Equal ≠ The Same: Sex Differences in the Human Brain

By Larry Cahill, Ph.D.

Editor's Note: While advances in brain imaging confirm that men and women think in their own way and that their brains are different, the biomedical community mainly uses male animals as testing subjects with the assumption that sex differences in the brain hardly matter. This month's Cerebrum *highlights some of the thinking and research that invalidates that assumption.*

Early in 2013, the Food and Drug Administration (FDA) ordered the makers of the well-known sleep aid Ambien (zolpidem) to cut their recommended dose in half—but only for women. In essence, the FDA was acknowledging that despite extensive testing prior to the drug's release on the market, millions of women had been overdosing on Ambien for 20 years. On February 9, 2014, CBS's *60 Minutes* highlighted this fact—and sex differences in general—by powerfully asking two questions: Why did this happen, and are men and women treated equally in research and medicine?[1]

The answer to the first question is that the biomedical community has long operated on what is increasingly being viewed as a false assumption: that biological sex matters little, if at all, in most areas of medicine. The answer to the second question is no, today's biomedical research establishment is not treating men and women equally. What are some of the key reasons for the biomedical community's false assumption, and why is this situation now finally changing? What are some of the seemingly endless controversies about sex differences in the brain generated by "anti–sex difference" investigators? And what lies at the root of the resistance to sex differences research in the human brain?

Why Sex Didn't Matter

For a long time, for most aspects of brain function, sex influences hardly mattered to the neuroscience mainstream. The only sex differences that concerned most neuroscientists involved brain regions (primarily a deep-brain structure called the hypothalamus) that regulate both sex hormones and sexual behaviors.[2] Neuroscientists almost completely ignored possible sex influences on other areas of the brain, assuming that the sexes shared

anything that was fundamental when it came to brain function. Conversely, the neuroscience mainstream viewed any apparent sex differences in the brain as not fundamental— something to be understood after they grasped the fundamental facts. By this logic, it was not a problem to study males almost exclusively, since doing so supposedly allowed researchers to understand all that was fundamental in females without having to consider the complicating aspects of female hormones. To this day, neuroscientists overwhelmingly study only male animals.[3]

To make matters worse, studying sex differences in the brain was for a long time distasteful to large swaths of academia.[4] Regarding sex differences research, Gloria Steinem once said that it's "anti-American, crazy thinking to *do* this kind of research."[5] Indeed, in about the year 2000, senior colleagues strongly advised me against studying sex differences because it would "kill" my career.

Why Sex Matters

I survived after rejecting my colleagues' advice, and in fact, many neuroscientists have come to realize like me that their deeply ingrained assumption that sex does not matter is just plain wrong.

Let us start with animal research. Despite the fact that most neuroscientists still overwhelmingly use only males in their studies, other neuroscientists have generated considerable data demonstrating sex influences on brain function at all levels, including the molecular level[6-8] and ion-channel level.[7] Very often these sex influences are completely

unanticipated by investigators. Crucially, animal research clearly demonstrates that mammalian brains in particular are filled with sex influences that cannot be explained by human culture. Thus animal research proves that the human mammalian brain must contain all manner of biologically based sex influences—from small to large—that cannot be explained simply by human culture (even though there are certainly cultural contributions in many cases). Animal research has torpedoed the "it's all human culture" ship that ruled the academic seas since the 1970s when it came to sex differences.

But evidence of sex influences on brain function is not restricted to animal research. Research involving humans has generated equally impressive findings, two of which I highlight here, one regarding human brain structure, the other human brain genetics.[6-8]

One recent landmark study came from investigators from the University of Pennsylvania. They used a form of magnetic resonance imaging (MRI) called diffusion tensor imaging (a way to measure the brain's white matter, or axons by which neurons connect) in a large sample of men and women (428 males and 521 females, ages 8 to 22 years).[9] Across a number of different analytic approaches, they found a striking and consistent result: The brains of women exhibit significantly stronger patterns of interconnectivity across brain regions—including across the hemispheres—than do the brains of men, which conversely exhibit significantly greater average connectivity within local brain regions (what the authors refer to as modularity).

