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Sex on the brain: Contradictions in the neuroscience of sex

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A contradiction exists within the neurosciences on the issue of sex. On the one hand, it is increasingly clear that there are important differences in brains as a function of sex, and to ignore these differences is a disservice to both men and women. On the other hand, research that draws on findings in neuroscience to explain sex differences in behaviour has been called out as 'neurosexist'. In this article I'll make the case for keeping sex in the neurosciences, outline some of the ways research can be misinterpreted (by both scientists and the public), and clarify what neuroscience can, and can't, tell us about men and women.

There are several reasons why we should consider sex when studying the brain. Men and women differ across a host of biological and environmental variables. They differ genetically and hormonally, with consequences for almost all biological systems, including the brain (McCarthy *et al*. 2012). They also differ in peer and parental influences, socialisation, expectations, and life experiences (Fine 2013). Any of these factors (and others) can affect the brain and subsequent behaviour. Some behavioural sex differences are quite large; for example those in sexual attraction and behaviour, aggression, or interests (Carothers & Reis 2013). Others are quite small, including those in many cognitive abilities (Halpern 2012). The mere existence of these differences, of course, says nothing about their causes, consequences, or malleability. But to the extent that all thoughts, feelings, and actions are generated by the brain, we can learn more about these behaviours by considering sex differences in their neural correlates.

Sex differences are critical to understanding a number of brain-based disorders. Depression, for example, is twice as common in women as in men (Nolen-Hoeksema 2001). Women also suffer from higher rates of anxiety, eating disorders, multiple sclerosis, and Alzheimer's disease. Men in contrast have higher rates of impulsivity, autism, Parkinson's disease, and adolescent-onset schizophrenia (Abel *et al.* 2010; Arnett *et al*. 2014; Eaton *et al*. 2012; Miller & Cronin-Golomb 2010; Voskuhl & Gold 2012; Werling & Geschwind 2013). Any neuropsychologically valid theory of these disorders therefore has to consider the role of sex in etiology, manifestation, and treatment. Again, the existence of difference says nothing about cause. Consider depression, a complex disorder that surely has genetic, neurochemical, cognitive, experiential, psychosocial, and cultural determinants - any combination of which can differ for men and women. Regardless of its causes, the constellation of thoughts, feelings, and actions that define depression are instantiated in the brain, making the brain a critical component in any understanding of why depression so inequitably targets women.

Disregard for sex differences can have serious consequences. A well-publicised example is the dose recommendations for the sleep medication zolpidem (Ambien), the most widely-prescribed hypnotic drug worldwide (Greenblatt *et al.* 2000, 2013). Zolpidem was in wide use before it was recognised that women achieved higher blood concentrations of the drug than men, even after adjusting for bodyweight. More worrying, the drug also had more profound effects on fatigue and concentration in women, even after adjusting for blood concentrations. Thus men and women differ in both the metabolism of the drug and in its psychological effects. The US Food and Drug Administration only altered its recommended dosing for zolpidem in women in 2013, more than twenty years after it first appeared on the market (US FDA 2013).

Problems like these can arise because much medical (including neuroscience) research includes only male laboratory animals, based on the assumption that non-reproductive systems should not show sex differences. Using only one sex reduces variability between animals and so maximises ability to observe experimental effects. Female animals are assumed to have additional variability related to hormonal cycles, and co-housing of males and females introduces additional complications. The use of only male animals is therefore efficient and cost-effective, but only if effects in males generalise to females. But in many domains they don't. In response to this problem, the National Institutes of Health has recently called for a wholesale change in preclinical studies to include both male and female animals and cells (Clayton & Collins 2014).

