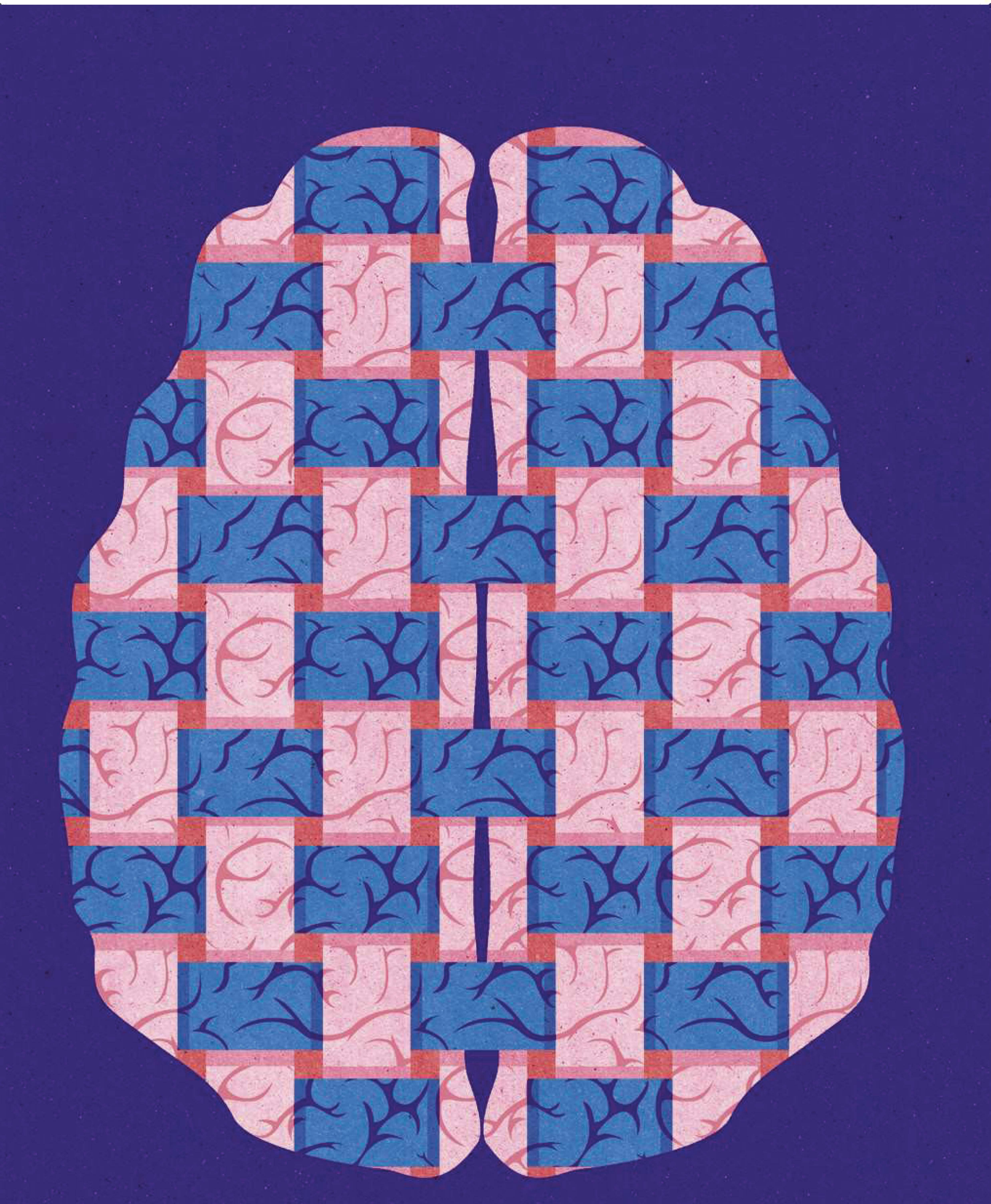
IS THERE A "FEMALE" BRAIN?

