

ANIMAL RESEARCH

Male Scent May Compromise Biomedical Studies

Jeffrey Mogil's students suspected there was something fishy going on with their experiments. They were injecting an irritant into the feet of mice to test their pain response, but the rodents didn't seem to feel anything. "We thought there was something wrong with the injection," says Mogil, a neuroscientist at McGill University in Montreal, Canada.

The real culprit was far more surprising: The mice that didn't show pain had been handled by *male* students. Mogil's group discovered that this gender distinction alone was enough to throw off their whole experiment—and likely influences the work of other researchers as well.

"This is very important work with wide-ranging implications," says M. Catherine Bushnell, a neuroscientist and the scientific director of the Division of Intramural Research at the National Center for Complementary and Alternative Medicine (NCCAM) in Bethesda, Maryland. "Many people doing research have never thought of this."

Mogil has studied pain for 25 years. He's long suspected that lab animals respond differently to the sensation when researchers are present. In 2007, his lab observed that mice spend less time licking a painful injection—a sign that they're hurting—when a person is nearby, even if that "person" is a cardboard cutout of Paris Hilton. Other scientists began to wonder if their own data were biased by the same effect. "There were whisperings at meetings that this was confounding research results," Mogil says.

So he decided to take a closer look. In the new study, Mogil told the researchers in his lab to inject an inflammatory agent into the foot of a rat or mouse and then take a seat nearby and read a book. A video camera trained on the rodent's face assessed the animal's pain level, based on a 0- to 2-point "grimace scale" developed by the team. The results were mixed. Sometimes the animals showed pain when an experimenter was present, and sometimes they seemed just fine. So, on a hunch, Mogil and colleagues rechecked the data, this time controlling for whether a male or a female experimenter was present. "We were stunned by the results," he says. The rodents showed significantly fewer signs of pain (an average of a 36% lower score on the grimace scale) when a male researcher was in the room than when a female researcher—or no researcher at all—was there.

Thinking back to his Paris Hilton

experiment, Mogil wondered whether the rodents were responding to the sight of a woman or man or to something more subtle. So he told the people in his lab to place their worn T-shirts near injected animals and then leave the room. Even when the humans weren't present, the results were the same. Rats and mice showed about a 36% lower score on the grimace scale when exposed to male versus female T-shirts, the team reported online this week in *Nature Methods*. (Female mice were

in the lab, from the effectiveness of experimental drugs to the ability of monkeys to do math, is affected by stress, notes Paul Flecknell, a veterinary anesthesiologist at Newcastle University in the United Kingdom who researches ways to alleviate pain in animals. "This could have an impact on just about everything."

Male odor could even influence human clinical trials. If a male doctor injects you with a new kind of pain medication, do you



What's that smell? The presence of a male scientist can influence research results.

slightly more sensitive to the effect.) Placing a woman's T-shirt next to a man's T-shirt negated the impact. Bedding material from unfamiliar male mice and guinea pigs, as well as pet beds slept in by unsterilized male cats and dogs, produced the same response: Male odors seemed to act like painkillers.

Further testing showed that the rodents exposed to male odors were actually feeling less pain, rather than simply hiding the pain they were in. The male aroma ramped up their stress levels, which deadened the hurt. "It's really astounding that such a robust effect could have been missed for so many years," Mogil says.

He suspects the rodents are reacting to scent chemicals that male mammals have produced for eons. "It's a primordial response," he says. "If you smell a solitary male nearby, chances are he's hunting or defending his territory." If you're in pain, you're showing weakness.

Almost every animal behavior studied

feel better because of the drug—or because of his gender? "It's not an unreasonable concern," Flecknell says.

The findings may also suggest why some labs have trouble reproducing the results of other groups. "Sometimes pharmaceutical companies can't replicate preclinical work," says Bushnell, who came to NCCAM to develop a pain research program. "This could help explain that."

Still, Mogil doesn't think scientists need to redo decades of animal research. "It's a confounding factor, but not a fatal one," he says. But going forward, he advises, researchers should pay more attention not to just what experiments they're doing, but also to *who's* doing the experiments. "I joke that the solution is to fire all the male researchers," Mogil says. "But at the very least, this is something teams should be noting in the methods sections of their papers. We can change the bath water without throwing out the baby."

—DAVID GRIMM