



TAMING STRESS

AN EMERGING UNDERSTANDING OF THE BRAIN'S STRESS PATHWAYS POINTS TOWARD TREATMENTS FOR ANXIETY AND DEPRESSION BEYOND VALIUM AND PROZAC
BY ROBERT SAPOLSKY

PHOTOGRAPHS BY JAMES SALZANO

OVER THE CENTURIES, SOCIETY'S APPROACHES TO TREATING the mentally ill have shifted dramatically. At present, drugs that manipulate neurochemistry count as cutting-edge therapeutics. A few decades ago the heights of efficacy and compassion were lobotomies and insulin-induced comas. Before that, restraints and ice baths sufficed. Even earlier, and we've entered the realm of exorcisms.

Society has also shifted its view of the causes of mental illness. Once we got past invoking demonic possession, we put enormous energy into the debate over whether these diseases are more about nature or nurture. Such arguments are quite pointless given the vast intertwining of the two in psychiatric disease. Environment, in the form of trauma, can most certainly break the minds of its victims. Yet there is an undeniable biology that makes some individuals more vulnerable than others. Conversely, genes are most certainly important factors in understanding major disorders. Yet being the identical twin of someone who suffers one of those illnesses means a roughly 50 percent chance of *not* succumbing.

Obviously, biological vulnerabilities and environmental precipitants interact, and in this article I explore one arena of that interaction: the relation between external factors that cause stress and the

biology of the mind's response. Scientists have recently come to understand a great deal about the role that stress plays in the two most common classes of psychiatric disorders: anxiety and major depression, each of which affects close to 20 million Americans annually, according to the National Institute of Mental Health. And much investigation focuses on developing the next generation of relevant pharmaceuticals, on finding improved versions of Prozac, Wellbutrin, Valium and Librium that would work faster, longer or with fewer side effects.

At the same time, insights about stress are opening the way for novel drug development. These different tacks are needed for the simple fact that despite laudable progress in treating anxiety and depression, currently available medications do not work for vast numbers of people, or they entail side effects that are too severe.

Research in this area has applications well beyond treating and understanding these two illnesses. The diagnostic boundary that separates someone who is formally ill with an anxiety disorder or major depression from everyone else is somewhat arbitrary. Investigations into stress are also teaching us about the everyday anxiety and depression that all of us experience at times.

Out of Balance

WHEN A BODY is in homeostatic balance, various measures—such as temperature, glucose level and so on—are as close to “ideal” as possible. A stressor is anything in the environment that knocks the body out of homeostasis, and the stress response is the array of physiological adaptations that ultimately reestablishes balance. The response principally includes the secretion of two types of hormones from the adrenal glands: epinephrine, also known as adrenaline, and glucocorticoids. In humans, the relevant glucocorticoid is called cortisol, also known as hydrocortisone.

This suite of hormonal changes is what stress is about for the typical mammal. It is often triggered by an acute physical challenge, such as fleeing from a predator. Epinephrine and glucocorticoids mobilize energy for muscles, increase cardiovascular tone so oxygen can travel more quickly, and turn off nonessential activities like growth. (The hormones work at different speeds. In a fight-or-flight scenario, epinephrine is the one handing out guns; glucocor-



EPINEPHRINE IS THE ONE HANDING OUT GUNS. Glucocorticoids are the ones drawing up blueprints for new aircraft carriers.

ticoids are the ones drawing up blueprints for new aircraft carriers needed for the war effort.)

Primates have it tough, however. More so than in other species, the primate stress response can be set in motion not only by a concrete event but by mere *anticipation*. When this assessment is accurate (“This is a dark, abandoned street, so I should prepare to run”), an anticipatory stress response can be highly adaptive. But when primates, human or otherwise, chronically and erroneously believe that a homeostatic challenge is about to come, they have

entered the realm of neurosis, anxiety and paranoia.