The debate over whether men and women have meaningfully different brains could have profound implications for health and personal identity

By Lydia Denworth

Illustrations by Kotryna Zukauskaite



IN 2009 DAPHNA JOEL, A NEUROSCIENTIST AT TEL AVIV UNIVERSITY, DECIDED TO teach a course on the psychology of gender. As a feminist, she had long been interested in questions of sex and gender, but as a scientist, her research had been mostly on the neural underpinnings of obsessive-compulsive behavior. To prepare for the class, Joel spent a year reviewing much of the extensive and polarized literature on sex differences in the brain. The hundreds of papers covered everything from variations in the size of specific anatomical structures in rats to the possible roots of male aggression and female empathy in humans. At the outset, Joel shared a popularly held assumption: just as sex differences nearly always produce two different reproductive systems, they would also produce two different forms of brains—one female, the other male.

IN BRIEF

A popularly held assumption asserts that male and female brains are markedly different.

Controversial new research, however, suggests that most brains are a mosaic of male and female characteristics.

Ensuing debate has roiled neuroscience and raised questions about ways in which sex and gender are considered outside the laboratory.

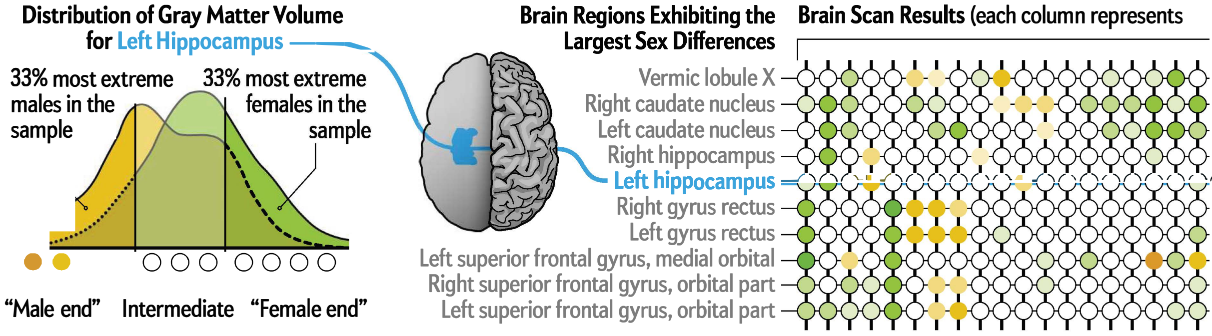
As she continued reading, Joel came across a paper contradicting that idea. The study, published in 2001 by Tracey Shors and her colleagues at Rutgers University, concerned a detail of the rat brain: tiny protrusions on brain cells, called dendritic spines, that regulate transmission of electrical signals. The researchers showed that when estrogen levels were elevated, female rats had more dendritic spines than males did. Shors also found that when male and female rats were subjected to the acutely stressful event of having their tail shocked, their brain responded in opposite ways: males grew more spines; females ended up with fewer.

From this unexpected finding, Joel developed a hypothesis about sex differences in the brain that has stirred up new controversy in a field already steeped in it. Instead of contemplating brain areas that differ between females and males, she suggested that we should consider our brain as a "mosaic" (repurposing a term that had been used by others), arranged from an assortment of variable, sometimes changeable, masculine and feminine features. That variability itself and the behavioral overlap between the sexes—aggressive females and empathetic males and even men and women who display both traits—suggest that brains cannot be lumped into one of two distinct, or dimorphic, categories. That three-pound mass lodged underneath the skull is neither male nor female, Joel says. With her colleagues at Tel Aviv, the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, and the University of Zurich, Joel tested her idea by analyzing MRI brain scans of more than 1,400 brains and demonstrated that most of them did indeed contain both masculine and feminine characteristics. "We all belong to a single, highly heterogeneous population," she says.

