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# Grandma's Experiences Leave a Mark on Your Genes

Your ancestors' lousy childhoods or excellent adventures might change your personality, bequeathing anxiety or resilience by altering the epigenetic expressions of genes in the brain.

By Dan Hurley | Tuesday, June 11, 2013

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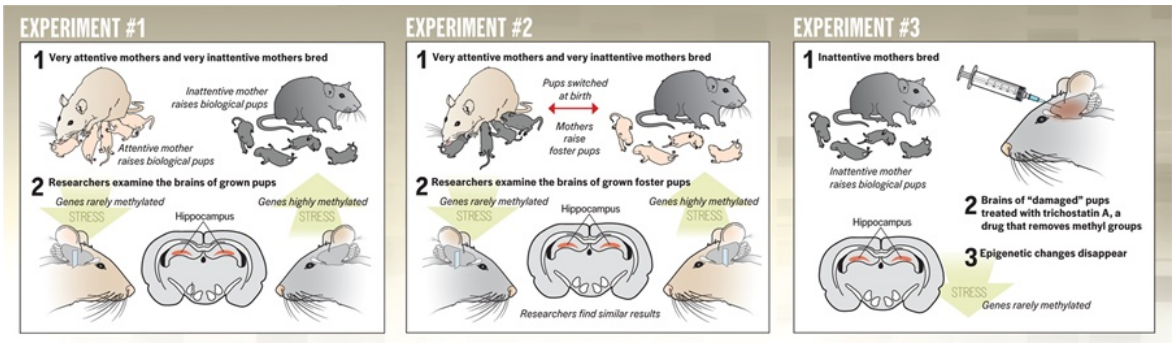


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Despite such seemingly overwhelming evidence, when the pair wrote it all up in a paper, one of the reviewers at a top science journal refused to believe it, stating he had never before seen evidence that a mother's behavior could cause epigenetic change.

"Of course he hadn't," Szyf says. "We wouldn't have bothered to report the study if it had already been proved."

In the end, their landmark paper, "Epigenetic programming by maternal behavior," was published in June 2004 in the journal *Nature Neuroscience*.

Meaney and Szyf had proved something incredible. Call it postnatal inheritance: With no changes to their genetic code, the baby rats nonetheless gained genetic attachments due solely to their upbringing — *epi*genetic additions of methyl groups sticking like umbrellas out the elevator doors of their histones, gumming up the works and altering the function of the brain.

## The Beat Goes On

Together, Meaney and Szyf have gone on to publish some two-dozen papers, finding evidence along the way of epigenetic changes to many other genes active in the brain. Perhaps most significantly, in a study led by Frances Champagne — then a graduate student in Meaney's lab, now an associate professor with

her own lab at Columbia University in New York — they found that inattentive mothering in rodents causes methylation of the genes for estrogen receptors in the brain. When those babies grow up, the resulting decrease of estrogen receptors makes them less attentive to *their* babies. And so the beat goes on.

As animal experiments continue apace, Szyf and Meaney have entered into the next great step in the study of behavioral epigenetics: human studies. In a 2008 paper, they compared the brains of people who had committed suicide with the brains of people who had died suddenly of factors other than suicide. They found excess methylation of genes in the suicide brains' hippocampus, a region critical to memory acquisition and stress response. If the suicide victims had been abused as children, they found, their brains were more methylated.

Why can't your friend "just get over" her upbringing by an angry, distant mother? Why can't she "just snap out of it"? The reason may well be due to methyl groups that were added in childhood to genes in her brain, thereby handcuffing her mood to feelings of fear and despair.

Of course, it is generally not possible to sample the brains of living people. But examining blood samples in humans is routine, and Szyf has gone searching there for markers of epigenetic methylation. Sure enough, in 2011 he reported on a genome-wide analysis of blood samples taken from 40 men who participated in a British study of people born in England in 1958.

All the men had been at a socioeconomic extreme, either very rich or very poor, at some point in their lives ranging from early childhood to mid-adulthood. In all, Szyf analyzed the methylation state of about 20,000 genes. Of these, 6,176 genes varied significantly based on poverty or wealth. Most striking, however, was the finding that genes were more than twice as likely to show methylation changes based on family income during early childhood versus economic status as adults.

Timing, in other words, matters. Your parents winning the lottery or going bankrupt when you're 2 years old will likely affect the epigenome of your brain, and your resulting emotional tendencies, far more strongly than whatever fortune finds you in middle age.

