# Neuro-endocrinology BRIEFINGS

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## SEX DIFFERENCES IN THE BRAIN


### SUMMARY

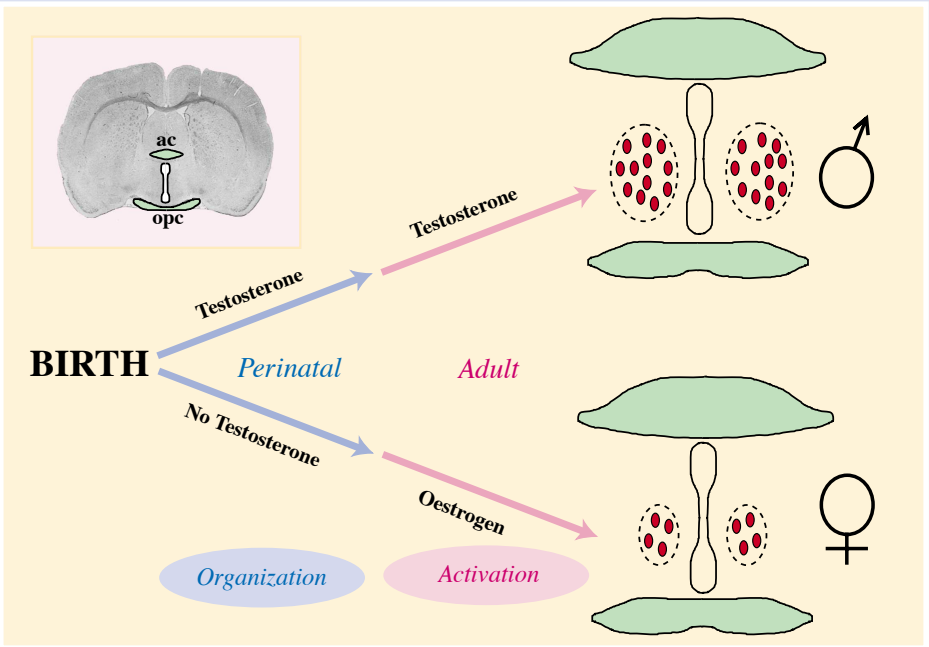
Males and females have evolved to perform quite different roles and marked sex differences are observed in the structure and functioning of their brains. These differences result from exposure to the gonadal steroid hormones, testosterone and oestrogen, in early life but have deeper implications for psychology and disease in later life.


## Sex on the brain

The differences between the sexes is a subject of enduring fascination, one which has inspired art and literature, is at the heart of our psychology, and which underlies the very structure of society. Males and females show profound differences in their physiology and, from an early age, in their behaviour. Boys, on average, are better at spatial skills and mathematical reasoning, while girls have greater perceptual speed and are better at verbal reasoning. Soberingly, men commit 80% of all murders, and 99% of all sexual crimes.

## Different, why?

Underlying these differences are believed to be sex differences in the brain. Indeed, when we peer inside the brains of males and females, we see differences in the size of regions, the number of nerve cells, the patterns of synaptic connections, and the distribution of the various neurotransmitters. For example, a striking sex difference is seen in the so-called 'sexually dimorphic nucleus' which is twice as large in males as females. One region of the suprachiasmatic nucleus contains twice as many neurones in men until middle age, when the sex difference reverses, and then ultimately disappears altogether! Males and females even use different parts of the brain: in verbal tests, females use parts of both brain hemispheres while males use almost entirely the left. Intriguingly, differences are




*The number of nerve cells in the sexually dimorphic nucleus in the hypothalamus of the rat brain is determined by the 'organizational' actions of testosterone around the time of birth. At puberty, and in adult life, testosterone and oestrogen act on sexually differentiated structures such as this to 'activate' appropriately different behaviours. The insert shows a frontal section of the rat brain with the hypothalamus, containing the sexually dimorphic nucleus, lying between the anterior commissure (ac) and the optic chiasm (opc).*

beginning to be identified between the brains of homosexual and heterosexual men – with differences in the size of some regions.

## Different, how?

But how do these sex differences come about? The answer seems to be the dramatic differences in the exposure of the brain to the gonadal hormones – testosterone and oestrogen – in early life. Males are exposed to high levels of testosterone secreted by their testes which show peaks in early embryonic life, just after birth, and then again at puberty. Females, in contrast, develop in the absence of these high testosterone levels.

*"In early life, the hormones are believed to 'organize' the brain"*

Only in recent times have we begun to understand how the gonadal hormones act to masculinize or feminize the brain. In early life, the hormones are believed to 'organize' the brain – essentially setting up the brain's circuitry as either male or female. Later in life, they 'activate' these sex-specific circuits to evoke the characteristic masculine or feminine behaviour patterns. In the rat, in which most research has been carried out, this 'organization' depends crucially on the hormonal exposure both pre- and post- natally. Paradoxically, masculinization of many aspects of the rat brain is controlled by the female hormone oestrogen which is made by conversion from testosterone within the brain – a sort of 'super dose' of oestrogen! Once the perinatal organizational phase is complete, the brain's 'sex' is fixed and simply requires the appropriate sex hormones at puberty to activate the appropriate behaviour.

This process, which has been revealed in the rat, is also thought to occur in humans although, intriguingly, the postnatal hormone exposure may be relatively more important. This is of particular interest because it allows the possibility that environmental factors and social stimuli – which are known to affect gonadal hormone levels – may also affect the sexual differentiation of the brain. Testosterone and oestrogen affect diverse processes to cause this differentiation including protein synthesis, cell division and migration, neuronal growth and axonal branching, and synaptic remodelling. Fascinatingly, one of the most significant mechanisms by which the gonadal hormones influence the brain may be by causing some cells to commit suicide while allowing others to live.

## Sexual (neuro)chemistry

One of the most exciting areas of research into brain sex differences is looking at sexually differentiated neurotransmitter systems to understand the sex-specific functioning of the brain:

- We can map out the circuits which use specific neurotransmitters and begin to construct structure-function relationships
- We can measure how neurotransmitter systems change under the influence of the sex hormones and correlate this with changes in behaviour
- We can alter the level of neurotransmitter and observe what effect this has

Even more fascinating is the finding that many diseases of the

*"Many diseases of the brain show marked sex differences in their sufferance"*

brain show marked sex differences in their sufferance – for example, autism, schizophrenia and Alzheimer's disease – and many such diseases have been associated with imbalances in specific neurotransmitters. The sexual disparities suggest an important role for the gonadal hormones in the aetiology of these diseases. Indeed, oestrogen has very recently been shown to protect cells against changes suspected of being causally linked to Alzheimer's disease, while low oestrogen is associated with increased risk of schizophrenia. An understanding of both the organizational and activational influences of the gonadal hormones on the neurotransmitter systems underlying these diseases may well prove to be a fruitful route towards treatment or a cure.

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