When Joel's work was published in 2015 in the *Pro-*

The Mosaic Brain

Sex differences found in the human brain have led to the perception that brains are either male or female. A study by Daphna Joel of Tel Aviv University and her colleagues tells a different story. Joel's research found that the typical brain is a "mosaic," combining some features more common in males and some that appear more frequently in females, pointing to the conclusion that human brains do not belong to two distinct types categorized by sex.



Graphic by Jen Christiansen

ceedings of the National Academy of Sciences USA, like-minded scientists hailed it as a breakthrough. "The result is a major challenge to the entrenched misconceptions," wrote Gina Rippon, a professor of cognitive neuroimaging at Aston University in England. "My hope is it will be a game-changer for the 21st century."

Longtime sex-difference researchers, meanwhile, disagreed strenuously, taking issue with Joel's methodology and conclusions, as well as her overt feminism. "The paper is ideology masquerading as science," says neurobiologist Larry Cahill of the University of California, Irvine, who argues that Joel's statistical methods were "rigged" (albeit not necessarily consciously) to favor her hypothesis. Other criticisms were more measured. "There's variability within individuals, and she shows that beautifully, but that doesn't mean there are no regions of the brain that, on average, are going to be different in men versus women," says neuroscientist Margaret M. McCarthy of the University of Maryland School of Medicine, who studies sex differences in rats.

Joel, for her part, agrees that genetics, hormones and environment do create sex differences in the brain. She even agrees that given enough information about specific features in any one brain, it is possible to guess, with a high degree of accuracy, whether that brain belongs to a female or a male. But what you cannot do, she points out, is the reverse: look at any one man or woman and predict the topography and molecular landscape of that individual's brain or personality just because you know the person's sex.

Controversial as her study is, the essence of what Joel is saying is true, says Catherine Dulac, a molecular biologist at Harvard University whose work in mice echoes Joel's findings: "There is huge heterogeneity between individuals." Acknowledging that fact has opened a new thread in the conversation about what it means to be male or female. For neuroscientists, it is no longer enough to ferret out sex differences in the brain. The debate now centers on the source, size and significance of those differences. It could have major implications for how sex and gender are considered inside and outside the laboratory—and it may have consequences as well for whether drug regimens and treatment protocols should be specialized for women and men. "Our entire society is built on the assumption that our genitals divide us into two groups not just in terms of reproduction ability or possibility but also in terms of our brain or behavioral or psychological characteristics," Joel says. "People assume the differences add up. That if you are feminine in one characteristic, you will be feminine in other characteristics. But it's not true. Most humans have a gender mosaic."