In the 1950s and 1960s pioneers such as John Mason, Seymour Levine and Jay Weiss—then at the Walter Reed Army Medical Center, Stanford University and the Rockefeller University, respectively—began to identify key facets of psychological stress. They found that such stress is exacerbated if there is no outlet for frustration, no sense of control, no social support and no impression that something better will follow. Thus, a rat will be less likely to develop an ulcer in response to a series of electric shocks if it can gnaw on a bar of wood throughout, because it has an outlet for frustration. A baboon will secrete fewer stress hormones in response to frequent fighting if the aggression results in a rise, rather than a fall, in the dominance hierarchy; he has a perception that life is improving. A person will become less hypertensive when exposed to painfully loud noise if she believes she can press a button at any time to lower the volume; she has a sense of control.

But suppose such buffers are not available and the stress is chronic. Repeated challenges may de-

mand repeated bursts of vigilance. At some point, this vigilance may become overgeneralized, leading an individual to conclude that he must always be on guard—even in the absence of the stress. And thus the realm of anxiety is entered. Alternatively, the chronic stress may be insurmountable, giving rise to feelings of helplessness. Again this response may become overgeneralized: a person may begin to feel she is always at a loss, even in circumstances that she can actually master. Depression is upon her.

Stress and Anxiety

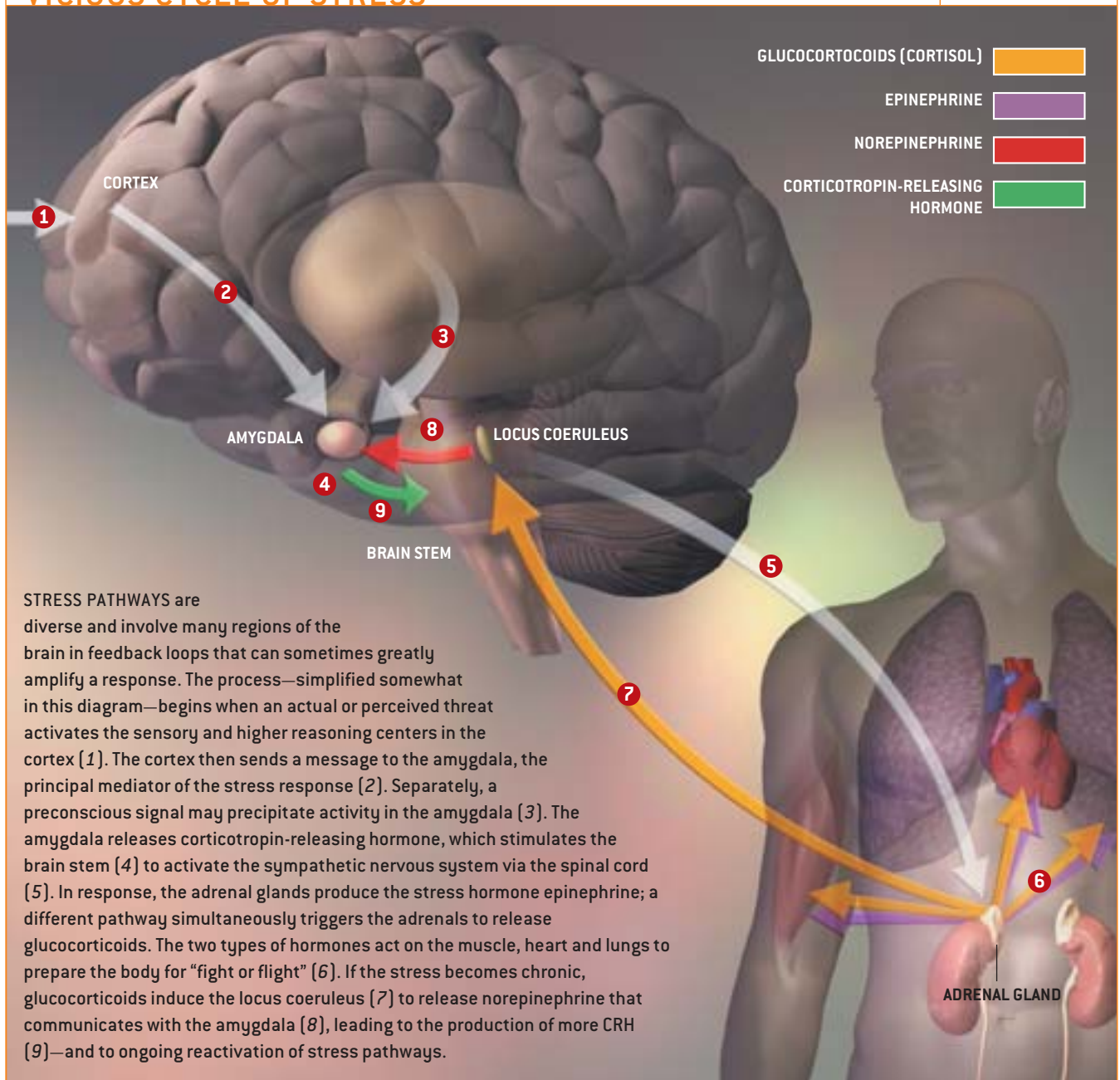
FOR ITS PART, anxiety seems to wreak havoc in the limbic system, the brain region concerned with emotion. One structure is primarily affected: the amygdala, which is involved in the perception of and response to fear-evoking stimuli. (Interestingly, the amygdala is also central to aggression, underlining the fact that aggression can be rooted in fear—an observation that can explain much sociopolitical behavior.)