This striking result fits very well with a highly consistent finding across the sex-difference literature: The brains of men tend to be more asymmetrically organized across the hemispheres than are those of women.[10] Importantly, the authors found no age-by-sex interactions despite having plenty of statistical power to find such interactions. This means we cannot explain the sex differences in their results as simply being due to different cultural experiences between males and females.

The Pennsylvania study results are also consistent with diffusion tensor imaging studies by Neda Jahanshad and colleagues, who found greater average interhemispheric connectivity in women compared to men.[11-12] (Impressively, with some analytic approaches, these investigators can accurately classify brain connectivity networks based on sex with 93 percent accuracy.[12]) While we can, and should, debate what these types of anatomical findings will ultimately prove to mean functionally, the evidence leaves little reasonable doubt that male and female brains exhibit, on average, differing patterns of structural interconnectivity, in particular between the hemispheres. In a comprehensive review of human-brain connectivity studies from several years ago, Gaolang Gong and colleagues concluded that "it should be mandatory to take gender into account when designing experiments or interpreting results of brain connectivity/network in health and disease."[13] The data since then confirms this view.

A second important study highlights the fact that sex differences exist down to the genetic level in humans. When David Cribbs and other researchers performed a comprehensive analysis of the patterns of expression in the brain of immune system–related genes in

human aging and Alzheimer's disease (AD), they found sex-specific patterns of gene expression in both conditions.[14] In particular, they compared patterns of gene expression in two regions that are critical for higher cognitive function and known to develop AD-type pathology: the hippocampus and a region of the frontal cortex called the superior frontal gyrus. The hippocampus was more prone to immune-type gene reactions in females than in males, while the superior frontal gyrus was more susceptible to immune-type gene reactions in males than in females. Studies such as this prove that the biological mechanisms of brain aging and disease cannot be assumed to be the same in men and women.

The Counter-reaction

Perhaps not surprisingly, the striking growth in sex-differences research appears to have elicited a counter-reaction from some academic quarters, especially among non-neuroscientists. In some cases this counter-reaction is justified, as when scientists object to gross overstatements about sex differences often made in best-selling books ("neurotrash," as it is sometimes called). But in the main, this counter-reaction appears to reflect a misunderstanding of some key facts of brain biology. Leaving aside the name-callers (such as the psychologist who calls people studying brain-sex differences "neurosexists"[15]), as well as the non-neuroscientists who hypercritically analyze a small fraction of the neuroscience literature while seemingly remaining unaware of the rest,[16] let's focus on key arguments made by "anti–sex difference" authors.

First, anti–sex difference authors argue that there are few (if any) meaningful behavioral differences between men and women. They invariably rely on meta-analyses—studies that analyze patterns across many published studies.[17] Typically, these meta-analyses examine the literature for the size of sex differences (in this case, the size of the difference in average performance between men and women) on isolated factors, such as reading comprehension or the ability to rotate a three-dimensional object in one's mind. And often (though not always), these meta-analyses suggest that, with a few exceptions such as sexual behavior and aggression, only very small (and by implication dismissible) differences exist in the behavior of men and women. But there are at least two problems with these sorts of analyses. First, as Sarah Burnett has illustrated very powerfully,[18] it is simply incorrect to conclude that because an average difference between men and women is quantitatively small, that difference will have few meaningful practical consequences. Second, claiming that there are no reliable sex differences on the basis of analyzing isolated functions is rather like concluding, upon careful examination of the glass, tires, pistons, brakes, and so forth, that there are few meaningful differences between a Volvo and a Corvette.

A more sensible analysis is one that better gauges the full behavioral patterns of men and women. In a fascinating study, Marco Del Giudice and his colleagues did just that.[19] Using a form of statistical analysis called multigroup latent variable modeling, which essentially assessed the size of sex differences by combining numerous isolated factors, they found very large sex differences in behavior with as little as a 10 percent overlap between the distributions of men and women. They powerfully conclude, "The idea that there are only

minor differences between the personality profiles of males and females should be rejected as based on inadequate methodology."

