New Evidence for the Necessity of Loneliness

A specific set of neurons deep in the brain may motivate us to seek company, holding social species together.

By Emily Singer

As social animals, we depend on others for survival. Our communities provide mutual aid and protection, helping humanity to endure and thrive. “We have survived as a species not because we’re fast or strong or have natural weapons in our fingertips, but because of social protection,” said John Cacioppo, the director of the Center for Cognitive and Social Neuroscience at the University of Chicago. Early humans, for example, could take down large mammals only by hunting in groups. “Our strength is our ability to communicate and work together,” he said.

But how did these powerful communities come to exist in the first place? Cacioppo proposes that the root of social ties lies in their opposite — loneliness. According to his theory, the pain of being alone motivates us to seek the safety of companionship, which in turn benefits the species by encouraging group cooperation and protection. Loneliness persists because it provides an essential evolutionary benefit for social animals. Like thirst, hunger or pain, loneliness is an aversive state that animals seek to resolve, improving their long-term survival.

If Cacioppo’s theory is correct, then there must be an intrinsic biological mechanism that compels isolated animals to seek out companionship. Something in our brains must make it feel bad to be alone and bring relief when we’re with others. Researchers at the Massachusetts Institute of

Technology think they've found the source of that motivation in a group of little-studied neurons in part of the brain called the dorsal raphe nucleus. Stimulating these neurons drives isolated mice to find friends, according to research published earlier this year in the journal *Cell*. The finding provides critical support to Cacioppo's theory and illuminates a deep connection that links specific structures in the brain to social behavior.

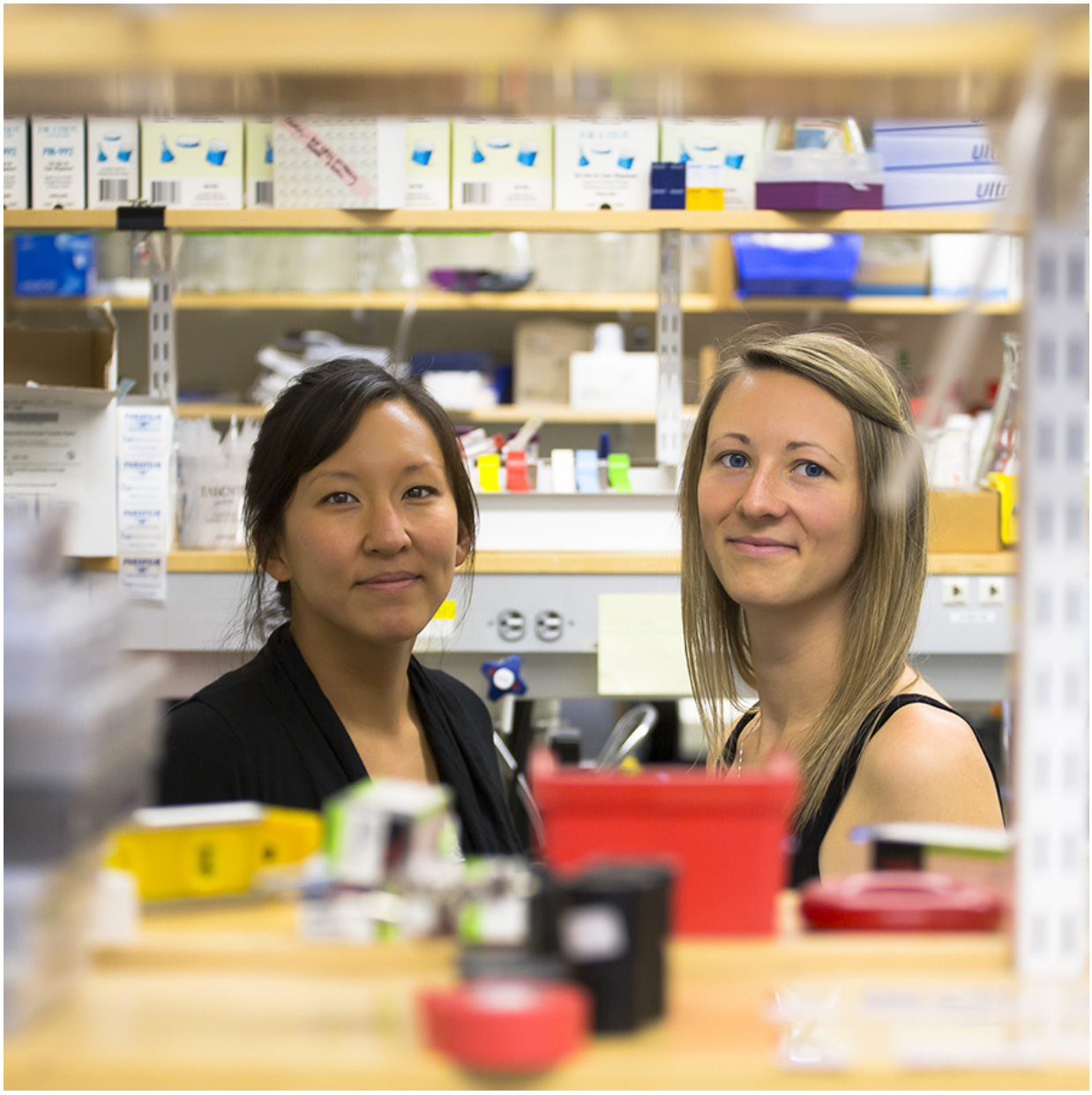
The new study — the first to link specific neurons to loneliness — is part of a growing effort to map out the genetics of social behavior and its underpinnings in the brain. "Over the last roughly 15 years, there has been a tremendous increase in the desire to understand the basis of social behavior, including caring for others, social rejection, bullying, deceit and so forth," said Patricia Churchland, a philosopher at the University of California, San Diego, who studies the brain and social behavior. "I think we have a good idea for the evolutionary basis for caring and sharing and mutual defense, but the brain mechanisms are bound to be very complex."