To carry out its role in sensing threat, the amygdala receives input from neurons in the outermost layer of the brain, the cortex, where much high-level processing takes place. Some of this input comes

OVERVIEW/*Battling Stress*

- Scientists understand a lot about the role stress plays in the development of anxiety disorders and major depression, which may affect as many as 40 million people in the U.S. And they are coming to see the ways in which unremitting stress can transform anxiety into depression.
- Insights into the neurochemistry of stress are allowing researchers to develop new ways of thinking about drug development. In addition to refining drugs that are already on the market, these findings are leading to entirely novel strategies for treatments.
- Finding these alternatives is crucially important because many people are not helped by currently available medications.

VICIOUS CYCLE OF STRESS



from parts of the cortex that process sensory information, including specialized areas that recognize individual faces, as well as from the frontal cortex, which is involved in abstract associations. In the realm of anxiety, an example of such an association might be grouping a gun, a hijacked plane and an anthrax-tainted envelope in the same category. The sight of a fire or a menacing face can activate the amygdala—as can a purely abstract thought.

The amygdala also takes in sensory information that bypasses the cortex. As a result, a subliminal preconscious menace can activate the amygdala, even before there is conscious awareness of the trigger.

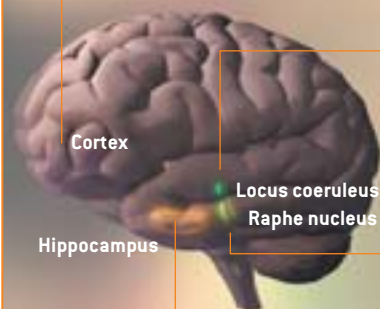
Imagine a victim of a traumatic experience who, in a crowd of happy, talking people, suddenly finds herself anxious, her heart racing. It takes her moments to realize that a man conversing behind her has a voice similar to that of the man who once assaulted her.

The amygdala, in turn, contacts an array of brain regions, making heavy use of a neurotransmitter called corticotropin-releasing hormone (CRH). One set of nerve cells projecting from the amygdala reaches evolutionarily ancient parts of the midbrain and brain stem. These structures control the autonomic nervous system, the network of nerve cells projecting to parts of the body over which you

DEPRESSION'S EFFECTS

DOPAMINE DEPLETION

Prolonged exposure to stress hormones can increase the risk of depression by depleting levels of dopamine. This neurotransmitter is integral to the pleasure pathway, which involves many brain structures, including the prefrontal cortex.



NOREPINEPHRINE DEPLETION

Because stimulation from the raphe nucleus falls off after chronic stress, the locus coeruleus secretes less norepinephrine, and attentiveness is accordingly diminished.

SEROTONIN DEPLETION

Stress brings about reduced secretion of the neurotransmitter serotonin from the raphe nucleus, which communicates with the locus coeruleus and the cortex.

