

FAULTY CIRCUITS

Neuroscience is revealing the malfunctioning connections underlying psychological disorders and forcing psychiatrists to rethink the causes of mental illness

By Thomas R. Insel

KEY CONCEPTS

- Because mental disorders such as depression display no conspicuous brain damage, they were long thought to stem from purely psychological processes.
- Neural imaging is revealing that abnormal activity along a circuit of brain structures involved in mental processing underlies many mental disorders, making the physical dysfunction causing the mental symptoms visible for the first time.
- Understanding the biology of mental disorders will clarify the sources of malfunction in a circuit, provide objective methods of diagnosis and lead to targeted treatments.

—The Editors

In most areas of medicine, doctors have historically tried to glean something about the underlying cause of a patient's illness before figuring out a treatment that addresses the source of the problem. When it came to mental or behavioral disorders in the past, however, no physical cause was detectable so the problem was long assumed by doctors to be solely "mental," and psychological therapies followed suit. Today scientific approaches based on modern biology, neuroscience and genomics are replacing nearly a century of purely psychological theories, yielding new approaches to the treatment of mental illnesses.

Many illnesses previously defined as "mental" are now recognized to have a biological cause: in autism, for example, it is an abnormality in the connections between neurons, often attributable to genetic mutations; schizophrenia is now viewed and treated as a developmental brain disorder. Yet the public and even clinicians have had difficulty accepting that certain other mental disorders such as depression, obsessive-compulsive disorder (OCD) or post-traumatic stress disorder (PTSD) could also be physiological disorders of the brain.

A primary reason that the understanding of such mental disorders has lagged so far behind other areas of medicine is that unlike classical

neurological illnesses such as Parkinson's disease or the aftermath of a stroke, where the damage is visible, mental disorders are not marked by conspicuous lesions in the brain—a physical cause is still not obvious. The newest imaging technologies for mapping function in the living brain, though, allow the detection of problems with activity levels in, or communication between, brain areas, even when there is no observable loss of cells.

Neuroimaging has opened up the black box of the brain so that mental disorders can, for the first time, be studied as abnormalities in the connections between distant areas of the brain or, in some cases, problems in the coordination of brain areas whose activity is normally synchronized. Brain regions that function together to carry out normal mental operations can be thought of as analogous to electrical circuits. And the latest research shows that the malfunctioning of entire circuits may underlie many mental disorders.

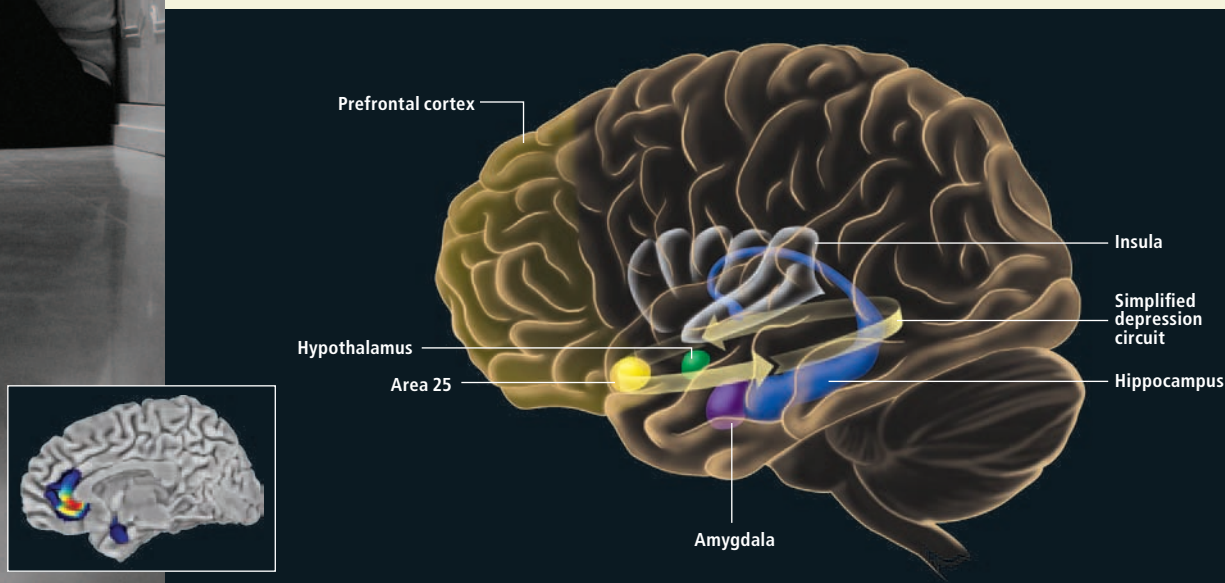
The details of each disorder's "circuit diagram" or map are still emerging. But this new view is already producing seismic shifts in psychiatry, opening avenues to more empirical diagnosis of mental illnesses and providing insights into their underlying causes, which promises more effective forms of treatment.



