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The New Genetics *of* Mental Illness

Life's experiences add molecular switches to the genes that control our brain activity, affecting how susceptible we are to depression, anxiety and drug addiction

By Edmund S. Higgins

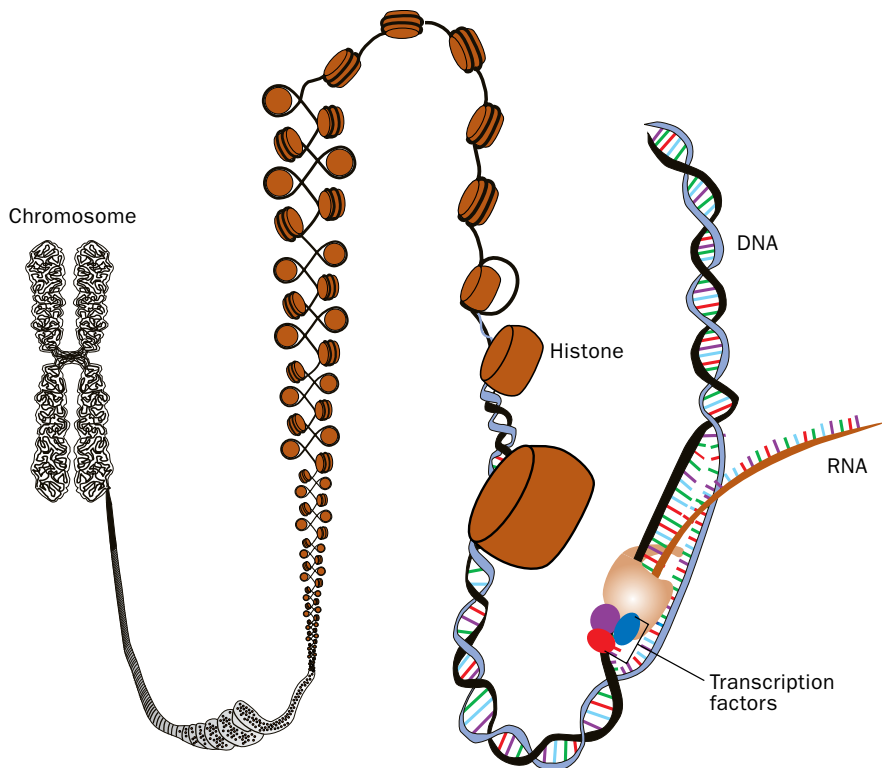
Throughout history shamans, clerics and physicians have tried to pin down what goes awry when a person slips into sadness, insanity or psychosis. Theorists have variously blamed mental illness on an imbalance of bodily fluids, the movement of planets, unconscious mental conflict and unfortunate life experiences. Today many researchers believe that psychiatric disorders arise in large part from a person's genetic makeup. Genes, after all, are

the blueprints for the proteins that create and control the brain.

And yet genetics cannot be the whole story: identical twins, who have virtually the same DNA, do not always develop the same mental disorders. For example, if one identical twin acquires schizophrenia, the other stands just a 50 percent chance of also suffering from the disease. Indeed, abundant data suggest that psychiatric ailments typically result from a complex

Unraveling the Chromosome

In the nucleus of every cell, the DNA in chromosomes is tightly wound around proteins, called histones, to make its considerable length fit inside the cell. DNA's protein packaging also controls the expression of genes. For a gene to be expressed, a chromosome must unravel so that a complex of proteins, including so-called transcription factors, can attach to the appropriate section of the DNA and create an RNA molecule. This RNA is then translated into a protein (*not shown*).



interplay between the environment and a number of different genes [see “The Character Code,” by Turhan Canli; *SCIENTIFIC AMERICAN MIND*, February/March 2008]. But only recently have scientists begun to grasp how the environment affects the brain to produce psychological changes.

Ushering in a new conception of mental illness, researchers are discovering that life experience can literally change a person's mind by chemically coating the DNA that controls its function—but in a way that does not alter the genetic code. Rather the experience of trauma, drug abuse or lack of affection somehow causes satellite molecules to latch onto a person's DNA. Instead of tinkering with the basic essence of a gene, these molecular hangers-on alter gene expression, shutting down or revving up the construction of proteins that affect an individual's mental state, the way the speed of an assembly line affects production and, ultimately, the company's bottom line.

