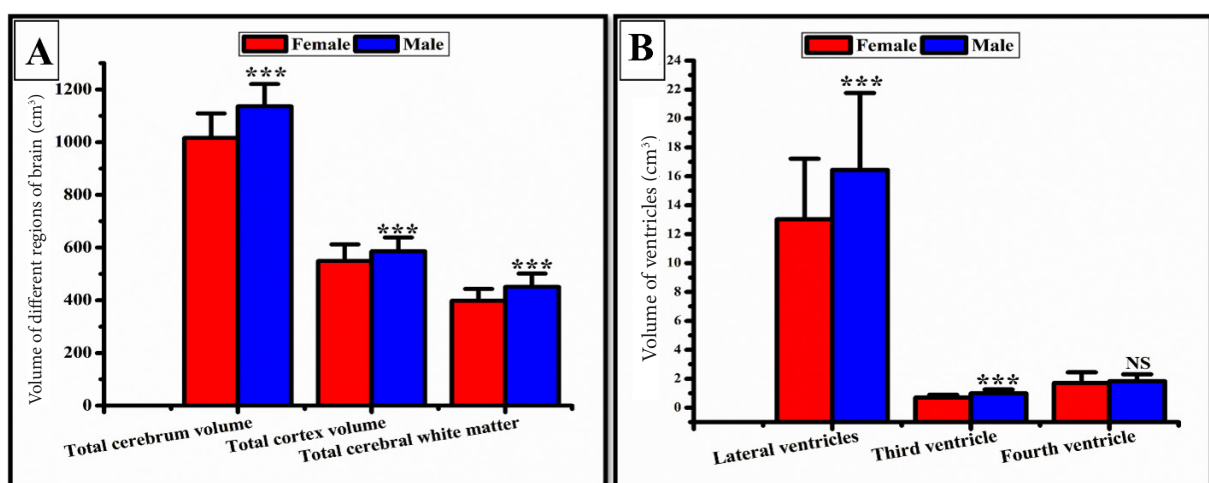


Figure 1. Volume (cm³) of different regions compared between females and males. (A) Volume of different regions of the brain, (B) Volume of the ventricle. *** $p < 0.001$.

Table 1. Volume (cm³) of different regions in developmentally low estrogen and androgen receptor regions compared between females and males

Brain region	Females Mean±SD	Males Mean±SD	t-value	p-value	Effect size (Cohen's d)
Superior occipital lateral gyri	37.58±7.11	38.35±8.02	-0.723	0.471	-0.10
Planum polare	3.19±0.61	3.44±0.81	-2.472	0.014	-0.35
Central operculum	7.56±1.03	8.17±1.39	-3.504	0.001	-0.50
Superior parietal lobule	10.85±2.00	12.39±2.70	-4.567	0.000	-0.65
Inferior occipital lateral gyri	17.73±4.04	18.62±4.18	-1.520	0.130	-0.22
Temporal pole	18.30±2.93	18.85±3.59	-1.181	0.239	-0.17
Temporooccipital fusiform gyrus	6.51±1.57	6.93±1.45	-1.933	0.055	-0.27
Frontal pole	55.04±9.51	61.08±9.41	-4.519	0.000	-0.64
Middle temporal gyrus	14.55±2.23	15.77±2.23	-3.857	0.000	-0.55
Precuneus	20.25±3.78	22.42±3.15	-4.428	0.000	-0.63
Superior temporal gyrus	10.47±1.45	11.64±1.74	-5.168	0.000	-0.73
Temporal fusiform gyrus	9.97±1.89	11.70±1.94	-6.364	0.000	-0.90
Inferior temporal gyrus	10.85±2.55	12.37±2.76	-4.065	0.000	-0.58
Subcallosal cortex	4.15±0.87	4.97±0.83	-6.763	0.000	-0.96

($t(198) = -0.723$, $p = 0.471$, $d = -0.1$). Similarly, the inferior occipital lateral gyri also showed no significant difference ($t(198) = -1.52$, $p = 0.13$, $d = -0.22$), indicating minimal sex-based variation in these regions (Table 1).