GOVERNOR OF MOOD



Depression sufferers have low energy and mood, and their reaction times and memory formation are inhibited, as though normal brain activity levels are suppressed. Yet common symptoms, such as anxiety and sleep disturbances, suggest certain brain areas are overactive. Imaging of the brain regions most disrupted in depression points to the source of such imbalances as a tiny brain structure called area 25, which acts as a hub for a depression circuit. Area 25 connects directly to structures such as the amygdala, which mediates fear and anxiety, and the hypothalamus, involved in stress responses. Those regions, in turn, exchange signals with the hippocampus, a center of memory processing, and the insula, where sensory perceptions and emotions are processed. A smaller than normal area 25 (*red in inset*) is suspected of contributing to a higher risk of depression in people with a gene variant that inhibits serotonin processing.



Stuck in Overdrive?

Depression offers perhaps the best example of the rapid progress being made in understanding the biology of mental illness. Major depressive disorder, the official diagnostic term for depression, affects 16 percent of all Americans, potentially leading to loss of work, substance abuse and suicide. It is also one of the most prevalent illnesses in the developed world, where it is the leading cause of medical disability among people between the ages of 15 and 44. The symptoms include not only a profound sense of despair with helplessness and hopelessness but also a range of physical symptoms such as loss of appetite, sleep disturbances, constipation and fatigue that is sometimes mixed with agitation. Depression is known to disturb the immune system and multiple hormonal systems and to increase one's risk for cardiovascular disease. Yet despite its widespread effects on the body, depression is fundamentally a brain disorder. And considerable evidence points to a tiny region in the brain's prefrontal cortex (PFC) called area 25 as a hub for the circuitry underlying depression.

The designation "area 25" comes from a Ger-

man neurologist, Korbinian Brodmann, who assigned numbers to various regions of the cortex in his classic 1909 atlas of the human brain. For the past 100 years this hard-to-reach region, which sits deep in the midline at the front of the brain, has garnered little attention. But over the past decade discovery of its critical role in depression has turned area 25 into high-interest real estate among clinical neuroscientists. Helen Mayberg and her colleagues at Emory University, for example, have shown that the region is overly active in depression and that symptom improvement after virtually all forms of treatment, from medication to psychotherapy, is accompanied by decreased activity in this same region.

Other clues also point to area 25 as having a pivotal role in depression. The region is exceptionally rich with serotonin transporters—molecules that manage the amount of the neurotransmitter serotonin available to neurons. (Many antidepressant medications are believed to act on these transporters, enhancing neural signaling through serotonin.) While at the National Institute of Mental Health, Lukas Pezawas, Andreas Meyer-Lindenberg and their col-

SAMI SARKIS/Getty Images (photograph); FROM "5-HTTLPR POLYMORPHISM IMPACTS HUMAN CINGULATE-AMYGDALA INTERACTIONS: A GENETIC SUSCEPTIBILITY MECHANISM FOR DEPRESSION," BY LUKAS PEZAWAS ET AL., IN NATURE NEUROSCIENCE, VOL. 8, MAY 8, 2005 (brain image); PRECISION GRAPHICS (illustration)

leagues studied brain scans from more than 100 nondepressed individuals to compare those with “short” and “long” variations of the serotonin transporter gene and found only a single but consistent difference in the subjects’ brains. Participants with the short variation of this gene, which causes less of the transporter protein to be manufactured and is believed to confer a higher risk of depression, had reduced brain tissue volume in area 25. Moreover, in the short-variant subjects, the activity of area 25 was functionally uncoupled from that of subcortical brain regions, such as the amygdala.

