"His and Hers: Sex Differences in the Brain"
With Catherine Woolley, Ph.D.

Transcript of Cerebrum Podcast

Guest: Catherine S. Woolley, Ph.D., is the William Deering Chair in Biological Sciences and a professor of neurobiology and neurology at Northwestern University. She is a researcher and teacher who has studied hormone actions in the brain for over 30 years. She founded Northwestern's neuroscience major in 2015 and was named a Charles Deering McCormick Professor of Teaching Excellence in 2018. In 2019, she was elected to the National Academy of Medicine "for pioneering research demonstrating estrogen-driven plasticity of neural circuitry and sex-dependent molecular signaling in brain areas related to cognition, epilepsy, and affective disorders." Woolley received her Ph.D. in neuroscience from Rockefeller University.

Host: Bill Glovin serves as editor of *Cerebrum* and as executive editor of the Dana Foundation. He was formerly senior editor of *Rutgers Magazine*, managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and a staff writer at *The Record* newspaper in Hackensack, NJ. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

[Intro] *Men are from Mars, Women are From Venus*. That 1990s bestseller, which is still being referenced today, address the reasons men and women behave differently. But it didn't address such things as brain structure or if men and women remember the same way, or why the brain of men and women deal differently with such things as addiction and psychiatric disorders. So what are the neurobiological differences in the male and female brain?

Bill Glovin: Hi, I'm your host Bill Glovin and welcome to the Cerebrum Podcast, brought to you by the Dana Foundation in New York City. This episode focuses on the controversial topic of differences in male and female brains. To help us sort it all out is Catherine Woolley, author of our cover story on the topic in the recent issue of *Cerebrum* magazine, titled "His and Hers: Sex Differences in the Brain." You can find Catherine's article and all of our magazine content at Dana.org.

Catherine Woolley: I think the fact that there are differences at a molecular level, between the way cellular level processes work in the male brain and the female brain, is important because those types of experiments at a cellular and molecular level really provide the pipeline of information that feeds into clinical and biomedical research aimed at developing new therapies or treatments for disease.

Bill Glovin: Believe me when I say we are very lucky to have Catherine Woolley as our guest. Catherine is the William Deering Chair in Biological Sciences at Northwestern University, and was elected to the National Academy of Medicine for pioneering research in an area where frankly, as she points out, there isn't enough of it. And, she tells us, sex differences might not need to be its own field, but most research that ignore sex differences is incomplete research. We already know that male and female brains are different when it comes to autism rates, drug effectiveness, and brain development.

Welcome Catherine, and thanks for being here. How did you get into this line of research?

Catherine Woolley: Well, I should explain that my entry into the field of sex differences in the brain was entirely serendipitous, and in fact, came after decades of intentionally and explicitly avoiding the issue of sex differences in the brain. I never wanted to study them, and I still have mixed feelings about it. But we began in this field because we couldn't replicate results in the published literature. And after ruling out several kinds of technical reasons that we might not be able to replicate others' findings, we realized that it could be because we were doing our experiments in female animals, and the vast majority of the published literature that we were trying to replicate had been done in male animals.

And when we then explicitly tested that idea by comparing our results in males and females, we found that was true, that the molecular mechanisms that we were studying operated differently between males and females. And I realized that we needed to start doing our experiments more routinely in both sexes. And since that time, we've found many things that are the same between the sexes and many other things that are different at a molecular level. So that has persuaded me that it's very important to include both sexes in basic research on cells and animals, because in some ways the sexes will differ at that level.

Bill Glovin: Could the reason be that in scientific, research men have outnumbered women when it comes to just the number of scientists out there?

Catherine Woolley: I actually doubt that that's the explanation. I think probably implied in the question is that women might care more about sex differences in the brain than men do, and I don't think that's the case. Some of the most vocal proponents of the need to include both sexes in scientific research have been in the past, and are today, men. So, I doubt that is the reason. I think it's more likely that there has been an assumption, until recently, that in most ways, the brains of males and females are the same. Females are sort of just like males plus some hormones.

