Volume 23 | Issue 8 | Page 18
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Reprints | Issue Contents

By Elie Dolgin

Epigenetic suicide note

Epigenetic patterns in this brain could reveal suicidal tendencies.

Courtesy of the Douglas Mental Health University Institute. Photo by Raja Ouali, Bivouac Studio, 2008

Recently, Moshe Szyf, a McGill University epigeneticist, performed a series of experiments indicating that chemical marks on people's brain cells can reveal suicidal tendencies long before these people consider taking their own lives.

To start, Szyf and his colleague Michael Meaney compared two types of rats: those that received frequent licking and grooming as pups, and those that had been neglected as newborns by their deadbeat moms. Motherly love, they found, altered DNA methylation levels in the regulatory regions of the glucocorticoid receptor (GR) gene in the brains of young rats. These epigenetic changes, in turn, affected the regulation of stress hormone levels into adulthood, such that licked pups matured into calmer adults than their less-groomed, jittery counterparts (*Nat Neurosci*, 7:847–54, 2004).

Szyf had discovered a way in which the early environment stably altered the genome for the rest of a rat's life. "The question was," he says, "is this relevant [for humans]? And the only way to know if it's relevant is to look at human material." Fortunately, his colleagues across town at the Douglas Mental Health Institute (DMHI) kept just the perfect material.

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In 2005, Szyf and Meaney teamed up with Gustavo Turecki, director of the DMHI's Quebec Suicide Brain Bank, a repository of brains from hundreds of suicide victims, complete with medical records and postmortem interviews with friends and family members. These detailed records allowed the researchers to reconstruct the victims' personal histories, including whether they had been abused or neglected as children—the human equivalent of not getting licked and groomed. To test whether early childhood adversity left an epigenetic mark on the brain, the McGill team then compared cells from suicidal brains with those taken from people who died randomly in car crashes or other accidents.

First, the researchers investigated genes encoding ribosomal RNA because Szyf had already linked expression patterns with DNA methylation levels at these genes' promoter regions in cell cultures (*Mol Cell Biol*, 27:4938–52, 2007). Szyf and his coauthors applied the exact same primers to the human brain tissues, and found that suicidal brains had highly methylated—and, thus, inactive—

rRNA genes. What's more, the epigenetic differences between suicidal and healthy brains were manifested only in the hippocampus, the epicenter of stress hormone regulation, but not in the cerebellum, which directs motor control (*PLoS ONE*, 3:e2085, 2008).

The results suggested that early childhood adversity was leaving a specific epigenetic mark on people who ultimately killed themselves, but the researchers couldn't rule out other confounding life factors associated with suicide, such as depression or substance abuse. So, to tease apart the source of the environmental hardship, Szyf's team then compared the brains of suicide victims who were abused as children with those who were not.

This time, instead of the rRNA locus, for logistical reasons the researchers returned to the GR gene, which is known to be hyperactive in people with major depression and which Szyf had already implicated in the rat studies of maternal care. "It's the first suspect you would look at if you thought that epigenetics played a role in suicide," Szyf says. Abused suicide victims indeed had significantly different methylation patterns in their hippocampi from both nonabused suicide victims and those who died suddenly in accidents, and these differences were linked with reduced GR expression (*Nat Neurosci*, 12:342–48, 2009). The other perfect control—brains from abused people who didn't commit suicide—were not available because these people don't generally die of unnatural causes. As for the nonabused suicide victims, "they committed suicide so there must be a reason, but we can't pinpoint it," says Szyf.

"Psychiatry has been in search of causative mechanisms of mental illness for many, many decades without finding any concrete clear evidence," says Turecki. "[These findings] open the door to the development of treatment intervention and eventually prevention as well."

These suicidal brain studies provide an "important signpost," says Ezra Susser, an epidemiologist and psychiatrist at New York's Columbia University. "This is exactly the direction we have to go."

Szyf is now testing whether social adversity also leaves a chemical mark on T cells, since there is extensive crosstalk between the immune system and brain signaling. The goal is to identify markers that signal someone is at risk of suicide in nonbrain tissue (because once you have brain tissue, the patient is already dead). "Once this is possible it will change social studies forever," Szyf says.

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Comment on this article

Broad generalisations - futher investigation needed!
by Kanchana Pathirana

[Comment posted 2009-09-01 19:24:27]
Firstly, congradulations McGill team on your research. The findings are interesting and certainly do have some important implications in terms of future research for developing an understanding of the biological mechanisms of abuse and possible suicidal tendancies.

Perhaps my following comments are not a reflection upon the study itself but how we communicate our findings to the scientific community/public and how the media twists scientific findings to meet their own agendas.

