SEX: Mind the Difference

Yuri Koutcherov

Most people have at least a vague idea about how men and women are different. Well, they look different. Given sufficient time to think, most of us would also suggest that men and women behave somewhat differently, though the majority would find it quite hard to put their finger on particulars. There are, of course, vague commonly held preconceptions of a typical man: hard-working, football watching and lacking sensitivity vis-a-vis women who mind the house, drive badly and long for romance. Most of these are just suppositions, some, however are real phenomena which may reveal not only behavioural and underlying neurological differences between the genders, but also give hints as to how the brain works.

Fortunately, there are essential methodological criteria by which scientists can distinguish between genuine behavioural evidence and anecdotal observations. Collecting and analyzing such evidence for the past fifty years has helped to work out many neural differences in the brain, which underlie variations in sex specific behaviours. Thus, we can say with certainty now that the brains of men and women are very similar, but there is a great range of structural, chemical and functional differences. Besides being a good source of topics for dinner table conversation, these differences suggest a neural basis for sexual behaviour (whether hetero homo or trans-sexual) and provide reasons why we need to develop sex-specific treatments for a host of conditions, including depression, addiction, schizophrenia and post-traumatic stress disorder.

So, what are these behavioural differences and what are the structural differences in the brain that lie behind them?

Few would argue that the most obvious behavioural sex difference is their actual sexual behaviour. Men are attracted to women and women are attracted to men but they behave differently in going about the business of mating. In fact scientists have known since the mid sixties, with a high degree of certainty, which brain regions are responsible for mating behaviour and for the emotional and sensory cues underlying this behaviour.

As hard as it is to deviate from the subject of sexual behaviour, there is something that should be explained fi rst. The story takes us back in time to when the analogue of the olfactory (smell, or chemical sensor) system developed to give early animals clues about their surrounding environment and the best way to survive and reproduce. This early neural guidance system learned to recognize what is good and what is bad and transmitted this information to the rest of the body. The good and the bad, in neural terms, were then translated into pleasant and unpleasant, desirable and revolting. This formed the basis of what we now call emotions and emotional learning. We also know that this system of emotional learning is strongly connected to the hypothalamus, a small structure at the base of the brain that is involved in regulating hormone production, control of the body's physiology and basic behaviours such as eating, drinking, aggression and sex. Thus, emotional activity has a profound influence on the regulation of our basic bodily functions and our motivation and basic autonomic (not controlled by cognition) behaviours. In terms of gender specific reproductive behaviours in, for example, rats, such influence could be seen in males engaging in mounting and females arching their backs and raising their rumps to attract a suitor when they sense one. The main areas that constitute the emotional learning system include the amygdala – a walnut size structure located roughly behind the ear – and the horn shaped, ventral striatum extending from the amygdala towards the middle of the brain. These structures also form the core of the so-called limbic system, if you have ever come across the term. Simply put, animals had to recognize somehow who to mate with to produce offspring and the limbic structures did just that. We now know that in many animals the amygdala, ventral striatum and hypothalamus constitute the main elements of the neural pathway for pheromones – chemicals produced by animals to give messages, including sexual messages, to other animals. Consistent with their origin, the amygdala and ventral striatum are also central to the action of psychotropic drugs and to addiction, reward and fear. The human olfactory system is quite poor compared to say other mammals or rodents and our pheromonal system lacks major parts, so it does not really work, if you are wondering. That is because we have now evolved to use other sensory modalities such as vision and hearing a lot more than smell. Nevertheless, the human limbic system, including the amygdala and ventral striatum, as well as the hypothalamus, appear to be just as robust in their function of emotional learning and regulation of sexual behaviour in each one of us.

This brings us to a series of discoveries in the early nineties of the structural and chemical differences in those areas of the brain that regulate sexual behaviour and the motivating emotional cues for this behaviour in the hypothalamus, amygdala and ventral striatum of the human. Originally, a Dutch research group led by Professor Dick Swaab identifi ed five neural structures within the hypothalamus and ventral striatum that differ dramatically in size and chemical content between males and females. Some are as much as five times bigger in males, while others are bigger in females. Swaab's group and other scientists have also shown that in homosexual males these structures approximate to female size and chemical content, and even more so in male to female trans-sexual brains. These size differences, as well as others mentioned throughout the article, are relative: they refer to the overall volume of the structure relative to the overall volume of the brain.

