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Sex differences in brain structures throughout the lifetime

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The neuroanatomical characteristics of the brain exhibit variations between females and males, encompassing both healthy and pathological conditions [1]. Bethlehem et al. (2022) recently developed a human brain chart based on Magnetic Resonance Imaging (MRI) data from over 100,000 participants ranging in age from 115 days post-conception to 100 years [2]. This study discovered that males and females have significantly different brain tissue volumes throughout their lives and that these differences can also be seen in the brain growth patterns of people with psychiatric and neurologic conditions. Based on this growth chart trajectory, males have larger brain tissue volumes and more significant variance across MRI phenotypes, compared to females. It is critical to understand the effects of biological sex on brain development as it can significantly affect the physical and mental health of different psychiatric and neurologic patients.

Numerous studies have been conducted to compare brain volumes between healthy males and females. These studies have consistently found that males tend to have larger Total Cerebral Volume (TCV), total Grey Matter Volume (GMV), subcortical Grey Matter Volume (sGMV), total White Matter Volume (WMV), and Cerebrospinal Fluid Volume (CSFV). On the other hand, females generally demonstrate a higher mean Cortical Thickness (CTh) [3]. Abe et al. (2010) examined a population of individuals ranging in age from 21 to 71, revealing that males possess larger total GMV and WMV [4]. Additionally, males exhibited higher rates of decline in GMV and WMV with aging compared to females. This suggests that males and females have distinct brain structures, and the patterns of age-related brain changes are also different.

The precise etiology behind the lifelong disparities in brain structure between males and females remains incompletely understood. Emerging evidence suggests that these variations may have developmental origins. Certain investigations have identified different phenotypes in male and female brain cells, indicating a critical role of sex chromosomes in the emergence of sex-based brain differences. For instance, in vitro research has revealed that embryonal brain cells with XX and XY chromosomal configurations exhibit divergent behaviors [5]. XY cell cultures demonstrate a propensity to yield a higher number of dopamine neurons compared to their XX counterparts [5]. This emphasizes the genetic origin of the sex differences in brain structure. Consistent with this perspective, male infants exhibit larger total GMV and WMV compared to their female counterparts [6]. Moreover, these discrepancies persist into puberty, with males exhibiting greater total GMV, WMV, and TCV [7]. These findings underscore the significance of sex chromosomes in the development and perpetuation of brain differences between males and females.

While numerous studies have provided substantial evidence supporting the genetic origin of brain differences between males and females, a considerable body of research has demonstrated significant effects of sex hormones on brain development. Previous research revealed that testosterone acts as a human fetal brain programming system, leading to fetal dimorphism in brain structure and function

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[8,9]. Also, noteworthy sex-by-age interaction between testosterone levels and mean CTh across various brain regions was identified [10]. Furthermore, women with complete androgen insensitivity syndrome, characterized by the absence of androgen action despite a 46XY karyotype, exhibit comparable white matter structure to typical females [11]. This highlights the more prominent influence of sex hormones compared to genetics on brain development.

According to Bethlehem et al. (2022) growth charts for total GMV, WMV, sGMV, and CSFV, the disparities between males and females exhibit the smallest magnitude during the neonatal stage [2]. However, these differences tend to increase notably during post-pubertal periods and subsequently decrease during advanced stages of life, particularly in the postmenopausal periods for females. These observations suggest that although sexual dimorphism is evident at birth, the magnitude of these differences undergo dynamic changes throughout the lifespan, likely influenced by the impact of sex hormones.

Hagemann et al. (2011) revealed that GMV and CSFV undergo alterations throughout the menstrual cycle in women, highlighting the dynamic nature of these brain measures in relation to hormonal fluctuations [12]. Also, postmenopausal women experience a steeper decline in TCV and GMV compared to pre/perimenopausal individuals, implying that sex hormones may have a direct effect on brain growth patterns [13]. These findings collectively contribute to our understanding of the role of sex hormones in brain development, complementing the existing evidence on the developmental origin of brain differences between males and females.

