Male mice hard-wired to recognize sex of other mice, study finds

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A male mouse identifies the sex of an unfamiliar mouse because of hard-wired brain physiology, not previous experience, Stanford University School of Medicine investigators have found.

Female mice also quickly determine a stranger's sexual identity. But the circuitry in their brains that guides those decisions remains to be located.

"Surprisingly, recognition of a stranger's sexual identity works completely differently in male and female mice," said Nirao Shah, Ph.D., professor of psychiatry and behavioral sciences and of neurobiology.

The findings, described in a study to be published Jan. 31 in *Cell*, add to a small but growing list of mammalian brain circuits known to work differently in males and females. They inform a long-standing debate about the relative contributions of inherently hard-wired predispositions versus socially acquired influences in molding sex-specific behaviors.

Shah is the study's senior author. The lead author is postdoctoral scholar Daniel Bayless, Ph.D.

"Our findings show that males, at least, don't need prior sexual experience in order to make fast, reliable decisions about closely approaching strangers," Shah said.

That makes good evolutionary sense. In its lifetime, a wild male mouse may get just a few shots at sexual reproduction, ratcheting up the advantage of being able to correctly identify a newcomer's sex in short order without having to learn how first. If that ability is innately programmed, even a sexually inexperienced mouse can rapidly discern males from females of its species.

The findings are likely to apply to humans, Shah said, because we share with mice much of the same hard-wired brain circuitry they use for recognizing a stranger's sex and because human studies of this circuitry indicate significant structural and physiological differences between men and women.

"All social and sexual encounters are predicated on first correctly identifying the sex of the other agent," Shah said. "It's a fundamental decision animals make."

Where and how mammals make such decisions was completely unknown prior to this study. But the investigators did have some ideas about where to start looking.

Indispensable subset of neurons

Numerous tissues responsive to sex hormones produce aromatase, an enzyme that converts androgens into estrogens—the active form of these sex hormones inside many cells. Aromatase turns up in about a half-dozen mouse-brain regions that Shah and his colleagues identified a decade ago. Some of these brain regions differ in their anatomy, physiology and behaviors they govern, depending on whether the brain is that of a male or a female.

One such region is called the bed nucleus of the stria terminalis. This structure is twice as large and more densely populated with neurons in men than in women. Human studies have revealed different patterns of gene-activation levels in men's versus women's bed nucleus of the stria terminalis—a reliable clue that this structure's function differs by sex.

A tiny fraction of this structure's neurons, called AB neurons, produce aromatase. It's these cells, about 1,000 on each side of a mouse's 75-million-neuron brain, that Shah's team has tied to sex recognition. "Prior to this study, AB neurons were for the most part unexplored territory," he said. "They've been particularly hard to study because they're interspersed among other superficially identical-appearing neurons."

But Shah's group has developed tools that let them both monitor

signaling activity in AB neurons in freely moving mice and remotely stimulate or inhibit activity in just those neurons.

They used these tools to study and manipulate the AB neurons of male mice that had never been exposed to a female mouse besides their mothers and sisters during their first few weeks of life. Immediately after being weaned (and well before puberty), they'd been transferred to male-only housing and then, several days prior to the experiments, to solo housing.

It's long been known that a male mouse on its own turf, whether it's sexually naïve or experienced, responds predictably to the intrusion of another mouse. That response depends on the stranger's sex, Shah said. "If it's a female, the resident male will try to woo her. If it's a male, he'll pick a fight."

Hard-wired differences

As expected, when the researchers introduced a female into the naïve male's habitat, not much more than a few minutes of sniffing and exploring passed before he tried to mate with her. When they introduced another male into the bachelor pad, the resident male went on the attack, also as anticipated. In both cases, the scientists observed an early uptick in the resident male's AB neuron activity. But this increase was much greater when the stranger was a female. During the sexual behavior following the resident male's recognition of a female, those neurons got even more excited. By contrast, their activity subsided during the ensuing fights with a male.

Even neutering a male didn't affect the AB neurons' ability to distinguish between the two sexes, further supporting the idea that this ability is developmentally hard-wired.

When the researchers experimentally stifled AB neurons' action during a male resident mouse's encounter with a stranger of either sex, he morphed into a kind of wimp due to his suppressed sex-recognition capacity. "He wouldn't fight with the males, and he wouldn't mate with the females," Shah said.

Conversely, when the investigators stimulated activity in a resident male mouse's AB neurons' to mimic what happens when a male encounters a female, the resident was fooled into thinking that another male approaching him was a female. As a result, he tried to mate with the approaching male.

Female mice's AB neurons responded somewhat to the introduction of a strange mouse of either sex, but showed no particular difference in activity whether the stranger was male or female. Even experimental manipulations that eliminated the females' AB neurons had no obvious effect on their social behaviors.

"These nerve cells' role in the female brain is mysterious," Shah said. "Females apparently use a different neural system to recognize sex of other individuals. What that system might be is still anybody's guess." He said he intends to find out.

Provided by Stanford University Medical Center

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