And so, if you're interested in understanding fundamental mechanisms of how the brain works, it's perfectly fine to study the male brain. And then if you're interested on top of that in sort of the specialty area of what hormones do, then you could add females if you wanted to. I can tell you a little story to illustrate

that. Maybe about 10 years ago, when my lab first started to recognize that there were quite profound sex differences at a molecular level, I asked a bunch of my colleagues at Northwestern how important they thought it was to include both sexes in their experiments.

And one of my colleagues captured, I think very well, the view of the people who said they didn't think it was very important, when this person said, "Well, I think it's fine to include both sexes if you're interested in sex differences, but I'm more interested in understanding how the brain works normally. And then later, we can worry about variations on normal." So that sort of implies that understanding differences between males and females are just variations on normal. And what we know now is that, at least in some ways, that the brain works normally differently in one sex from the way the brain works normally in the other sex. So that's why it's important to do experiments in both sexes so that you can find out when are the results applicable similarly to both sexes and when are the results applicable to one sex and not the other one.

Bill Glovin: Initially, when I first approached you on writing on the topic, you wrote: "Most of the public, as well as scientific discussion on whether or not there are meaningful sex differences in the brain, is about the wrong thing." What are they getting wrong?

Catherine Woolley: Yeah. If you were to Google "sex differences in the brain," I think you would find a lot of divergent opinion about whether or not there are meaningful sex differences in the brain. And most of that would be about structural differences in a human brain and their purported relationship to differences between men and women in behavior or cognition. And there are sort of two extreme views out there. One group of scientists who find, actually quite small, statistically or quantitatively, differences in the brains of men compared to women. And then they use those differences as evidence for a neural basis of sex differences in sometimes complex behaviors without any real scientific link made between a difference in something like who's better at reading a map and the differences that they see in the brain. No causal link established between them. It's just purely speculative.

And then the other view is from also a group of neuroscientists who say that there are no meaningful differences in the brain, because the differences that have been found, the structural differences in the human brain, are very small and there's no scientific reason to link those to any known behavioral difference. And so, then they leap to the conclusion that there are no meaningful sex differences in the brain. So, you have these two sort-of-polarized extremes out there, neither of which, in my opinion, is about the right thing.

I think the fact that there are differences at a molecular level between the way cellular level processes work in the male brain and the female brain is important because those types of experiments at a cellular and molecular level really

provide the pipeline of information that feeds into clinical and biomedical research aimed at developing new therapies or treatments for disease. That is much more scientifically tractable, and I think fundamentally important level to understand sex differences in the brain, as opposed to arguing about whether these very small average differences in the structure of a human brain do or do not have anything to do with what I see as gendered stereotypes about the behavior of men and women.

Bill Glovin: For example, like being better at math, or like you pointed out, reading a map, or being sensitive or good at multitasking, those kinds of things? I guess the tractable stuff is tied into drug development and the reaction to those drugs on the molecular level. That's something we can actually investigate. The other stuff is very, just kind of guesswork?

Catherine Woolley: Let's back up for a second and recognize that when we talk about sex differences, we're talking about categorical differences. We can divide most people, not all people, but most people into two categories, male and female. And on average, there are some structural differences between brains of males and brains of females, but those differences are not categorical. So for example, let's use an analogy. Say, you're redecorating your house and you need to paint a room. You go to the hardware store and you want to pick out a paint color. When you look at paint colors, you see all these chips of paint. And within any color, let's say blue, there's a range of shades of blue from very light to very dark. And let's say there's seven shades of blue. And so you can number them. The palest one is number one, the darkest one is number seven.

You could take two groups of people and you could hand out paint chips. And you could give one group, each member of that group a chip. Range numbers one through six, and you could give the other group chip, numbers two through seven. On average, if you then measured darkness of the shades of paint chips that each group has, there would be a statistical difference. One group on average would have darker paint chips than the other group on average, but there'd be a huge amount of overlap between the groups because it's just a shift in the distribution. One through six compared to two through seven. So that is what sex differences in the brain, the structural sex differences in the brain are like that.

