Scientists uncover a difference between the sexes

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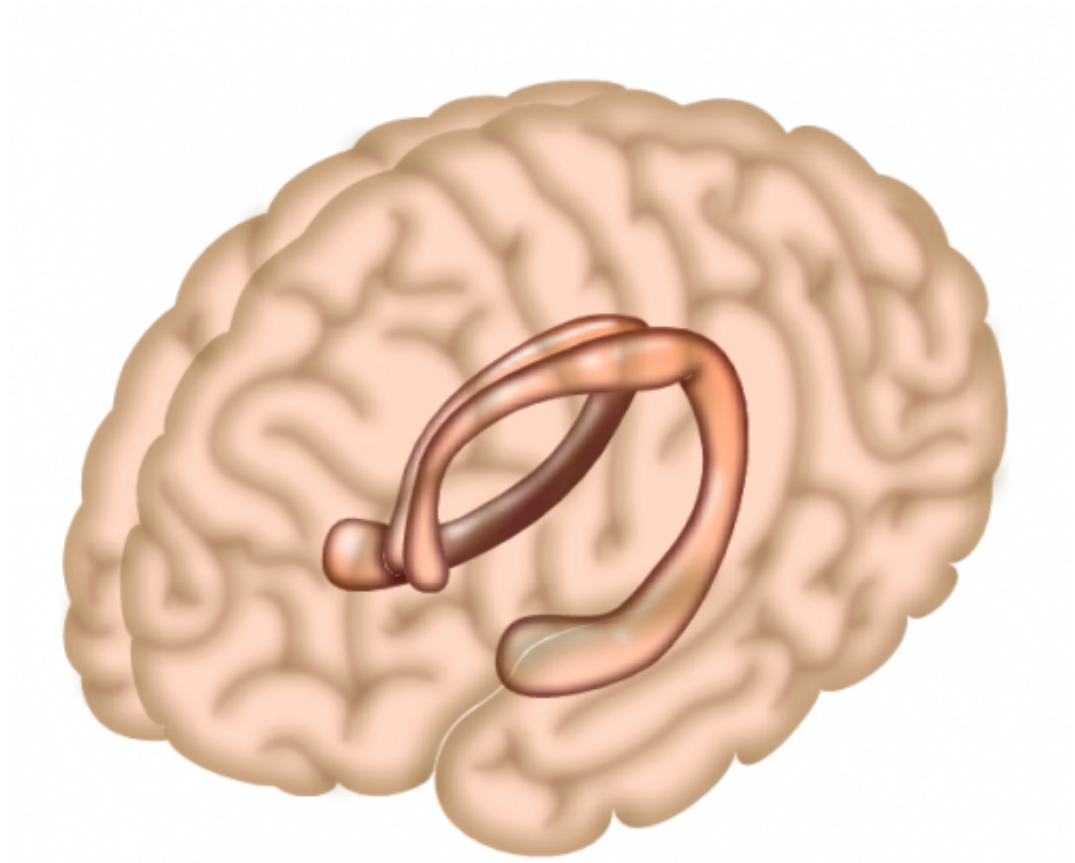

The hippocampus is a region of the brain largely responsible for memory formation. Credit: Salk Institute

Male and female brains operate differently at a molecular level, a Northwestern University research team reports in a new study of a brain

region involved in learning and memory, responses to stress and epilepsy.

Many brain disorders vary between the sexes, but how biology and culture contribute to these differences has been unclear. Now Northwestern neuroscientists have found an intrinsic biological difference between males and females in the molecular regulation of synapses in the hippocampus. This provides a scientific reason to believe that female and male brains may respond differently to drugs targeting certain synaptic pathways.

"The importance of studying sex differences in the brain is about making biology and medicine relevant to everyone, to both men and women," said Catherine S. Woolley, senior author of the study. "It is not about things such as who is better at reading a map or why more men than women choose to enter certain professions."

Among their findings, the scientists found that a drug called URB-597, which regulates a molecule important in neurotransmitter release, had an effect in females that it did not have in males. While the study was done in rats, it has broad implications for humans because this drug and others like it are currently being tested in clinical trials in humans.

"Our study starts to put some specifics on what types of molecular differences there are in male and female brains," Woolley said.

Woolley is the William Deering Chair in Biological Sciences, professor of neurobiology in the Weinberg College of Arts and Sciences and a member of the Women's Health Research Institute at Northwestern University Feinberg School of Medicine.

The study of inhibitory synapses and endocannabinoids, which regulate neurotransmitters, was published today (Aug. 12) in *The Journal of*

Neuroscience. It is the first study to detail where males and females differ in a key molecular pathway in the brain.

"We don't know whether this finding will translate to humans or not," Woolley said, "but right now people who are investigating endocannabinoids in humans probably are not aware that manipulating these molecules could have different effects in males and females."

Specifically, Woolley and her research team found that in female brains the drug URB-597 increased the inhibitory effect of a key endocannabinoid in the brain, called anandamide, causing a decrease in the release of neurotransmitters. In male brains, the drug had no effect. (The difference is not related to circulating reproductive hormones.)

The subject of many clinical trials, endocannabinoids are molecules that help regulate the amount of certain neurotransmitters released at synapses, the gap between neurons. These molecules are involved in a variety of physiological processes including memory, motivational state, appetite and pain as well as in epilepsy, a neurological disorder. (Their name comes from the fact that endocannabinoids activate the same neural receptors as the active ingredient in marijuana.)

Understanding what controls the synthesis, release and breakdown of endocannabinoids has broad implications both for normal and pathological brain function, Woolley said. This study contributes an important piece of knowledge.

For 20 years, Woolley actively avoided studying sex differences in the brain until her own data showed her that differences between females and males were real. Her discovery, reported in 2012, that estrogens decreased inhibitory synaptic transmission in the brains of female rats but not in males, changed her thinking.

"Being a scientist is about changing your mind in the face of new evidence," Woolley said. "I had to change my mind in the face of this evidence."

Building on these earlier findings, Woolley and her team used a series of electrophysiological and biochemical studies to pinpoint what causes this effect. The researchers found the difference between males and females lies in the interaction between the molecules ERalpha and mGluR1. Details of the molecular pathway are reported in the new study.

To find out what is the same and what is different between males and females, scientists need to study both sexes, Woolley maintains. Currently, about 85 percent of basic neuroscience studies are done in male animals, tissues or cells.

"We are not doing women—and specifically women's health—any favors by pretending that things are the same if they are not," Woolley said. "If the results of research would be different in female animals, tissues and cells, then we need to know. This is essential so that we can find appropriate diagnoses, treatments and, ultimately, cures for disease in both sexes."

More information: "Sex Differences in Molecular Signaling at Inhibitory Synapses in the Hippocampus," *The Journal of Neuroscience*, 2015.

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