SEXUAL BEHAVIOR

Bisexual Fruit Flies Point to Brain Courtship Centers

In the world of fruit flies, there are no forward females. All the courting, tender touching, and serenading are done by the male; his mate's main role, like that of a proper Victorian lady, is merely to sit still and accept his advances.

Researchers know all that. What they don't know is how a male chooses the object of his affection. Some researchers have tried to identify the brain regions that govern courtship and mating behavior in the fruit fly *Drosophila melanogaster*, but their success has been limited by the available techniques. Now, in work described on page 902, a team led by neurogeneticist Ralph Greenspan of New York University has used a new genetic trick to identify two brain areas that seem to control mate selection by male fruit flies. Indeed, the researchers found that by causing those areas to undergo the female developmental pattern, they can create bisexual male flies that pour out their passions to males and females alike.

This isn't the first observation of bisexual fruit flies; at least one mutation that causes bisexuality had previously been identified. But unlike earlier work, this study shows "that there are likely distinct anatomical regions involved in ... reacting to male versus female," says Cold Spring Harbor behavioral geneticist Tim Tully. The finding is encouraging to researchers who seek to understand the roots of sexual orientation in humans. "The message is that there are a set of switches that can, at some critical point in a behavior, channel it in a different direction," says Simon LeVay of the West Hollywood Institute for Gay and Lesbian Education, the neuroscientist who 4 years ago found a feminized region in the brains of homosexual men.

The paper is also important, adds Tully, because it demonstrates a general method for identifying brain regions involved in specific forms of behavior: "To my knowledge, this paper is the first one that has successfully analyzed a behavioral phenotype using this general approach."

Researchers have studied courtship in fruit flies for decades, using it as an experimental model for understanding how genes govern behavior. By seeking out mutations that change courtship behavior, they have identified a myriad of genes that have a role in courtship, including one, called *fruitless*, which, when mutated, causes bisexual behavior in male flies. But mutation analysis can't provide all the answers about how behavior is controlled. For example, researchers studying *fruitless* don't know exactly where in the fly's nervous system the gene acts to influence sexual behavior.

Until now, to identify the areas of the nervous system where genes such as *fruitless* act, researchers have had to rely on an old technique for making a type of mosaic flies, called gynandromorphs. These flies start out female, but during development some of their cells lose one of their two X chromosomes. The tissues that descend from those cells become islands of maleness in an otherwise female fly.

In the 1970s, Jeff Hall of Brandeis University in Waltham, Massachusetts, was the first of several researchers to use gynandromorphs to try to find the parts of the brain that govern courtship. "I found that if a certain region of the brain is male genetically," Hall says, "then you get certain male behaviors" even if the fly is mostly female. But it was difficult to narrow down the key brain structures responsible for the behaviors, because the patches of male tissue in gynandromorphs are large. An added problem is the fact that each gynandromorph has a unique pattern of maleness and femaleness, shared with no other fly. So experiments have to be done entirely on single flies. One mistake and all the data on that fly could be lost, with no hope of recovery. "It was an ordeal," says Greenspan, who has also worked with gynandromorphs. "It was a miracle that we ever got any data from them."

REINHARD STOCKER

Wired for sex. The antennal lobes of the fruit-fly brain, marked here by blue stain, may help control sexual orientation.

But in 1993 Andrea Brand and Norbert Perrimon of Harvard Medical School in Boston made an advance that paved the way for the current work. They demonstrated a clever new way to turn on a gene in discrete parts of a fruit fly. First the researchers inserted a yeast gene for a gene-activating protein called Gal4 into fruit flies, creating a collection of fruit-fly strains, each of which expresses Gal4 in a unique pattern of tissues. Those flies were mated to a second fly strain engineered to contain a gene of the researcher's choice, connected to a control switch activated by the Gal4 protein. In the progeny produced by these matches, that gene would then be turned on in all the tissues that make Gal4.