There's a great deal of overlap between these two categories that you can define male and female, but they're actually much more the same than they are different. So then that kind of overlapping, even though a statistically significant difference, is often used to demonstrate a biological basis, the possibility of a biological basis for gendered stereotypes. For example, that men are better than women at navigating directions. Yet, there's zero scientific basis to connect the structural sex differences in the brain to the complex behavior of reading a map, or let's say playing chess. That's another one that comes up.

I remember five years ago now I was contacted by a reporter for the Christian Science Monitor who was writing an article centered around comments by a chess grandmaster who'd said that it was well-known that the brains of men and women were hardwired differently, and that those differences accounted for the fact that there were many more men who were masters in chess than there are women. And so the implication was sex differences in the brain constrain the ability of women to be good at chess.

Of course, that is a ridiculous idea. And one way to think about why or how it's ridiculous is to think about other differences in chess. For example, if we were to look at the distribution of chess masters across countries, I think Russia has far more chess masters than the United States does. Okay. Do we expect that there are differences in the brains of people from Russia, that account for the fact that there are more Russian chess masters than American chess masters, is there some bias by virtue of their nationality? Are there differences in the brains of Russian people compared to American people that explain the fact that Russia produces more chess masters? I don't think so.

I think it's much more likely that something like chess occupies a different place in Russian culture. And I don't know what the specific mechanisms might be. Maybe Russian kids are more encouraged to play chess or maybe chess is more respected in Russia than it is the United States. I don't know, but most likely there's a cultural explanation for this outcome that Russia has more chess masters in the United States, not a brain-based difference. Conversely, if we found a brain-based difference between people from Russia and people from the United States, would we then back calculate that that brain difference is the reason there are more Russian chess masters than American chess masters? Probably not.

And so there are differences that I think are probably largely culturally derived and don't have anything to do with national or sex-based differences in the hard wiring of the brain. These things are just not related. There are certainly differences among individuals. I'm sure there is likely to be some difference in the brain of someone who an intrinsic talent for chess compared to another person who does not have an intrinsic talent for chess. Likewise, when you practice chess and become better at chess, there are surely changes in the brain that account for you getting better at chess. But that doesn't mean that you can categorize people as having brains that are intrinsically hardwired to be one way versus another way groups of people.

Bill Glovin: Right. So, it does seem like a lot of the stereotypes are tied to cultural or behavioral type things. That popular a Netflix show with *Queen's Gambit* kind of points to that.

Catherine Woolley: Yeah.

Bill Glovin: But how about the idea about males being more innately aggressive than females? That's a little bit different. Is that something that has been explored at all or explained, or is it even true?

Catherine Woolley: I'm not an expert on human aggression, so I won't comment on that. But at the level that, that I work, for example, on animals like rats and mice, it is true that male rats and mice are more aggressive than female rats and mice, except for when females have a litter of pups. And females can be very aggressive in defense of their pups. And maternal aggression is just as robust as male aggression. So again, it's much less about a sex difference as it is about a circumstantial one.

Bill Glovin: I've read, and lots of other people probably have read, that females begin talking before males, for example, and they seem to physically develop faster than males, especially where height is concerned. Do female brains develop faster than male brains?

Catherine Woolley: There are sex differences in the rate of brain development. That's one reason that people studying the developing brain have to be cautious about evaluating sex differences, because developmental age may be somewhat different from chronological age. So if you just took a snapshot in time, you might see a difference between males and females that was related to a difference in the trajectory of their development and rather than something that would ultimately turn out to be different. So there are differences in the rate of brain development. That's true.

Bill Glovin: You're right that in 2012, you accidentally discovered a sex-specific molecular mechanism for turning synapse strength while studying how estrogens might affect the part of the brain involved with learning and memory. Why is this important?

