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Brains apart: The real difference between the sexes

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ANYONE in a long-term relationship will tell you that, at times, men are indeed from Mars, and women are almost certainly from Venus. It's common knowledge that the sexes often think very differently, but until recently these differences were explained by the action of adult sex hormones or by social pressures which encouraged males and females to behave in a certain way. For the most part, the basic architecture of the brain, and its fundamental workings, were thought to be the same for both sexes.

Increasingly, though, those assumptions are being challenged. Research is revealing that male and female brains are built from markedly different genetic blueprints, which create numerous anatomical differences. There are also differences in the circuitry that wires them up and the chemicals that transmit messages between neurons. All this is pointing towards the conclusion that there is not just one kind of human brain, but two.

It's giving neuroscientists something of a headache. Most of what we know about the brain comes from studies of male animals and male human volunteers. If even a small proportion of what has been inferred from these studies does not apply to females, it means a huge body of research has been built on shaky foundations. Working out exactly how women are different could explain some long-running mysteries, such as why men and women are prone to different mental health problems and why some drugs work well for one sex but have little effect on the other.

It has long been known that some differences exist between male and female brains, but they were widely believed to be restricted to the hypothalamus, which is involved in regulating food intake and controlling sex drive, among other things. Unless they were studying the hypothalamus, researchers generally

avoided using female animals in their experiments because the ups and downs of oestrogen and progesterone during the female menstrual cycle made interpreting results more complicated. So, hypothalamus aside, neuroscientists continued to believe that male and female brains were the same.

But it's becoming obvious that the hypothalamus is only the beginning of the story. For a start, the relative sizes of many of the structures inside female brains are different from those of males. In a 2001 study, Jill Goldstein of Harvard Medical School and colleagues measured and compared 45 brain regions in healthy men and women. They found that parts of the frontal lobe, which houses decision-making and problem-solving functions, were proportionally larger in women, as was the limbic cortex, which regulates emotions. Other studies have found that the hippocampus, involved in short-term memory and spatial navigation, is proportionally larger in women than in men, perhaps surprisingly given women's reputation as bad map-readers. In men, proportionally larger areas include the parietal cortex, which processes signals from the sensory organs and is involved in space perception, and the amygdala, which controls emotions and social and sexual behaviour. "The mere fact that a structure is different in size suggests a difference in functional organisation," says neurobiologist Larry Cahill at the University of California, Irvine.

Cahill has found evidence that sex also influences how some brain regions are used. In brain-imaging experiments, he asked groups of men and women to recall emotionally charged images they had been shown earlier. Both men and women consistently recruited the amygdala - a pair of almond-sized bundles of neurons which make up part of the limbic system - for the task. However, the men enlisted the right side of it, whereas women used the left. What's more, each group recalled different aspects of the image. The men recalled the gist of the situation whereas the women concentrated on the details. This suggests men and women process information from emotional events in very different ways, using different mechanisms, says Cahill.

The same may be true for the brain circuits used to dampen pain. It is well known that women are more likely to seek help for chronic pain than men. Some of this can be chalked up to the fact that women use healthcare services more than men, but even taking this into account, there's strong evidence that women - and female animals - experience more pain than males. Not all studies show sex differences but, when they do, it's always the females that feel more pain.

Anne Murphy at the University of Georgia in Athens is trying to find out why chronic pain affects women more than men. She is particularly interested in a pain-suppressing circuit that links two parts of the brain - the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) - with the spinal cord. When this circuit is activated by a pain signal it can dampen pain by setting off a chain reaction that leads to the release of endorphins, which bind to opioid receptors and inhibit the pain signal. "This circuit is the Mecca of pain modulation in

humans and all vertebrates, yet no one has asked how it is organised in females," says Murphy.

There is no clear answer yet, but Murphy's investigations have yielded some intriguing results. Females have a denser connection between PAG and RVM than males, yet Murphy's work suggests that this pathway is not activated in females to suppress pain. "This pathway is obviously not being used for pain in females, so what's the function for it and why is it so much bigger?" she asks.

That question remains unanswered for now, but Jeff Mogil at McGill University in Montreal, Canada, thinks he may have found at least part of the female pain circuitry. In experiments in mice, he chemically blocked a particular receptor found on neurons in the mouse PAG and spinal cord. Mogil discovered that male mice use these *N*-methyl-D-aspartate (NMDA) receptors to dampen pain, but that blocking this pathway had little impact on females' ability to deal with pain. "It suggests that females have a separate pathway that doesn't involved the NMDA receptor," he says.