Temporal lobe regions

The planum polare exhibited a small but significant difference, with males having a larger volume ($t(198) = -2.472$, $p = 0.014$, $d = -0.35$). The superior temporal gyrus ($t(198) = -5.168$, $p < 0.001$, $d = -0.73$), middle temporal gyrus ($t(198) = -3.857$, $p < 0.001$, $d = -0.55$), inferior temporal gyrus ($t(198) = -4.065$, $p < 0.001$, $d = -0.58$), and temporal fusiform gyrus ($t(198) = -6.364$, $p < 0.001$, $d = -0.9$) were all significantly larger in males, with effect sizes ranging from moderate to large. The temporal pole, however, did not show a statistically significant difference ($t(198) = -1.181$, $p = 0.239$, $d = -0.17$) (Table 1).

Parietal lobe regions

The superior parietal lobule showed a moderate sex difference, with males exhibiting larger volumes ($t(198) = -4.567$, $p < 0.001$, $d = -0.65$). The precuneus was also significantly larger in males ($t(198) = -4.428$, $p < 0.001$, $d = -0.63$), indicating consistent sex-related volumetric variation in parietal structures (Table 1).

Frontal lobe regions

The frontal pole was significantly larger in males ($t(198) = -4.519$, $p < 0.001$, $d = -0.64$). The central operculum also showed a notable sex difference, favoring males ($t(198) = -3.504$, $p = 0.001$, $d = -0.5$) (Table 1).

Subcortical and limbic regions

The subcallosal cortex exhibited one of the largest sex differences, with males having significantly larger volumes ($t(198) = -6.763$, $p < 0.001$, $d = -0.96$) (Table 1). Overall, males exhibited larger volumes in most examined brain regions, with particularly strong differences in the subcallosal cortex, temporal fusiform gyrus, and superior temporal gyrus. In contrast, some regions, such as the superior occipital lateral gyri and temporal pole, did not show significant sex-based differences. These findings suggest that sex-related differences in brain volume may be more pronounced in certain cortical and subcortical structures.

Comparison of brain region volumes in developmentally high-density estrogen and androgen receptor regions

Frontal lobe regions

The precentral gyrus showed no significant difference between males and females ($t(198) = 0.082$, $p = 0.935$, $d = 1.0132$). However, the front orbital cortex was significantly larger in females ($t(198) = 2.98$, $p = 0.003$, $d = 0.8539$), while the superior frontal gyrus showed a trend toward a difference but did not reach statistical significance ($t(198) = 1.877$, $p = 0.062$, $d = 1.3961$). The middle frontal gyrus was significantly larger in males ($t(198) = -5.146$, $p < 0.001$, $d = 1.1409$), as was the frontomedial cortex ($t(198) = -6.134$, $p < 0.001$, $d = 0.971$) (Table 2).

Table 2. Volume (cm³) of different regions developmentally high-density estrogen and androgen receptor regions comparing in females and males

Bain region	Female Mean±SD	Male Mean±SD	t-value	p-value	Effect size (Cohen's d)
Precentral gyrus	35.94±0.95	35.93±1.08	0.082	0.935	1.0132
Frontoorbital cortex	13.73±0.83	13.37±0.88	2.980	0.003	0.8539
Superior frontal gyrus	25.20±1.37	24.83±1.42	1.877	0.062	1.3961
Lingual gyrus	14.12±1.36	13.63±1.21	2.704	0.007	1.2866
Anterior cingulate gyrus	12.63±1.17	13.03±1.14	-2.482	0.014	1.1566
Posterior cingulate gyrus	11.24±1.25	11.59±1.11	-2.093	0.038	1.1827
Posterior supramarginal gyrus	11.31±1.18	10.44±1.20	5.140	0.000	1.1871
Middle frontal gyrus	23.22±1.20	24.05±1.08	-5.146	0.000	1.1409
Frontal operculum	3.07±0.68	3.06±0.62	0.064	0.949	0.6512
Caudate nucleus	6.60±0.98	6.85±0.98	-1.786	0.076	0.9770
Superior calcarine sulcus	2.89±0.82	2.84±0.72	0.487	0.627	0.7712
Hippocampus	7.82±1.02	8.50±1.03	-4.691	0.000	1.0276
Putamen	9.37±1.16	9.85±1.08	-2.991	0.003	1.1204
Basal forebrain	2.81±0.78	2.80±0.91	0.044	0.965	0.8505
Insula	14.30±1.14	15.34±1.08	-6.600	0.000	1.1130
Posterior parahippocampal gyrus	3.29±0.97	3.37±0.94	-0.555	0.579	0.9575
Nucleus accumbens	1.14±0.76	1.27±0.80	-1.173	0.242	0.7807
Anterior parahippocampal gyrus	5.55±1.04	5.80±1.10	-1.607	0.110	1.0703
Thalamus	13.35±1.26	14.52±1.31	-6.433	0.000	1.2821
Heschl's gyrus	2.97±0.90	3.32±0.70	-2.999	0.003	0.8025
Supplementary parietal cortex	10.99±0.94	12.15±1.01	-8.381	0.000	0.9731
Paracingulate cortex	11.80±1.06	12.36±1.19	-3.525	0.001	1.1271
Pallidum	3.34±0.70	3.45±0.74	-1.058	0.292	0.7171
Anterior supramarginal gyrus	7.66±1.17	8.26±1.34	-3.377	0.001	1.2569
Postcentral gyrus	26.05±1.22	28.80±1.80	-12.631	0.000	1.5361
Occipital pole	18.02±1.20	21.29±1.47	-17.263	0.000	1.3423
Amygdala	3.12±0.90	4.32±0.86	-9.667	0.000	0.8815
Angular gyrus	10.13±1.20	12.65±1.17	-15.088	0.000	1.1827
Hypothalamus	0.80±0.63	0.97±0.70	-1.792	0.075	0.669
Frontomedial cortex	4.26±0.90	5.10±1.04	-6.134	0.000	0.9710