Another way to defeat the idea that there are no behavioral sex differences between men and women is to consider stereotypical male and female behaviors. Bobbi Carothers and Harry Reis did just this when they analyzed the size of sex differences in a variety of stereotypically gender-driven behaviors, such as playing golf or video games, watching pornography or talk shows, taking a bath, and talking on the phone.[20] Using this analysis, they report extremely large, bimodal (also called taxonic) sex differences that, as they correctly note, say absolutely nothing about the degree to which those taxonic behaviors result from biological or environmental factors. It may not be fairly assumed that stereotypical behaviors result solely from environmental factors. (Indeed, it has been shown that male and female stereotypical occupational preferences are strikingly consistent across 53 countries, ranging from Pakistan to Norway, under hugely variable cultural conditions.[21,]) Carothers and Reis powerfully invalidate the idea that there are no large, group-average sex differences in human behavior outside a few limited domains.[20]

Worse still for the anti–sex difference authors is the fact that a complete, fully-agreed-upon-by-all lack of a sex difference in a particular behavior means absolutely nothing about whether or not sex differences exist in the neural substrates of that behavior. Neuroscientist Geert de Vries most convincingly makes this case, which even his own colleagues occasionally forget.[22] Focusing on a variety of animal models, de Vries shows that sex differences in the mammalian brain often exist to prevent behavioral level sex

differences (by compensating for underlying neural or hormonal differences) rather than to create behavioral level sex differences. But understanding these compensatory sex differences is every bit as important to properly treating brain dysfunction in men and women as is understanding sex differences that induce behavioral differences.

A second argument that the anti–sex difference authors sometimes make is that there really aren't male and female brains; rather, men and women have a single "intersex" brain. In attempting to support this view, Daphna Joel,[23] who has stated that sex-difference research can make her "blood boil,"[24] correctly points out what neuroscientists have known from animal research since the 1970s or earlier: Both males and females are exposed to both masculinizing and feminizing influences. She also correctly refers to both male and female brains as "mosaics" of such influences—and she is far from the first person to do so.[6] But because most of these influences can vary by degree and circumstances, she concludes, "We all have . . . an intersex brain (a mosaic of "male" and "female" brain characteristics)." The fallacy in her argument lies in the implication that "we all" (men and women) have a *single* mosaic "intersex" brain. What she clearly means by the term *intersex* is "unisex"—there is only one. However, zero evidence supports the view that, through the normal course of development, male and female mammals, including humans, possess brains that have on average the *same* combination of masculine and feminine traits—that they possess a single unisex mosaic brain. Also, the unisex view fails to accommodate a host of facts, such as the remarkable hemisphere differences in X inactivation seen only in female brains, the consequences of incomplete X inactivation (again, only in female brains), direct Y-chromosome-linked effects on brain function in males, or dyslexia's incidence in up to 10

times as many males as females, to name just a few.[25-28] We aren't unisex, and every cell in the brain of every man and every woman knows it.

"But wait," argue the anti–sex difference authors, "the brain is plastic"—that is, molded by experience. One group of authors uses the word *plasticity* in the title of their paper three times to make sure we understand its importance.[29] (As someone who has studied brain plasticity for more than 35 years, I find the implication that it never occurred to me amusing.) By the plasticity argument—also made explicitly by neuroscientist Lise Eliot in her book *Pink Brain Blue Brain*—small sex differences in human brains at birth are increased by culture's influence on the brain's plasticity.[30] Eliot further argues that we can avoid "troublesome gaps" between the behaviors of adult men and women (a curious contradiction, by the way, of the view that there are no behavioral differences between the sexes) by encouraging boys and girls to learn against their inborn tendencies.

It is critical to understand where the fallacies in this argument lie. First, it is false to conclude that because a particular behavior starts small in children and grows, that behavior has little or no biological basis. One has only to think of handedness, walking, and language to see the point. Second, this argument presupposes that human "cultural" influences are somehow formed independent of the existing biological predispositions of the human brain. But third, and most important, is the key fallacy in the plasticity argument: the implication that the brain is *perfectly* plastic. It is not. The brain is plastic only within the limits set by biology.