As a result of this study and others, neuroscientists now think of depression as a circuitry disorder involving abnormal activity in area 25 that disrupts its vast connected network, including the hypothalamus and brain stem, which influence changes in appetite, sleep and energy; the amygdala and insula, which affect anxiety and mood; the hippocampus, which is critical to memory processing and attention; and parts of the frontal cortex, which mediate insight and self-esteem.

The brain, after all, is an information-pro-

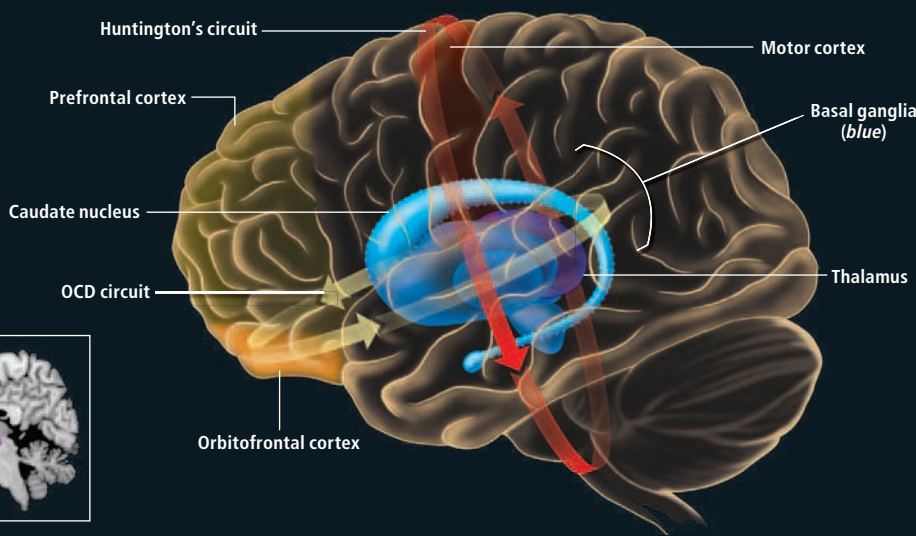
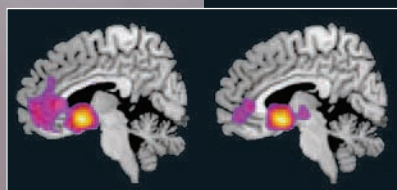
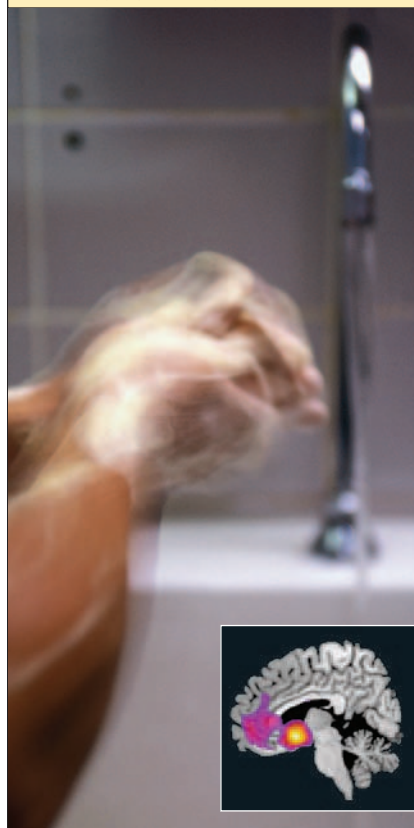
cessing organ, constantly integrating sensory inputs and coordinating responses. To extend the circuitry analogy, area 25 is believed to serve as a governor for a vast network, sensing and modulating the activity levels of other brain centers for fear, memory and self-esteem. A dysfunctional area 25 might therefore fail to coordinate the activity of these other centers so that information processing is biased, leading to distorted assessments of the internal and external world. If this conception is correct, resetting the firing of area 25 should moderate each of these downstream centers, thereby lessening the symptoms of depression. Indeed, Mayberg has demonstrated that direct electrical stimulation near area 25 reduces the activity of this node and can lead to recovery in people with depression who did not respond to standard therapies.