Cingulate and paracingulate cortex

The anterior cingulate gyrus was significantly larger in males ($t(198) = -2.482, p = 0.014, d = 1.1566$), as was the posterior cingulate gyrus ($t(198) = -2.093, p = 0.038, d = 1.1827$). The paracingulate cortex also showed a significant difference, with males having larger volumes ($t(198) = -3.525, p = 0.001, d = 1.1271$) (Table 2).

Parietal lobe regions

The postcentral gyrus exhibited a large effect size, with males having significantly greater volumes ($t(198) = -12.631, p < 0.001, d = 1.5361$). The supplementary parietal cortex ($t(198) = -8.381, p < 0.001, d = 0.9731$) and the anterior supramarginal gyrus ($t(198) = -3.377, p = 0.001, d = 1.2569$) were also significantly larger in males. The angular gyrus showed a substantial difference, with males having significantly greater volumes ($t(198) = -15.088, p < 0.001, d = 1.1827$) (Table 2).

Temporal lobe regions

Heschl's gyrus was significantly larger in males ($t(198) = -2.999, p = 0.003, d = 0.8025$). The hippocampus also showed a notable sex difference, with males exhibiting larger volumes ($t(198) = -4.691, p < 0.001, d = 1.0276$), as did the anterior and posterior parahippocampal gyrus, though the latter did not reach statistical significance ($t(198) = -0.555, p = 0.579, d = 0.9575$). The insula was significantly larger in males ($t(198) = -6.6, p < 0.001, d = 1.113$) (Table 2).

Occipital regions

The occipital pole was significantly larger in males ($t(198) = -17.263, p < 0.001, d = 1.3423$), while the superior calcarine sulcus showed no significant difference ($t(198) = 0.487, p = 0.627, d = 0.7712$). The lingual gyrus was significantly larger in females ($t(198) = 2.704, p = 0.007, d = 1.2866$) (Table 2).

Subcortical structures

The thalamus was significantly larger in males ($t(198) = -6.433$, $p < 0.001$, $d = 1.2821$), as were the putamen ($t(198) = -2.991$, $p = 0.003$, $d = 1.1204$), caudate nucleus ($t(198) = -1.786$, $p = 0.076$, $d = 0.977$), and nucleus accumbens, though the latter did not reach statistical significance ($t(198) = -1.173$, $p = 0.242$, $d = 0.7807$). The amygdala was also significantly larger in males ($t(198) = -9.667$, $p < 0.001$, $d = 0.8815$). The hypothalamus showed a trend toward a difference but did not reach statistical significance ($t(198) = -1.792$, $p = 0.075$, $d = 0.669$) (Table 2).