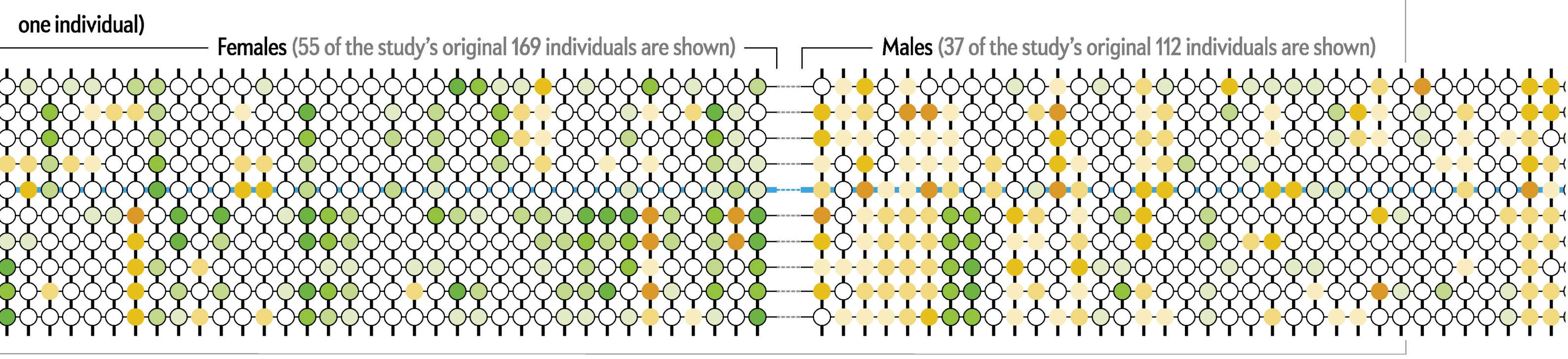
CLAIMS AND COUNTERCLAIMS

IN THE LATE 1800S, long before MRI was a gleam in any scientist's eye, the primary measurable difference in male and female brains was their weight (assessed postmortem, naturally). Because women's brains were, on average, five ounces lighter than men's, scientists declared that women must be less intelligent. As journalist Angela Saini recounts in *Inferior: How Science Got Women Wrong—and the New Research That's Rewriting the Story,* women's-rights advocate Helen Hamilton Gardener (a pseudonym) took on the experts of the day, arguing that the ratio of brain weight to body weight, or brain size to body size, had to be more relevant to intelligence than brain weight alone or "an elephant might out-think any of us." Fittingly, Gardener left her own brain to science. It was found to be five ounces lighter than the average male brain, but it was the same weight as that of the eminent male scientist who had founded the brain collection at Cornell University where her brain was stored. (For the record, Gardener was on to something. "Once you correct for brain size, most of these sex differences disappear, or they become very small," says Lise Eliot, a neuroscientist at the Chicago Medical School at Rosalind Franklin University of Medicine and Science.)

For much of the next century concrete sex differences in the brain were the province not of neuroscientists but endocrinologists, who studied sex hormones and mating behavior. Sex determination is a complex process that begins when a combination of genes on the X and Y chromosomes act in utero, flipping the

NEURAL SIGNATURES OF THE SEXES

In her 2015 study, Joel examined MRIs of more than 1,400 brains and found significant overlap among the areas of neural tissue (gray matter) showing the largest differences between males and females. In brain scans of the left hippocampus, most females and males had a volume of gray matter toward the middle on a continuum of "maleness" or "femaleness" (*graph at left and white dots from a subset of the study data below*). In addition, about a third of individuals had features at both the maleness and femaleness extremes, shown below as green (femaleness) and orange (maleness) in dots of varying shades. Only 2.4 percent, meanwhile, had just features from one extreme. The trend was also reflected in the other data sets used by the researchers, and the findings were corroborated by a subsequent analysis of personality traits, attitudes and behaviors.



switch on feminization or masculinization. But beyond reproduction and distinguishing boy versus girl, reports persisted of psychological and cognitive sex differences. Between the 1960s and early 1980s the late Stanford University psychologist Eleanor Maccoby found fewer differences than assumed: girls had stronger verbal abilities than boys, whereas boys did better on spatial and mathematical tests. Predictably, critiques followed. Janet Hyde, a psychologist at the University of Wisconsin–Madison, has conducted meta-analyses, combining the results of previous studies, and found, as she wrote in a 2016 study, that females perform as well as males in math and that "males and females are quite similar on most—but not all—psychological variables." Based on these results, Hyde developed what she calls the gender similarities hypothesis, which posits that the psychological makeup of men and women is more alike than different.

Once technology made it possible to peer inside a living brain, a long list of sex differences appeared that had nothing to do with mating or parenting. Writing in 2006 in *Nature Reviews Neuroscience,* Cahill described "a surge of findings from animals and humans concerning sex influences on many areas of brain and behaviour, including emotion, memory, vision, hearing, processing faces, pain perception, navigation, neurotransmitter levels, stress hormone action on the brain and disease states." In rats, McCarthy measures everything from the size of the collections of neurons that make up cell nuclei to the number of astrocytes and microglia, cells that form a support system for neurons. "There's irrefutable evidence of a biological basis for sex differences in the brain beginning from animals all the way up to humans," she says. But McCarthy also emphasizes that the source of sex differences in humans is more complicated than in animals that do not contend with gender, the psychological and social attributes of sex. "In humans, the fact that you're raised as a particular gender from the instant that you're born of itself exerts a biological impact on your brain," she says. In her 2009 book *Pink Brain, Blue Brain,* Eliot agrees, arguing that plasticity, the way the brain changes in response to experience, drives sex differences in behavior more than hardwired biology does.

