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Mice Inherit the Fears of Their Fathers

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6–7 minutes

- Science
- Only Human

UPDATE (12/1, 2:37pm): This study was just published in Nature Neuroscience; you can read all of the juicy details here.

UPDATE (11/17, 11:22 am): I just published a new post showing how scientists reacted to this study on Twitter, with comments ranging from "awe-inspiring biology" to "deep skepticism."

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There's no question that trauma gets handed down from one generation to the next.

In one highly publicized example, researchers in New York studied several dozen women who were pregnant on September 11, 2001, and had been in the vicinity of the terrorist attacks. Some of these women developed post-traumatic stress disorder (PTSD), and this group shows lower levels of the stress hormone cortisol in their saliva than do those who did not develop PTSD. But here's the rub: At 9 months old, the *babies* of the women with PTSD have significantly lower cortisol levels than babies of healthy mothers.

In earlier work, the same researchers had reported low cortisol levels in adult children of Holocaust survivors with PTSD. And in yet another study, Kerry Ressler's group at Emory University showed that the so-called "startle response" to a sudden stimulus — a marker of anxiety — is more pronounced in kids whose mothers were physically abused as children then in those whose mothers were not abused. I could go on.

But how, exactly, does a parent's stress leave such a deep impression on its progeny?

Part of it is nurture. A parent's sadness and stress naturally affects how they interact with other people, including their children. The Holocaust study, in fact, found that the survivors with PTSD tended to emotionally abuse or neglect their children. And we know from some remarkable experiments in rats that parental care affects the offspring's genes: Rat pups that get a lot of licking and grooming from their mothers show distinct changes in their epigenome, the chemical markers that attach to DNA and can turn genes on and off. Neglected pups, in contrast, don't show these epigenetic tweaks.

Now a fascinating new study reveals that it's not just nurture. Traumatic experiences can actually work themselves into the germ line. When a male mouse becomes afraid of a specific smell, this fear is somehow transmitted into his sperm, the study found. His pups will also be afraid of the odor, and will pass that fear down to their pups.

"Parents transfer information to their offspring, and they do so even before the offspring are conceived," said Brian Dias, a postdoctoral fellow in Ressler's lab, at an engaging talk about this unpublished data on Tuesday at the Society for Neuroscience meeting in San Diego.

And why, evolutionarily, would a parent pass down such specific information? "So that when the offspring, or descending generations, encounter that environment later in life, they'll know how to behave appropriately," Dias said.

The researchers made the mice afraid of certain odors by pairing them with a mild shock to the foot. In a study published a few years ago, Ressler had shown that this type of fear learning is specific: Mice trained to fear one particular smell show an increased startle to that odor but not others. What's more, this fear learning changes the organization of neurons in the animal's nose, leading to more cells that are sensitive to that particular smell.

Dias trained mice to fear acetophenone — which, according to this chemist, smells "like orange blossom with a bit of artificial cherry" — over three days, then waited 10 days and allowed the animals to mate. The offspring (known as the F1 generation) show an increased startle to acetophenone (with no shock) even though they have never encountered the smell before. And their reaction is specific: They do not startle to a different odor, propanol (which smells like alcohol). What's more, the researchers found the same thing in the F1 generation's offspring (known as F2).

The scientists also looked at the F1 and F2 animals' brains. When the grandparent generation is trained to fear acetophenone, the F1 and F2 generations have more "M71 neurons" in their noses, Dias said. These cells contain a receptor that detects acetophenone. Their brains also have larger "M71 glomeruli," a region of the olfactory bulb that responds to this smell. "Like father like son, we're getting some ancestral information," Dias said. "But how is that occurring?"

His team performed an *in vitro* fertilization (IVF) experiment in which they trained animals to fear acetophenone and then 10 days later harvested their sperm. They sent the sperm to another lab across campus where it was used to artificially inseminate female mice. Then the researchers looked at the brains of the offspring. "What is striking is that the neuroanatomical results still persist after IVF," Dias said. "There's something in the sperm."

I've been to a lot of scientific talks. The excitement around this one was notable, with many scientists whispering about it in the room and more loudly buzzing in the hallways outside.

But I know what you're wondering. It was the first question that Dias received from the audience after the talk: "Do you have any idea of how this information being stored in the brain is being transmitted to the gonads?" the questioner asked.

The short answer is that the researchers don't have any idea, though they've thought about several possible explanations. Apparently a study in cats and pigeons showed that after smelling an odor, the odorant receptor molecules can get into the blood stream, and other studies have reported odorant receptors on sperm. So maybe the odor molecules get into the bloodstream and make their way to sperm. Another possibility is that microRNAs — tiny RNA molecules involved in gene expression — get into the bloodstream and deliver odor information to sperm.

For now, though, Dias said, "those are two science-fiction hypotheses."

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Read more about Ressler's work in a feature on stress and resilience that I wrote for Nature *last year.*