Catherine Woolley: This is important, I think, getting back to the issue of the basic science information that feeds into the translational and clinical pipeline for drug development. So that was the experiment that opened my eyes to the importance of using both sexes in basic science, because they can differ in some ways. And in those experiments, we were testing effects of a drug that regulate the levels of a group of molecules called endocannabinoids. And we found that this drug had very different effects on synaptic connections in the brains of males compared to synaptic connections in the brains of females. And that drug was a FAH inhibitor, a fatty acid amide hydrolase inhibitor. And that drug had been used already in clinical trials, presumably without any awareness that it could affect the brains of males and females differently.

I think what that shows is that we can't assume that drugs, either drugs that are tested in human beings or drugs to be developed, will have the same effects in each sex. So it's important to get information about the possibility of differences between the sexes and the ways the brain responds to drugs as early as possible

in that long and expensive process of drug development. Because if those drugs do affect males and females differently, we should know that at the beginning, not at the end. And this is one reason that I think arguments that the study of sex differences in the brain is harmful, potentially harmful, to women because they might provide a rationale for sexism. I think those arguments are hollow, because we really are not doing women or women's health any favors by pretending the brain is the same if it's not. The dangers related to sex differences in the brain are really in the interpretation of the results of studies on the brains of males and females, not in the results themselves or the data.

Bill Glovin: One of the areas that you just in the article is sort of neuropsychiatric disorders, which seem to be more common in one sex over another. What are they and why is that?

Catherine Woolley: Yeah, so this is very interesting. The most commonly given rationale for the importance of considering both sexes in basic science is the fact that the vast majority of neuropsychiatric or neurological disorders do differ between the sexes, either in their incidence, or their age of onset, or in some cases, maybe their presentation or responses to treatment. And probably the biggest difference is in the rate of autism. So autism is about three or four times more common in boys than in girls. And conversely, disorders, mood disorders like depression and anxiety are more common girls than boys or women than in men.

Catherine Woolley: And one thing that seems to be true, one principle that seems to hold true, is that disorders that are related to show up earlier in life like autism and are related in some way to neuro development, those tend to be more common in boys or men. And disorders that show up later in life and that may be more related to circumstance are more common in women. And many people are interested in trying to understand why that is. I don't think that's not known, but the comparison between the sexes does give us an additional tool to use to try to understand the origins of these disorders. Why is it that females are relatively protected against development of autism? If we understood that, that might help us to understand how autism develops in the first place. And we don't know the answers to those questions yet.

Bill Glovin: About the idea of addiction rates between the sexes, is that a factor?

Catherine Woolley: Well, that one is a little bit harder. There are differences in the numbers of men and women, boys and girls, who develop substance use disorders. One complication in interpreting those differences is that it may be the case that men and boys are more likely to engage in risk-taking behaviors. Therefore, maybe given the opportunity to try drugs, maybe there's a sex difference in the likelihood that someone will. And so it is difficult to sort of parse the causes of sex differences in the rates of addiction. If you look at experimental animals and ask about how experimental animals respond to drug exposure, there are sex differences there. And so that's another way, exploring those differences. What

is the neural basis of differences in the way male and female animals respond to, let's say psychostimulants, could give us insight into how drug addiction occurs in both sexes? And there are people who, not me, but there are people who study that.

Bill Glovin: Is that where you think the research needs to go next? Or just generally, where do you think it needs to go next?

Catherine Woolley: Well, I think two ways. One, far more scientists than currently do need to consider the possibility of sex differences in what they are studying. And the way to do that is simply to do experiments in both sexes. Just do your experiments in both sexes. Find out if the sexes are the same or if they're different. And either, way report the results in, in both sexes. And that way we will know what elements of basic science, what molecular mechanisms, what cellular mechanisms, what behaviors are the same and are different between the sexes. I really look forward to a day when it becomes routine to do all basic science studies in both sexes with the minor exception of studies on things that are necessarily sex specific, like for example, research on prostate cancer. Wouldn't be important to do research on prostate cancer also in females, but for the majority of research, it really would be a benefit to do all experiments in both sexes and report the data by sex.