Jean-François Ferveur, a postdoc with Greenspan, used this approach to design what Greenspan calls "a new version of the gynandromorph studies." Ferveur and Greenspan got a collection of Gal4 strains from Brand, now at the Wellcome Institute in Cambridge, United Kingdom, and picked out the strains in which Gal4 is made in various parts of the brain. They bred flies from each of these strains to flies of a strain into which they had introduced a fruit-fly gene called *transformer*, linked to the Gal4 switch. They chose *transformer* because it switches cells to the female pattern of development, thus feminizing the tissues in which it is turned on.

By feminizing parts of the brain with *transformer*, they didn't necessarily expect to make male flies act like females—the rest of the brain and body of the fly was, after all, male—but they thought they might disrupt certain aspects of normal male courtship. Their hunch was right: Ferveur found that males of some of the transformed strains courted male as well as female flies.

With the help of fruit-fly neuroanatomist Reinhard Stocker of Fribourg University in Switzerland, Ferveur and Greenspan checked the distribution of *transformer* expression in the bisexual flies and found that all the bisexual strains were making *transformer* in either the antennal lobe, which receives olfactory information, or the mushroom bodies, higher areas of the brain that process olfactory information from the antennal lobe.

This tie to the sense of smell makes sense, says Ferveur, because mate choice in flies probably depends on detecting volatile chemical pheromones. One possibility, says Ferveur, is that the *transformer* males "are not able to distinguish males from females, so they court both." Indeed, adult male flies make two compounds that inhibit courtship by other males, says Laurie Tomkins, a behavioral geneticist at Temple University in Philadelphia. Feminization of the olfactory system by *transformer* may destroy male flies' ability to detect the inhibitory compounds, she says, robbing the flies of "information about the maleness of [their] sex objects."

Another scenario, Greenspan adds, is that "the flies find both sexes positively attractive" as a result of the changes wrought by *transformer*. Ferveur, who is now at the University of Paris at Orsay, is investigating those possibilities.

Other researchers are also interested in following up on the Greenspan group's work. It provides useful clues to researchers studying genes that affect courtship in fruit flies, says Barbara Taylor, who studies *fruitless* at Oregon State University. "It suggests a place [in the brain] to look for changes in *fruitless* that we might not have looked at [otherwise]," she says.

And what does it say about sexual orientation in higher animals, including humans? Greenspan cautions that care must be taken in drawing parallels to humans from studies of fruit flies. "There isn't a lot of indication that the organization of a fly brain is relevant to a noninsect brain," says Greenspan, so the details of the conversion to bisexuality in flies are probably not applicable to humans.

But, says Dean Hamer, a researcher at the National Institutes of Health who is searching for a gene linked to homosexuality, the fly study does support "the general principle that the brain is the locus of sexual behavior, and that the brain is wired differently in males and females, under a program of genetic control, and that variations in that [wiring] can cause variations in sexuality. We think that general rule holds in humans as well."

–Marcia Barinaga

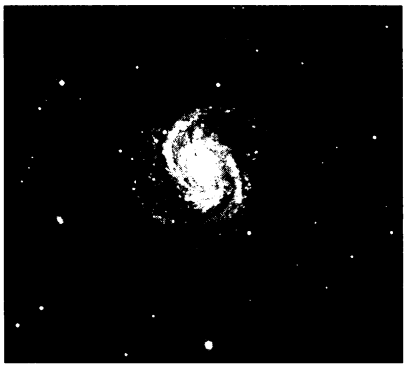
ASTRONOMY

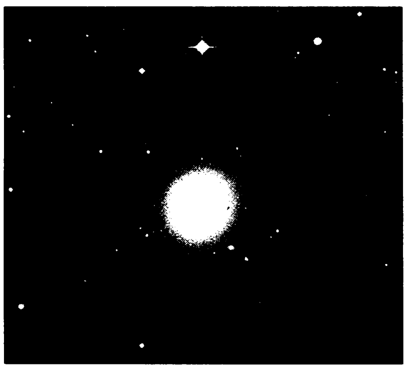
Galaxy Experts Train Electronic Stand-Ins

University of Alabama astronomer Ronald Buta does a job few of his colleagues in the field care to do. Like a naturalist classifying a butterfly collection, Buta pores over thousands of galaxies imaged in telescope surveys and assigns each one a number that indicates whether it is a spiral galaxy, an elliptical galaxy, or something in between. Perhaps fewer than a dozen scientists in the world are formally trained in this deceptively simple task, which Buta calls "very tedious and time-consuming." Still, he feels it's a vital job. "Buried in the morphology of galaxies is information about how they formed and how they evolved," he says. Now Buta and his fellow classifiers may be getting some help from electronic apprentices, as he and other astronomers report on page 859 of this issue of *Science*.