If area 25 can cause the brain, like a computer, to get stuck in a loop of abnormal activity, then the goal of treatment might be akin to “rebooting” a computer that has become frozen. The same principle can be applied to other mental disorders, particularly OCD, which appears even to a casual observer as though the suf-

[OCD CIRCUIT]

A CONSTANT PROD

People with obsessive-compulsive disorder (OCD) liken their intrusive thoughts and powerful urges to perform an action repeatedly to uncontrollable tics. A connection does exist: involuntary movements such as those seen in Huntington’s disease originate in the basal ganglia, a group of structures involved in initiating and coordinating basic motor actions. The caudate nucleus of the basal ganglia is also part of the brain circuit that drives OCD, along with the orbitofrontal cortex, a region critical to decision making and moral judgment, and the thalamus, which relays and integrates sensory information. In OCD sufferers (*left inset*), overactivity is evident in parts of the frontal cortex and basal ganglia, and firing of those regions is more synchronized than in normal subjects (*right inset*).



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ferer is trapped in a cycle of abnormal thoughts and behaviors.

Relentless Repetition

In an earlier era, obsessive-compulsive disorder was considered the prototypic neurosis, caused by psychic conflict, and ideal for treatment by psychoanalysis. People with OCD suffer from intrusive, repetitive thoughts (obsessions) and may be impaired by the need to perform stereotypic, repetitive rituals (compulsions). Some people may feel they are contaminated and will wash repetitively, to the point of abrading their skin. Others have a nagging sense of having failed to carry out some responsibility and will need to check the stove or the faucets or the doorknobs repeatedly before leaving the house. While people with this condition generally realize that their thoughts are senseless, they cannot control either the obsessions or compulsions, and in severe cases they may become completely disabled.

Patients with OCD often describe their symptoms as “mental tics,” as though they were physical movements that are not under voluntary control. Indeed, many people with OCD have actual tics as well as obsessive thoughts. Most

neuroscientists believe the regulation of movement involves a series of loops in the brain linking the cortex with brain areas such as the basal ganglia, which are centers for initiating and coordinating various aspects of movement. The involuntary motions seen in motor tics or more dramatically in Huntington’s disease reflect abnormal activity in this circuit, usually originating in the basal ganglia. Neuroimaging studies of patients with OCD have discovered abnormal activity in an adjacent loop that includes the orbitofrontal cortex, which is involved in complex tasks such as decision making, the ventral caudate nucleus within the basal ganglia, and the thalamus, which relays and integrates sensory information.

