Mouse social behavior can reveal genetic links to disease and early signs of neuropsychiatric disorders.

TRACKING MOUSE BEHAVIOR REVEALS NEW DISEASE CLUES

AUTOMATED MONITORING of unstressed mice yields new insights and reproducible results.

Brun Ulfhake spent decades studying aging in mice before he discovered a treasure trove of new data, one that many researchers overlook.

Until this trove became available, researchers had a hard time obtaining reliable data on how animals scamper, sleep, eat, and otherwise act naturally. Lab mice scare easily when they're handled and moved, especially during the day when mice, naturally nocturnal creatures, would normally be resting. This stress alters behavior in unpredictable ways, which has often made it impossible to tell whether an animal's altered behavior was due to a disease, drug or other intervention, or to frazzled nerves.

"We have this reproducibility problem when it comes to animal behaviors," says Ulfhake, a senior professor of laboratory medicine at Stockholm's Karolinska Institute. Irreproducible results also made it difficult to investigate long-term behavior patterns, such as changes in sleep-wake cycles. "Before, we had just glimpses of their behaviors," Ulfhake says.

To overcome these problems, researchers are turning more to automated systems that monitor mice in their home cages, where they are least stressed. This improves the animals' welfare, offers more reliable measurements of normal behavior, and makes it easier to spot deviations that signal disease onset, progression, or recovery, says Joanna Moore, an investigator and information officer for GlaxoSmithKline (GSK), whose work is focused on maximizing animal welfare in the company's medicine research. "For reproducibility, whatever's best for the animal is best for the science, too."

Keeping Close Tabs

For decades, lab mice were kept in shoebox-sized home cages, and then temporarily transferred to other cages for tests and behavioral observations. But as scientists developed more genetically modified mouse strains in the 1990s to model human diseases and brain disorders, they struggled to reproduce phenotyping studies, which discern how genetic changes in animals affect their physiology and behavior.

In response, several companies developed automated home-cage monitoring platforms. Some used infrared sensors to detect when mice ate or drank. Others monitored movements with infrared beam-break set-ups akin to building security systems, or used video cameras to record their behaviors. These measurements led to important discoveries on the links between disease and behavior. Researchers found that reduced activity signaled Autism Spectrum Disorder,[1] that pups of nicotine-exposed mothers faced an increased risk of ADHD,[2] and that social withdrawal was an early warning sign of neuropsychiatric disorders.[3]

But as automated cages grew more sophisticated, they also grew bigger and more expensive, making it difficult to scale up and monitor scores of animals in large, statistically powerful studies. This limitation in turn fueled demand for smaller, affordable and scalable automated cages.

In response, Tecniplast, an Italian company that specializes in automated mouse cages, introduced the Digital Ventilated Cage (DVC®). Unlike earlier systems with video cameras that produced so much data that they were difficult to scale, the DVC® uses a grid of 12 electromagnetic sensors underneath each cage that monitor mice round the clock. This produces less data than a video system, which reduces the data storage space needed, and it collects a comparable amount of information, including how far a mouse has traveled, its average speed, and where in the cage it spends most of its time, says Guido Gottardo, DVC® Product Manager at Tecniplast.

Beyond these baseline measures of mouse movement, today researchers can use a growing selection of add-on features to collect more revealing data. They can now program lighting in cages, as opposed to entire rooms, thereby controlling what individual mice experience as night and day. They can use a tool like the DVC® to monitor spontaneous movement, or use

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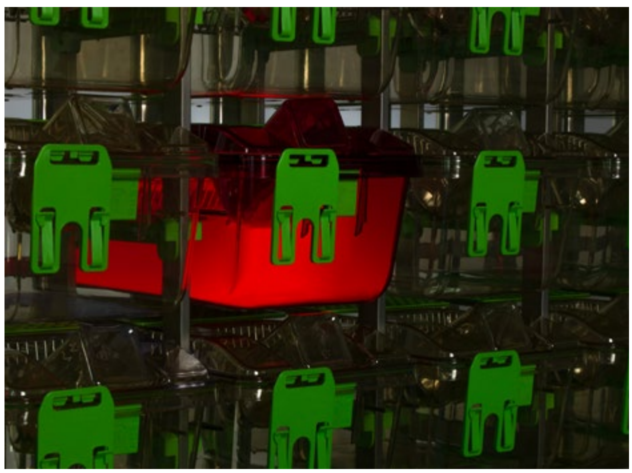
cage wheels that count rotations to track voluntary movement — an often-used model for an active lifestyle in humans. They can track how mice respond to altered eating and sleeping schedules and what affects their memory. Soon they'll be able to follow individual mice as they spontaneously explore and socialize, using a system of tubes called the Interlink that connect cages and have antennae to track RFID-tagged mice, according to Ulfhake, who is collaborating with Tecniplast on this new feature.

The rhythm of disease

With access to 24/7 behavioral data, researchers can monitor the rhythms of normal and diseased mice to gain clues to their health status. At Munich's Helmholtz Diabetes Center, for example, postdoctoral researcher Kenneth Dyar follows patterns of mouse activity and rest to learn how circadian clock disruptions raise the risk of metabolic diseases such as type 2 diabetes.

To understand how the central body clock in the brain and peripheral body clocks in organs and tissues affect metabolism, Dyar compared mice with and without a gene required for the skeletal muscle circadian clock. "Just based on their activity patterns, we can determine if they have some kind of deficit in their clock mechanism," he says.

When Dyar used a beam-break tracking system[4] and surgically implanted telemetry sensors[5] to record the home-cage behavior of the transgenic mice, along monitoring metabolite levels in the blood and tissues, the experiments offered tantalizing results. Unlike mice with a faulty central body clock, which move less than normal mice and in ways that are uncoupled with normal circadian rhythms, mice with a defective muscle clock were no different than normal mice in their overall activity levels or rhythm of activity. But they did have less fat, suggesting that they had adapted to their genetic defect by changing their metabolism to pick up the metabolic slack.



TECNIPLAST

Programmable lighting like Tecniplast's Leddy lets scientists control each mouse's experience of night and day.

More recently, Dyar's group has been digging into the reasons why restricting the food intake of mice can alter metabolism in ways that increase longevity. Because hungry mice will also move more to search for food, Dyar and his team are using a DVC® tracking system to sort out the effects of diet from those of activity changes. "To tease out these types of influences, you have to monitor not only when they're eating, but also when they're moving and how much they're moving," he said.

Libraries of behavior

Since turning to automated home cage monitoring, Ulfhake has used the DVC® system to catalogue how mouse behavior changes as the animals age. By tracking the routine habits of hundreds of mice round the clock for more than 700 days — about the entire mouse lifespan — he found, in unpublished work, that activity declined in old age, as expected. But Ulfhake also discovered weekly and seasonal variations in normal behavior, and he found that male mice took longer than females to act normally after cage cleanings and other routine disturbances.

By using automated cages to observe enough mice, and a large enough variety of mice, researchers could collaborate to build libraries of expected mouse behaviors, sorted by genetic strain, sex and age. This library could provide virtual control groups for future studies, Ulfhake says.

Virtual controls or not, more researchers than ever before are using cage-monitoring systems to monitor behavior. And within a decade, Ulfhake predicts, automated monitoring could make undisturbed home cage environments the primary location for nearly every mouse study. ■

To learn more about Tecniplast's Digital Ventilated Cage (DVC®) system, click here.

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