HIPPOCAMPAL SHRINKAGE

Stress brings about cell death in the hippocampus—and studies have found that this brain region is 10 to 20 percent smaller in depressed individuals. Such impairment can lead to memory problems.

normally have no conscious control (your heart, for example). One half of the autonomic nervous system is the sympathetic nervous system, which mediates “fight or flight.” Activate your amygdala with a threat, and soon the sympathetic nervous system has directed your adrenal glands to secrete epinephrine. Your heart is racing, your breathing is shallow, your senses are sharpened.

The amygdala also sends information back to the frontal cortex. In addition to processing abstract associations, as noted above, the frontal cortex helps to make judgments about incoming information and initiating behaviors based on those assessments. So it is no surprise that the decisions we make can be so readily influenced by our emotions. Moreover, the amygdala sends projections to the sensory cortices

procedural memory: recalling how to ride a bike or play a passage on the piano. And it is involved in fear. Remember the woman reacting to the similarity between two voices without being aware of it. In that case, the activation of the amygdala and the sympathetic nervous system reflects a form of implicit memory that does not require conscious awareness.

Researchers have begun to understand how these fearful memories are formed and how they can be overgeneralized after repeated stress. The foundation for these insights came from work on declarative memory, which is most likely situated in a part of the brain called the hippocampus. Memory is established when certain sets of nerve cells communicate with one another repeatedly. Such communication entails the release of neurotransmitters—chemical messengers that travel across synapses, the spaces between neurons. Repeated stimulation of sets of neurons causes the communication across synapses to be strengthened, a condition called long-term potentiation (LTP).

Joseph LeDoux of New York University has shown that repeatedly placing rats in a fear-provoking situation can bring about LTP in the amygdala. Work by Sumantra Chattarji of the National Center for Biological Science in Bangalore extends this finding one remarkable step further: the amygdalic neurons of rats in stressful situations sprout new branches, allowing them to make more connections with other neurons. As a result, any part of the fear-inducing situation could end up triggering more firing between neurons in the amygdala. A victim—if he had been robbed several times at night, for instance—might experience anxiety and phobia just by stepping outside his home, even under a blazing sun.

LeDoux has proposed a fascinating model to relate these changes to a feature of some forms of anx-

SEVERE STRESS can harm the hippocampus, preventing the consolidation of a conscious, EXPLICIT MEMORY OF THE EVENT.

as well, which may explain, in part, why sensations seem so vivid when we are in certain emotional states—or perhaps why sensory memories (flashbacks) occur in victims of trauma.

Whether it orchestrates such powerful reimmersions or not, the amygdala is clearly implicated in certain kinds of memory. There are two general forms of memory. Declarative, or explicit, memory governs the recollection of facts, events or associations. Implicit memory has several roles as well. It includes

ity. As discussed, the hippocampus plays a key role in declarative memory. As will become quite pertinent when we turn to depression, glucocorticoid exposure can impair LTP in the hippocampus and can even cause atrophy of neurons there. This phenomenon constitutes the opposite of the stress response in the amygdala. Severe stress can harm the hippocampus, preventing the consolidation of a conscious, explicit memory of the event; at the same time, new neuronal branches and enhanced LTP facilitate



the amygdala's implicit memory machinery. In subsequent situations, the amygdala might respond to preconscious information—but conscious awareness or memory may never follow. According to LeDoux, such a mechanism could underlie forms of free-floating anxiety.

It is interesting that these structural changes come about, in part, because of hormones secreted by the adrenal glands, a source well outside the brain. As mentioned, the amygdala's perception of stress ultimately leads to the secretion of epinephrine and glucocorticoids. The glucocorticoids then activate a brain region called the locus coeruleus. This structure, in turn, sends a powerfully activating projection back to the amygdala, making use of a neurotransmitter called norepinephrine (a close relative of epinephrine). The amygdala then sends out more CRH, which leads to the secretion of more glucocorticoids. A vicious circle of mind-body feedback can result.

Assuaging Anxiety

AN UNDERSTANDING of the interactions between stress and anxiety has opened the way for new therapies, some of which hold great promise. These drugs are not presumed better or safer than those available today. Rather, if successful, they will give clinicians more to work with.