I agree with previous comments in regards to the complex nature of the human body/mind and how one single atribute can not be a sole precursor for deciding diagnosis or treatment pathways. Though it is certainly exciting findings, as scientists one has to be critical of certain generalised statements made such as the following:
- ?This is exactly the direction we have to go.?
- 'The goal is to identify markers that signal someone is at risk of suicide in nonbrain tissue (because once you have brain tissue, the patient is already dead). ?Once this is possible it will change social studies forever,?'
That rule out any other avenues of investigation or associations (not causality - as this article does not conclusively illustrate causality).

As far as I am aware, this is the 1st study that was conducted with human brains in regards to activity of rRNA and GR gene expression and it's relationship (not causality) to suicidal tendancies. The analysis was done post suicide, longitudinal analyses has not yet been conducted, and as Doug pointed out the findings are more about abused pathology rather than suicide/suicidal tendencies. Surely further studies are required prior to making such broad claims that this will lead to diagnosis, treatment and eventually prevention. One can not simply give a pill and make it all go away! Treatment and prevention needs to be multifaceted for long term benefits - especially when dealing with a topic such as suicide, which the research world (including psychiatry) has not been able to get a comprehensive understanding of.

Saying that, I think this research is a first in understanding the adult epigenetics of people with abused childhoods and I look forward to future research in this area. I would be curious to find whether there is a possible linkage of the abused biological mechanisms/epigenetics that predisposes individuals for suicidal tendencies, but much more work is needed before we even try to attempt to answer that question!

Thank you

.The data beg an explanation.
by Douglas Easton

[Comment posted 2009-09-01 09:18:22]
I think the point of the research is not to predict who might be suicidal; rather the researchers are getting a toe hold on one aspect of the molecular biology underlying some cases of suicide.
Actually I find it surprising that such an important gene or set of genes as rRNA genes would be underexpressed. Obvious questions are; are there fewer ribosomes in the hippocampal neurons in abused animals? Does this affect the rate of protein synthesis in the neurons? Eventually this research may lead to a better understanding of the pathology induced by abuse.

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psycological view
by ANKIT SHROFF

[Comment posted 2009-09-01 00:17:38]
the article opens doors for more questions like "whether there is difference in perceiving a particular situation by those who have different epigenetics of the neurons of the brain?"

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diagnosis will be not effective
by andrew silvanus

[Comment posted 2009-08-31 23:48:38]
suicidal cases don't have a single reason to commiit suicide .there are other cofactors that turn around them totally.saying "physical abuse" or "mothers love "is totally unacceptable.

The future of healthcare
by anonymous poster

[Comment posted 2009-08-31 16:48:37]
Unfortunately, as science marches forward the ever growing question arises regarding "managed health care" not only in this country, but worldwide.

We will know so much about our physical and mental future there won't be an insurance company out there that will cover us.

Blood samples, cord blood at birth, routine exams - all will disclose so much of our biological fingerprint are we doomed as a society to use this information as a means to exclude those with such markers from existence?

Here is a clue
by John Norton

[Comment posted 2009-08-31 16:34:19]
Let's see, "The goal is to identify markers that signal someone is at risk of suicide.."

How about asking: "Were you abused? Do you destructively self-medicate? Are you deeply unhappy and unwilling to remain alive?"

Can you imagine the day when someone will exclaim, "I'm sure glad I had that genomics test! Otherwise, I never would have known that I was so unhappy!"

How to diagnose?
by Ranjith Pathirana

[Comment posted 2009-08-31 15:59:24]
I would have liked to see an account on how these brain changes can be diagnosed in living people with depression.

The scientists have found these epigenetic changes in the brain cells, obviously after suicide. For diagnosing and cure one should be able to take a sample of blood, urine etc and analyse for the presence of any changes. Can anyone in the field of medical diagnosis suggest how this can be done? Any links to brain changes in other body parts?
Thanks
Ranjith Pathirana
Senior Scientist

Why Blame Mom?
by Cheryl Soehl

[Comment posted 2009-08-31 14:55:52]
It's careless to reference mothers as the only source of childhood adversity. The biggest stress risk factor for mothers and children is an abusive father in the home. Children who simply witness abuse of one parent by the other will have structural brain changes. Mothers who are stressed by abuse will have stressed children and be more prone to abuse as well.

If you're going to talk about non-nurturing mothers, give equal time to cruel and abusive fathers and father surrogates...

C. Soehl
Certified Rehabilitation Counselor

Thank you!
by Christina Sponias

[Comment posted 2009-08-31 13:09:47]
Thank you for this great article! This is really valuable information!

The truth is that there is really too much absurdity inside the human brain, and it is inherited.

On the other hand, the emotional balance of any creature depends basically on affection. So, the social factor is also very important: the present experience, the contact with the external world, their parents, and the personal characteristics of everyone.

I believe that it is obvious that only love can bring mental health and happiness to the human being, but humanity is so far from this simple truth, that each 40 seconds someone commits suicide on Earth.

I truly hope that these brilliant scientists will really discover a way to prevent all suicidal attempts.

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