Scientists mimic natural conditions in the lab to more accurately test stress

August 26 2013, by Seth Palmer

Lauren Chaby handling lab rats. Credit: Seth Palmer

(Medical Xpress)—With a unique focus on methodology, Huck Institutes researchers studying rat behavior show that chronic, unpredictable stress during adolescence causes long-term changes in cognitive bias and coping response.

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Events of adolescence can change individuals in dramatic ways that persist well into adulthood, according to a study by Penn State researchers, who used rats as a model for investigating long-term effects of stress.

"The results of our study suggest that exposure to chronic, unpredictable stress during adolescence leads individuals to respond more negatively and impulsively to letdown and ambiguity as adults," says Victoria Braithwaite, professor of fisheries and biology and co-director of the Center for Brain, Behavior and Cognition, part of the Huck Institutes of the Life Sciences.

A team led by Braithwaite and graduate student Lauren Chaby recently published their results in the journal *Frontiers in Human Neuroscience*.

"Even though we've only done this work with rats, it's still interesting as it shows that stress during the really vulnerable stage of adolescence can have a huge long-term impact," Braithwaite says. "Lots of people have looked at the short-term consequences, but very few have followed them through to adulthood and seen these effects."

Naturalistic design

Animal models play a crucial role in our understanding of human biology, and the validity of conclusions drawn from studying these models is highly dependent on scientists' developing appropriate, accurate paradigms through conscientious methodology. This is especially true for studies of animals' cognition and behavior, where such due diligence is critical in avoiding anthropomorphic bias.

Braithwaite and Chaby stress the importance of designing studies naturalistically to avoid distorting their results.

"Some of the stuff we're trying to get at here is quite complicated—we're basically trying to peer into the mind of the animal—and so we've got to ask the animal questions in ways that it can understand what the question is," Braithwaite explains. "It can be really difficult getting at that. Interestingly, some of our more successful tests have ended up using simple things that the animals are naturally doing and that we can easily measure. But when we're looking at choice behavior—how the animals are choosing to do one thing or the other—that gets more complicated, and we have to be quite careful how we set that up and interpret the results."

Researchers must consider such factors as variation in predation pressure and variability of the environment, and develop a lab model that can mimic them.

"It's how we got the idea for this study of using multiple stressors—both social and physical—which makes this study different from a lot of others, since most labs tend to concentrate on one or the other," Braithwaite explains.

Chaby, the lead author of the paper and a dual-degree candidate under Braithwaite's mentorship in the Huck Institutes' ecology and neuroscience graduate programs, thinks about experimental design in terms of the rodent's natural life cycle.

"We try to mimic relatively realistic circumstances that you could imagine a rat encountering, which is difficult," she says. "This isn't always done in other studies, and it's another aspect that makes this study unique."

The researchers used such physical and social stressors as damp or foreign bedding, crowding and other stimuli that rats are likely to come across naturally.

Laboratory ecology

Braithwaite and Chaby have also observed a relationship between naturalistic laboratory ecology and quality data, where environmental complexity and social interplay—both among the animals, themselves, and between the animals and the researchers—can have a significant affect.

"While the natural world varies, these lab animals are often put in constant, homogeneous conditions—the most mundane, boring environment you can imagine—and then tested as though they will truly reflect the way that people might behave given lots of change and variation," Braithwaite says. "There's a mismatch there, and even though we're using domesticated strains of lab rodents, I think that in many of those cases you've got animals that aren't behaving in the way they've been selected to do in a natural environment."

As a direct result of this line of thinking, the animals, upon delivery to the lab, are paired in object-enriched environments and given time to explore and adjust to their new surroundings before any tests are initiated.

"A social partner gives these animals a certain amount of stimulation," Braithwaite notes, "but even then, it's important to have enrichment items in the cages—something for them to do, something to chew on or play with, a tube to hide in and run in and out of—to help keep them occupied. We know that these sorts of things promote neural growth in key areas of the brain that are important for decision-making and even cognitive bias, so providing these enrichment items makes a big difference that can affect your results: the behaviors you see from these animals are going to be more robust and more reliable."

Chaby explains that enrichment also affects physiological measures.

"It's been shown that even basic enrichment can change the structural representation of the forepaw in the brain of a rodent," she says, "so when you're talking about sensory capacity and acuity, these things can differ depending on the amount of enrichment and stimulation an animal was exposed to during its development."

Leading up to and through the course of a given study, the researchers make a point of interacting frequently with the animals for further socialization and to help them acclimate to the goings-on of the lab.

"We handle the animals regularly," says Braithwaite, "because we've found that the more they're handled, the more they become used to us and to the experimental paradigms and setups. If they're not handled very much, they find anything new to be stressful and they don't learn things very well."

Results and follow-up

To minimize the influence of any unintended stressors on their results, the researchers allowed a week for the animals' socialization and acclimation after their delivery to the lab and prior to the stress phase, which lasted 40 days—until the onset of adulthood—and was followed by nearly two months of normal, stressor-less conditions before the final tests.

"All the tests of cognitive bias and impulsivity were done after about two months of the test animals' being back on standard conditions," Braithwaite says, "so that they were just like the control animals during that phase, doing what rats normally do in a lab. We wanted to be absolutely sure that any effects we observed during the testing phase were associated solely with the stressors from the adolescent phase, which really is important because this shows that what's happening during adolescence—during that sensitive developmental phase—has

long lasting effects.

"In the end, we were surprised that it had as big of an impact as it did over so many different tests—the differences we were able to detect in terms of things like the animals' emotional state, how sensitive it was to not getting an expected reward, and whether it had a more negative interpretation of ambiguous situations."

Braithwaite and Chaby plan to continue their current investigations, but with an additional focus on neural connectivity, which may help them to explain the physiology underlying the behaviors they've observed.

"The speed with which the animals corrected the wrong choice is much faster in those animals that have had this chronic, unpredictable stress," says Braithwaite. "We think that this could be an indication of impulsivity, and there are a number of mechanisms that might underpin that."

Chaby points out that adolescence is a period when people typically exhibit a high level of impulsivity. "If we're seeing a scenario where impulsivity is retained into adulthood, then this could have serious consequences for risk-seeking and other behaviors that can potentially be detrimental to the welfare of an animal or a human being," she says. "We're interested in looking in more detail at what's happening with impulsivity—what types of impulsivity might be affected and what kind of an impact increased impulsivity may have on other behaviors."

More information: www.frontiersin.org/Human_Neur …
.2013.00328/abstract

Provided by Pennsylvania State University