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In humans, sex differences can go unnoticed because researchers simply do not look for them. Researchers may include both men and women in their studies, but then not analyse sex differences or even report the sex of their participants. An example can be drawn from the area of pain research, where research prior to the 1990s rarely considered the sex of participants (Berkley 1997). But it is now clear that women have lower pain thresholds than men in experimental settings, are more likely to report clinical pain, and show a reduced therapeutic response to analgesics (Bartley & Fillingim 2013; Mogil 2012). This 'don't ask, don't tell' approach is still common in many research areas in psychology and the neurosciences. Most concerning is that scientists may actively avoid sex difference research because they are concerned about the consequences of their findings. Sex differences are likely to draw unwelcome media attention that can drown out more important scientific findings or distort results to create controversy. Scientists can be stigmatised simply for pursuing sex difference research. Larry Cahill, a neuroscientist who studies sex differences in the amygdala (a brain structure that plays an important role in emotional processing) writes that he was advised by senior colleagues that studying sex differences would 'kill' his career (Cahill 2014). I was similarly advised that sex differences are peripheral to important questions in cognitive neuroscience and not a suitable topic of study for a serious scientist.

An avoidance of sex difference research in the neurosciences stems partly from concerns about neurosexism (Fine 2013) – the use of neurological findings to support a sexist status quo. Neurosexism reflects some important misunderstandings about brain research and about what neuroscience can, and can't, tell us. A recent study on sex differences in connectivity illustrates some of these misunderstandings. In a study published in the Proceedings of the National Academy of Sciences, Ingalhalikar and colleagues (2013) used a process called diffusion tensor imaging (DTI) to map the major myelinated pathways in the brain. The process produces a structural connectivity map (or *connectome*) that quantifies the strength of connections between different brain areas. They divided the brain up into 95 small segments, or parcels, and examined the connection strength between each pair. This produced almost 9000 potential connections.

In a large sample of 949 adolescents and young adults (ages 8–22), they found that some (but certainly not all) of these pathways showed sex differences that emerged in adolescence. Of the pathways that were stronger in men than women, almost all were intrahemispheric; they connected brain areas within the same cerebral hemisphere. In contrast, most of the pathways that were stronger in women than men were interhemispheric; connecting homologous areas in the left and right hemispheres. This structural map is largely consistent with decades of research suggesting that women are less lateralised than men, and that they have better communication between left and right hemispheres. The study makes some important contributions to the literature. DTI is a relatively new technique that allows us to map structural connections between brain areas, which are emerging as important factors in understanding brain function. This research team are pioneers in the technique, and this is one of the largest studies conducted to date to produce such a detailed map.

The media response was swift, and came in two phases. The first appeared in the mainstream press: *Vive la difference* (*Economist* 2013). *Male and female brains wired differently, scans reveal* (*The Guardian* 2013). *Differences in how men and women think are hard-wired* (*Wall Street Journal* 2013). *The Independent* (2013) led with a wordy headline, *The hardwired differences between male and female brains could explain why men are better at map-reading*. The second wave consisted of the backlash: *Getting in a tangle over men's and women's brain wiring* (*Wired* 2013). *Be wary of studies that claim men and women's brains are wired differently* (*New Republic* 2013). *The most neurosexist study of the year*? (*Slate* 2013). *Men are NOT from Mars after all* (*Daily Mail* 2014).

The media attention (both pro and con) focused largely on 'hardwiring' – a term that does not appear anywhere in the published article. The term reflects the assumption that brain structure and function are innate, coded in our DNA, as nature intended us to be. The extension of this assumption is that men's and women's innately different brains provide an explanation for all the myriad ways that men and women are different. But this assumption is wrong on a number of counts. Most importantly, brains reflect both genetic and environmental influences. Brains are certainly constrained by our biology. I can talk and my dog cannot, and I am fairly confident that the difference stems from fundamental differences in our brains that are coded in our genomes. But, brains (especially human brains) are also plastic. Every skill we learn, every fear we acquire, every memory we create, alters brain structure and function (Zatorre *et al.* 2012). The fact that connectivity differences emerged in adolescence is consistent with the idea that they reflect, at least partially, the different experiences of boys and girls. However, it is also consistent with hormonal differences with adolescent onset. To the extent that two groups of people (like men and women) think or act differently, *for whatever reason*, those differences will show up in their brains – it is inevitable. It would be much more remarkable if two groups of people exhibited different behaviours yet had identical brains! The focus on the brain as hardwired reflects the hope that somehow the brain could give us the answer to the age-old (but ill-conceived) question of nature vs. nurture. But neuroscience can't answer that question, because nature and nurture will both be reflected in the brain, intimately entwined. Neuroscience can't explain the 'why' of sex differences, but it can help us to understand 'how'. And understanding 'how' is a critical step toward the goal of better understanding of the human condition.