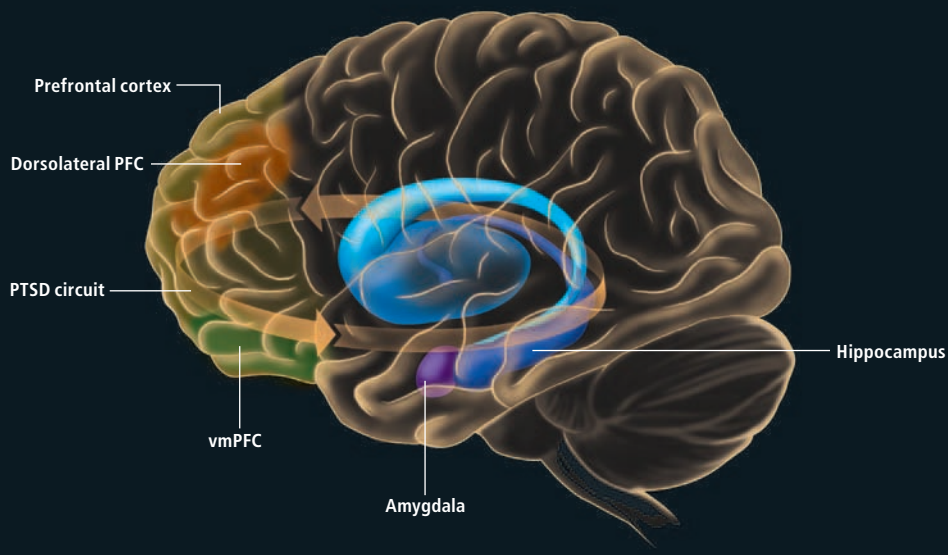
Evidence for overactivity in this circuit in OCD comes from more than just neuroimaging research. Most people with OCD report a profound reduction in symptoms with treatment, whether behavior therapy or medication, and this symptom improvement consistently goes along with a decrease in orbitofrontal cortical activity. In patients who do not respond to medication or behavior therapy, actually disconnecting the orbitofrontal cortex from the cau-

[PTSD CIRCUIT]

PERPETUATOR OF FEAR



In post-traumatic stress disorder (PTSD), cues that evoke a traumatic experience induce fear reactions long after the event. Malfunctioning of a brain structure called the ventromedial prefrontal cortex (vmPFC) is thought to increase vulnerability to the condition because it modulates the amygdala, a driver of fear and anxiety. Normally recovery after trauma, known as extinction, replaces a fear response with a neutral one through a learning process that engages the hippocampus and the dorsolateral prefrontal cortex. The vmPFC is believed to serve as the critical link between the dorsolateral PFC and the amygdala, allowing such extinction learning to quiet the amygdala.



date either by cutting the axons, or nerve fibers, that link them or by inhibiting electrical activity along the fibers also reduces the symptoms of severe OCD. Such a clear effect produced by physically altering the connections within a brain circuit offers strong evidence for the principle that symptoms of mental disorders can arise from the dysfunction of a specific circuit.

The underlying cause of the original circuit malfunction in OCD and other mental disorders is a separate question and may have complex answers. In some cases, a preexisting vulnerability may be present. Just as predispositions to high cholesterol or high blood glucose can run in families, individual genetic variations can influence the brain's development and operation. As in other complex health disorders, however, a genetic vulnerability does not produce illness alone—environment and experiences usually interact with genetic variations and may cause disease in some people but not others. This recognition that the brain's individual biology may interact with experiences to cause or exacerbate disordered circuits is particularly helpful in understanding the aftermath of trauma.

Unlearning Fear

Post-traumatic stress disorder is one of the most common afflictions of veterans returning from war. Once called combat neurosis or battle fatigue, it is now classified as an anxiety disorder that includes disturbing intrusive thoughts, such as flashbacks to a specific traumatic event, nightmares, a high state of vigilance and sleep disturbance. The disorder is also increasingly recognized in nonveterans who are victims of civilian violence such as rape or terrorism and even automobile accidents.

At first glance, PTSD seems unlikely to be a disorder caused by abnormal brain circuitry. Even its name describes the “cause” as an external event—a specific trauma. Symptoms such as disturbed sleep and increased vigilance are to be expected immediately after a traumatic experience, and for most people they naturally fade with time. PTSD, however, develops weeks and months later in about 20 percent of trauma victims. They continue to experience acute stress responses—in essence, intense fear reactions—to memories or other cues evocative of the original trauma.

In psychotherapy, the process of reducing fear is called extinction. It means specifically that through repeated exposure to a particular trauma-related memory or cue, without adverse

consequences, a patient is able to sever that cue from an automatic extreme fear response and to learn a new, neutral response to it. PTSD can thus be considered a failure of extinction. And recovery, whether natural or through therapy, requires new learning. Recent evidence from studies of animals and of people suggests that a dysfunctional circuit may make extinction harder to achieve, leaving a person vulnerable to developing PTSD.