The medicines that already exist do target aspects of the stress system. The minor tranquilizers, such as Valium and Librium, are in a class of compounds called benzodiazepines. They work in part by relaxing muscles; they also inhibit the excitatory projection from the locus coeruleus into the amygdala, thereby decreasing the likelihood that the amygdala will mobilize the sympathetic nervous system. The net result is a calm body—and a less anxious body means a less anxious brain. While effective, however, benzodiazepines are also sedating and addictive, and considerable research now focuses on finding less troublesome versions.

In their search for alternatives, researchers have sought to target the stress response upstream of the locus coeruleus and amygdala. Epinephrine activates a nerve called the vagus, which projects into a brain region that subsequently stimulates the amygdala. A new therapy curtails epinephrine's stimulation of the vagus nerve.

Chemical messengers such as epinephrine exert their effects by interacting with specialized receptors on the surface of target cells. A receptor is shaped in such a way that it can receive only a certain messenger—just as a mold will fit only the statue cast in it. But by synthesizing imposter messengers, scientists have been able to block the activity of some of the body's natural couriers.



Drugs called beta blockers fit into some kinds of epinephrine receptors, preventing real epinephrine from transmitting any information. Beta blockers have long been used to reduce high blood pressure driven by an overactive sympathetic nervous system, as well as to reduce stage fright. But Larry Cahill and James McGaugh of the University of California at Irvine have shown that the drugs also blunt the formation of memories of emotionally disturbing events or stories. Based on their findings and others, clinicians such as Roger Pitman of Harvard University have started studies in which beta blockers are given to people who have experienced severe trauma in the hope of heading off the development of post-traumatic stress disorder.

Other therapies are being designed to act in the amygdala itself. As described, the amygdala's shift from merely responding to an arousing event to be-

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SOME NOVEL THERAPEUTIC STRATEGIES



Substance P. This compound is released during painful sensations and stress and acts on neurokinin-1 receptors, which are found throughout the central nervous system but in greater amounts in the amygdala and locus coeruleus (*highlighted*), among other stress-related areas. Current work—including one clinical trial—suggests that blocking the action of Substance P may blunt anxiety and depression. But another clinical trial did not support this finding.



Corticotropin-Releasing Hormone. This hormone is released by the amygdala and initiates the stress cascade. Research efforts now include trying to block receptors for CRH in the brain stem. Without information from CRH, the brain stem will not set the sympathetic nervous system in motion, thus preventing the release of epinephrine by the adrenal glands. This blockade could curb both anxiety and depression.



Brain-Derived Neurotrophic Factor. This substance is important to the creation of new nerve cells. By injecting BDNF into brains, researchers hope to counteract the deleterious effects of glucocorticoids on neurogenesis in the hippocampus, thereby maintaining healthy memory function and preventing the hippocampal atrophy often seen in depressed people.



Gene Therapy. This treatment can introduce novel genes to specific regions of the brain; these genes can then produce proteins that can undo or prevent the effects of stress. Current studies aim to figure out which genes are active in the amygdala during stress. Introducing genes that inhibit unwanted neural branching in the amygdala might then thwart the anxiety-inducing effects of stress. For depression, the goal is different: genes placed in the hippocampus could produce proteins that would break down glucocorticoids, preventing damage to nerve cells—and, accordingly, the memory impairment—that can accompany depression.

coming chronically overaroused probably involves memory formation as well as the growth of new synapses. Work in my laboratory is exploring the molecular biology underlying those changes. Because prolonged stress has opposite effects on synapse formation in the hippocampus and the amygdala, we would like to know how the profiles of genes turned on and off by stress differ in those two structures. Our goal is to then try to block the changes by introducing genes into the amygdala that might give rise to proteins that could inhibit synapse formation during stress. In this work, viruses that have been rendered safe are used to ferry genes to the amygdala [see “Gene Therapy in the Nervous System,” by Dora Y. Ho and Robert M. Sapolsky; *SCIENTIFIC AMERICAN*, July 1997].