Last year, Szyf and researchers from Yale University published another study of human blood samples, comparing 14 children raised in Russian orphanages with 14 other Russian children raised by their biological parents. They found far more methylation in the orphans' genes, including many that play an important role in neural communication and brain development and function.

"Our study shows that the early stress of separation from a biological parent impacts long-term programming of genome function; this might explain why adopted children may be particularly vulnerable to harsh parenting in terms of their physical and mental health," said Szyf's co-author, psychologist Elena Grigorenko of the Child Study Center at Yale. "Parenting adopted children might require much more nurturing care to reverse these changes in genome regulation."

Alison Mackey/DISCOVER

A case study in the epigenetic effects of upbringing in humans can be seen in the life of Szyf's and Meaney's onetime collaborator, Frances Champagne. "My mom studied prolactin, a hormone involved in maternal behavior. She was a driving force in encouraging me to go into science," she recalls. Now a leading figure in the study of maternal influence, Champagne just had her first child, a daughter. And epigenetic research has taught her something not found in the *What to Expect* books or even her mother's former lab.

"The thing I've gained from the work I do is that stress is a big suppressor of maternal behavior," she says. "We see it in the animal studies, and it's true in humans. So the best thing you can do is not to worry all the time about whether you're doing the right thing. Keeping the stress level down is the most important thing. And tactile interaction — that's certainly what the good mother rats are doing with their babies. That sensory input, the touching, is so important for the developing brain."

**The Mark Of Cain**

The message that a mother's love can make all the difference in a child's life is nothing new. But the ability of epigenetic change to persist across generations remains the subject of debate. Is methylation transmitted directly through the fertilized egg, or is each infant born pure, a methylated virgin, with the attachments of methyl groups slathered on solely by parents after birth?

Neuroscientist Eric Nestler of the Icahn School of Medicine at Mount Sinai in New York has been seeking an answer for years. In one study, he exposed male mice to 10 days of bullying by larger, more aggressive mice. At the end of the experiment, the bullied mice were socially withdrawn.

To test whether such effects could be transmitted to the next generation, Nestler took another group of bullied mice and bred them with females, but kept them from ever meeting their offspring.

Despite having no contact with their depressed fathers, the offspring grew up to be hypersensitive to stress. “It was not a subtle effect; the offspring were dramatically more susceptible to developing signs of depression,” he says.

In further testing, Nestler took sperm from defeated males and impregnated females through in vitro fertilization. The offspring did not show most of the behavioral abnormalities, suggesting that epigenetic transmission may not be at the root. Instead, Nestler proposes, “the female might know she had sex with a loser. She knows it’s a tainted male she had sex with, so she cares for her pups differently,” accounting for the results.

Despite his findings, no consensus has yet emerged. The latest evidence, published in the Jan. 25 issue of the journal *Science*, suggests that epigenetic changes in mice are usually erased, but not always. The erasure is imperfect, and sometimes the affected genes may make it through to the next generation, setting the stage for transmission of the altered traits in descendants as well.

Alison Mackey/DISCOVER

**What’s Next?**

The studies keep piling on. One line of research traces memory loss in old age to epigenetic alterations in brain neurons. Another connects post-traumatic stress disorder to methylation of the gene coding for neurotrophic factor, a protein that regulates the growth of neurons in the brain.

If it is true that epigenetic changes to genes active in certain regions of the brain underlie our emotional and intellectual intelligence — our tendency to be calm or fearful, our ability to learn or to forget — then the question arises: Why can’t we just take a drug to rinse away the unwanted methyl groups like a bar of epigenetic Irish Spring?

The hunt is on. Giant pharmaceutical and smaller biotech firms are searching for epigenetic compounds to boost learning and memory. It has been lost on no one that epigenetic medications might succeed in treating depression, anxiety and post-traumatic stress disorder where today’s psychiatric drugs have failed.

But it is going to be a leap. How could we be sure that epigenetic drugs would scrub clean only the dangerous marks, leaving beneficial — perhaps essential — methyl groups intact? And what if we could create a pill potent enough to wipe clean the epigenetic slate of all that history wrote? If such a pill could free the genes within your brain of the epigenetic detritus left by all the wars, the rapes, the abandonments and cheated childhoods of your ancestors, would you take it?