The key hubs in the brain for fear are the amygdala and an adjacent galaxy of cells called the bed nucleus of the stria terminalis. These regions drive virtually all the symptoms of fear: racing heart, increased sweating, freezing and exaggerated startle responses. Nerve cells in the amygdala project their long, slender axons to centers in the brain stem that control those autonomic functions and also to areas in the forebrain that influence motivation, decision making, and the saliency of specific stimuli. But if the amygdala is the engine of fear, something in the brain should be responsible for turning it off when conditions change and fear is no longer necessary or appropriate.

Studies by Greg Quirk and his colleagues at the University of Puerto Rico show that a tiny area within the prefrontal cortex of rodents, known as the infralimbic region, is central to fear extinction. After teaching the animals to be afraid of a certain stimulus and then using extinction training so the animals could overcome their fear, Quirk's group found that activity in the infralimbic area increases during extinction, serving as a brake on the amygdala. Experimental microstimulation of cells in the infralimbic appears to cause extinction behavior, even in animals that have not been trained to overcome their fear. Furthermore, blocking neural function in this tiny prefrontal region impairs extinction in animals that have been trained, suggesting that the activity of this brain region is both necessary and sufficient to overcome fear.

In PTSD sufferers, neuroimaging studies point to abnormal activity in the ventromedial prefrontal cortex (vmPFC), which is comparable to the rat's infralimbic region. Five different studies have found that when exposed to trauma-related cues, people with PTSD show reduced activity in the vmPFC. They also have a smaller vmPFC relative to trauma-exposed control subjects without PTSD. Indeed, Mohammed Milad and his colleagues at Massachusetts General Hospital in a study of healthy volunteers recently reported that the thickness of this region was

[THE AUTHOR]



Thomas R. Insel, a psychiatrist and neuroscientist, is director of the National Institute of Mental Health, the federal agency that supports the study of mental illnesses. His early clinical research revealed the role of serotonin in obsessive-compulsive disorder, and his animal studies of the neurobiology underlying social attachment identified the importance of brain receptors for oxytocin and other substances in forming social bonds. In describing new findings in the neurocircuitry of mood disorders, as in all his work, Insel endeavors to bridge divisions between biology and psychology by highlighting the reciprocal relations between neural activity and behavior.

Studies of circuit functioning have shown not only that certain treatments work but *how* they may work by altering brain activity.

correlated directly with the capacity to extinguish fear memories. Elizabeth Phelps and her colleagues at New York University have demonstrated that extinction learning in humans, just as in rodents, involves an increase in vmPFC activity and a decrease in amygdala activity.

Neuroimaging has begun to identify the biological basis for improvements through cognitive-behavioral therapy, a form of talk therapy that emphasizes changing a patient's responses to difficult situations. The imaging shows the importance of the hippocampus for assessing context and of the dorsolateral prefrontal cortex for learning to tolerate and overcome fear. Because the dorsolateral prefrontal cortex does not connect directly to the amygdala, however, the vmPFC is thought to be the critical link between them that allows cognitive treatment to produce new learning and recovery.

Fundamental Shifts

The examples I have described from studies of people with depression, OCD and PTSD all suggest a correlation between the activity of interconnected regions of the brain and the abnormal behavior and feelings that characterize those disorders. In each case, the prefrontal cortex is involved, which is not surprising. The PFC is a brain region that is less developed in other mammals, which makes it difficult to study in

laboratory animals but also suggests that it is central to what makes us human. Scientists' best estimation is that the PFC acts as an overall governor for the brain and is the place where our most complex goals and motivations are processed so that we can make decisions and plan for the future.

In each of the disorders described, though, a different PFC structure and different connected regions appear to be involved. Beyond these examples, abnormal activity has also been seen in the dorsolateral prefrontal cortex in schizophrenia, and delayed maturation of the entire PFC between the ages of seven and 12 has been seen in attention-deficit hyperactivity disorder.

