



Obsessions

Revisited

Scientists are taking a fresh look at obsessive-compulsive disorder, identifying its likely causes—and hints for new therapies

By **Melinda Wenner Moyer**

One day 12-year-old Elizabeth McIngvale became obsessed with the number 42, which happened to be her mother's age at the time, 11 years ago. When she washed her hands, she had to turn the sink on and off 42 times, get 42 pumps of soap and rinse her hands 42 times. Sometimes she decided that she actually needed to do 42 sets of 42. When she dressed, she put her right leg in and out of her pant leg 42 times, then the left. Even getting up from a chair took 42 attempts. She was afraid that if she did not follow her

self-prescribed ritual, something terrible would happen to her family—they might die in a car accident, for instance. “Everything I did was completely exhausting and grueling,” she recalls. “I was probably doing 12 to 13 hours a day of rituals.”

McIngvale was diagnosed with obsessive-compulsive disorder (OCD), a psychiatric illness that afflicts 2 to 3 percent of Americans, not all of them as severely as McIngvale. Individuals with OCD experience debilitating recurrent and persistent thoughts, or obsessions, which they try to suppress or eliminate with rituals, known as compulsions. Compared with people who have other anxiety or mood

disorders, adults with OCD are more likely to be single and unemployed. In fact, OCD is among the 10 most disabling medical and psychiatric conditions.

Current psychotherapy techniques and drugs help reduce or extinguish obsessive thoughts, but only rarely do patients overcome the disorder. Part of the problem, scientists now believe, is that researchers have had little grasp of OCD's true nature. Now, however, they may be reaching a turning point in their understanding, a change they hope will lead to new therapies.

Identifying the neural circuits involved provides possible targets for medi-

cines. With the help of genetic studies, researchers have learned that a brain-signaling chemical, or neurotransmitter, called glutamate plays a role, for example. Glutamate drives a brain circuit involved in making decisions that are associated with positive outcomes—one that operates abnormally in individuals with OCD. Perturbations of the immune system can also affect the same neuronal wiring, predisposing some people to OCD and related conditions. “This circuitry, which we're defining, is important for lots of different things that cross diagnoses,” says Benjamin Greenberg, a research psychiatrist at Brown University. The new data point away from the long-held notion that OCD results mainly from anxiety. Instead the disorder seems to spring from a drive to revisit thoughts and perform tasks over and over again.

Repetition and Reward

For centuries scientists have sought the roots of the affliction we now know as OCD. In the 1600s people who suf-

The essence of obsessive-compulsive disorder is now thought to be a repetitious stuttering of thoughts or actions, such as organizing and reorganizing a closet.

ferred from repetitive obsessions and compulsions were assumed to be afflicted with “religious melancholy.” By the mid-20th century psychiatrists in the tradition of Sigmund Freud described OCD symptoms as signs of “neuroses” that result from repressed instinctual or sexual drives. Vaguely echoing the Freudian view, the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, the “bible” of mental health diagnoses, currently classifies OCD as an anxiety disorder based on the persistent nervousness that patients typically display.

That thinking has begun to change, however. In a 2007 international survey, 60 percent of 187 authors of OCD publications challenged this rationale, with many arguing that no data show that anxiety actually causes the disorder. They believe anxiety is more of a side-light than a defining feature of OCD, and as a result, studying and treating anxiety may not be the best way forward. Instead, these experts contend, researchers should consider OCD as a problem based on urges that cause repetitive thoughts and behaviors. With that understanding, they think OCD should be officially grouped with illnesses such as body dysmorphic disorder (BDD), a preoccupation with an imagined defect in appearance [see “Imagined Ugliness,”



by Susanne Rytina; SCIENTIFIC AMERICAN MIND, April/May 2008]; Tourette’s syndrome, which causes physical and vocal tics; and hypochondriasis, excessive fear about having a serious illness. After all, these three disorders often develop in concert: about one third of BDD patients and up to half of Tourette’s sufferers also have OCD; meanwhile up to 15 percent of OCD patients are hypochondriacs.

This proposed new grouping—which could be penned in the next iteration of the *DSM* due out in 2013—may even have an important biological basis. Relatives of people with OCD are more

likely than average to have Tourette’s and BDD, suggesting that these ailments may have common genetic roots. (OCD itself is known to run in families: relatives of people with OCD are eight times more likely than others to also have the disorder.) And genetic clues are beginning to reveal the biology of OCD.

