Social influences can override aggression in male mice, study shows

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Stanford University School of Medicine investigators have identified a cluster of nerve cells in the male mouse's brain that, when activated,

triggers territorial rage in a variety of situations. Activating the same cluster has no such effect on female mice.

Moreover, whether a male mouse displays territorial aggression depends on whether it's recently been the sole occupant of a bachelor pad or living in the mouse equivalent of boarding school. The latter makes for good manners; the former, not so much.

In a study to be published online July 27 in *Neuron*, the researchers used sophisticated laboratory techniques to determine how much this aggressive behavior owed to environmental factors and how much was genetically hard-wired. Their findings suggest that social forces can override genetically programmed behavior. The findings also could potentially help explain the ill effects of solitary confinement on prisoners, as well as what underlies psychiatric disorders characterized by bursts of violent anger.

Male mice are naturally territorial. In the wild or in the lab, they attack other male mice even if plenty of room, food and females are available.

A typical male mouse who's been dug in for a while as the sole occupant of a chunk of turf will normally attack any other male placed into that territory, said Nirao Shah, MD, PhD, professor of psychiatry and behavioral sciences and of neurobiology.

"But selectively activating just this tiny cluster—about 5,000 nerve cells in a brain with 80 million nerve cells—escalates the level and extent of male mice's aggressiveness dramatically," said Shah, the study's senior author. The lead author is postdoctoral scholar Taehong Yang, PhD.

The cells, designated as PR+ VMHvl nerve cells, are found in a part of a brain structure called the ventromedial hypothalamus and are distinguished by the fact that they contain receptors for sex hormones.

Turning mouse Jekyll into mouse Hyde

Stimulating PR+ VMHvl cells in a male lab mouse who's spent a week to 10 days in a cage of its own triggers fierce displays of territorial aggression even when such behavior would rarely occur, the scientists found. This mouse not only will attack a female, which male mice never do, or a member of another species, which mice also rarely do, but will threaten a mirror placed in its cage or even an inflated surgical glove. Even if neutered, the resident male will launch an attack on another mouse introduced to its cage. (Circulating testosterone is normally indispensable for displays of male territorial aggression.) In effect, stimulating these cells makes the solitary male lash out violently and indiscriminately.

In an earlier study, Shah and his colleagues showed that selectively killing PR+ VMHvl nerve cells radically reduces territorial aggression in male mice. This cluster therefore appears to be essential to a male mouse's display of territorial aggressiveness. The new study indicates that the circuitry's activation is also sufficient to trigger territorial aggression in a broad range of circumstances.

Nevertheless, this genetically hard-wired behavior seems to be subject to complex social etiquette. For one thing, the study showed, a solitary-resident male mouse wouldn't start exhibiting displays of aggression if it was all alone, regardless of how amped up its PR+ VMHvl circuitry was. But the sighting of an unfamiliar object—even the nonreflective side of a mirror—in its cage was enough to trigger tail-rattling threats. Such a mouse would also attack when inserted into the turf of another aggressive, solitary male. On the other hand, a male mouse that had been housed with other males would not attack the aggressive solitary male on the latter's home turf, even when the researchers revved up PR+ VMHvl activity in the socially housed male. Something about social housing, Shah said, seems to powerfully temper male mice's aggressiveness—so

much so that even directly activating the intruders' "rage center" wasn't enough to coax it into attacking.

That something, said Shah, is likely to be related to mice's acute ability to sense pheromones, which are chemical compounds released by members of a species to signal their social and reproductive status to other members of the species.

"You can tell male and female mice apart by the way they smell," said Shah, an experienced rodent researcher. Unlike female mice, males smell "pretty offensive." Ponder the scent of moldy socks and dirty T-shirts in a teenage boy's gym locker.

Previous work showed that a solitary male hanging out on his home turf attacks a male intruder because of the intruder's pheromones. The new study showed that pheromones exuding from such a solitary male on his home turf deter aggression from a socially housed male intruder. Strikingly, if the socially housed male could no longer sense the solitary male resident's pheromones, he would attack the resident once his PR+ VMHvl cells were revved up.

'Nature versus nurture is a false dichotomy'

"Nature versus nurture is a false dichotomy," said Shah. "We've showed, on the one hand, that genetically programmed circuitry massively influences mammalian behavior. And we've seen that, under certain circumstances, nurture wins: Your social conditions can override your natural impulse to fight."

The human brain, like that of the mouse, also features a ventromedial hypothalamus. While this brain region's functions haven't been fully elucidated in humans, Shah said, case studies suggest at least a degree of similarity to those of a mouse.

The study's findings, therefore, may bear on the question of whether solitary confinement of aggressive male criminals is counterproductive. In addition, some 5 percent of adults are estimated to experience, at some time in their lives, episodes of a psychiatric condition called intermittent explosive disorder—impromptu outbursts of ferocity in the face of what would usually be considered inadequate triggers for that ferocity. It could be, Shah speculated, that the human equivalent of PR+ VMHvl nerve cells are involved, and that learning how to modulate their activity in mice could lead to treatments for this disorder in people.

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