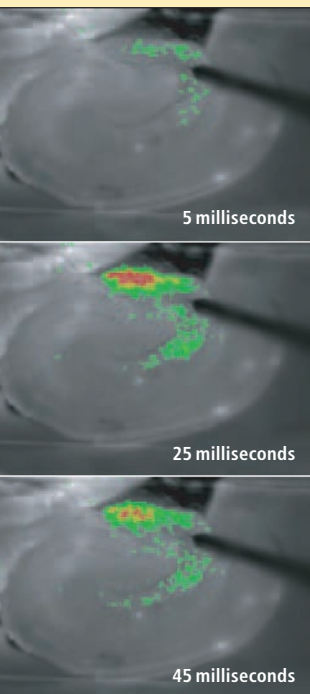
Although these correlations are compelling, further research is required to establish precisely which aspects of brain activity underlie these and other mental disorders. Data about genes that may increase risk for a given disorder will also help unravel the physiological mechanisms involved.

An ability to identify the brain circuit malfunctions underlying mental illness could have broad implications for diagnosis and treatment. At present, mental disorders are classified by their symptoms, which may overlap in many conditions and are not linked to any particular biological evidence. Reclassifying disorders based on brain function could yield a system of diagno-

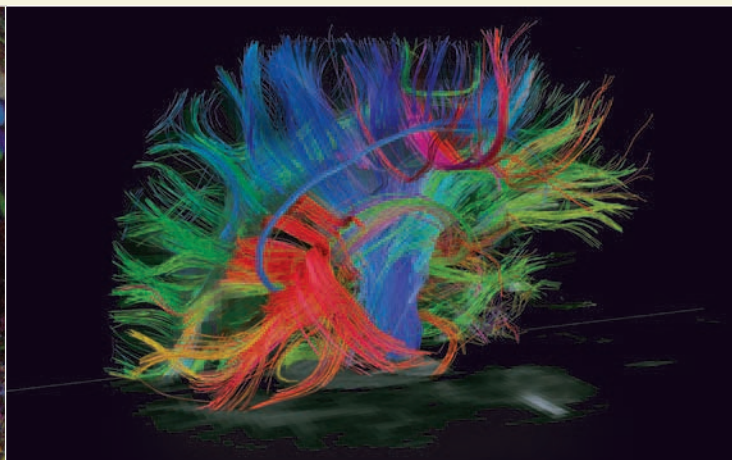
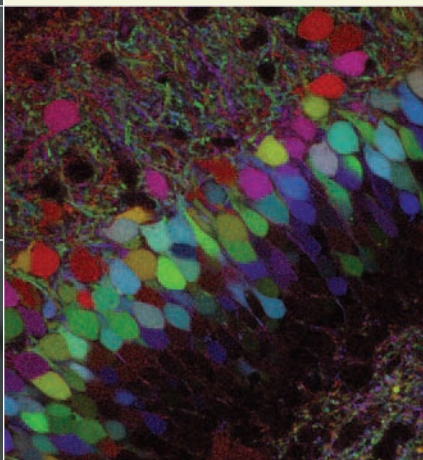
FROM "HIGH-SPEED IMAGING REVEALS NEUROPHYSIOLOGICAL LINKS TO BEHAVIOR IN AN ANIMAL MODEL OF DEPRESSION," BY KARL DEISSEROTH ET AL., IN SCIENCE, VOL. 317, AUGUST 10, 2007. REPRINTED WITH PERMISSION FROM AAAS (hippocampus); GETTY IMAGES (brainbow); COURTESY OF VAN J. WEDEEN (Massachusetts General Hospital) (connecting fibers)

[IMAGING]

