EXPERIMENTAL ORGANISMS

Neural control of duets between Alston's singing mice, an emerging vocalization model

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The little brown Alston's singing mouse (*Scotinomys teguina*) is ready for his moment. He rears up on his hind legs, throws his head back, and belts out a series of trills and chirps, notes distinctive enough to distinguish one mouse from another. Whether in the wilds of the Costa Rican cloud forest or the concrete jungle of Manhattan, male Alston's singing mice will sing their hearts out.

The Manhattan population lives in the lab of Michael Long, a neuroscientist at New York University School of Medicine who has spent the past few years setting up the vociferous colony, part of a collaboration with Steve Phelps at the University of Texas at Austin. Long had been working with a classic vocalization model, the zebra finch, but in Alston's singing mouse he's found a mammal with an equally tractable vocal behavior. "We originally wanted to ask a motor control question," Long says, "How does the brain generate that kind of organized song?" But the operatic displays aren't the only intriguing feature of Alston's singing mice, as the lab discovered by happenstance when a student had several cages out at once. Their song isn't just a solo: it's a duet.

When humans talk, the pause time between speakers averages just a fifth of a second, Long says, but that can be disrupted in disorders that affect the ability to communicate, such as stroke or autism. Male singing mice take turns in their songs, akin to humans having a conversation. One mouse will sing and when finished, another will pick up its own song without missing a beat, 'talking' back and forth in rapid exchanges without overlap or interruption. In a new study published in *Science*, Long and his colleagues take a first look at the neural underpinnings of the ability.

Vocal interactions are composed of two distinct tasks: there's the singing itself and then the coordination with a partner. "It turns out that two different brain areas are actually mediating these two tasks," Long says. In the current paper, the researchers identify the orofacial motor cortex (OMC) as the area of the brain responsible for song coordination. Electrical stimulation produced pauses, and focal cooling of the OMC slowed the songs down, suggesting that it controls singing behavior. To test the OMC's role in dueting, the researchers temporarily silenced that region with a compound called muscimol that inactivates neurons around where it's injected. The mice could still sing just fine, but they lost the ability to coordinate their songs with a partner until the muscimol wore off.

A singing Alston's singing mouse. Credit: C. Auger-Dominguez

"We turned off social interaction, the social back-and-forth that exists with their song. That was a very satisfying result for us" Long says. "That was kind of the end of the paper, but certainly not the end of what we hope to do with these guys."

There's still that second component of vocal interaction—producing the song—to investigate (Long suspects its origins lie in subcortical regions of the brain). And the lab already has translation in mind too. Long works with both animal models and humans—the focal cooling technique, for example, was developed in song birds and is now, with collaborators at the University of Iowa, being applied to humans to study how the human brain produces speech. Inspired by what they've observed in the brains of singing mice, Long says they're changing their focus from the production of simple speech sounds to the generation of conversational exchanges. "We're seeing a richer representation in the brain of how speech works, and how speech is perceived, and how that kind of turn taking happens," he says. With a singing mouse genome in the works and CRISPR/Cas9 tools under development, they soon hope to be able to start manipulating genes too, he says, to make singing mouse models of conditions that come with communication deficits.

The vocal interaction that the Alston's singing mouse displays is not all that novel, Long says—from crickets to bottlenose dolphins, there are a number of species that take turns when they communicate. Turn-taking is not apparent, however, in the lab mouse. "They don't actually vocally communicate in this clear way that matches up to human conversation," he says.

"Alston's singing mice and house or laboratory mice have a very different singing behavior," commented Kurt Hammerschmidt, a researcher at the German Primate Research Center who has studied vocal communication in both lab mice and nonhuman primates. "The songs of Alston's singing mice have only minor structural variation but precise temporal charateristics, in addition to the robust and rapid counter singing, he notes."Ultrasonic songs of laboratory mice are characterized by a high variation of elaborating frequency modulated notes, but fail to show specific temporal characteristics or counter singing." The Alston's singing mice could be an important new model to study the cortical control mechanisms that underly vocal communication in mammals.

For their vocalization advantages over their lab mouse brethren, the singing mice do come with some extra husbandry requirements: they need ample space to run around or they'll quickly pack on the grams, and chow doesn't quite cut it—they are insectivores and (pregnant females in particular) demand a regular diet of live meal worms. In the wild, a singing mouse might occupy an area as large as half a football field; the New York City real estate market is not quite so generous, Long laments, but he says that the mice are thriving—and singing—nonetheless in the terrariums they've built in the lab.

Now several generations in, the singing mice remain a bit wild—"they can bite, they can be a little bit ornery, but I've seen my student put his hand out flat, and the animal ran, hopped up, and stood up on his hind legs on his hand. And my student fed him with a dropper, and then the animal ran back down into the cage," Long recalls. "The fact that the behavior is still so rich is something that I really love."

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