Sexual differences of human brain

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ABSTRACT

During the last decades there has been an increasing interest in studying the differences between males and females. These differences extend from behavioral to cognitive to micro- and macro- neuro-anatomical aspects of human biology. There have been many methods to evaluate these differences and explain their determinants. The most studied cause of this dimorphism is the prenatal sex hormones and their organizational effect on brain and behavior. However, there have been new and recent attentions to hormone's activational influences in puberty and also the effects of genomic imprinting. In this paper, we reviewed the sex differences of brain, the evidences for possible determinants of these differences and also the methods that have been used to discover them. We reviewed the most conspicuous findings with specific attention to macro-anatomical differences based on Magnetic Resonance Imaging (MRI) data. We finally reviewed the findings and the many opportunities for future studies.

Introduction

Sexuality affects the human brain and behavior, as other species. Men and women are dimorphic in many aspects; their physics, sexual orientation, gender identity, cognitive features, the preferences for short- and long- term partner, the rate by which they are afflicted with psychological and physical health conditions (1). The key question is what are the causes of these differences? The supremacy of behaviorism of the 20th century left no doubt; "One is not born, but rather becomes, a woman" (2).

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However, more than 50 years ago, Phoenix et al. (1952) in a revolutionary study, showed that early exposure of female guinea pigs to androgens, has masculinized their sexual behavior (3). This study was the first which showed that a biological factor such as sex hormones can influence behavior as well as reproductive anatomy and function. Since then there have been many studies trying to understand the behavioral and cognitive differences between human males and females as well as the responsible factors.

In addition to hormonal influences, there are rich evidences about the effects of genetics. One of the most important is the study of Arnold and Chen et al. in 2008 which used the mouse model for evaluating genetic association in sexual differences (4). This model is consisted of mice whose sex chromosome complement had been separated from their gonads. The four resulted types are as follows: XX males (new type), XX females (normal females), XY males (normal males) and XY females (new type). Other studies that have used this model, have shown that some sexually dimorphic features of mice, previously considered as hormone based, are actually influenced by sex chromosomes and genetic imprinting (4).

Question about the dimorphic behaviors between human males and females has been debated and the study about sexual differences has particular difficulties (5). One problem is the researcher's own preconceptions or sex-related stereotypes influence on their work. Another one is that a finding of differences between groups is easier to publish than a finding of no differences. Therefore, in this review we only rely on those differences that have been replicated in numerous studies.

Any conclusion about behaviors or psychological characteristics which are sexually different does not necessarily mean that males and females are dramatically different. Typically it means that when groups of men/women or boys/girls are compared, the groups show average differences. The size of these average differences is different. The measure by which we quantify the magnitude of differences between males and females is d, which is calculated through obtaining the difference of means for the two groups (males minus females) and then dividing it by the combined standard deviation. A d values which is 0.8 or greater means that the difference should be considered large, a d around 0.5 means the difference is moderate, and those features that their d is 0.2, are considered small (6). Effect size values smaller than 0.2 are considered negligible.

Sex Differences in Brain

Structural magnetic resonance imaging studies have provided striking evidence for sex differences in the human brain. The most consistent macroscopic observation is a larger brain volume and weight in men compared to women (7), which is partly explained by larger body dimensions of men (4). Other sex differences have been observed with respect to the dimensions of cortical and sub-cortical regions. For example, the planum temporale and sylvian fissure were found to be larger and longer in males vs. females (8). In contrast, the volumes of the superior temporal cortex, Broca's area, the hippocampus and the caudate (expressed as a proportion of total brain volume) were significantly larger in females (9). The mid-sagittal areas and fiber numbers of the anterior commissure (connecting the temporal lobes) as well as the massa intermedia (connecting the thalami) were larger in women vs. men, where the massaintermedia was also more often absent in males than in females.

The cortical cortex of the brain has attracted considerable attention over the past decades. The cerebral cortex contains approximately 80 % of the central nervous system neurons. Over the course of evolution, the cerebral cortex has grown considerably in surface area. The cortex in human is only 15% thicker than Macaque monkeys but has at least, 10 times more surface area. This enormous enlargement in surface area seems to be the result of larger brain and perhaps more importantly, an increased folding of the brain's surface. Given that men usually have larger brain than women, researchers have suggested possible compensatory mechanisms in female brain that might have occurred during human evolution (10). Sex differences in the anatomy of the cerebral cortex might constitute parts of such compensatory mechanisms.

A study about the sex differences of cortical depth, which is defined as approximately half of the cortical thickness (11) did not reveal any significant differences between men and women. Recent methods with much higher precision revealed that adult women have significantly thicker cortices than adult men (12).

These sexual differences were identified in all four lobes in each hemisphere, with temporal regions being least different. No regions with significantly thicker cortices were detected in males. When the actual brain sizes of men and women were preserved, the same pattern and general direction of the sex difference (females>males) were noticed, but the effect was considerably less pronounced. A small cortical region in the left lateral temporal lobe showed greater thickness in men (12).