BETTER WINDOWS INTO THE BRAIN

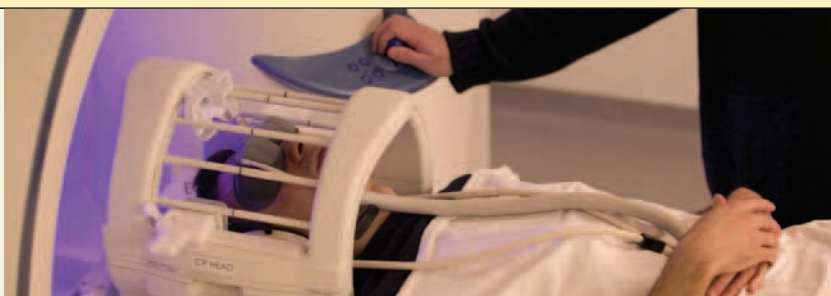


New neural-imaging techniques will expand and refine scientists' understanding of the malfunctions underlying circuit disorders by providing detailed views of brain activity and structure. Voltage-sensitive dye fluoresces red where neural firing is most intense in the hippocampus of a rat (*left panel*). Genetic engineering produces mice whose neurons fluoresce in multiple colors, yielding a "brainbow" picture of developing structures in the mouse brain (*below center*). Diffusion spectrum imaging, which uses MRI data to highlight the nerve fibers connecting different parts of the human brain, can aid in the study of disordered circuits (*below right*).



BRIDGING THE GAP

Disparities between medical treatment of a mental disorder such as depression and that of heart disease, for example, stem from differences in knowledge about the biological underpinnings of disease. Understanding the causes and nature of malfunctioning circuits in mental disorders will make earlier diagnosis possible through brain imaging and potentially blood testing for genetic and protein “markers” that signal a problem. Interventions can then be tailored to address the underlying cause directly and quickly.



DEPRESSION TREATMENT PAST, PRESENT AND FUTURE

	1960	2010	GOAL FOR 2020
Predictors of risk	None	Weak (family history, history of trauma)	Strong (genes, proteins, imaging)
Diagnosis	By interview	By interview	By imaging, biomarkers, interview
Interventions	Institutionalization, electroconvulsive therapy, insulin coma	Antidepressants, cognitive therapy	<ul style="list-style-type: none"> ■ Preventives: cognitive therapy or vaccine ■ Treatment options tailored to individual need: improved medications, cognitive therapy, brain stimulation
Outcomes	Relapse risk high, mortality high	50 percent response after 12 weeks, relapse risk high, mortality high	Response in 24 hours, relapse risk low, mortality low

sis based on biomarkers—biological signs such as brain activity patterns or chemical or structural changes specific to the condition. Just as blood tests of cholesterol or prostate-specific antigen levels and physiological measures such as electrophysiology and imaging scans are used in the rest of medicine, mental disorders could be diagnosed with greater precision and possibly identified earlier by their distinctive biological markers.

Currently a defining criterion for diagnosing schizophrenia is an episode of psychosis, just as heart disease was once defined by a person having suffered a heart attack. For brain disorders, behavioral and cognitive symptoms may be late manifestations of dysfunction in a circuit, and symptoms may appear only after compensatory mechanisms no longer suffice. In Parkinson's, observable symptoms emerge only after 80 percent of the dopamine-producing cells in the substantia nigra deteriorate. In Huntington's, motor problems become evident after 50 percent of basal ganglia neurons are lost.

Interventions will depend on the nature of the disorder. Studies of circuit functioning have shown not only that certain treatments such as cognitive-behavioral therapy work but *how* they may work by altering brain activity, and these insights might be used to improve existing ther-

apy techniques. Many current antidepressant and antipsychotic medications are also effective, but no more so than the drugs available 40 years ago. A better understanding of the physiological malfunctions in the brain underlying depression will likely lead to more targeted and curative treatments.

Perhaps the most immediate result of approaching mental disorders as brain circuit disorders will be changing public perception of these illnesses. In different generations, people with mental illness have been stigmatized as possessed, dangerous, weak-willed or victimized by bad parents. Science supports none of this. A scientific approach to mental disorders could allow those who struggle with these illnesses to receive full acceptance and the high-quality care that they deserve.

From the scientific standpoint, it is difficult to find a precedent in medicine for what is beginning to happen in psychiatry. The intellectual basis of this field is shifting from one discipline, based on subjective “mental” phenomena, to another, neuroscience. Indeed, today's developing science-based understanding of mental illness very likely will revolutionize prevention and treatment and bring real and lasting relief to millions of people worldwide. ■

➔ MORE TO EXPLORE

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