Another strategy—for both anxiety and depression—targets CRH, the neurotransmitter used by the amygdala when it sends information elsewhere. Based on insights into the structure of CRH and its receptors, scientists have developed chemical imposters to bind with the receptors and block it. In research by Michael Davis of Emory University, these compounds have proved effective in rat models of anxiety. They have reduced the extent to which a rat

anxiously freezes when placed in a cage where it was previously shocked.

Stress and Depression

IN CONTRAST TO ANXIETY, which can feel like desperate hyperactivity, major depression is characterized by helplessness, despair, an exhausted sense of being too overwhelmed to do anything (psychomotor retardation) and a loss of feelings of pleasure. Accordingly, depression has a different biology and requires some different strategies for treatment. But it, too, can be related to stress, and there is ample evidence of this association. First of all, psychological stress entails feeling a loss of control and predictability—an accurate description of depression. Second, major stressful events seem to precede depressive episodes early in the course of the disease. Finally, treating people with glucocorticoid hormones to control conditions such as rheumatoid arthritis can lead to depression.

One way in which stress brings about depression is by acting on the brain’s mood and pleasure pathways. To begin, prolonged exposure to glucocorticoid hormones depletes norepinephrine levels in the locus coeruleus neurons. Most plausibly, this means that

the animal—or person—becomes less attentive, less vigilant, less active: psychomotor retardation sets in.

Continued stress also decreases levels of serotonin—which may be important in the regulation of mood and sleep cycles, among other things—as well as the number of serotonin receptors in the frontal cortex. Serotonin normally arrives in the frontal cortex by way of the raphe nucleus, a structure that also communicates with the locus coeruleus. You can probably see where this is going. Normally, serotonin stimulates the release of norepinephrine from the locus coeruleus. When serotonin becomes scarce, less norepinephrine is released—exacerbating the shortage caused by earlier unremitting glucocorticoid bombardment.

Stress affects dopamine, the main currency of the pleasure pathway, in a way that seems counterintuitive at first. Moderate and transient amounts of stress—and the ensuing presence of glucocorticoids—increase dopamine release in the pleasure pathway, which runs between a region called the ventral tegmentum/nucleus accumbens and the frontal cortex. More dopamine can lead to a feeling of well-being in situations of moderate or tran-

gression turned inward—an enormous emotional battle fought entirely internally—and the disease’s physiology supports this analysis.

Memory and New Cells

STRESS ALSO ACTS ON the hippocampus, and this activity may bring about some of the hallmarks of depression: difficulty learning and remembering. As I explained before, stress and glucocorticoids can disrupt memory formation in the hippocampus and can cause hippocampal neurons to atrophy and lose some of their many branches. In the 1980s several laboratories, including my own, showed that glucocorticoids can kill hippocampal neurons or impair their ability to survive neurological insults such as a seizure or cardiac arrest.

Stress can even prevent the growth of new nerve cells. Contrary to long-held belief, adult brains do make some new nerve cells. This revolution in our understanding has come in the past decade. And although some findings remain controversial, it is clear that new neurons form in the olfactory bulb and the hippocampus of many adult animals, including humans [see “Brain, Repair Yourself,” by Fred H.

The helplessness of DEPRESSION is not a quiet, passive state. The dread is active, twitching, ENERGY-CONSUMING.

sient stress during which a subject is challenged briefly and not too severely. For a human, or a rat, this situation would entail a task that is not trivial, but one in which there is, nonetheless, a reasonably high likelihood of success—in other words, what we generally call “stimulation.” But with chronic glucocorticoid exposure, dopamine production is curbed and the feelings of pleasure fade.

Not surprisingly, the amygdala also appears relevant to depression. Wayne Drevets of the National Institute of Mental Health reports that the images of the amygdala of a depressed person light up more in response to sad faces than angry ones. Moreover, the enhanced autonomic arousal seen in anxiety—thought to be driven by the amygdala—is often observed in depression as well. This fact might seem puzzling at first: anxiety is characterized by a skittish torrent of fight-or-flight signals, whereas depression seems to be about torpor. Yet the helplessness of depression is not a quiet, passive state. The dread is active, twitching, energy-consuming, distracting, exhausting—but internalized. A classic conceptualization of depression is that it represents ag-

Gage, on page 46]. Many things, including learning, exercise and environmental enrichment, stimulate neurogenesis in the hippocampus. But stress and glucocorticoids inhibit it.

