Sex and Drugs and Singing Mice

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Mice can whistle and chirp like birds--and researchers now say their songs seem to be happy ones. New experiments associate the rodents' ultrasonic chatter with the brain's dopamine-based reward system, and investigators hope that studying the songs may eventually point toward genes behind human emotional disorders such as schizophrenia and autism.

Researchers have known for nearly 50 years that rodents produce ultrasonic calls. In 2005, they discovered that mice even sing complex songs (*Science*NOW, 1 November 2005). Their sparrowlike whistles and twitters are a couple of octaves too high for human ears to hear. No one knew exactly why mice sing, but rats make similar calls during sex, pleasant brain stimulation, and drug use, so psychologists thought the songs might be a sign of happiness. If this held true in mice, then powerful genetic tools available only in mouse studies could help researchers discover new genes that affect emotion and pleasure.

A team of researchers led by brain scientist Haoran Wang at the University of Toronto in Canada used special microphones to eavesdrop on mice during sex. When they let a male mouse into a female's cage, he approached her with a series of whistle calls and then, during intercourse, sang more complex chirp songs until ejaculation. (Females sing during social reunion with other females but only squeak uncomfortably during sex). Even without sex, the male mice sang complex chirps after the researchers injected them with a low dose of amphetamine, which activates the brain's reward circuitry by boosting levels of the neurotransmitter dopamine.

The researchers also listened to several types of genetically engineered mice, each of which lacked a single gene for a receptor that forms part of the dopamine circuitry. They knew animals missing these genes should have less interest in pleasure--and indeed, some strains of modified mice sang less than their wild-type counterparts, the team reports in the April issue of *PLoS*

One. "They're still beautiful calls," says John Yeomans, senior author of the study. "There are just a lot less of them."

The team thinks the songs are a window into mouse pleasure, and that they can now find more of the genes involved. That, in turn, could help understand how human feelings are regulated. "Whether it relates to human emotions, we'll see, but that's the hope," Yeomans says.

Neurobiologist Timothy Holy of Washington University in St. Louis, Missouri, who first described mouse songs in 2005, says the study is "far more authoritative than anything that's been done previously" in describing them. But neurobiologist Timothy DeVoogd of Cornell University cautions that "the brain can go wrong in all sorts of odd ways" when a receptor is missing for the animal's entire life, so changes in the songs may be difficult to interpret. He would like to see additional studies in which the receptor genes are silenced only at the time of the experiments.

Still, the work is "extremely useful to the field," says behavioral neuroscientist Jacqueline Crawley of the National Institute of Mental Health in Bethesda, Maryland, because the songs offer a relatively simple way to test for genes that change the expression of emotion and reward.