This was similar to the outcomes of another study which showed thicker cortex in numerous brain regions of female after image scaling, with smaller effects in the temporal lobe (13). Here again, putting

the brain sizes into account, the sex effects (females>males) were still observed but considerably decreased. No cortical regions were thicker in males. Similarly, when analyzing brains in their native dimensions (i.e., without correcting for individual brain size), another study revealed thicker cortices in right inferior parietal, left ventral frontal and posterior temporal regions of female brains. Thicker cortices in male brains were only detected in small clusters within right anterior temporal and orbitofrontal regions (14).

Sex difference determinants

Researchers are confounded by many ethical, methodological, and practical obstacles when studying sex differences in humans (15). Typical manipulations in nonhuman subjects such as castration, reducing or increasing androgens and genetic engineering are clear violations in humans. There would remain a gap in understanding the mechanisms by which sex differences in the human brain are developed. Solving this challenge is critical not only for answering the fundamental questions on why men and women differ, but also for understanding the underlying mechanisms of neuro-developmental conditions, specifically those presented with different rate in males and females (16).

Considering the importance of this question, there have been several strategies for understanding human neural and behavioral sexual differentiation. These include two general types of studies. The first examines individuals who have experienced dramatic alterations in hormones prenatally, for instance, because of genetic disorders or because their mothers were prescribed hormones during pregnancy. The second relates normal variability in the early hormone environment to normal variability in subsequent behavior. Here, we reviewed

some of the most studied conditions in which the evaluation of sexual difference determinants is possible.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), in its classic form, is an autosomal recessive condition which is due to overproduction of androgens. The condition begins prenatally. The problem is originated in deficiency of enzymes which are responsible for production of adrenal steroids. In more than 90% of patients, the deficient enzyme is 21-hydroxylase (21-OH). The incidence of CAH caused by 21-OH deficiency in Europe and the United States is estimated between 1 in 5000 and 1 in 15000 births (17). Lack of 21-OH prevents cortisol production. The negative-feedback system detects the low levels of cortisol then the additional metabolic precursors are produced. Because of the blockage in cortisol production, the precursors are shunted into the androgen pathway, resulting in an overproduction of adrenal androgens, as well as progesterone and 17-hydroxyprogesterone. Female fetuses who are afflicted with classical CAH have androgen level which is clearly elevated than normal female population (18) and girls with the condition are typically born with a conspicuously virilized phenotype. In very rare conditions, the masculination is so severe that girls are mistaken and socialized as boys (19). Typically however they are diagnosed with CAH near the time of birth, and are assigned and reared as girls. Then, they are treated with hormones to regulate hormones postnatally, and their genitalia are usually feminized surgically.

Androgen Insensitivity Syndrome

Androgen insensitivity syndrome is resulted from the inability of androgen receptors to react to androgens (20). The insensitivity can be complete androgen insensitivity Syndrome (CAIS) or partial androgen insensitivity Syndrome (PAIS). Both forms are transmitted as X-linked recessive traits which occur almost exclusively in genetic males. Individuals with CAIS appear as female at birth and are raised as girls without any symptom suggesting of an underlying pathology.

At puberty, estrogen derived from testicular androgen leads to normal telarc. CAIS patients are, typically, referred to endocrinologist or gynecologist for their primary amenorrhea. Their primary amenorrhea is due to lack of female internal reproductive structures. Estimates of the CAIS prevalence vary widely, although it appears to be far rarer than CAH.

Androgen biosynthesis deficiencies (5 alpha R and 17-HSD deficiencies)

These deficiencies are transmitted as autosomal recessive traits. They were first discovered in area of the Dominican Republic (21). They are rare in general population, but can occur frequently in population where inbreeding is common. The enzyme 5-aR converts testosterone (T) to dihydrotestosterone (DHT), and patients deficient in the enzyme have low levels of DHT but normal-to-high levels of T (22). Because DHT is needed for normal virilization of the external genitalia prenatally (23), 5-aR deficiency results in female-appearing or ambiguous genitalia at birth, and individuals with the disorder are usually assigned and reared as girls. At puberty, however, T and other androgens cause virilization, including growth of the phallus and scrotum, deepening of the voice and development of male-typical musculature.

The enzyme 17-HSD is needed to produce T from its immediate precursor, androstenedione. Patients deficient in this enzyme have low levels of T and DHT,

but elevated levels of androstenedione. The natural history of 17-HSD is similar to that of 5-aR deficiency. These natural experiments have been mostly studied for psychological traits such as gender identity (24), sexual orientation (25), childhood play (26), personality types (27), cognitive abilities (28) and etc. Most of these studies have been focused on CAH patients due to their much more prevalence; therefore they could have only evaluated the androgen effects. To our knowledge there has been no imaging study, neither on CAH nor on 5ARD or CAIS patients. Regarding the prevalence of these conditions in our region, these would be of immense importance for future studies.

Clearly, sex differences that arise before birth must be a consequence of prenatal or perinatal sex-specific hormonal action and genetic determination rather than differential social stimulation. In contrast, morphological sex differences which arise after birth could be the result of prenatal, perinatal, or postnatal influences. However, except for the larger brain weight and volumes (16) in males compared to females, it is not known conclusively whether any of the sexual dimorphisms in the human brain are present at birth or not. Thus, the exact underlying mechanisms and determinants remain to be assessed in future work, where interplay between genetic determination, hormonal exposure, and environment is very likely.

Acknowledgement

Conflict of Interest

The authors declare no conflict of interest.

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