Experiments in laboratory animals, mainly rats, and studies in primates, including humans, established that these, sexually dimorphic brain structures are responsible for the regulation of hormonal and neural circuits underlying sexual behaviour. Moreover, we now know that structural and chemical gender differences in these structures, also called sexual dimorphism, develop in the fi rst two years after birth under the influence of steroid hormones, primarily testosterone. Androgens, including testosterone produced mainly by the testes in foetal and neonatal life, act on the brain to produce sex differences in neural structure and function. Testosterone affects neural development by averting programmed cell death, infl uencing neural connectivity, and altering neurochemical profi les. In humans, exposure to atypically high levels of prenatal androgens results in masculine behaviour and ability patterns. For example, females with congenital adrenal hyperplasia, a genetic condition that elevates foetal testosterone, show tomboy behaviour. It is too simple to say that men have more of it, while sexually dimorphic structures in the amygdala, ventral striatum and hypothalamus have evolved to become sensitive to these hormones. The effects of hormones are more complicated than that. They are produced in both sexes, may be converted into one another, and can have varying effects in different species, sexes, and individuals. The moral is that it is not hormones themselves but the neural circuitry, shaped by natural selection and modulated by the hormones, that explains our thoughts and feelings.

To remove any ambiguity, there is no scientifi cally credible data that would suggest that homosexuality or trans-sexuality are anything but the result of hormonal influence on the amygdala, ventral striatum and hypothalamus. The fate of these structures is predisposed genetically and chemically during early development. As far as I am aware all previous suggestions that environmental influences may affect sexual identity and behaviour are initially false or invalidated.

Here is a good example of environmental infl uence on sexual behaviour. In a small group of villages in the Dominican Republic, there is a developmental oddity of "male" children with undescended testes and clitoris-sized penises until they reach puberty. They do not produce much testosterone, look pretty much like girls (without hints from the external reproductive organs young boys and girls look rather similar) and are brought up like girls. Then, at puberty the process completes with a sudden rush of testosterone and development of testes and penises, and they are transformed from female to male in the culture without comment. They get married and there were no reported cases of homosexuality. In Spanish they are called guevedoces – balls at twelve.

Thus, sex hormones play an essential role in the development of sexual dimorphism in limbic and hypothalamic brain structures that, in turn, underlie divergent reproductive behaviours and basic emotional processing. Sex differences in the brain, however, are not limited to mating behaviours, sex hormones and the hypothalamus.

The basic developmental rule of the brain "use it or lose it" refers to the neural mechanism that promotes the development of brain circuitries that are utilized more. This mechanism makes sexual dimorphism of the amygdala, ventral striatum and hypothalamus seminal to the development of sexual differences in other brain structures. It is thought that between birth and about two years of age, when the amygdala, ventral striatum and hypothalamus become structurally different in boys and girls, this difference affects the development of neural connections between these (evolutionary old) structures and other (evolutionary younger) structures, and as a consequence causes gender difference in the latter. This developmental influence has particular behavioural consequences in the cortex – the main bulk of the brain tissue covering the outer surface of the brain in two massive hemispheres. Cortical functions are diverse, vary dramatically between species and include memory, attention, sensory awareness, moto-control, "thinking", language and consciousness. The human cortex, unlike the amygdala, ventral striatum and hypothalamus, is in evolutionary terms the youngest part of the brain and differs dramatically (particularly in areas associated with cognitive processing) from the cortex of other species. In humans the cortex develops slowly and reaches its adult configuration by 18 – 20 years of age, but throughout development we can already see strong trends for behavioural differences between the sexes reflected in sex variation in sensory perception, and higher emotional and cognitive control of complex behaviours.

There is a large amount of scientifi c evidence showing differences in cognition and behaviour between boys and girls. For example, the hands of newly born girls are signifi cantly more sensitive than those of newly born boys. Baby girls are much more irritated and anxious about noise, pain and discomfort than boys. Baby girls identify emotional content in speech better than boys. At four months a girl can distinguish photographs of familiar people, boys cannot yet. Psychologists from Cambridge recently reported that one-year-old girls spend more time looking at their mothers than boys. And when these babies are presented with a choice of films to watch, the girls look longer at a film of a face, whereas boys lean toward a fi lm featuring cars. Boys are more active than girls. At the school gates it takes girls on average 92.5 seconds to say goodbye to their mothers, while for the boys it is a brief 36 seconds' ciao. Boys occupy more space on the playground then girls. Strangers in the playground are more welcomed by girls but ignored by boys who also express irritation when followed by a stranger. Boys tend not to be bothered whether or not they like a particular member of the group – they are just there. Girls exclude other girls because "they are not nice". By the age of four, boys and girls usually start to play apart. Not that it's unexpected, but to be consistent with our preference for evidence over anecdotal observations, many researchers have also demonstrated that when selecting toys, young boys and girls part ways. Boys tend to gravitate toward balls or toy cars, whereas girls more typically reach for a doll. But no one could really say whether those preferences are dictated by culture or by innate brain biology.