To understand this critical point, consider handedness. It is indeed possible, thanks to the brain's plasticity, to force a child with a slight tendency to use her left hand to become a right-handed adult. But that does not mean that this practice is a good idea, or that the child is capable of becoming as facile with her right hand as she might have become with her left had she been allowed to develop her natural tendencies unimpeded. The idea that we should use the brain's plasticity to work against inborn masculine or feminine predispositions in the brains of children is as ill conceived as the idea that we should encourage left-handed children to use their right hand.

The presence of biological limits to plasticity—and hence the presence of limits to how much experiences can affect the brain—is perhaps made most clear in elegant studies by J. Richard Udry. In his important but underappreciated paper entitled "Biological Limits of Gender Construction," Udry examines the interaction between two factors—how much a mother encouraged her daughter to behave in "feminine" ways, and how much the daughter had been exposed to masculinizing hormonal influences in the womb—on how "feminine" the daughter behaved when she was older.[31] The figure below illustrates the key findings.

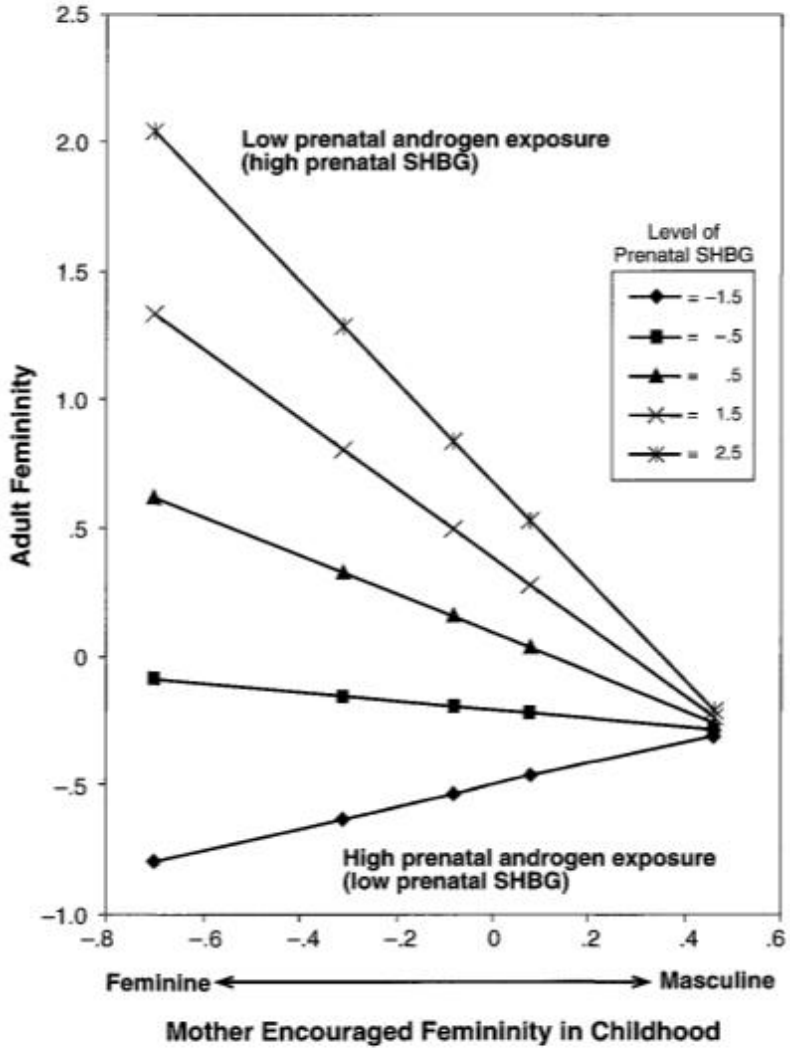

Figure 1. Effect of Childhood Gender Socialization on Adult Gendered Behavior by Level of Prenatal Androgen Exposure. Sex hormones (androgens, estrogens and progestins) operate in both males and females; in the brain, both sexes have receptors for these hormones that are found not just in brain areas associated with reproduction and related behaviors (eg hypothalamus) but in virtually all brain areas, including those involved in higher cognitive functions. These hormones, receptors for which are found not only in the cell nucleus, but also in many other cellular compartments often near membranes, influence many neurobiological events via the genome, epigenome and non-genomic cellular signaling. The process of sexual differentiation involves virtually the whole brain and is a seamless ongoing interaction over the lifecourse between hormones and experiences.

