Uncovering a flaw in drug testing for chronic anxiety disorder

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Pre-clinical trials—the stage at which medications or therapies are tested on animals like laboratory mice—is a crucial part of drug development. It's only then that scientists can assess benefits and side effects before a drug is administered to patients.

Now, Prof. Ilan Golani of Tel Aviv University's Department of Zoology and Sagol School for Neuroscience and his fellow researchers Prof. Yoav Benjamini of TAU's Department of Statistics and Operations Research and the Sagol School of Neuroscience, and Dr. Ehud Fonio of the Weizmann Institute are questioning the animal models used for measuring chronic disorders such as Generalized Anxiety Disorder. Using a hundred-times longer experimental time-frame and comparing lab mice with wild mice, the researchers found that the lab mice used do not actually experience chronic anxiety.

Instead, the researchers found that the behavior exhibited by the mice in the first minutes of an experiment is only a temporary response to a new environment. With time, the mice revert back to their true temperaments—lab mice have calm temperaments and wild mice are anxious. This discovery, which has been reported in the journals *PLOS One* and *Nature Methods*, could explain why most candidate drugs developed using this mouse model have poor therapeutic value in treating human brain disorders, says Prof. Golani.

Back to the wild

Because of their genetic similarity to humans, mice are the most commonly used lab animals. Countless hours and billions of dollars have been spent developing mouse models, whose genes can be engineered to mimic human diseases and disorders. And while many of these models have made invaluable contributions to the advancement of research into Parkinson's disease and various cancers, others have proven less effective.

A chronically anxious mouse model is crucial to test anti-anxiety therapies, says Prof. Golani. Currently, scientists use a specific strain of lab mice thought to be particularly anxious. During experiments, the mice are placed in a novel environment and monitored for signs of anxiety such as staying in sheltered rather than exposed space, for example. After drugs are administered, the mice are observed for a reduction in anxious behaviors.

The researchers compared the lab mouse strain now used for Generalized Anxiety Disorder testing to a strain of first-generation wild mice born in captivity. The time-frame of the experiment was extended from a few minutes to as long as 45 hours. Though the lab mice appeared more anxious at first, the scientists discovered that the lab mice eventually settle into calm behavior, while the wild mice exhibit consistently more anxious behavior: "In nature, mice must always be on high alert or they will get preyed upon," explains Prof. Golani.

They believe that the current Generalized Anxiety Disorder methodology for animal models should be revised because of three main experimental fallacies: use of the wrong animal, too short a time-frame, and analysis made at the wrong points in the experiment. These prevent the diagnosis of true chronic mal-behavior, they say.

Replicating results

In their Nature Methods article, the researchers call for similar scrutiny of other behavioral animal models. One important criterion is that findings from experiments conducted using an animal model must be replicable in other labs. The lack of replicability is a problem in the field, they note, which is currently insufficiently addressed by complicated and costly efforts to standardize experimental protocols.

Not every experiment needs to be replicated in many labs, sacrificing more animals, time and money, says Prof. Benjamini. "Developing a collaborative database that draws on the different experiments conducted across the globe, as well as using appropriate data mining tools, can yield the needed yardstick to check for replicability of findings for scientists in isolated labs," he adds. Such a community-based effort can help researchers better identify valid experimental results.

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