

# The sex of the researcher can influence results of mouse experiments

Ketamine appears to be more effective as an antidepressant in mouse experiments if they are conducted by a male researcher, raising questions about other studies in mice

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**A researcher holding a mouse**

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Laboratory mice tend to be more stressed when they can smell men, making them behave differently in experiments depending on whether they are handled by a man or a woman. The finding raises important questions about past research using mice, since animal studies generally don't control for an experimenter's sex.

[Todd Gould](#) at the University of Maryland began investigating this issue after his team

couldn't replicate a simple lab result. The experiment involved a "forced swim test", in which researchers place mice in a tank of water and see how long they keep trying to swim for. When they stop swimming, the researchers take them out, unharmed.

In previous tests with male experimenters, mice tried to stay afloat for longer if they were given ketamine, an antidepressant. But when Polymnia Georgiou, a female researcher who was working in Gould's team, carried out the test, the mice gave up quickly regardless of whether they were given ketamine.

"The first feeling was of surprise," says Gould. He had read a [study published in 2014](#) that showed mice were generally more stressed and less responsive to pain when handled by men than women. To see if this explained the surprise result, Gould and his colleagues designed a series of tests to explore whether the sex of the experimenter influenced how mice behaved.

Mice were exposed to T-shirts worn by male and female experimenters, as well as cotton swabs rubbed across the experimenters' wrists, elbows or behind the ears. They found that mice would avoid sniffing and engaging with scents from male experimenters and were either impartial or showed a slight preference for those linked to female experimenters.

The team also repeated their experiments with ketamine to see whether the sex of the experimenter affected the drug's apparent effectiveness as an antidepressant.

Paradoxically, when men administered ketamine injections, mice were more anxious but showed a stronger response to the treatment on various tests, including the forced swim test and a test that looked at their preference for sugary food.

Gould's team showed that being handled by male experimenters caused the release of hormones known as corticotropin releasing factors, which activated a pathway critical for ketamine's efficacy.

Targeting that pathway in humans may be important for the antidepressant effect of ketamine in humans too, says Gould, but more research is needed to investigate this. In the meantime, he says it is important for scientists working with animals to really consider whether the sex of the experimenter is influencing their results.

"What it suggests is that every experiment that's ever been done with male experimenters has happened with the mice in a different state than experiments that have been done with female experimenters," says [Jeffrey Mogil](#) at McGill University in Montreal, Canada, who was part of the team behind the 2014 study. "And so, yeah, you're going to get different results."

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The problem could apply to any animal with an acute sense of smell, including rats, says Gould. If so, a large proportion of critical scientific research on subjects from Alzheimer's disease to cancer may be subject to this bias. Mogil goes so far as to say that this finding may, in part, explain why science is facing a [replication crisis](#) where attempts to repeat key experiments often produce different results.

The sex of experimenters may be just one of many biases that we should account for, says [Gerlinde Metz](#) at the University of Lethbridge in Canada, who wasn't involved in the research. [Her team published a study in July](#) showing that male and female rats showed different stress and behavioural responses to human experimenters.

The shipment, the breeding and handling of animals and their diet could all have an effect too, she says. "Even seasons can induce different effects."

Metz says scientists should try to control for as many of these variables as possible. People could wear gowns, clean up cages well in advance of an experiment and allow mice to get used to the experimenter so that the effect of their presence diminishes, says Mogil. But it is near impossible to keep things totally controlled, says Metz, especially when dealing with a creature with such a sophisticated sense of smell.

As a minimum, researchers should be reporting the sex of experimenters in their studies so that they can later account for potential differences in results. "That's something that we've all been ignoring completely because no one thought it was even remotely possible that it could matter," says Mogil. "But it does."

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