A further misconception surrounding the study by Ingalhalikar and colleagues is that their reported sex differences in structural connectivity explain any sex differences in behaviour. The study did not assess behaviour, and so it is impossible to make that link – although that should be a goal in future research. The authors are guilty of making this assumption themselves. Although the research team may have considerable expertise in structural imaging, they do not appear to know much about sex differences. They speculate that 'male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes'. Although they may not use the term hardwired, they imply that behavioural differences arise through pre-existing neurological mechanisms. More seriously, they link their structural differences to popular (mis)conceptions of sex differences in athletic skills and intuition, and not to those in well-documented (and well-defined) constructs. They also draw on folk theories of the cerebral hemispheres when they refer to women's ability

to connect the 'analytical and sequential reasoning modes of the left hemisphere with the spatial, intuitive processing of the right'. In the media these claims were exaggerated even further, with this structural difference explaining why women are more nurturing and men are better hairdressers.

And yet a further misconception is that these connectivity effects are large or profound. This misconception stems partly from sloppy language – we say 'women have stronger interhemispheric connections' by which we mean that people differ in their interhemispheric connections, but the mean connection strength in women is greater than the mean connection strength in men. The connection strengths can be described by two overlapping distributions. A study with a sample size of greater than 900 can reveal very small but statistically significant differences. Although the authors don't report an effect size for any of their sex differences, Ridgway (2013) calculated them based on the statistics in the paper, and found that for the largest interhemispheric difference, connection strength was 0.3 of a standard deviation greater in women than men. We can consider what that means in real terms. If I assumed that anyone with values greater than the overall mean was a woman, and anyone with values less than the mean was a man, I would be right 56% of the time.

The magnitude of the effect is exaggerated by a figure that is included in the paper, and that was widely reproduced in the media. It presents a brain showing only those connections that are stronger in men than in women (almost all of which are intrahemispheric) and another showing only those connections that are stronger in women than in men (almost all of which are interhemispheric). The resulting image looks like a pair of wiring diagrams of the typical male and female brain, which are so strikingly different 'that they might almost be separate species' (*Daily Mail* 2013, 2014). Of course, the reality is that men and women have all the same connections, and the figure is just presenting those connections that are slightly stronger in men or women. The authors were criticised in the scientific literature for this misrepresentation (Joel & Tarrasch 2014). Although they explain the figure accurately in the text of the article, that explanation was lost when the brain diagrams were presented to the public.

Clearly then, neuroscience findings can be used to draw unjustified conclusions about sex differences in behaviour, and those distortions can be magnified when findings reach the public. It is worth noting that the original finding of a sex difference in connectivity is not particularly controversial and is a valuable contribution to a growing literature on sex differences in brain structure and function. Neurosexism arises through the inappropriate extrapolation of findings to provide simplistic explanations for complex and multiply-determined behaviour. The biggest danger of incidents like these is that they can lead us to brand neuroscience itself as an enemy of feminism and equality. One of the most disturbing media headlines appeared in *Popular Science* (2014): *Stop looking for 'hardwired' differences in male and female brains*. A neuroscience that ignores sex is incomplete and ineffective. The stakes are too high, for both men and women, for us to stop.

Given recent findings of important sex differences, and changes in government funding policies, I expect (and hope) that we will see more sex difference research in the neurosciences in future. The challenge will be for researchers to conduct and communicate that research responsibly. Fine and colleagues (2013) laid down this challenge: 'Scientists who work in politically sensitive and important areas have a responsibility to realise how social assumptions influence their research and, indeed, public understanding of it. Moreover, they should also recognise that there are important and exciting opportunities to change these social assumptions through rigorous, reflective scientific inquiry and debate'. A neuroscience that tackles the important question of sex does indeed seem a worthy pursuit for a serious scientist.

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