The graph illustrates that, indeed, the more mothers encouraged "femininity" in their daughters, the more feminine the daughters behaved as adults, but only in those daughters exposed to little masculinizing hormone in utero. Crucially, the greater the exposure to masculinizing hormonal effects in utero (the progressively lower lines), the less effective was the mother's encouragement, to the point where encouragement either did not work at all (line with squares) or even tended toward producing the *opposite* effect on the daughters' behavior (line with diamonds).

All those wishing to understand sex influences on the human brain need to fully grasp the implications of the animal literature, and then think about the Udry data, which captures an incontrovertible fact from brain science: Yes, brains are plastic, but only within the limits set by biology. It is decidedly *not* the case that environmental experience can turn anything into anything, and equally easily, in the brain. The specious plasticity argument invoked by anti–sex difference authors appears to be just a modern incarnation of the long-debunked "blank slate" view of human brain function, the idea that all people's brains start out as blank slates, thus are equally mold-able to become anything through experience.[32]

What Darwin Actually Said

We should have expected all along that the brains of men and women are a complex mix of similarities and differences, at least if we believed in evolution as Charles Darwin described it. Darwin did not believe that evolution proceeded by natural selection. In fact, he was

completely clear that, in his view, evolution by natural selection alone must fail. He knew that natural selection alone failed to explain far too many phenomena (most famously the male peacock's tail). What Darwin actually said was that evolution proceeded largely through two distinct mechanisms: natural selection and sexual selection. The former acted on the basis of whether an organism survived; the latter acted on whether it made a baby. In his second book, *The Descent of Man, and Selection in Relation to Sex*, Darwin developed this idea (first presented in the original edition of *The Origin of Species*) and made explicit his view that the beneficial effects of sexual selection must at times outweigh the negative effects of natural selection (again, think of the male peacock's tail).

After receiving much criticism for this concept, as he also did for natural selection, Darwin said, "My conviction in the power of sexual selection remains unshaken."[33] Sexual selection is a force that, by definition, often acts male on male or female on female. It is therefore a force that must produce sex differences of many sorts in brain and mind, as Darwin discussed in great detail. Thus, if we believe in evolution as Darwin described it (as a complex mix of natural and sexual selection forces), then we *must* believe that it produced in men and women bodies and brains that are a complex mix of similarities and differences, small to large—exactly what it appears to have produced.

Evolution has produced mammalian brains that are filled with biologically based sex similarities and differences, down to the molecular level. Evolution also has produced in men and women bodies that are filled with similarities and differences, including in the heart, liver, lungs, immune system, and even knees.[34] To insist that somehow—magically—

evolution did not produce biologically based sex influences of all sizes and sorts in the human brain, or that these influences somehow—magically—produce little or no appreciable effect on the brain's function (behavior) is tantamount to denying that evolution applies to the human brain.

False Assumptions

At the root of the resistance to sex-influences research, especially regarding the human brain, is a deeply ingrained, implicit, false assumption that if men and women are equal, then men and women must be the same. This is false. The truth is that of course men and women are equal (all human beings are equal), but this does not mean that they are, on average, the same. 2 + 3 = 10 – 5, but these expressions are not the same. And, in fact, if two groups really are different on average in some respect, but they are being treated the same, then they are not being treated equally on average.

Sadly, this is exactly the case in research and medicine today. Women and men are *not* being treated equally, because by and large women are being treated as if they were the same as men. To make real progress in improving *both* men's and women's health, and to avoid more Ambiens or worse, we need neuroscientist and non-neuroscientist alike to determine whether they too operate on the false assumption that "equal" means "the same." If so, toss that assumption aside. True equality for the sexes demands it.

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