Spiny mice point the way to new path in social neuroscience

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Spiny mice evolved to live in the wild in large, mixed-sex groups. Credit: Aubrey Kelly

Scientists have zeroed in on brain circuitry powering the desire of spiny mice to live in large groups, opening the door to a new model for the study of complex social behaviors in mammals.

The journal *Current Biology* has published the work led by researchers at Emory University. It shows that neural signaling from the brain's anterior cingulate cortex to the lateral septum drives the preference for spiny mice (Acomys) to affiliate with large peer groups.

"To our knowledge, this is the first study to identify neural circuitry that promotes group-size preferences in a mammal," says Aubrey Kelly, senior author of the study and associate professor of psychology at Emory. "We hope that our work paves the way for new insights into complex social behaviors in a range of mammals, including humans."

The Kelly lab made the breakthrough by developing methods to use spiny mice as a laboratory model for social neuroscience.

Unlike the rats and mice commonly used in laboratory research, spiny mice evolved to live in the wild in large, mixed-sex groups—they even allow unrelated newcomers to join their groups.

"A spiny mouse colony is not just one big family," Kelly explains. "It's more like a little society."

Brandon Fricker, first author of the study, worked on the research as a Ph.D. student at Emory. He graduated in May and now works as a postdoctoral fellow at Harvard University.

"It was challenging, but fun, to design experiments and validate our methods for a species that is new to social neuroscience," Fricker says. "I really enjoyed working with spiny mice. They have a very different temperament than I've seen in other lab rodents. They don't show nearly as much fear or aggression towards each other, or even towards humans."

Despite the prevalence of communal living across the animal kingdom—from ants to birds to humans—methods to study the neural mechanisms that make group living possible have been lacking.

One major limitation is that the species of rats and mice commonly used in lab research do not get along well in large, mixed groups. In the wild, for instance, the classic lab rat Rattus norvegicus domestica primarily lives in groups of one male and many females. When males get together, they tend to fight.

The prairie vole—a small, mouse-like rodent that mates with a partner for life—has emerged in recent decades as an excellent laboratory model for the neuroscience of pair-bonding. While they are notable for their lifelong mates, however, wild prairie voles live in small family groups and are quite aggressive toward strangers.

As a graduate student, Kelly, who has a Ph.D. in evolutionary biology, explored the neural evolution of flocking behavior in birds using several finch species that ranged from being solitary to highly social.

She wanted to examine group living in mammals, but was stumped by the lack of a good animal model.

Communal living comes naturally to the spiny mouse. Credit: Aubrey Kelly

"It's important to consider how an animal behaves in the real world when trying to understand how the brain works," Kelly says. "You need to have the right animal for your particular question."

Enter the spiny mouse.

Kelly first heard about these quirky rodents through a chance conversation with Ashley Seifert, a biology professor at the University of Kentucky and a co-author of the current paper.

More than a decade ago, scientists learned that the spiny mouse, which lives in arid environments in Africa, the Middle East and southern Asia, has remarkable powers of wound healing, including the ability to regenerate large suites of tissue. If a predator grabs a spiny mouse, its skin slips off, allowing the mouse to escape. It then regenerates its skin, complete with stiff, spiny hairs.

Studies have also shown that the spiny mouse has unique adaptive responses related to damage to the heart, kidney and the spinal cord.

Seifert is among a growing number of scientists using the spiny mouse as a biomedical model for regeneration research. Spiny mice have also recently emerged as a model for type 2 diabetes studies. And a handful of labs have published work on the prosocial behaviors of spiny mice and their developmental traits.

When Seifert learned that Kelly wanted a better rodent model for social neuroscience, he suggested spiny mice.

"I was feeling bold and decided to try to build a social neuroscience program around them," Kelly says.