As more and more studies show, in the human adult, sex has influence on many areas of cognition and behaviour, including memory, emotion, vision, hearing, the processing of faces and the brain's response to stress hormones. This progress has been accelerated in the last ten years by the growing use of sophisticated non-invasive imaging techniques such as positron-emission tomography and functional magnetic resonance imaging, which can peer into the brains of living subjects. The major advantage of these technologies for studying sexual dimorphism is that they permit comparison in cortical activity during specific cognitive tasks and thus provide evidence for a neural basis of sexual differences in cognition.

There is no credible evidence that males and females differ in general intelligence. However, specifi c cognitive tasks, often used by psychologists to gather statistically analysable information, reveal sex differences. Most notably, females score higher on tests of emotion recognition. They also demonstrate significant language and verbal fl uency tasks (such as listing as many words as you can, beginning with the letter 'A'). Females start to talk earlier than boys, and demonstrate a lower risk of language impairment. They also demonstrate social sensitivity better than men and do better in tests of social judgement, measures of empathy and cooperation. Women are better in rapid identification of matching items, ideational fluency (for example listing as many things as you can that are the same colour), fine-motor coordination (like placing pegs in pegboard holes), mathematical calculation tests and pretend play in childhood.

On the other hand, men in general, are superior to women in mathematical reasoning, especially geometry and mathematical word problems (for example at high-level mathematics, the male-female ratio has been reported at 13:1). They are also superior to women in solving engineering and physics problems. Men are also better at geometrical tasks like finding a part of a figure within a whole, imagining how an object will look when it is rotated, or how a sheet of paper will look when folded. There is also a clear male bias in some spatial skills – mostly geometric navigation, including map reading (spatial superiority in males is even found in childhood), target-directed motor skills, such as guiding or intercepting projectiles – irrespective of the amount of practice. Males are also more likely to play with mechanical toys, both as children and as adults.

These tasks may appear somewhat trivial but they underlie greater cognitive functions such as emotional intelligence, ability to analyse the surrounding environment and hypothesising. It is also important to point out that all of these differences exist at the level of populations, not individuals; from such population differences, no inferences can or should be made about individuals.

Pronounced cognitive differences in the way males and females go about solving general psychological tasks led psychologists from Cambridge to propose an "empathizing-systemizing" theory of psychological sex differences. Such differences reflect stronger systemizing in males and stronger empathizing in females. Systemizing is the drive to analyze a system in terms of the rules that govern the system, in order to predict the behaviour of the system. Empathizing is the drive to identify another's mental states and to respond to these with an appropriate emotion, in order to predict and to respond to the behaviour of another person. Other people's emotional states and behaviour cannot easily be predicted and responded to using systemizing strategies.

In addition to psychological studies of humans, experiments with animals suggest a biological foundation for sex differences in cognition. Male rats perform significantly better than females in navigating the water maze. This sex difference is eliminated by castrating males or by treating females with testosterone just before birth. Human males also are better and faster than females at completing maze tasks. Young male monkeys prefer to play with toy trucks, whereas young female monkeys prefer dolls. Castrated male monkeys spend significantly more time with their mothers and are a lot less aggressive than their peers. These findings suggest that sex differences in toy preferences and social behaviour in children are, in part, the result of innate biological differences. Studies of human infants suggest there is also a biological contribution to social interest. When newborn babies are presented with either a live face or a mechanical toy, girls spend more time looking at the face, whereas boys prefer the mechanical object.

One obviously wants to know the cause of these discrepancies. In the past twenty years there has been an ardent search for some neural, anatomical substrate for cognitive sex differences. Anatomical variations occur in an assortment of regions throughout the brain, and in the sizes of many cortical and subcortical areas. Among other things, investigators have found that parts of the frontal cortex, the engine of many higher cognitive functions, are bigger in women than in men, as are parts of the limbic system, which, as mentioned previously is involved in emotional responses. In men, on the other hand, parts of the parietal cortex, which is thought to deal with space perception, are bigger than in women, as is the amygdala.