Making the leap from brain to behavior provokes the most strident disagreements. One recent high-profile study accused of playing to stereotypes (and labeled "neurosexist") was a 2014 paper by Ruben Gur, Raquel Gur and Ragini Verma, all at the University of Pennsylvania. The group used diffusion tensor imaging, a technique showing the strength of connections among neurons, to look at nearly 1,000 brains of subjects between the ages of eight and 22. It found that males had stronger connections within the left and right hemispheres of the brain and that females had more robust links between hemispheres. The researchers concluded that "the results suggest 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." (Counterclaim: the study did not correct for brain size.)

IN SEARCH OF VARIABILITY

INTO THIS MAELSTROM stepped Joel. Many previous studies have identified differences in single brain features and then used those differences to make claims about entire populations—the averages for women and men. Joel and her colleagues did the opposite: they used a picture of the population-level differences encountered across an entire group to ask what claims can be made about individual brains. "These are two different descriptions of the world," Joel says. Both show the same group-level differences. The critical question is: Which better describes human brains—the first, in which one type of brain is typical of males and another of females, or the second, in which most people's brains are mosaics of male and female characteristics?

Specifically, Joel's 2015 study asked two questions: How much overlap is there in features that show differences between females and males? And are brains "internally consistent"? The latter is a measure Joel developed to determine if all features in any one brain were masculine or feminine. Using four large sets of MRI data, her team identified, in each data set, several features with the greatest difference between males and females, such as the collective volume of the nerve cells' central bodies and dendritic extensions (gray matter) and their connecting fibers (white matter). They found a continuum of features. Definitive feminized and masculinized features occupied the extremes, and an intermediate zone exhibited a mix of attributes.

The researchers then assessed every brain in the data sets region by region and coded each feature [*see box on preceding pages*]. They reasoned that if brains are internally consistent, elements that show sex differences should reliably take on male or female forms. It followed that few brains should exist with both feminine and masculine traits. But between 23 to 53 percent of brains (depending on the data set) contained features from both ends of the spectrum. Brains that were internally consistent were rare—from 0 to 8 percent of those examined.

Joel cites arguments for the desirability of single-sex classrooms as a real-world example of why variability matters. "[Single-sex education] assumes that boys have one set of characteristics—for example, they are more active and have less patience—and girls have another set of characteristics. Therefore, we should separate them and treat each group differently. What we are showing is that although this is true at the group level, it's not true at the individual level. You can't divide students into a group that is very active, likes sports, is very good at mathematics, and doesn't like poetry and another group that is the mirror image. There are very few kids like this."

Most scientists find Joel's work demonstrating variability convincing. "Daphna's contribution was to show, individual by individual, the variability within gender," Eliot says. "Nobody ever publishes [those] data." But many find the measurement of internal consistency problematic. One response to Joel's *PNAS* paper was from Marco Del Giudice of the University of New Mexico and his colleagues. They argued that the definition Joel and her colleagues used for internal consistency was so extreme as to be biologically implausible, if not impossible. To prove it, they reran Joel's analysis using entirely different sets of biological variables—for example, comparing variability among facial features of three very different-looking monkey species. If Joel's method were valid, Del Giudice reasoned, the monkeys should show clear ("internally consistent") facial distinctions across species.

Despite notably varied appearances among the three species, the distinguishing facial features of any one monkey rarely resulted in internal consistency, as defined by Joel—hence, Cahill's view that the study is "rigged." In response, Joel and her colleagues used different analytical techniques in a 2018 study. Measuring similarity and difference mathematically rather than biologically in 2,176 human brains, they found that brains from females were almost as likely to be classified as "male" as brains from males are and that a male and a female are almost as likely to have the same brain types as two females or two males are.