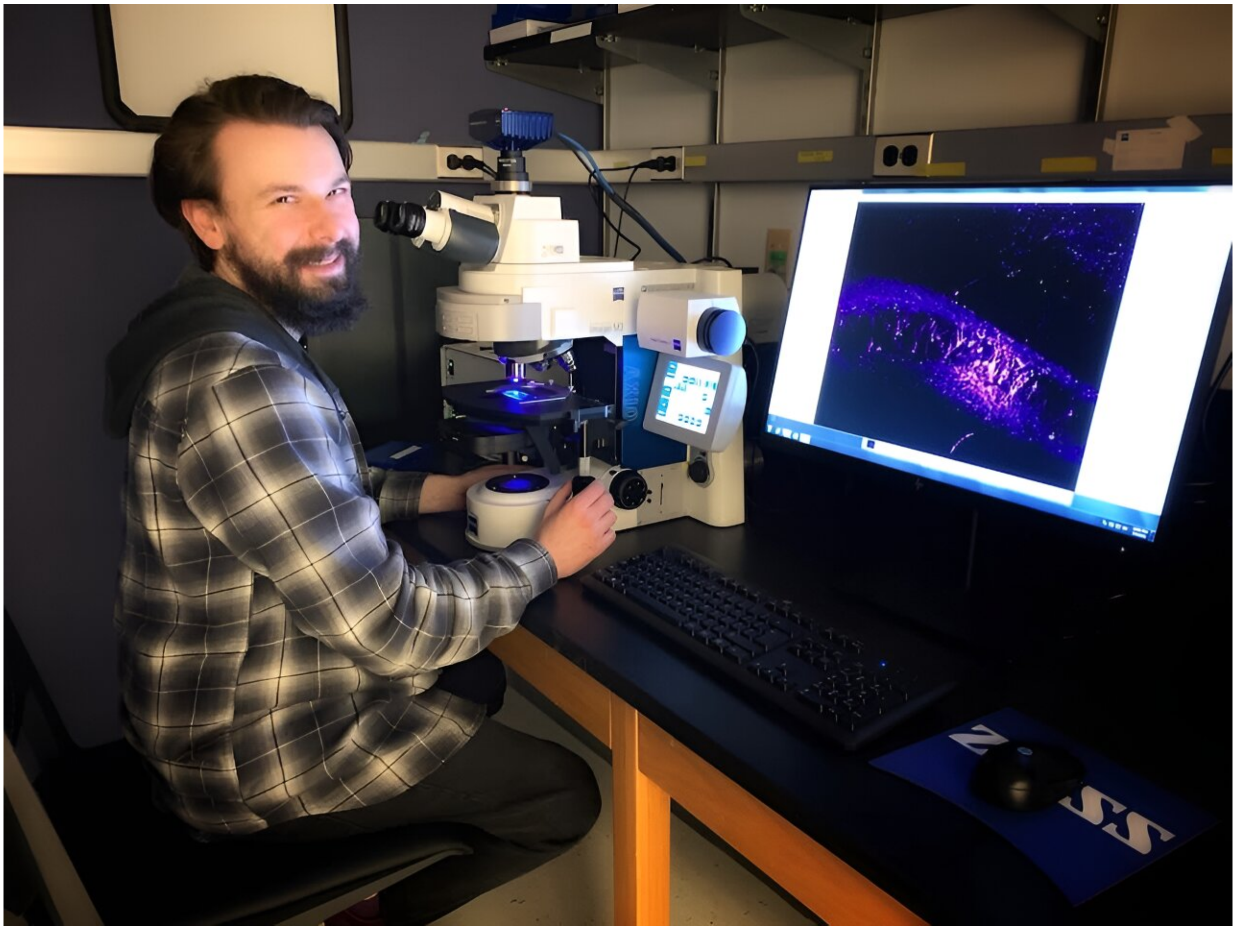
Fricker came to Emory as a graduate student five years ago shortly after Kelly launched her lab's spiny mice program, intrigued by this new approach.