Some of the new insights confirm what we already suspected. Psychiatrists know that serotonin reuptake inhibitors (SRIs), drugs that increase the amount of the neurotransmitter serotonin (a regulator of mood, appetite and sleep) outside of neurons, are among the most effective medications for OCD; that fact suggests that serotonin signaling could be malfunctioning in OCD. A statistical analysis in 2008 added weight to this idea. In that study, James Leckman and his colleagues at the Yale University Child Study Center analyzed data from 19 studies involving 1,797 individuals with OCD and 3,786 people who did not have the disorder.

The researchers looked at variation in a single gene—the one for the serotonin transporter, a protein that mops up serotonin from between neurons. When too much of this protein is made, too little serotonin is left in the spaces

FAST FACTS

Compulsive Circuitry

- 1>> Scientists are now challenging the long-held notion that anxiety is the defining feature of obsessive-compulsive disorder (OCD).
- 2>> The neurotransmitter glutamate plays a role in OCD. It is critical to a brain circuit involved in making rewarding decisions that is abnormal in OCD patients.
- 3>> Immune system abnormalities could predispose some individuals to OCD by perturbing the same brain network.

between neurons, suppressing signaling. The researchers found that certain variations in the gene that increase the production of the protein are indeed more common in some OCD patients—in particular, Caucasians and those with childhood-onset OCD. In a 2005 experiment radiologist Georg Berding and his colleagues at Hannover Medical School in Germany reported that the serotonin transporter also binds abnormally to serotonin in unmedicated Tourette's patients and that BDD is sometimes successfully treated with SRIs as well.

Although the effectiveness of SRI drugs suggested that serotonin (and dopamine, another brain chemical) played a role, researchers have long suspected that glutamate might be important, too, based

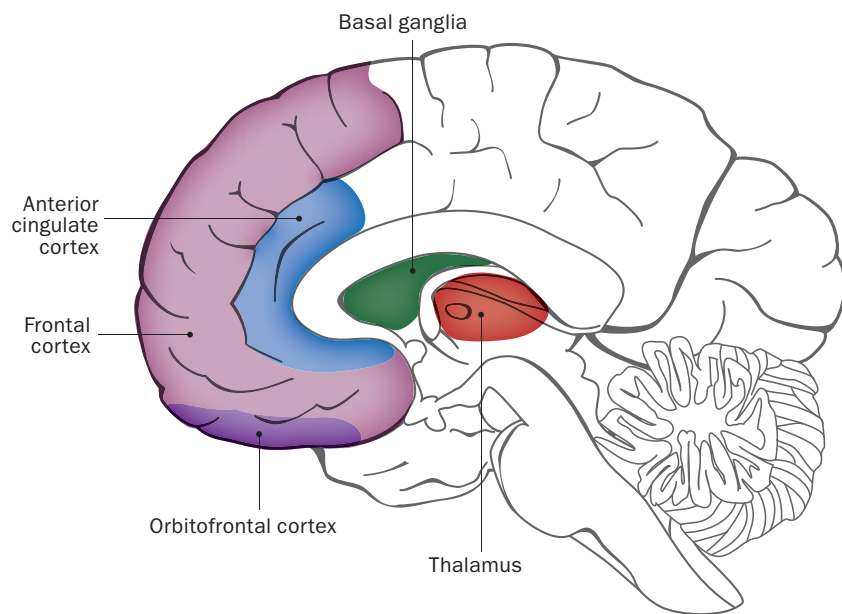
2002 by psychiatrist Edwin Cook, Jr., and his colleagues at the University of Chicago and the University of Michigan at Ann Arbor, have associated OCD with variations in the gene for a protein that removes glutamate from outside neurons. And in 2007 neurobiologist Guoping Feng, now at the Massachusetts Institute of Technology, and his colleagues reported that turning off a structural protein in mice that regulates activity at the glutamate receptor led to compulsive grooming.

Among other functions, glutamate fuels a brain circuit involved in making decisions that will lead to positive, or rewarding, outcomes, particularly when the choice requires sifting through data and experience. The so-called cortical-basal ganglia circuit comprises the orbit-

Relatives of people with OCD are more likely than average to have Tourette's syndrome and body dysmorphic disorder.

circuit, leading to nonsensical decisions and behaviors. Although investigators are loath to propose a precise mechanism, glitches in this neural wiring could alter a person's ability to sift through information or make decisions based on experience, leading them to sometimes see danger when none is present—and obsess over it. Other anomalies could in theory alter the experience of reward, such that repetitive behaviors trigger it.