Buta was one of "six hotshots who understand galaxy morphology," as another astronomer describes them, who were enlisted to teach their classification skills to the brain-inspired computer programs known as artificial neural networks. When these electronic pupils were then left free to classify galaxies on their own, the networks did their teachers proud. "A computer algorithm can replicate the expert [who trained it] as well as another expert can," says Ofer Lahav of the Institute of Astronomy in Cambridge, United Kingdom, who recruited Buta and the other classifiers for the unusual experiment.

The work reported in this issue isn't the only attempt to automate galaxy classification: Stephen Odewahn, a University of Minnesota astronomer, is leading a similar project in training neural networks, for example. That's all to the good, because Buta and other human classifiers will need all the help they can get to cope with the flood of data that's expected from efforts like the Sloan Digital Sky Survey, which by itself is expected to image more than a million galaxies. "We're going to be overwhelmed with data," says Lahav, who devised the networks with his colleagues Avi Naim, Laerte Sodre, and Michael Storrie-Lombardi.





Shapely galaxies. Neural networks can learn to tell a spiral *(top)* from an elliptical.

PHOTOS BY ROYAL OBSERVATORY/PHOTO RESEARCHERS

If ways can be found to analyze such masses of information, it could be very valuable. Studies of galaxy morphology have hinted, for instance, that elliptical-shaped galaxies are more common in regions packed with other galaxies, suggesting that a region's density somehow influences galactic shape. And some astronomers peering back in time by looking into the far reaches of the universe wonder whether spiral galaxies were more prevalent early in cosmic history than they are now. But pursuing such questions means classifying a deluge of galaxy images. And as Odewahn puts it, "You can't get Harold Corwin [a co-author of the *Science* paper] to look at a half-million images. We need an automated way of extracting type."

In spite of this need, classifying the shape of galaxies might seem an unpromising target for automation, because it is more art than science. In 1936, the pioneering astronomer Edwin Hubble suggested a classification scheme that placed elliptical galaxies at one end of a sequence and spirals similar to the Milky Way at the other. Over the years, Hubble's scheme was refined to take into account characteristics including the size of a galaxy's central bulge and the dimensions of a spiral galaxy's arms. But exactly where a galaxy's shape fits in the scheme comes down to a matter of expert—and therefore subjective—judgment.

Fortunately for astronomers, neural networks are good at replicating human skills that can't easily be quantified, because instead of being rigidly programmed from the start, they learn from experience. The networks designed by Lahav and his colleagues classify each galaxy based on more than a dozen morphological features, but the weights they assign to each feature can change in the course of their training. Each galaxy expert trained a network on anywhere from 300 to 600 galaxy images by giving it the "correct" answer for each image. As the networks analyzed more and more images, they modified the weights assigned to each feature in order to produce answers as close as possible to the "correct" ones.

Once the training was finished, the researchers staged a competition between the electronic apprentices and their teachers. Each neural network classified 100 to 200 galaxies on its own, and its judgments were then compared with those of the expert who had trained it. The networks didn't exactly replicate their tutors' choices—but then again, the experts didn't always agree among themselves. In short, says Lahav, a neural network could match, say, Buta's classification of a galaxy as well as any other of the world's top classifiers could.

"There's still a role for the experts," says Buta, who notes that a neural network may fail to flag those galaxies with unusual features that, in the past, have proven so informative to astronomers. "Sometimes it's the exception to a rule that reveals the rule," he says. Still, Buta welcomes electronic apprentices for their speed and endurance. They "will provide a huge database on morphology that no human could find the time to do," he says. Adds Odewahn, "Edwin Hubble would have been doing it this way if he could have."

–John Travis