Investigators in this new field, called epigenetics (“epi” meaning “above” or “beyond”), have discovered that a mother rat's nurturing behavior can bolster emotional resilience in her pups by boosting the expression of a gene that modulates stress and anxiety. Distressing events, on the other hand, seem to turn off the expression of a neuronal growth protein by epigenetic mechanisms, thereby promoting depression.

Recent work similarly suggests that epigenetic changes may also underlie the pathology of drug addiction and schizophrenia as well as the retain-

FAST FACTS

Doctoring DNA

1>> Experiences can literally change a person's mind by chemically coating the DNA that controls its function. Instead of tinkering with the genetic code, the coating alters gene expression, shutting down or revving up the construction of proteins that affect a person's mental state.

2>> A female rat's nurturing behavior bolsters emotional resilience in her pups by boosting the expression of a gene that modulates anxiety. Distressing events can turn off the expression of a neuronal growth protein by epigenetic mechanisms and thereby trigger depression.

3>> Epigenetic changes may also underlie the pathology of schizophrenia and drug addiction.

ing of long-term memories [see “Unmasking Memory Genes,” by Amir Levine, on page 48].

Identifying such molecular mishaps on the road to mental illness may enable scientists to develop a host of new treatments for psychiatric diseases. Future drugs might, for example, be designed to pharmacologically scrub DNA to eliminate the molecular alterations that led to the slide into schizophrenia, depression, anxiety or drug addiction.

Expressive Genes

Our genes, embedded in the DNA at the center of every cell in the body, form the blueprints for proteins, the cellular workhorses. Protein molecules build and maintain our brains and our bodies, shaping our personalities as well as our physical characteristics. The study of genetics is largely a discipline of correlating changes in the genetic code—that is, in its sequence of chemical units (A, T, C and G)—with changes in a person’s or animal’s appearance or behavior.

But to have an effect, a gene must actually be used as a template for a protein. In this process, called gene expression, various (previously fabricated) proteins attach to the DNA and use it to transcribe an intermediate molecule termed RNA, which is then translated into a protein. A cell does not transcribe and translate every gene, however. Each cell in an individual contains the same genes, but different cells use different sub-

sets of them. Such selective gene expression is what makes a liver cell, say, different from a brain cell. Similarly, a person could take on different physical or emotional characteristics if gene expression were to change in his or her cells.

How might this happen? The primary mechanism for silencing a gene involves preventing the necessary molecular machinery from accessing it. Like a long wire wound into a Slinky toy, the DNA molecule is tightly coiled—much of it around protein “spools,” or histones—a necessary measure if its considerable length is to fit inside a cell’s nucleus [see box on opposite page]. In its condensed state, DNA cannot be actively used as a protein template. To be expressed, a gene’s DNA segment must be unraveled and exposed.

Epigenetic mechanisms ease or block access to a cell’s genes, thereby controlling gene expression. Such mechanisms include the addition or removal of molecules to or from the DNA or histones. For instance, attaching so-called methyl groups, which consist of a carbon atom attached to three hydrogen atoms (CH_3), to DNA limits access by physically hampering the ability of the transcription machinery to bind to that DNA, thus silencing or at least quieting the gene. On the other hand, affixing acetyl groups (COCH_3) to the histones expands the chromosome’s structure, facilitating gene expression [see box below]. Experimenters are increasingly finding that such chemical changes can occur in response to par-

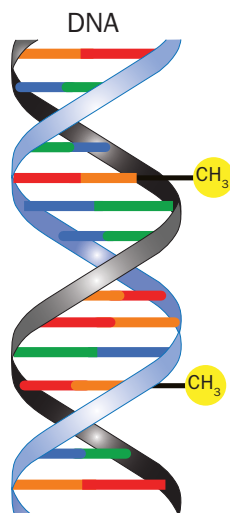
Beyond Genetics

Epigenetics is the study of certain kinds of chemical switches that turn genes on or off, thereby altering gene expression (how actively a gene is used to make protein).

