Making monkeys just to suffer: Is new autism model ethical?

Chinese scientists at the Shanghai Institutes for Biological Sciences created a stir in February 2016, when they used genetic modification to give monkeys a form of autism called Rett* syndrome. These modified monkeys showed social anxiety and repetitious behaviors. The impetus for creating this model was the belief among scientists that autism must be studied in more advanced animals than mice.

But other researchers warned that creating animals specifically to suffer was unethical. Others have suggested the transgenic monkeys were not close enough to human autism to warrant the experiments.

Most basic research starts with experiments with mice, even with complex human psychiatric conditions like schizophrenia and autism. But mice are a lot different than humans. They develop quickly, over just a few months, and this condensed time scale makes it difficult to properly observe a complex disease develop. Mice have less developed social networks and they have a limited behavioral repertoire: eat, sleep, clean oneself, maybe run on a wheel. So there is inarguably a desire in the research community to develop better models in different animals to study conditions with social components like autism, as Pam Bellock explained in the *New York Times*:

> Though mice engineered with other genes have developed some autism-like behaviors, the complexity and variability of autism are difficult to study in those less-advanced animals. “Mice are not in the same league when you’re talking about doing models of social cognition and interaction,” said Jonathan Sebat, chief of the Beyster Center of Psychiatric Genomics at the University of California San Diego, who was not involved in the monkey research. “They’re not even close.”

And so, the Shanghai team introduced repeating copies of the human *MECP2* gene into macaque embryos. Duplicates of this gene are found in 90 percent of people with Rett syndrome, an extremely rare condition that causes autism-like symptoms especially in women. They then transferred the embryos to a pregnant female and let them develop.

Most of the monkey embryos did not survive to birth. Those that did showed behaviors that the researchers called autism-like. They repetitively circled their cages, even jumping over other animals in their paths. They didn’t groom other group members as often as monkeys without the human gene copies, an important part of social bonding within macaque communities. And the transgenic monkeys became more scared and agitated on stress and threat tests.

But there are at minimum of 50 gene variants that have been robustly associated with autism so far. The *MECP2* duplications the Chinese researchers used in this study represent a tiny part of the puzzle. And the transgenic monkeys might not be accurately reflecting what’s happening in the human brain as Tanya Lewis reports at Business Insider:

> Huda Zoghbi, a professor at Baylor College of Medicine who was not involved with the study

> but who has studied the MeCP2 duplication syndrome in mice, told Business Insider we should be cautious about calling these transgenic monkeys a true model for the disorder, however, because the genes they modified didn't exactly mirror the effects of the human version of the disease, such as cognitive problems and seizures. "We need to develop criteria before generating a non-human primate model so that the model is as optimal as possible and it can be useful for preclinical research," Zoghbi said.

Others bioethicists worry that creating animals to suffer is unethical, especially when those animals are so genetically similar to us. From Gizmodo:

> What's concerning about this particular study is that the researchers assessed anxiety levels by frightening the monkeys in various ways, and then monitoring the intensity of their shrieks and screams. "Clearly from our own human moral perspective we have harmed them by the very rules we use to define what makes us human and worthy of elevated moral status," said [University of Toronto bioethicist Kerry] Bowman. "In turn, as an ethical construct, the more social and cognitive capacities primates possess, the greater our obligations to them. Creating social impairment and anxiety in a primate is clearly a highly significant harm."

A simian model of Huntington's disease had been created, but that case is a little simpler. Huntington's disease is caused by defaults in just one, well studied gene. The genetics of autism is far from that level of clarity. It may be worth waiting for a clearer understanding before we use genetic modification to develop these autism models in higher order mammals.

The Chinese scientists say they will look to find the faulty neurological circuits that underly the repetitive behaviors and social disorders in their transgenic monkeys. Identifying that circuitry would provide valuable information to autism researchers as long as they translate to the condition in humans. But some doubt this connection, explains Sam Wong at New Scientist:

> The idea that all conditions that involve autistic features must have the same underlying brain circuitry is also contentious. The human brain has evolved to allow us to become a very social animal, so it's possible that changes in a wide range of pathways can lead to altered social communication. "Expecting to find a single biological pathway that functions abnormally and leads to autistic symptomatology is in my opinion naive and untrue," says [University College London autism expert David] Skuse.

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3/28/16: We corrected a misspelling of Rett Syndrome in the story.