

The role of sex and gender in neuropsychiatric disorders

Florence Thibaut, MD, PhD – *Editor in chief*

Abstract

The prevalence, age of onset, and clinical symptoms of many neuropsychiatric diseases substantially differ between males and females. Factors influencing the relationships between brain development and function and sex or gender may help us understand the differences between males and females in terms of risk or resilience factors in brain diseases.

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Author affiliations: University Hospital Cochin (Site Tarnier), Faculty of Medicine Paris Descartes), INSERM U 894, CNP, Paris, France

Address for correspondence: Dept of Psychiatry and Addictive Disorders, Hôpital Tarnier, 89 rue d'Assas, 75006 Paris, France

(email: florence.thibaut@aphp.fr)

The role of sex and gender is a fundamental issue in medicine. The prevalence, age of onset, and clinical symptoms of many neuropsychiatric diseases substantially differ between males and females. Examples of male-biased conditions include early-onset disorders that involve some kind of neurodevelopmental impairment, such as autism, attention deficit/hyperactivity disorder, conduct disorder, specific language impairment, Tourette syndrome, dyslexia, or schizophrenia; examples of female-biased conditions include emotional disorders such as depression, anxiety disorder, and anorexia nervosa, which usually start during puberty or later in life.^{1,2} Factors influencing the relationships between brain development and function and sex may help to understand the differences between males and females in terms of risk or resilience factors to brain diseases.

Unfortunately, in preclinical research, in most cases, researchers avoid experimenting with female animals and consider that there are no sex differences in brain function outside of reproductive behavior, with single-sex studies of male animals outnumbering those of females by 5.5 to 1.³ Moreover, studies of both sexes frequently fail to analyze results by sex. Yet, Ruygrok et al⁴

have conducted a metaanalysis of sex differences in brain structure and observed that, on average, males have larger total brain volumes compared with females. Regional sex differences in volume and tissue density include the amygdala, hippocampus, and insula, which are known to be involved in sex-biased neuropsychiatric conditions.

Because sexual differentiation of the genitals takes place earlier in intrauterine life than sexual differentiation of the brain, these two processes can be influenced independently of each other. In the male brain, testosterone can be converted via aromatase to estradiol, which exerts its actions via estrogen receptors (ERs); or via 5 α -reductase to dihydrotestosterone (DHT), which exerts its effects via androgen receptors. Testosterone and its aromatization to estradiol play a specific organizational role during a critical period of development in sexing of the human brain, with a greater degree of exposure enhancing masculinization. Estradiol is not necessary for the organizational effects of testosterone, whereas androgen receptors are responsible for brain masculinization in humans. It seems that the brain will develop as a female brain in the absence of testosterone. However, according to Joel et al⁵ the brain could be a mixture of relative degrees of masculinization in certain areas and feminization in others. Activational actions of testosterone occur after puberty when the hormone acts transiently and reversibly on circuits that have already been established.⁶ After puberty, androgen receptors are required for activation of male-typical behavior, in both males and females (see Morford and Mauvais-Jarvis, in this issue, p 415). In females, apart from sexual behavior, many other aspects of brain functioning such as fine motor control, pain mechanisms, seizure activity, mood, cognitive function, and neuroprotection are influenced by estrogens. Females also produce androgens, both as a necessary precursor to estradiol and from the adrenal glands.

Astrocytes and microglia, the latter being the brain's innate immune system, also play an important role in brain sexual differentiation. The developing male brain is naturally in a state of both higher excitation and inflammation compared with the female brain, which may be a contributing factor to greater male vulnerability to neurodevelopmental disorders.⁷

More surprisingly, placental sex (XX vs XY) is a major determinant in the magnitude and functional responses of the placenta to maternal perturbations dur-

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ing pregnancy, where the female placenta appears to be protective. Placental cellular mechanisms give rise to sex-specific neurodevelopmental changes and are also expected to provide novel insight into disease risk and resilience (see Bale, in this issue, p 459).

Additionally, epigenetic modifications involving DNA methylation and histone deacetylation are essential for feminization or masculinization of sexual behavior.^{8,9} Sex differences at the molecular level of cell signaling and protein trafficking are amplified to create a state of vulnerability which may also interact with stress and contribute to sex differences in vulnerability for psychiatric disorders¹⁰ (see Ramikie and Ressler, in this issue, p 403).

Finally, sex-specific variance has been identified in numerous biological functions influencing pharmacokinetic determinations, including plasma levels, production of gastric acid, gastric emptying times, levels of plasma protein, enzyme activity, drug transport, and clearance rates. However, it is not clear that such differences translate into clinical practice guidelines (Sramek et al, in this issue, p 447). Finally, a sex difference in the dopamine response in the nucleus accumbens may also contribute to the different vulnerability of males and females to addictive disorders.

This issue will explore how sex differences in the brain may contribute to gender biases in neuropsychiatric disorders. □

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