In any event, these brain regions and their communications suffer a range of abnormalities in OCD. In a 2009 statistical analysis of 21 studies comparing the brains of mentally healthy people with those of OCD patients, psychiatrist Bruno Aouizerate and his colleagues at the University of Bordeaux in France reported that the OFC and part of the anterior cingulate cortex tend to be smaller in OCD patients. And in a 2008 study neuropsychologist Barbara Sahakian and her co-workers at the University of Cambridge used functional MRI scans to show that 14 OCD patients had reduced OFC activation, compared with



Obsessions and compulsions may stem from glitches in a brain circuit governing decision making and reward. The circuit includes the orbitofrontal cortex, a decision-making hub; part of the basal ganglia that mediates rewarding feelings; the fact-filtering thalamus; and the anterior cingulate cortex, which monitors mistakes.

on the fact that these neurotransmitter systems frequently work together. Glutamate is the brain's primary excitatory neurotransmitter: it tends to stimulate (rather than inhibit) neuronal signaling. As it turns out, glutamate facilitates neuronal communication in brain regions that have been implicated in OCD. Several family genetic studies, including one published in

orbitofrontal cortex (OFC), a decision-making hub; the striatum, a section of the basal ganglia involved in learning and the experience of reward; the thalamus, a region that filters facts and other data; and the anterior cingulate cortex, which detects errors. Mutations in the glutamate transporter gene might impair the protein's ability to regulate activity in this

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control subjects, while performing a computer task that required them to update their behavioral responses based on new information.

Imaging studies hint that the repetitive thoughts and behaviors that characterize disorders such as Tourette's and BDD are similarly driven by problems with this brain circuit. In Tourette's patients, data published in 2008 point to abnormalities in the connections between different nodes in the circuit; these are formed by so-called white matter, which is made up of the long axons that link one neuron to another. And a 2010 study hints that an abnormally small OFC and anterior cingulate cortex may underlie some cases of BDD.

Infectious Behavior?

Recent work has implicated another possible culprit in OCD: the body's immune system. For instance, a 2002 study reported that mice missing a gene involved in immune function demonstrated OCD-like behaviors. Molecular geneticist Mario R. Capecchi and his col-



The immune system may play a role in compulsions. Mice lacking one type of immune cell groomed themselves excessively.

leagues at the University of Utah bred mice lacking a gene for a protein called *Hoxb8* that was known to regulate the development of body shape in mice. Previous research had shown that the gene also helps to maintain myeloid progenitor cells, which mature into immune cells in the brain called microglia. The researchers were curious to see what happened to mice in the gene's absence. They found that the mice were surprisingly healthy—but groomed themselves and one another twice as often as mice typically do.

In a follow-up study published in May 2010 Capecchi's team discovered that these *Hoxb8*-deficient mice had 15 percent fewer microglia in their brains than normal, confirming that *Hoxb8* is important for microglia development. Then, when the scientists replaced the missing microglia by giving the mice bone marrow transplants, the rodents groomed themselves the ordinary amount, hinting that an adequate number of microglia are critical for staving off the repetitive actions characteristic of OCD. No one is yet sure of the connection between microglia and the disorder, but in addition to scavenging infectious material, microglia may also release immune chemicals called cytokines that control activity at neuronal junctions known as synapses [see "The Hidden Brain," by R. Douglas Fields, on page 52]. These immune cells are abundant in the cortical-basal ganglia circuit and make direct contact with synapses. Other studies reveal that microglia regulate neuronal cell death during development, and the absence of normal cellular pruning may create structural oddities that spawn behaviors characteristic of OCD.

Other types of abnormal immune responses seem to incite OCD as well. In 1998 pediatrician Susan Swedo of the National Institutes of Mental Health (NIMH) identified a group of children who had acquired OCD or related tic disorders immediately after suffering group A streptococcus infections, the cause of strep throat. Her work suggests that in the process of fighting the infection, the brain can accidentally develop antibodies against—and begin attacking—basal ganglia neurons, which are mistaken for the bacteria. These immune attacks may ultimately disrupt the cortical-basal ganglia circuit, leading to OCD symptoms. Swedo has found that severe tics characteristic of Tourette's disorder can also appear suddenly after strep throat infections.

The overactive immunity described in strep sufferers contrasts with the apparent underactive immunity Capecchi's group saw in their hyperhygienic ro-

Studies suggest that either overly vigorous or weakened immunity could put a person at risk for obsessive behavior.

dents. Other studies that have assessed the levels of immune cells and proteins in patients with OCD have produced similarly conflicting results, suggesting that either overly vigorous or weakened immunity could put a person at risk. That said, most OCD cases are probably not caused by infection or immune system irregularities. "There are so many patients [with strep infections], and not all of them get obsessive," says Aye-Mu Myint, a neuroimmunologist at Ludwig Maximilian University in Munich.