Together, Cacioppo's work and the new findings from MIT are helping to move loneliness from the realm of psychology and literature to biology. "I think the bigger picture is not to understand why loneliness is painful but rather how our brain is set up to move us out of that lonely state," said Steve Cole, a genomics researcher at the University of California, Los Angeles. "Instead of thinking about loneliness, we could think about social affinity."

Social Creatures

Gillian Matthews stumbled across the loneliness neurons by accident. In 2012 she was a graduate student at Imperial College London who had been studying how cocaine changes the brain in mice. She would give the animals a dose of the drug, place each one alone in a cage, and then examine a specific set of its neurons the next day. She did the same for a control group of mice, injecting them with saline instead of cocaine.

When Matthews returned to her mice 24 hours after dosing them, she expected to see changes in their brain cells, a strengthening of neuronal connections that might help explain why cocaine is so addictive. To her surprise, both the drug-treated mice and the control mice showed the same changes in neuronal wiring. Overnight, the neural connections onto a certain set of cells had grown stronger, regardless of whether the animals were given drugs or not. "We first thought there was something wrong, that we had mixed up our procedure," said Matthews, who is now a postdoctoral researcher at MIT.



Kay Tye (left) and Gillian Matthews, both neuroscientists at MIT, have found a set of neurons that compel mice to seek out companionship.

The brain cells she was interested in produce dopamine, a brain chemical typically associated with pleasurable things. Dopamine surges when we eat, have sex or use drugs. But it does more than simply signal pleasure. The brain's dopamine systems may be set up to drive the search for what we desire. "It's not what happens after you get what you want, it's what keeps you searching for something," Cole said.

The researchers focused on dopamine neurons in a brain region called the dorsal raphe nucleus, best known for its link to depression. (This may not be a coincidence — loneliness is a strong risk factor for depression.) Most of the neurons that reside there produce serotonin, the chemical messenger that drugs such as Prozac act on. Dopamine-producing cells make up roughly 25 percent of the region and have historically been difficult to study on their own, so scientists know little about what they do.

Matthews speculated that other environmental factors during the experiment might have triggered the changes. She tested to see if simply moving mice to new cages altered the dopamine neurons, but that couldn't explain the effect. Ultimately, Matthews and her colleague Kay Tye realized that these brain cells were responding not to the drug but to the 24 hours of isolation. "Maybe these

neurons are relaying the experience of loneliness," Matthews said.

Mice, like humans, are social creatures that generally prefer to live in groups. Isolate a mouse from its cage mates, and once confinement ends it will spend more time interacting with other mice, to a much greater extent than if it had been with its mates all along.