Basal ganglia and limbic system

The pallidum did not show a significant difference ($t(198) = -1.058$, $p = 0.292$, $d = 0.7171$), nor did the basal forebrain ($t(198) = 0.044$, $p = 0.965$, $d = 0.8505$) (Table 2). Overall, males exhibited significantly larger volumes in most high-density estrogen and androgen receptor regions, particularly in the postcentral gyrus, occipital pole, angular gyrus, thalamus, and amygdala. However, some regions, such as the front orbital cortex and lingual gyrus, were larger in females. These findings suggest that sex differences in brain volume may be more pronounced in specific cortical and subcortical structures related to sensorimotor and limbic functions.

DISCUSSION

The present study provides a comprehensive analysis of sex differences in brain region volumes, comparing male and female cohorts across multiple cortical and subcortical structures. Our findings align with previous literature highlighting consistent sex-based morphological differences, with males generally exhibiting larger brain volumes across most regions. However, the extent of these differences varies across specific brain structures, which may reflect underlying neurobiological mechanisms and functional implications.

Our results indicate that males have significantly larger total cerebrum and total cortex volumes compared to females, consistent with prior neuroimaging studies (2, 3). The effect sizes for these differences were large, underscoring the robust nature of these findings. The greater total cerebral white matter volume in males compared to females is also well-documented and may re-

flect sex differences in axonal connectivity and myelination (16). These differences in white matter organization may have implications for cognitive and functional lateralization between sexes.

Significant sex differences were observed in ventricular volumes, with males having larger lateral and third ventricles. This is consistent with prior research indicating greater cerebrospinal fluid (CSF) volume in males (17). Enlarged ventricular volumes have been associated with neurodevelopmental conditions, and the observed sex differences could have implications for susceptibility to neurological disorders. Notably, the fourth ventricle did not exhibit a significant difference, suggesting that not all ventricular structures are affected by sex-based morphological variations. Recent studies have revealed significant sex differences in brain structure volumes during adolescence and adulthood. Males generally exhibit larger volumes in white matter, gray matter, total brain, and CSF compared to females (18).

However, females show larger accumbens volumes (18). Deep learning analysis of pre-adolescent brains identified sex-specific patterns in cerebellar and subcortical structures, which accurately predicted sex and correlated with working memory performance (19). Ventricular indices, particularly the bicaudate ratio, demonstrate age-related changes and sex differences, with males showing higher values (20). Longitudinal studies of subcortical volumes in adolescents and young adults consistently found larger volumes in males across all seven subcortical regions examined, with sex differences in age-related trajectories observed in both European cohorts studied (21). These findings contribute to our understanding of sex-specific neurodevelopment and may have implications for neuropsychiatric disorders.

In regions characterized by low receptor density, males exhibited significantly larger volumes in several areas, including the superior parietal lobule, precuneus, and superior temporal gyrus. These findings support previous studies demonstrating male-biased volumetric differences in these regions (4). These regions play key roles in visuospatial processing, sensory integration, and auditory functions, suggesting that structural sex differences may contribute to variations in cognitive abilities. However, no significant differences

were noted in the superior occipital lateral gyri and inferior occipital lateral gyri, suggesting that occipital regions may be less influenced by sex-related neurodevelopmental factors.

Research has consistently shown sexual dimorphism in brain structure and development. Males typically have 10% larger total brain volume across all ages (22). Specific regions, including the amygdala, hippocampus, and cerebellum, show sex differences and have high sex steroid receptor density (4, 22). Cortical gray matter development follows an inverted U-shaped trajectory, peaking earlier in females (22). Androgen receptors are present in developing rat visual and prefrontal cortex, with higher expression in males (23). In humans, androgen receptor genotype influences cortical maturation, with more efficient alleles associated with “masculinization” of development (24). These findings suggest that sex and sex steroids shape brain development in a spatiotemporally specific manner, potentially contributing to cognitive and behavioral differences between males and females (4, 24).

Recent studies have explored sex differences in brain structure and development, particularly in relation to sex hormones and their receptors. While males generally exhibit larger brain volumes across many regions (25, 26), sex-specific developmental trajectories in early childhood are less pronounced (25). Androgen receptor (AR) expression shows sex-specific patterns in certain brain areas during prepubertal development (27), and testosterone levels may influence amygdala subregion volumes in adolescents, moderated by AR sensitivity (28). Sex differences in cortical and hippocampal microstructure have been observed, with variations related to hormone levels and receptor gene expression (26). These structural differences are most evident in areas of low laminar cortical complexity. Overall, these findings suggest complex interactions between sex hormones, their receptors, and brain structure throughout development, contributing to our understanding of sex-specific neurodevelopmental processes.