As would be expected, depression is associated with impaired declarative memory. This impairment extends beyond remembering the details of an acute trauma. Instead depression can interfere with declarative memory formation in general—in people going about their everyday routine or working or learning. Recent and startling medical literature shows that in those who have been seriously depressed for years, the volume of the hippocampus is 10 to 20 percent smaller than in well-matched control subjects. There is little evidence that a small hippocampus predisposes someone toward depression; rather the decreased volume appears to be a loss in response to depression.

At present, it is not clear whether this shrinkage is caused by the atrophy or death of neurons or by the failure of neurogenesis. Disturbingly, both the volume loss and at least some features of the cognitive impairments persist even when the depression



resolves. (It is highly controversial whether new neurons are required for learning and memory; thus, it is not clear whether an inhibition of neurogenesis would give rise to cognitive deficits.)

Glucocorticoids may act on the hippocampus by inhibiting levels of a compound called brain-derived neurotrophic factor (BDNF)—which may aid neurogenesis. Several known antidepressants increase amounts of BDNF and stimulate hippocampal neurogenesis in laboratory animals. These findings have led some scientists to speculate that the stress-induced inhibition of neurogenesis and of BDNF are central to the emotional symptoms of depression. I find it to be somewhat of a stretch to connect altered hippocampal function with the many facets of this disease. Nevertheless, these hippocampal changes may play a large part in the substantial memory dysfunction typical of major depression.

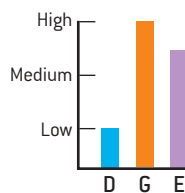
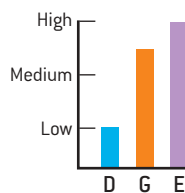
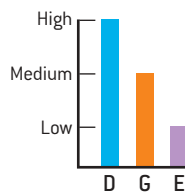
New Drugs for Depression

THE CURRENT GENERATION of antidepressants boost levels of serotonin, dopamine and norepinephrine, and there is tremendous ongoing research to develop more effective versions of these drugs. But some novel therapies target steps more intimately related to the interactions between stress and depression.

Not surprisingly, some of that work focuses on the effects of glucocorticoids. For example, a number of pharmaceuticals that are safe and clinically approved for other reasons can transiently block the synthesis of glucocorticoids in the adrenal glands or block access of glucocorticoids to one of their important receptors in the brain. Fascinatingly, the key compound that blocks glucocorticoid receptors is RU486, famous and controversial for its capacity to also block progesterone receptors in the uterus and for its use as the “abortion drug.” Beverly Murphy of McGill University, Owen Wolkowitz of the University of California at San Francisco and Alan Schatzberg of Stanford have shown that such antiglucocorticoids can act as antidepressants for a subset of severely depressed people with highly elevated glucocorticoid levels. These findings are made even more promising by the fact that this group of depressed individuals tend to be most resistant to the effects of more traditional antidepressants.

Another strategy targets CRH. Because depression, like anxiety, often involves an overly responsive amygdala and sympathetic nervous system, CRH is a key neurotransmitter in the communication from the former to the latter. Moreover, infusion of CRH into the brain of a monkey can cause some depressionlike symptoms. These findings have prompted

Anxiety becomes depression if stress is chronic and levels of dopamine [D], glucocorticoids [G] and epinephrine [E] change accordingly [graphs]. If a rat knows how to press a lever to avoid a shock, it can feel pleasure in that mastery [1]. If the lever no longer works, however, anxiety sets in and the animal desperately tries different strategies to avoid the shock [2]. As coping proves elusive, hypervigilance is replaced by passivity and depression [3].



studies as to whether CRH-receptor blockers can have an antidepressant action. It appears they can, and such drugs are probably not far off.

Using the same receptor-blocking strategy, researchers have curbed the action of a neurotransmitter called Substance P, which binds to the neurokinin-1 (NK-1) receptor. In the early 1990s workers discovered that drugs binding with NK-1 prevent some aspects of the stress response. In one trial and several animal studies, Substance P has worked as an antidepressant.