Genetics

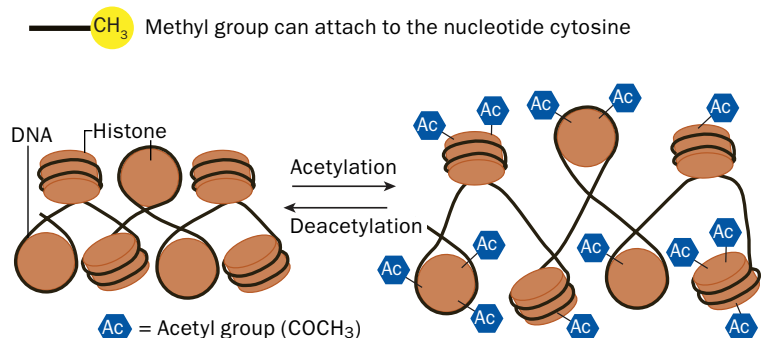
Changes in the genetic code—the sequence of nucleotides A, T, C and G in DNA—affect appearance and behavior.

Adenine (A) — Green
Thymine (T) — Blue
Guanine (G) — Red
Cytosine (C) — Orange



Epigenetics

Some chemical changes alter gene expression without affecting the genetic code. For example, affixing methyl groups to DNA inhibits gene expression, whereas adding acetyl groups to proteins called histones loosens chromosome structure, making the underlying genes easier to transcribe.



Certain parenting practices that profoundly shape a child's mental health may do so by altering DNA.

Children who receive a lot of affection and attention may be less prone to stress as adults.

ticular life experiences, and some of these modifications influence a person's mental stability.

Product of Parenting

Certain parenting practices can profoundly shape a child's emotional development and mental health—and some evidence suggests they can do so through epigenetics. For example, women with a history of childhood sexual and physical abuse have an exaggerated stress response: the amount of the stress hormone cortisol in their blood becomes abnormally elevated in the face of even minor stresses, such as speaking and performing mental arithmetic in front of an audi-



ence for 10 minutes. On the other hand, children who receive a lot of normal physical affection and care may end up more emotionally resilient and less prone to stress as adults than those who receive less attention and nurturing—at least that is what some animal studies suggest.

In 1997 neuroscientist Michael J. Meaney of McGill University and his colleagues compared the stress response of rats whose mothers had vigorously licked and groomed them during the first 10 days of their lives with that of rats whose mothers rarely licked and groomed them as pups. Meaney and his co-workers found that the progeny of high lickers and groomers displayed less anxiety and stress than the pups of low lickers

and groomers when they were confined to a small plastic tube for 20 minutes. Levels of the rat stress hormone, corticosterone, shot up noticeably higher and stayed elevated for longer in the rodents that had low-licking and low-grooming mothers than they did in the animals whose mothers had been high lickers and groomers.

But how did affection and nurturing, or the lack thereof, shape the rat pups' physiological reaction to stress? When a person or animal perceives a threat, the cognitive and emotional parts of the brain alert the hypothalamus, an almond-size structure at the base of the brain. The hypothalamus then sends chemical signals to the adrenal glands, by way of another gland called the pituitary, telling them to release cortisol or (in a rat) corticosterone. That hormone then eventually provides feedback to the hypothalamus, binding to specialized molecular receptors on neurons there, to inhibit further activity [see box on opposite page]. This feedback loop prevents the body from producing an overly intense and extended reaction to stress. In the anxious rats, however, that loop apparently did not work well, so the hypothalamus remained active and continued to trigger corticosterone release in response to the stress of confinement.

Meaney and his colleagues wondered whether the problem in these rats could be traced back to the corticosterone receptors in the hypothalamus. If a rat's brain lacked them, the researchers reasoned, that deficit might create a glitch in the feedback system. So Meaney, along with graduate student Ian Weaver, now at the University of Toronto, and others took a closer look at the gene for this corticosterone receptor in rats that received either a lot or very little licking and grooming from their mothers.

In 2004 Meaney's team reported that the corticosterone receptor gene in the pups of the low lickers and groomers bore many more methyl groups than did the same gene in their better-cared-for counterparts. As a result, the pups that received less nurturing only sluggishly expressed this gene and thus produced fewer corticosterone receptors in the hypothalamus. The lack of receptors weakened the ability of corticosterone to calm the hypothalamus after a stressful event, exaggerating the stress response and making for overly stressed and anxious rodents. On the oth-

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er hand, the nurturing behavior of the high-licking and high-grooming mothers kept their pups' corticosterone receptor gene relatively clear of methyl groups, and these pups were thus better able to handle stress as adults.