So I look forward to that day. And I think we will have better information that feeds into that pipeline of biomedical research if we do that. Secondly, when sex differences are discovered, when we find one, that gives us an extra tool to understand the fundamental process that is operating in each sex, go back to autism. The fact that autism is so much more common in boys than girls, if we understood why, that would help us to understand autism generally for both boys and girls. And so understanding the mechanistic basis of sex differences at the level of cells and animals, and at the level of human disease, will help us to understand that disease much better, which is good for both sexes.

Bill Glovin: Your article points out that NIH requires that grant applicants explain how they would consider sex as a biological variable in animal research. So, I guess that's some progress that even many scientific journals also require it, but you also point out that neither policy requires comparison of the sexes. So, I guess there still is a way to go.

Catherine Woolley: I will say that the NIH policy has had a very positive effect to raise awareness among many different types of scientists about the importance of considering sex as one of many biological variables relevant to an experiment. And so, in that way, it's been quite beneficial. I'd say still there is some reluctance among scientists to fully embrace that policy. And I think that comes largely from a presumption that it's not going to make that much difference. And the solution to that, in my mind, is for more and more scientists to include both sexes and then show that it does make a difference, in some cases it is meaningful. And I think over time, the sincere interest in sex differences will be piqued among a

greater and greater fraction of scientists. And so I think it probably will happen, that including both sexes and reporting the data by sex, irrespective of whether there is a difference, will become the norm. It isn't the norm yet.

Bill Glovin: So the research environment for this topic, or the fact that there might not be enough neuroscientists even studying the topic is not anywhere where it needs to be at this point?

Catherine Woolley: No, it's not anywhere where it needs to be. And I will say that I don't think it's necessary or even relevant to study sex differences as a topic. I don't think sex differences should be a topic. One should simply, as a matter of course, do experiments in both sexes. And so rather than talking about sex differences, I think it's maybe more helpful to talk about sex inclusion, to include both sexes in scientific research. Sometimes there will be differences. Sometimes there will not be differences. But either way, we'll have more and better information to pass on to our colleagues in more translational fields.

Bill Glovin: And lastly, for people who are interested in this topic, is there anything in the culture or in the literature that you might recommend to them to explore?

Catherine Woolley: Well, there's no shortage of popular level science books on the topic of sex differences in the brain. But just like I said at the beginning, if you were to Google "sex differences in the brain," you'd find the full spectrum of sex differences in the brain are extremely important all the way down to there are no sex differences in the brain that are meaningful. And you will find the very same spectrum in popular science books, ranging from books that accuse neuroscientists who study sex differences of being sexist, that just the study of sex differences is a sexist act, to people who put forward theories for which there is very little scientific basis about extreme differences between the sexes.

And so, I think this remains a very... It's a complex field, but it's in its infancy. So that there's sort of a very large pool of ideas and thoughts, little of which is grounded in scientific truth. And the solution to that is for more scientists to gather more data and to report those data responsibly, to not go wild with interpretations about what the data might mean, but to keep close to the results and be honest about what they can and cannot say about the significance of their findings. And I think over time, we will begin to get clarity about what is and isn't different between the brains of males and females and what the significance of those differences are and are not.

Bill Glovin: Well, I think that's a great place to end. And for our listeners, Catherine is the author of our cover story for our winter 2021 issue, His and Hers: Sex Differences in the Brain. Your article is fascinating and it's a fascinating topic. So I thank you again, and I wish you all the best.

Catherine Woolley: Thank you. It's been a pleasure talking with you and a lot of fun.

Bill Glovin: That was Catherine Woolley, who just did an amazing job explaining one of the more interesting and controversial topics in brain science. It's easy to hear why she has won two major teaching awards at Northwestern and a boatload of research awards. I've done many of these podcasts, and she just did as good a job explaining this topic as anyone we've ever featured. You can find your article along with all of our content at Dana.org. We are the Dana Foundation in New York City, and please feel free to provide feedback to me bglovin@Dana.org. That's B-G-L-O-V-I-N@Dana.org. I'm your host, Bill Glovin. We appreciate you listening. Have a great day and a big thank you to Catherine Woolley.