Genetic experiments in mice have since led him to suspect that female pain inhibition may be linked to sex-specific variations in the gene for the melanocortin-1 receptor (Mc1r), which regulates hair and skin colour in humans and is also expressed in the PAG. Female mice that lacked a functional version of these genes were less able to block pain, as were female human volunteers with red hair, who also lack functional Mc1r genes. Male redheads had no problems blocking pain, presumably because they were using the NMDA circuit instead.

It's early days, but if women do have a different pain-damping circuit to men, it could explain why there are sex differences in responses to opioid painkillers. Women get more relief from the opioid painkiller nalbuphine compared to morphine, whereas in men morphine is more effective and nalbuphine actually increases the pain intensity. The findings could eventually lead to new painkillers tailored to be more effective in women, but Mogil isn't holding his breath. "For now there isn't a big enough and uncontroversial enough literature in any of these differences to justify drug development of any single one of them," he says.

Similar difficulties have blighted developments in mental health - another area where there are known to be sex differences. Women are diagnosed with depression twice as often as men, for example, and their brains typically produce about half as much serotonin - a neurotransmitter linked to depression. Earlier this year, Anna-Lena Nordström, from the Karolinska Institute in Stockholm, Sweden, found that healthy women have more of the most common type of serotonin receptor than men but fewer serotonin transporters, which are needed to recycle serotonin. It hasn't been shown that variations of this set-up make some women more prone to depression, but Nordström points out that transporter differences between men and women are of particular interest because this is where antidepressants like Prozac act, and because there is

evidence that women respond better to such drugs than antidepressants that act on neurotransmitters other than serotonin.

Males may be less likely to suffer depression, but that doesn't mean they get an easy ride. Boys are more likely to be diagnosed with autism, Tourette's syndrome, dyslexia, stuttering, attention-deficit disorder and early-onset schizophrenia. Margaret McCarthy of the University of Maryland in Baltimore believes that hormone-like substances called prostaglandins, which help masculinise the male brain shortly before or after birth may be at least partly to blame. Prostaglandins are also known to cause inflammation, so McCarthy is investigating whether their action, if altered by infection or certain drugs, could cause inflammation and damage to the developing brain.

The ways in which men and women abuse drugs is another area that could reveal brain differences. While men are almost twice as likely as women to use cocaine, possibly due to social factors, when women take it they get addicted more quickly and have a more severe habit when they seek treatment.

Jane Taylor from Yale University suggested in 2007 that genetic differences may help to explain why. She compared mice that were engineered to either be genetically male with testes, genetically male with ovaries, genetically female with testes or genetically female with ovaries. She found that genetically female mice formed drug habits more quickly than the genetically male mice, regardless of which gonads they carried (*Nature Neuroscience*, vol 10, p 1398).

Jill Becker at the University of Michigan, Ann Arbor, has found something similar. She trained rats to poke their noses into a hole to get a dose of cocaine and compared the cocaine intake of female rats which had had their ovaries removed with castrated male rats. The females were bigger bingers. But when these females were given oestrogen, their total intake nearly tripled. That means that a genetic vulnerablility plus circulating sex hormones can add up to a crippling addiction.

Several studies have since found that women report that cocaine has a bigger positive effect when their oestrogen levels are high and their progesterone levels low. Suzette Evans at the Columbia University College of Physicians and Surgeons in New York City is running a clinical trial to test whether cocaine-dependent women can be treated by increasing their progesterone levels.

There's much left to learn, but as the evidence mounts for sex-related influences on brain structure and function, the development of medicines better suited to a woman's biology may yet take off. Before that can occur, however, more work is needed to uncover the differences between the brains of male and female animals. Despite recent progress, such work is very much in the minority.

Mogil, who has demonstrated big differences in pain processing in males and females, is astonished that so many researchers have failed to include female

animals in their studies, especially when it comes to pain research. "It's scandalous," he says. "Women are the most common pain sufferers, and yet our model for basic pain research is the male rat." On the flip side, it's also an area ripe for exploration: "Every year or two we write a paper that says that something someone reported earlier is actually only true in males. We keep making people look bad. They are missing stuff completely."

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