"I'm really interested in the neuroscience of social behaviors," he says. "How do neurons react to stimuli from others that we encounter and then signal how we should respond? It's critical both to our survival and to our emotional well-being. Like on the first day of school when there is a lot of pressure to make friends. Misreading a situation during that time is not ideal."

The researchers further characterized the social behaviors of spiny mice in the lab. They found that regardless of familiarity, spiny mice rapidly approach peers, demonstrating high social boldness. They are significantly more prosocial than aggressive towards one another. Spiny mice also showed a strong preference for hanging out with large over small groups.

For the current paper, they wanted to determine the neural circuitry behind this large-group preference.

In one experiment, the researchers exposed some spicy mice subjects to small groups of their peers and others to larger groups. They then scanned the brains of the subjects to look for expression of the Fos protein, a product created when neurons fire. This neuroscience technique showed that activity in the lateral septum (LS) region of the brain was higher in the spiny mice hanging out in the larger groups.



Social behaviors are "critical both to our survival and to our emotional well-being," says Brandon Fricker, shown using a compound fluorescent microscope when he worked on the project at Emory. Credit: Aubrey Kelly

It is well-established that the lateral septum is involved in a variety of functions, including aggression and other social behaviors. In previous research, Kelly had found that this brain region is associated with flocking behavior in zebra finches.

"A brain region can be involved in so many different things, from aggression to flocking, depending on how it is interacting with other regions," Kelly says. "As technology has advanced, neuroscience is going beyond looking at single brain regions to studying the connections between different regions."

To identify circuitry involved in the large-group preference, the researchers repeated the previous experiment with the addition of neuronal tracers in the subjects. These chemical probes can map where in the brain a signal originates and the direction it travels.

The results showed a stronger signal from the anterior cingulate cortex (ACC) to the LS for the spiny mice exposed to larger—versus smaller—groups of their peers. Previous work has associated the ACC with consoling and other social behaviors in prairie voles. In humans, the ACC is involved in attention, decision-making and emotion.

The researchers then conducted experiments using chemogenetic tools that allowed them to temporarily switch off the ACC-to-LS circuit. The results showed that when this circuit was switched off, female spiny mice showed no preference when given a choice to hang out with a smaller versus a larger group. The males, however, actually flipped their preferences and chose to spend more time with a smaller group.

"I was surprised to see how strong of a change in behavior shutting down this circuit caused," Fricker says. "That shows that the ACC-LS circuit exerts a lot of influence over group-size preference."

Co-author Malvika Murugan, assistant professor in Emory's Department of Biology and an expert in viral chemogenetic techniques for neuroscience, assisted with troubleshooting the validation of the methods in the spiny mice.

The researchers used the inanimate objects of rubber ducks to test whether the ACC-LS circuit specifically promotes social preferences or just any preference for a large group of objects. While spiny mice prefer investigating a larger over a small group of rubber ducks, manipulation of this brain circuit had no effect on rubber duck preferences.

"That really highlighted that the neural circuit we identified was modulating social group-size preferences rather than something broader," Fricker says.

The researchers have now set the stage for delving deeper into the neuroscience of mammalian grouping behaviors using spiny mice as a model.

"From here, we're going to collect more behaviorally rich datasets by allowing the spiny mice to freely interact together in large groups and analyze the activity in their brains," Kelly says. "That will give us a better idea of how neural activity maps onto complex, dynamic, social behaviors."

Among the questions she wants to explore are what factors facilitate cooperative group-living and what are the environmental tipping points that lead to group dissolution and selfish behaviors.

"Studying the evolution of the social brain may generate insights into how our own brains promote getting along in groups," Kelly says. "What is the brain circuitry involved in welcoming a newcomer or cooperating and sharing food when resources are depleted?"

These are the kinds of questions the affable spiny mouse may help to answer.

More information: Brandon A. Fricker et al, Cingulate to septal circuitry facilitates the preference to affiliate with large peer groups, *Current Biology* (2024). DOI: 10.1016/j.cub.2024.08.019

Provided by Emory University

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