To better understand the role the dorsal raphe neurons play in loneliness, the researchers genetically engineered the dopamine cells to respond to certain wavelengths of light, a technique known as optogenetics. They could then artificially stimulate or silence the cells by exposing them to light.

Stimulating the dopamine neurons seemed to make the mice feel bad. Mice actively avoided stimulation if given the choice, just as they might avoid physical pain. Moreover, the animals appeared to enter a state of loneliness — they acted like they had been alone, spending more time with other mice.

The Danger of Solitude

Loneliness not only feels bad, it can have profound health consequences. Animals raised in isolation, from flies to mice to chimps, have shorter life-spans. Solitary confinement — considered one of our harshest criminal punishments — boosts stress in humans and other animals, weakening the immune system and increasing the risk of death. Indeed, some estimates suggest that loneliness raises risk of mortality by nearly 30 percent — as much as obesity — even when controlling for confounding factors like age and depression.

Scientists hope that better understanding the neural circuits underlying loneliness will not only help explain why it exists but also ultimately point to new treatments. "Is there a way," Hawkley asked, "of moderating activity in the brain like we do for depression?"

"I think this reveals something about how our brains may be wired to make us innately social creatures and protect us from the detrimental effects of loneliness," Matthews said.

Spectrum of Loneliness

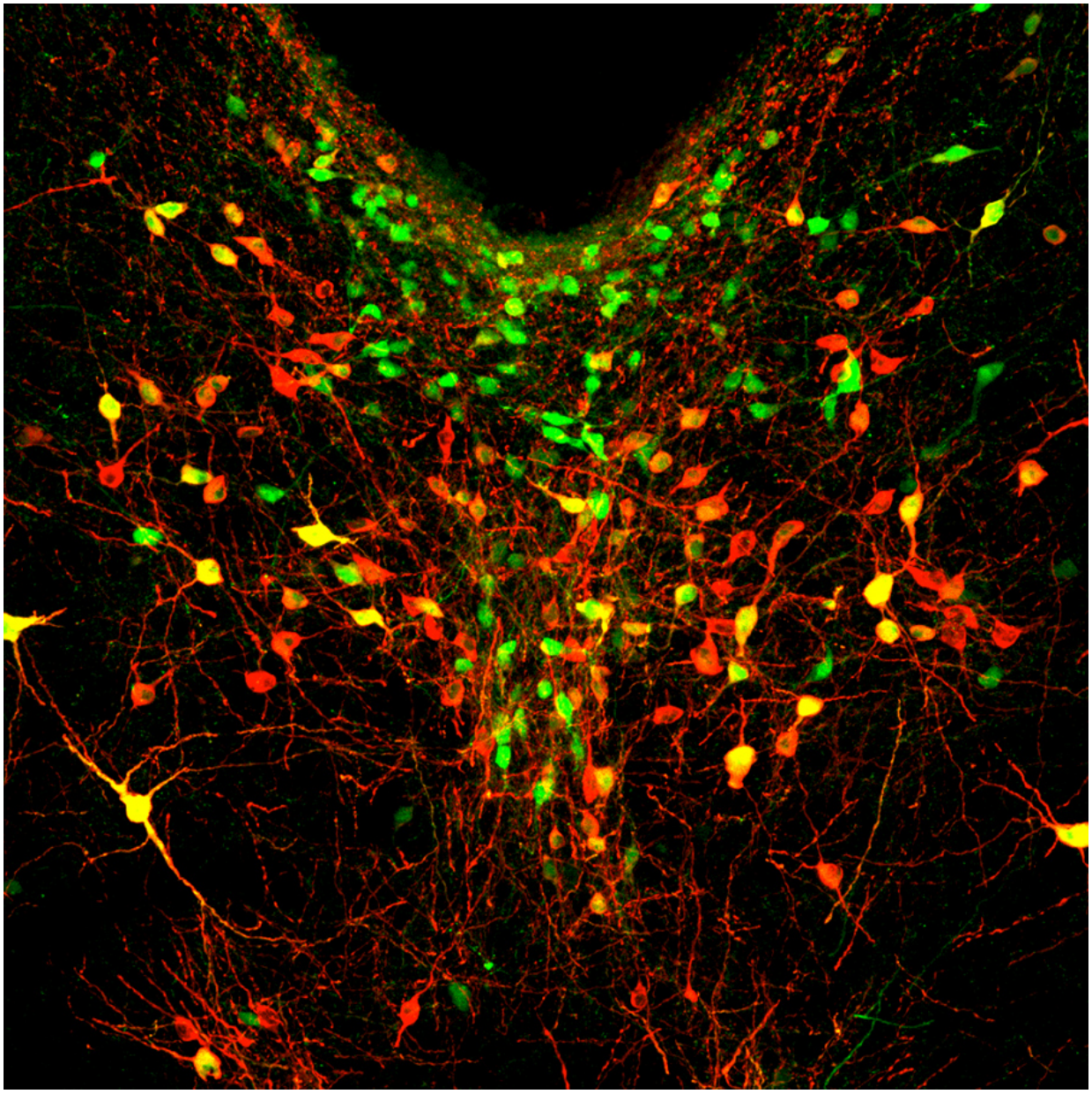
Cacioppo first formally proposed his evolutionary theory of loneliness a decade ago. Strong support comes from the fact that our sensitivity to loneliness is heritable, like height or risk of diabetes — about 50 percent of an individual's level of loneliness can be tied to their genes. "If it was really bad, it would have been bred out, so it must be adaptive," said Louise Hawkley, a psychologist at NORC at the University of Chicago, who has collaborated with Cacioppo in the past. The evolutionary theory for loneliness "forms a very coherent story about how loneliness might have come to exist," she said.