Other approaches center on the hippocampus. Investigators are injecting BDNF into the brains of rats to counteract the inhibitory effects of glucocorticoids on neurogenesis. My own laboratory is using gene therapy to protect the hippocampus of rats from the effects of stress—much as we are doing in the amygdala to prevent anxiety. These genes are triggered by glucocorticoids; once activated, they express an enzyme that degrades glucocorticoids. The net result blocks the deleterious effects of these hormones. We are now exploring whether this treatment can work in animals.

As is now clear, I hope, anxiety and depression



are connected. Yet a state of constant vigilance and one of constant helplessness seem quite different. When does stress give rise to one as opposed to the other? The answer seems to lie in how chronic the stress is.

The Stress Continuum

IMAGINE A RAT trained to press a lever to avoid a mild, occasional shock—a task readily mastered. The rat is placed into a cage with the lever, and the anticipatory sense of mastery might well activate the pleasurable dopaminergic projections to the frontal cortex. When the increase in glucocorticoid secretion is moderate and transient—as would likely be the case here—the hormone enhances dopamine release.

Suppose that in this circumstance, however, the lever has been disconnected; pressing it no longer prevents shocks. Initially this alteration produces a wildly hypervigilant state in the rat as it seeks a new coping response to stop the shocks. The animal presses the lever repeatedly, frantically trying to regain control. This is the essence of anxiety and of the mul-

pamine, serotonin and glucocorticoids. They also code for the enzymes that synthesize and degrade those chemical messengers, for the pumps that remove them from the synapses, for growth factors like BDNF, and so on.

But those genetic influences are not inevitable. Remember, if an individual has one of the major psychiatric disorders, her identical twin has only about a 50 percent chance of having it. Instead the genetic influences seem to be most about vulnerability: how the brain and body react to certain environments, including how readily the brain and body reequilibrate after stress.

Experience, beginning remarkably early in life, also influences how one responds to stressful environments. The amount of stress a female rat is exposed to during pregnancy influences the amount of glucocorticoids that cross the placenta and reach the fetus; that exposure can then alter the structure and function of that fetus's hippocampus in adulthood. Separate a newborn rat from its mother for a sustained period and it will have increased levels of

A GENETIC LEGACY of anxiety or depression does not confer a life sentence on sufferers of these TRAGIC DISEASES.

multiple, disorganized attempts at coping. Physiologically, this state is characterized by massive activation of the sympathetic nervous system by epinephrine and of the norepinephrine projection from the locus coeruleus, as well as moderately increased glucocorticoid secretion.

And as the shocks continue and the rat finds each attempt at coping useless, a transition occurs. The stress response becomes more dominated by high glucocorticoid levels than by epinephrine and the sympathetic nervous system—which are largely in control of the immediate fight-or-flight reaction. The brain chemistry begins to resemble that of depression as key neurotransmitters become depleted and the animal ceases trying to cope. It has learned to be helpless, passive and involuted. If anxiety is a crackling, menacing brushfire, depression is a suffocating heavy blanket thrown on top of it.

Stress and Genes

I DO NOT WANT to conclude this article having given the impression that anxiety and depression are “all” or “only” about stress. Obviously, they are not. Both illnesses have substantial genetic components as well. Genes code for the receptors for do-

CRH as an adult. Seymour Levine, one of the giants of psychobiology, illustrates this point with a quotation from William Faulkner: “The past is not dead. It’s not even the past.”

An understanding of the role of stress in psychiatric disorders offers much. It teaches us that a genetic legacy of anxiety or depression does not confer a life sentence on sufferers of these tragic diseases. It is paving the way for some new therapies that may help millions. Given that there is a continuum between the biology of these disorders and that of the “normal” aspects of emotion, these findings are not only pertinent to “them and their diseases” but to all of us in our everyday lives. Perhaps most important, such insight carries with it a social imperative: namely, that we find ways to heal a world in which so many people learn that they must always feel watchful and on guard or that they must always feel helpless. SA

MORE TO EXPLORE

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