Dialing Down Depression

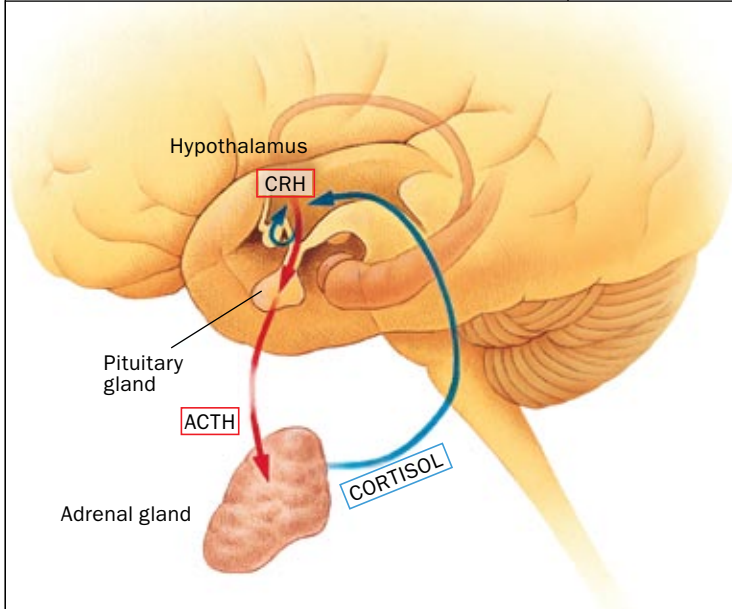
Another epigenetic modification may play a critical role in the development of depression. Although many people conceptualize depression as a chemical imbalance, nobody knows the exact mechanism for the disorder. Some investigators now theorize that depression can result from insufficient quantities of growth factor proteins such as brain-derived neurotrophic factor (BDNF), which, like other growth factors, sustains and nourishes nerve cells. In a 2006 study researchers found that concentrations of BDNF were abnormally low in the blood of depressed women. What is more, treatment with antidepressants brought the amount of BDNF in these women's bloodstreams back to normal. Likewise, other experiments demonstrate that treatments such as antidepressant medications, electroconvulsive therapy (ECT) and exercise increase concentrations of BDNF in the brains of rodents.

Until recently, no one knew the molecular mechanism of the BDNF depletion, but in the early part of this decade psychiatrist and neuroscientist Eric J. Nestler of the University of Texas Southwestern Medical Center at Dallas and his colleagues theorized that distressing experiences might alter the DNA that codes for BDNF. In a 2006 study Nestler and his colleagues paired "bully" mice with smaller mice in cages for five minutes a day. Face to face with their bully, the smaller mice acted anxious and submissive: they squeaked, cowered and tried to get out of the cage.

The scientists put a stop to the encounter by separating the two mice by a wire mesh, which still enabled the smaller mouse to smell the bully until the next go-round. After 10 days of such treatment, the small rodents acted defeated: like depressed humans, they would not interact with other mice and displayed unusual anxiety in novel settings, standing stock-still rather than exploring them. These mice also had abnormally low levels of BDNF in their brains.

To find out how bullying might lower BDNF concentrations, the researchers examined the gene for BDNF in cells from the hippocampus in the brains of both bullied and better-treated mice. They found a greater density of methyl groups on histones near the BDNF gene in the defeated mice than in normal mice, suggesting

Stress Response System



When a person faces a frightening or stressful situation, cognitive and emotional brain areas (*not shown*) alert the hypothalamus, which secretes corticotropin-releasing hormone (CRH) into the blood vessels that feed the pituitary gland. In response to the CRH, the pituitary releases adrenocorticotropic hormone (ACTH) into the bloodstream—and that substance prompts the adrenal glands to secrete the stress hormone cortisol. Cortisol not only prepares the body to confront or flee a challenge, it also acts on the hypothalamus to dampen the stress response. The effectiveness of this feedback may depend on epigenetic changes in the gene for the cortisol receptor in the hypothalamus.

that the threatening experiences had chemically closed off the BDNF gene, silencing the blueprint and squelching production of BDNF. What is more, treating the defeated mice with an antidepressant, imipramine, every day for a month boosted production of BDNF (and alleviated the depression), apparently by adding acetyl groups to the BDNF gene.