Regions with high estrogen and androgen receptor densities showed mixed sex differences. While males had significantly larger postcentral gyrus, occipital pole, and thalamus volumes, females exhibited larger volumes in the front

orbital cortex and lingual gyrus. These results align with studies suggesting that hormonal influences shape regional brain development differently across sexes (29). The larger front orbital cortex in females has been associated with increased emotional regulation and social cognition, while the greater male thalamic volume may be linked to sensory processing and attentional control. The amygdala and hippocampus were significantly larger in males, consistent with prior findings on sex differences in emotional and memory processing regions (22). These structural differences may contribute to known sex differences in emotional reactivity, memory performance, and vulnerability to psychiatric disorders.

Recent studies have revealed significant sexual dimorphism in brain structure and microstructure. Küchenhoff et al. found sex differences in cortical and hippocampal microstructure, which varied with hormone levels and overlapped with sex hormone receptor gene expression (26). Tan et al. demonstrated that microsatellite polymorphisms in sex steroid receptor genes influence gray and white matter volumes differently between sexes (30). Eijk et al. identified region-specific sex differences in hippocampal subfields, with males showing larger volumes in some areas after controlling for total hippocampal volume (31). López-Ojeda & Hurley discussed how these structural differences may contribute to sex-specific vulnerabilities in affective disorders, particularly noting the role of the amygdala in anxiety (32). These findings collectively suggest that sex hormones and their receptors play a crucial role in shaping brain structure and potentially influencing sex-specific behavioral and psychiatric outcomes.

The observed volumetric differences likely reflect a combination of genetic, hormonal, and environmental influences. Testosterone exposure during neurodevelopment is associated with larger brain volumes in males, while estrogen-related mechanisms may contribute to regional differences favoring females (4). These morphological variations may underlie sex-based cognitive and behavioral differences reported in the literature. Additionally, these differences may have implications for sex-specific risks for neurological and psychiatric disorders, such as autism spectrum disorder, schizophrenia, and major depressive

disorder, which exhibit distinct prevalence rates across sexes.

While our study provides valuable insights, certain limitations should be acknowledged. First, we did not control for potential confounding variables such as total intracranial volume (TIV), which could influence volumetric comparisons. Future studies should incorporate TIV-adjusted analyses to ensure more precise sex comparisons. Second, our findings are based on cross-sectional data; thus, longitudinal studies are needed to establish developmental trajectories of these sex differences. Third, environmental and lifestyle factors, such as education and socioeconomic status, were not examined but may contribute to observed structural variations. Future research should also explore the functional implications of these structural variations, particularly in relation to cognitive performance and neuropsychiatric conditions.

CONCLUSIONS

This study confirms and extends previous findings on sex differences in brain morphology. Males exhibit larger total brain and regional volumes across most areas, with notable exceptions in certain frontal and occipital regions where female-biased differences emerge. These findings contribute to our understanding of sex-based neuroanatomical diversity and highlight the importance of considering sex as a biological variable in neuroscience research. Further research integrating multimodal neuroimaging and longitudinal designs will be crucial in elucidating the developmental and functional significance of these structural differences.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest related to this study.

AUTHOR CONTRIBUTIONS

S.N.: conceptualization, methodology, data acquisition, statistical analysis, writing – original draft preparation, writing – review and editing; Z.B.: conceptualization, methodology, statistical analysis, writing – review and editing, supervision; K.T.: methodology, data acquisition, statistical analysis, writing – original draft preparation, writing – review and editing, supervision; R.P.J.: data acquisition, writing – review and editing; U.K.: writing – original draft preparation, writing – review and editing, supervision; Trained MRI technicians under the supervision of U.K., K.T., S.N.: MRI segmentation and parcellation.

All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Mamata Medical College (Approval/Reference Number: [MMC/IEC/2022/2945/03/2025; approved April 4, 2025])

INFORMED CONSENT STATEMENT

Written informed consent was obtained from all participants prior to inclusion in the study.

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

No generative AI tools were used in the writing, analysis, interpretation, or preparation of this manuscript. All scientific content and writing were completed exclusively by the authors.

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