It is generally believed that differences in the size of brain structures reflect their relative importance to the animal. For example, as I mentioned earlier, primates, including humans, rely more on vision than on smell; for rats, the opposite is true. As a result, primate brains maintain proportionately larger cortical regions devoted to vision, and rats' brains devote more space to smell. So the existence of widespread anatomical differences in the cortical and subcortical areas of men and of women, suggests that sex does influence the way the brain works. It is known that the brain as a whole is about 10% larger in men and is also larger in boys. This is consistent with fi ndings that increased brain size predicts decreased inter-hemispheric connectivity (neural connections between the right and left halves of the brain). These anatomical differences are likely to be the result of differences in micro-organisation. There are more neurons (brain cells) in the male cerebral cortex and in general, these neurons are more densely packed, albeit with some regional exceptions. Overall, greater numbers and denser packing of neurons, together with more projections between the two halves of the brain from these neurons, indirectly suggest a pattern of increased local connectivity and decreased inter-hemispheric connectivity in the male brain. Physiological observations, though sparse, seem consistent with this picture; language-related activation in female brains is more bilateral, suggesting greater interhemispheric connectivity.

Several recent investigations reported anatomical sex differences at the cellular level, and these differences appear to be region specific, which again points to functional diversification. For example, a recent study discovered that women possess a greater density of neurons in those parts of the temporal lobe cortex that are associated with language processing and comprehension. As I mentioned before, such anatomical diversity may be caused in large part by the activity of the sex hormones in early development. These steroids help to direct the organization and wiring of the brain during development and infl uence the structure and neuronal density of various regions. Interestingly, scientists from Dick Swaab's group in Amsterdam showed that the brain areas that differ between men and women are the ones that in experimental animals and humans contain the highest number of sex hormone receptors during development. This correlation between brain region size in adults and sex steroid action in utero support the notion that sex differences in cognitive function do not result from cultural influences or the hormonal changes associated with puberty – they are there from birth.

Importantly, we know that sex differences in the brain's chemistry and organisation influence how males and females respond to the environment or react to, and remember, stressful events. The amygdala, which was mentioned earlier in relation to basic emotional perception, is larger in men than in women, and this variation supposedly brings about differences in the way that males and females react to stress. For example, if you remove dog pups from their mother and measure the concentration of serotonin – a neurotransmitter important for mediating emotional behaviour (antidepressants in general act by increasing the amount of serotonin) you will find an increase in the serotonin receptor (target for the neurotransmitter) concentration in the males' amygdala, yet a decrease in the concentration of these same receptors in females. The results hint that if something similar occurs in children, separation anxiety might differentially affect the emotional well-being of male and female infants. Experiments such as these are necessary if we are to understand why, for instance, anxiety disorders are far more prevalent in girls than in boys and such discrepancy is increasingly reported in adults.

Another brain region now known to diverge in the sexes both anatomically and in its response to stress is the hippocampus, a structure crucial for short term memory storage. Imaging studies consistently demonstrate that the hippocampus is larger in women than in men. These anatomical differences might well relate somehow to differences in the way males and females navigate. Many studies suggest that men are more likely to navigate by estimating distance in space and orientation, whereas women are more likely to navigate by monitoring landmarks. Interestingly, a similar sex difference exists in rats. Such differences are also consistent with the systemizing pattern of male and the empathizing pattern of female cognition, mentioned earlier.

We also know that there is a difference in the way men and women remember emotional incidents—a process known to involve activation of the amygdala. The magnetic resonance imaging emotional memory experiments showed the right amygdala in men while women tend to use the left amygdala. The realization that male and female brains were processing the same emotionally arousing material into memory differently may lead us to question what this disparity might mean. Here again we must turn to a fundamental theory of brain function proposing that the right hemisphere processes general aspects of a situation, whereas the left hemisphere processes the finer details. Mostly, anyway. So, it is reasonable to argue that a drug that inhibits the amygdala also impairs a man's ability to recall the general plot of an emotional story by subduing the right amygdala, but should hinder a woman's ability to come up with the details by affecting the left amygdala. And funnily enough, scientists have found that so-called beta blockers (drugs usually associated with blood pressure regulation) quiet the activity of adrenaline and noradrenaline and, by doing so, subdue the activity of the amygdala and weaken recall of emotionally arousing memories. In a recent experiment, beta blockers were given to men and to women before they viewed a short slide show about a young boy caught in an accident while walking with his mother. One week later their memories were tested. The results showed that a beta blocker made it harder for men to remember the essence of the story—that the boy had been run over by a car. In women, propranolol did the converse, impairing their memory for details—that the boy had a ball.