Other depression treatments may have a similar effect on the BDNF gene. For example, in a 2004 study Nestler's team found that ECT, when applied to depressed rodents, also increased acetylation of the histones around the BDNF gene.

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Neuroscientists speculate that psychotherapy might have the same effect, but no one knows because no one has yet developed effective talk therapy for a rodent.

Branching Out

Epigenetic mechanisms also may lie at the root of our addictions to substances such as alcohol and illicit drugs. Drug addiction is probably fueled by genetic factors; that is, genetically susceptible individuals are more easily addicted than others. But the use of a substance is necessary to switch the brain to an addicted state, and epigenetics likely plays a role in that transformation.

Addictive drugs exert their insidious effects by hijacking the brain's reward centers, including a midbrain structure called the nucleus accumbens. This structure normally responds to ordinary delights, including eating and sex, but a drug of abuse such as cocaine can corrupt the brain's reward circuitry such that the drug becomes a person's sole source of pleasure [see "New Weapons against Cocaine Addiction," by Peter Sergo; *SCIENTIFIC AMERICAN MIND*, April/May 2008]. At the cellular level, the nucleus accumbens of cocaine-dependent rodents contains neurons that appear "bushier," with more branches, or dendritic spines, that connect to other neurons, than those of animals that have never been exposed to cocaine. Drug abuse seems to spur this branching, which may abnormally enrich the communication between neurons in the brain's reward circuitry.

One protein that may be stimulating the cellular changes is cyclin-dependent kinase-5 (Cdk5), an enzyme that seems to be involved in adjusting how well two neurons communicate at junctions called synapses. In 2003 Nestler and

his colleagues reported that injecting rats with a drug that inhibits the activity of Cdk5 reduced cocaine's effect on neuronal branching: the rats' nucleus accumbens neurons sprouted fewer branches and thus appeared less bushy. The study authors concluded that "cocaine-induced proliferation of dendritic spines in [the] nucleus accumbens is dependent on the activity of cyclin-dependent kinase-5."

In 2004 Nestler, along with University of Texas Southwestern Medical Center neuroscientist Arvind Kumar and others, reported that rats that were chronically exposed to cocaine had more than four times as many acetyl groups (which loosen the chromosome structure and make genes more accessible) on the histone at the *Cdk5* gene as compared with rats that imbibed a saline solution. The cocaine exposure thus appeared to boost the expression of the *Cdk5* gene, raising production of the Cdk5 protein, which in turn stimulated or enabled the growth of neuronal connections in the nucleus accumbens. Such an epigenetic change may therefore contribute to addictive behavior.

Making Connections

In contrast to the obvious environmental contributors to drug addiction, the causes of the hallucinations, apathy and distorted thinking characteristic of schizophrenia remain relatively opaque. At the cellular level, investigators have noted an anomaly in brains of deceased schizophrenics: the neurons in some of their cognitive and visual brain regions are smaller, thinner and less densely connected with other neurons than are their counterparts in people who had been mentally healthy. Although no one is sure what might account for this anatomical curiosity, it could arise in part from aberrations in certain proteins critical for modulating or forming neuronal connections. One such protein is reelin, an enzyme that acts on the structural matrix of molecules that stretches between neurons.

Researchers have found reelin concentrations to be about 50 percent reduced in various regions of the brains of deceased patients who suffered from schizophrenia [see *illustration on opposite page*]. In 2005 two scientific teams simultaneously reported a probable cause for the reelin deficit. In one of these studies molecular biologist Dennis R. Grayson and his colleagues at the University of Illinois at Chicago compared the gene for reelin in brain tissue from 15 deceased schizophrenia patients with the same gene in the brains of 15 people who had not been mentally ill. The

After repeated encounters with "bully" mice, smaller mice may display behaviors akin to those of depressed humans. Epigenetic alterations affecting a gene for a nerve growth substance are likely to partly underlie this change in mental state.