The debate comes down to which matters more: the average or the individuals within the population under study. The answer often depends on the question being asked. But researchers can and do look at the same evidence and draw different conclusions. "The human brain may be a mosaic, but it is one with predictable patterns," wrote Avram Holmes of Yale University and his colleagues in response to Joel in 2015, and they believe those patterns demand statistical consideration. Biologist Anne Fausto-Sterling, a professor emerita of biology and gender development at Brown University and a critic of sex-difference research, has another perspective. "Talking about average differences is misleading if that's all we do," she says. "The brain is not a uniform entity that behaves as something male or something female, and it doesn't behave the same way in all contexts. Daphna is trying to get at the complexities of what brains actually do and how they function."

The implications of this controversy for science, especially clinical research aimed at treating disease, are considerable. Between 1997 and 2000, 10 drugs were withdrawn from the U.S. market because they carried side effects that were dangerous, even fatal. Eight of the 10 had greater health risks for women than for men. In 2013 the U.S. Food and Drug Administration reduced by half the prescription dosage of zolpidem, the generic name for Ambien, for women. After registering patients' complaints about drowsy morning commutes, researchers had discovered that the drug was still present in some women's bodies on waking. Here, too, counterclaims appear. Eliot and Sarah Richardson, a historian of science and gender at Harvard, suggest that much of the differences in zolpidem's side effects could be accounted for by body weight disparities. Weight is not the whole story, because women's higher body fat levels cause some drugs to metabolize more slowly, but precision in identifying the truly critical variables for drug dosing should be possible.

Partly in response to such concerns, starting in January 2016, the National Institutes of Health required that all preclinical research, the phase before testing in humans, must include female animals. Janine Clayton, director of the NIH Office of Research on Women's Health, was careful to say, in explaining the new policy, that including both sexes in studies does not necessarily mean looking for sex differences. Many regard this directive as an important step. McCarthy points out that various neurological diseases or disorders with an early onset, such as attention deficit hyperactivity disorder and autism spectrum disorder, are more common in males, whereas those that appear later, such as depression and anxiety, are more common in females. "In the face of that, we are compelled to look at the brain as a biological organ that differs in males and females," she says. "To not do it would be a travesty." But Joel, Fausto-Sterling and others worry that the pendulum will swing too far. They argue for research that includes sex as a variable, with an even number of male and female subjects, but that recognizes in analyzing results that "male" and "female" categories may reflect variables that have nothing to do with sex.

More broadly, if this work is to change the way society thinks about sex and gender, it might begin with terminology. "It's time to dump the word 'dimorphism,'" Eliot says. "A dimorphic structure is an ovary versus a testis. A 2 percent difference in gray matter to white matter ratio is not dimorphic. It's just a sex-related variance."

Dulac argues that we need "a more refined way to define these differences." In mice, she has found that neural circuits governing male mating behavior are also found in females, whereas maternal behavior circuits can be found in males. "It would be wrong to conclude from our work that there are no differences between males and females," Dulac says. "But the very interesting question is: How are these differences emerging, and how subtle or significant are they?"

McCarthy and Joel joined forces in 2017 to lay out a more sophisticated framework for defining what is being measured in sex-difference research and what it means. They suggest four possible dimensions: whether a trait is persistent or transient; whether it depends on context; whether it takes only one of two forms—and is thus truly dimorphic—or else falls on a spectrum; and whether it is a direct or indirect consequence of sex. This way of describing the world of sex differences is not nearly as catchy as the long-standing Mars versus Venus metaphor, but it is probably much more accurate. As a rule, complexity more closely reflects who people really are. "My mother is very nurturing, but she's a lot better at spatial navigation than my father," Eliot says. "That's a mosaic, right?" SA

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MORE TO EXPLORE

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