It was also reported that the hemispheric differences between the sexes in response to emotional events are detectable very shortly following the event. Volunteers shown emotionally unpleasant photographs react within 300 milliseconds, demonstrating sharp activation of the brain's electrical activity. In men, this activation is more exaggerated when recorded from the right hemisphere; in women, it is larger when recorded from the left. Hence, sex-related hemispheric disparities in how the brain processes emotional images begins very fast, long before people have had a chance to interpret consciously what they have seen. These discoveries might have ramifications for the treatment of post traumatic stress disorder. It is now well established that beta blockers reduce memory for traumatic events in women but not in men.

As I mentioned at the beginning, sex also plays a major role in predisposition to mental disorders. Serotonin production is twice as high in men as in women, which may explain why women are more prone to depression, with most antidepressant drugs affecting serotonin metabolism. A similar situation might prevail in addiction. Take, for example, dopamine — a chemical involved in the feelings of pleasure associated with psychostimulants. In our laboratory we recently showed that cocaine and amphetamine regulated transcript – the main neural target of cocaine in the brain and a major modulator of dopamine – is found mainly in sexually dimorphic structures and at much higher quantity in foetal and adult human females than in males. We also know that in females, estrogen boosted the release of dopamine in those brain regions that are important in regulating drug-seeking behaviour. Furthermore, the hormone had long-lasting effects, making the female rats more likely to pursue cocaine weeks after last receiving the drug. Such differences in susceptibility – particularly to stimulants such as cocaine and amphetamine – could explain why women might be more vulnerable to the effects of these drugs and why they tend to progress from initial use to dependence more rapidly than men.

The brain abnormalities underlying schizophrenia also appear to differ between men and women. A recent study measured the size of the orbito-frontal cortex – a region involved in regulating emotional thinking – and compared it with the size of the amygdala, implicated in producing emotional reactions. The investigators found that women possess a significantly larger orbitofrontal-to-amygdala ratio than men do. It was thus speculated from these fi ndings that women might on average prove more capable of controlling their emotional reactions. Other studies showed that this balance appears to be altered in schizophrenia, though differently for men and women. Women with schizophrenia have a decreased orbitofrontal-to-amygdala ratio relative to their healthy peers, while men have an increased orbitofrontal-to-amygdala ratio relative to healthy men. These findings appear odd, but they imply that schizophrenia is a somewhat different disease in men and women.

A group of psychologists from Cambridge recently proposed a systematizing versus empathizing theory of psychometric gender differences to explain the nature of autism conditions. They argued that neural connectivity in the autistic brain represents an exaggerated version of the typical male brain. Classic autism and Asperger's syndrome (a mild version of autism) are two subgroups on the autistic spectrum of psychological conditions. The researchers point out that people with classic autism have empathy deficits, or degrees of "mind blindness," shown in delayed development of joint attention in infancy and a "theory of mind" in childhood. There is also a strong male bias in the sex ratio of autism. Normal males are slower to develop language than normal females, and children with autism are even more delayed in language development. Normal males are slower to develop socially than normal females, and people with autism are even more delayed in social development. Normal females are superior to males in mind reading tasks, and people with autism are severely impaired in mind reading. Left handedness is more common among males and people with autism. In the normal population, the male brain is heavier than the female brain, and people with autism have even heavier brains than normal males. Characteristic behaviours such as "insistence on sameness," repetitive behaviour, obsessions with lawful systems (e.g. train timetables), islets of ability (calendrical calculation), precocious understanding of machines, and superior attention to the detection of change, all involve a strong interest in rule-based prediction and therefore can be read as signs of hypersystemizing.

Neuroanatomical abnormalities associated with autism appear consistent with a deficit in empathizing, because empathy activates brain regions that integrate information from multiple neural sources. Young children with autism tend to have larger-than-average heads. Magnetic resonance imaging confirms that these large heads contain abnormally large brains. The development of the amygdala in autism likewise seems an extreme of typical male brain development. In children with autism between 18 and 35 months old, the amygdala is abnormally large, even when corrected for total brain volume. This enlargement persists through early childhood, exactly during the period of sex-differential amygdala growth in normal boys. By the time children with autism reach adolescence, the enlargement has disappeared; by early adulthood, the amygdala in autism is abnormally small. Thus, at least in development, the neuroanatomical characteristics of sexually dimorphic structures are affected in autism.

In conclusion, it is wise to mind the sex, that is, the difference between being male or being female. Scientifically put, it is an important basic human variable that should be considered when making scientifi c, medical, educational or other conclusions about human behaviour. We are still far from completing the puzzle of the human mind, including all the gender variations in the brain. Nevertheless, it is increasingly clear that gender differences exist at many levels including the organisation of the brain, behaviour, cognition and pathology.