Bethlehem et al. (2022) also investigated the sex differences in the brain changes observed in patients with psychiatric and neurologic disorders [2]. Their study reveals that sex differences are apparent in Anxiety Disorders (ANX) and Major Depressive Disorders (MDD), with males demonstrating a significant increase in global measures such as total GMV, sGMV, WMV, and TCV, while females tend to display non-significant decline in these measures [2]. This study marked the first exploration of sex differences in alterations in total GMV, sGMV, WMV, and TCV in ANX and MDD patients, aligning with prior research showing structural brain differences in specific regions between males and females. den Braber et al. (2013) found that male subjects with obsessive–compulsive disorders exhibited larger GMV in the left middle temporal gyrus, while females displayed larger GMV in the right precuneus [14]. Also, Yang et al. (2017) explored patients with MDD and discovered that males exhibited decreased GMV in the bilateral temporal gyri, whereas females demonstrated decreased GMV in the left lingual gyrus [15]. This suggests that different brain regions may contribute to the development of ANX and MDD in each biological sex, potentially influenced by sex hormones affecting brain structures and functions in these patients.

Based on the Bethlehem et al. (2022) article, male patients with Autism Spectrum Disorders (ASD) exhibit a more pronounced decline in WMV and a greater increase in mean CTh, whereas females demonstrate a more notable increase in CSFV [2]. Interestingly, total GMV and TCV experience a significant decrease in males, while females show a non-significant increase. Conversely, sGMV increases in males but significantly decreases in females [2]. Nevertheless, a systematic review presents contradictory evidence, suggesting that the age-related GMV decline in male ASD patients is less pronounced [16]. This review reveals significant sex differences at different life stages. Specifically, in youth, males have higher CTh in the parahippocampus, whereas in adults, females display higher CTh [16]. Additionally, Zhang et al. (2018) reported a significant sex-age interaction for total WMV in ASD patients, with males exhibiting greater values, especially in adulthood [17]. However, this interaction was not evident for total GMV. In summary, these findings emphasize sex-related discrepancies in lifelong brain alterations among ASD patients, though precise distinctions in each brain region remain a subject of debate.

Regarding patients with Schizophrenia (SCZ), females tend to show a more prominent decline in total GMV, WMV, sGMV, and TCV, while males demonstrate a steeper CTh decline [2]. Research on adolescents and adults with SCZ highlights distinct GMV patterns between sexes [18,19]. However, a study on children with SCZ found no significant sex differences in GMV across brain regions, suggesting that sex hormones, rather than genetics, likely underlie these variations in SCZ patients' brain regions [20].

In the realm of neurological disorders, sex-related patterns in brain metrics in Alzheimer's Disease (AD) patients resembled those seen in SCZ patients, according to Bethlehem et al. [2]. Among individuals with Mild Cognitive Impairment (MCI), both males and females exhibited brain metric alterations similar to AD, although males showed a non-significant increase in total WMV, while females displayed a non-significant decline [2]. However, some studies did not report significant sex-age interactions in GMV, sGMV, and CTh alterations among AD patients [21–23]. Sangha et al. (2021) found that in AD and MCI patients, CTh was thinner in elderly males, but these changes paralleled those observed in healthy controls, suggesting they may reflect broader population alterations rather than disorder-specific effects [24].

Reviewing the existing literature emphasizes the significance of comprehending lifelong brain differences between males and females. These disparities offer critical insights into brain development, aging, and neuropsychiatric disorders. Our discussion highlighted significant variations in brain structures among patients with psychiatric disorders across their lifespans, distinct from sex-specific patterns in healthy individuals. This implies a pivotal role for the sex hormones in psychiatric disorders. Conversely, in neurologic disorder patients like AD and MCI, brain structure sex differences largely mirrored those in the general population, suggesting a diminished impact of sex hormones on these conditions. Some studies have unveiled sex-specific genetic contributors to AD, potentially explaining distinctions between biological sexes [25]. Future research can further illuminate the interplay of sex hormones and genetics in neurologic disorder development, shedding light on brain changes in these patients compared to healthy controls.

Various studies have investigated the effects of sex on brain structure in healthy individuals, while there is a lack of research on individuals with neuropsychiatric disorders in this regard. It is important for future research to focus on the impact of sex on brain structure, particularly in the context of psychiatric and neurological conditions. This will help to further our understanding of these disorders and potentially lead to more targeted and effective treatments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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