COURTESY OF ERIC J. NESTLER

Combating stress and anxiety might be partly a matter of **cleansing DNA** of its epigenetic markings.

experimenters detected a greater number of methyl groups attached to the reelin gene in tissue from a region at the back of the schizophrenic brains as compared with tissue from the normal brains, suggesting that schizophrenia could arise from an epigenetic change that depresses reelin gene expression. Although psychiatrist Ming Tsuang of the University of California, San Diego, and his colleagues obtained similar results, two other groups of scientists later failed to find an association between reelin gene methylation and schizophrenia.

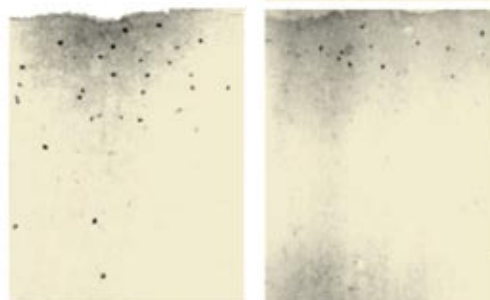
Even if reelin gene methylation is one cause of schizophrenia, no one knows what environmental factors might produce this chemical perturbation of the DNA. Scientists are similarly unsure how diminished production of reelin might lead to schizophrenia. A lack of reelin, which participates in neuronal migration and the remodeling of neuronal connections, could render neurons incapable of forming the ordinary number of links with other neurons—but how this might lead to symptoms such as hallucinations is unclear. Nevertheless, accumulating evidence suggests that excess methylation of DNA in the brains of schizophrenics is not limited to reelin but extends to various other genes involved in neural communication and brain development. Thus, DNA methylation, spurred by unknown environmental occurrences, may play an important role in the development of schizophrenia.

Chemical Erasers

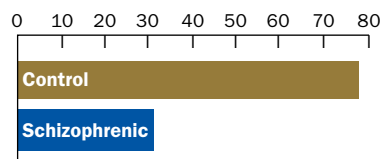
Researchers hope that illuminating the molecular path between experience and mental illness will ultimately pave the way toward better treatments for psychiatric disorders. Early work already suggests that combating stress and anxiety, at least in rats, might be partly a matter of cleansing DNA of its epigenetic markings.

In their 2004 paper Weaver, Meaney and their colleagues administered a histone deacetylase inhibitor—a compound that both boosts the number of acetyl groups and thins out methyl groups on chromosomes—to rats that had been raised by low-licking and low-grooming mothers. Meaney's group found that this treatment erased the emotional fallout from the rats' deficient upbringing. The treated rats were no longer especially anxious when they were trapped in the

Healthy Control Schizophrenic



Relative Concentrations
of Reelin RNA



tube: their stress hormone levels paralleled those of rats raised by high-licking and high-grooming mothers.

Eventually scientists might test a similar treatment in humans with intractable psychiatric disorders. Doctors might also advise patients at risk for mental disorders to engage in behaviors—say, changing their diet (which can alter gene expression in mice and thereby determine traits such as fur color), undergoing psychotherapy or taking medication—that could *prevent* deleterious epigenetic alterations to their DNA. A methylation antagonist blocker might, for example, help reduce the frequency or severity of post-traumatic stress disorder in rape and trauma victims. It might even be able to limit the psychological effects of combat in soldiers. Even though such therapies remain futuristic, the latest insights into the epigenetics of mental disorders are already prompting new notions about how the events and experiences of our lives can alter our minds. **M**

Concentrations of an enzyme called reelin (dark spots on images) involved in the remodeling of neuronal connections are about 50 percent lower in the brains of schizophrenics. The reduction may stem from epigenetic alterations of the gene for reelin, providing a possible clue to one cause of schizophrenia.

(Further Reading)

- ◆ **Genes and Behavior: Nature-Nurture Interplay Explained.** M. Rutter. Blackwell Publishing, 2006.
- ◆ **Epigenetic Regulation in Psychiatric Disorders.** N. Tsankova, W. Renthal, A. Kumar and E. J. Nestler in *Nature Reviews Neuroscience*, Vol. 8, No. 5, pages 355–367; May 2007.
- ◆ **Epigenetics.** C. D. Allis, T. Jenuwein, D. Reinberg and M.-L. Caparros. Cold Spring Harbor Laboratory Press, 2007.

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