Indeed, like diabetes, people have varying degrees of susceptibility to loneliness. "What's being inherited is not loneliness, it's the painfulness of the disconnection," said Cacioppo, who is now trying to nail down the specific genes linked to loneliness with studies of tens of thousands of people.

In evolutionary terms, it's helpful for a population to have some variability in this trait. Some members of a community would be "so pained by disconnection that they are willing to defend their village," Cacioppo said. "Others are willing to go out and explore but hopefully still have enough of a connection to come back and share what they found."

Mice also show this variability. In Matthews' experiments, the most dominant mice — those that win in fights against their cage mates and have priority access to food and other resources — show the

strongest reaction to having their loneliness neurons stimulated. At those times, the highest ranking animals search out companionship more fervently than animals on the lowest rungs of the social ladder. These mice also avoid stimulation of the loneliness neurons more avidly than the lower ranking members, suggesting that the dominant mice find it more unpleasant. The lowest ranked mice, in contrast, didn't seem to mind being alone. Perhaps they enjoyed isolation, being free of their harassers.



A subset of neurons (shown in red, green and yellow) in a brain region known as the dorsal raphe nucleus produce a chemical messenger called dopamine. Scientists think these neurons motivate isolated mice to spend time with others.

"It's extremely complex — they see a lot of variability just in rodents," Churchland said. "I think that's really very striking."

Tye and Matthews' findings suggest that these dorsal raphe nucleus neurons help to resolve the disconnect between the level of social connection the animal has and the level it wants. Imagine loneliness as a desire for ice cream — some animals love ice cream and some don't. The dopamine neurons drive the ice cream lovers to seek out the dessert but have little effect on everyone else. "We think that the [dorsal raphe nucleus] neurons are somehow tapping into that subjective social experience of the mouse, and only producing a significant effect on the behavior of mice who

perhaps previously valued their social connections, rather than those who did not," Matthews said.

The varying reactions suggest two intriguing possibilities: either neural wiring determines social rank, or social rank influences how these neurons get wired. Perhaps some animals are wired from birth to crave social contact. These animals then seek out others and become aggressive as they try to maintain their position in the group, eventually attaining top status. Alternatively, certain mice may start out with an aggressive personality, picking on other animals in their group. The brain wiring in these animals might change as a result, driving the mice to seek out others to bully. Tye and Matthews are planning additional experiments to distinguish those two possibilities.

Cacioppo said he almost "fell over" when he saw Tye and Matthews' results. He's done extensive research on loneliness in humans, using brain imaging to identify parts of the brain that are active when people feel lonely. But brain imaging has a coarse resolution and can't analyze specific cell types like Tye and Matthews did in mice.

Tye and Matthews' research helps to reframe loneliness from a state of profound despair to a motivational force encoded in our biology. "Instead of focusing on the aversive state of being alone, this study looks at how social contact gets rewarded in the nervous system," Cole said. "Then loneliness becomes understandable as a lack of reward."

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