Tweaking Treatments

Currently one of the most effective treatments for OCD is a therapy known as exposure and response prevention (ERP). The idea is simple: therapists repeatedly expose patients to the objects or other stimuli that trigger their repetitive behaviors—by making them touch toilets, say—without letting them perform their associated compulsions. Eventually the patients realize that nothing bad happens when they fail to perform their rituals, and "the stimulus is not linked to generating anxiety in the same way it was," says psychiatrist Helen Blair Simpson of Columbia University and also director of the New York State Psychiatric Institute's Anxiety Disorders Clinic. Simpson and her colleagues, along with researchers at the University of Pennsylvania,

have studied the effects of ERP in clinical trials. In one collaborative study published in 2005, they found that about 60 percent of patients who started ERP treatment improved. The severity of their symptoms, as measured through tests, typically diminished by up to 55 percent, with improvements—such as the reduced need to engage in rituals—seen in as little as four weeks.

Adherence can be a problem, though. Eight of the 37 subjects withdrew from the trial after learning that they were assigned to ERP, and another eight dropped out in the middle of the therapy. “The side effect of the therapy is anxiety,” Simpson says, even though the therapy reduces such distress in the long run.

The second-line therapies for OCD patients are SRIs. But the drugs typically take eight to 12 weeks to start working, if they ever do: on average, they reduce the severity of symptoms by only 20 to 40 percent. Combining SRIs with antipsychotic medications can, in some instances, boost response rates, as can using SRIs while undergoing ERP.

Individuals who do not respond well to SRIs might one day benefit from medications that calm glutamate activity in the brain. Several open-label trials and case reports have shown that drugs such as topiramate and riluzole—which work, in part, by blocking specific glutamate receptors—can improve symptoms when taken with SRIs. Scientists are now conducting placebo-controlled trials of these drugs to see how well they perform on their own. Another drug, D-cycloserine, which has been shown to help rats overcome conditioned fears by enhancing activity at receptors for the neurotransmitter N-methyl-D-aspartic acid, is now being tested in OCD patients in combination with ERP in hopes that it will help patients respond to therapy more quickly.

Greenberg and his colleagues are also studying whether deep brain stimulation



Using exposure and response prevention, a therapist might ask a patient who repeatedly checks the stove before she leaves the house to practice checking the stove only once.

(DBS)—a proven treatment for Parkinson’s disease that involves inserting electrodes into the brain—could treat OCD. A handful of small trials suggest DBS reduces symptoms for some people with severe OCD, perhaps by normalizing the cortical-basal ganglia circuit. “We’ve found that DBS seems to actually restore rhythmic activity in these areas,” says Anthony Grace, a neuroscientist at the University of Pittsburgh. In the ongoing trial, Greenberg is stimulating nerves that link to various parts of this circuit, pinpointing which components are the most important for regulating symptoms. “It gives us a tool to study the disease,” says Suzanne Haber, a neuroscientist at the University of Rochester.

Researchers suspect that OCD may represent a cluster of different conditions rather than just a single disorder; after all, sufferers may exhibit disparate obsessions and compulsions with activities

such as hoarding, cleaning, ordering and checking. “We’re assuming that OCD is one thing, and it probably is not,” says Gerald Nestadt, director of the Johns Hopkins University Obsessive-Compulsive Disorder Program. If a compulsion to order things, say, has a different biological cause than does obsessively collecting objects, researchers would like to identify those separate OCD conditions and tailor treatments to each one. To explore this approach, the NIMH is developing mental health research guidelines that will help scientists

better identify relevant OCD subtypes and classify patients for research studies. As part of this program, Greenberg and his colleagues currently have a \$10.5-million grant to identify the specific brain networks that affect treatment responses.

Some of these new and future approaches may ultimately benefit patients such as McIngvale. Thanks to ERP, McIngvale, now 23, is pursuing her Ph.D. in social work and is the spokesperson for the International OCD Foundation. She still contends with hand-washing compulsions, which she tries to hide from her colleagues, and struggles to stop herself from repeating fruitless tasks that consume her day. “There is no cure [for OCD],” she admits. But someday, McIngvale hopes, treatments stemming from a better understanding of OCD may make her life easier. She may even forget why she ever cared about the number 42. **M**

(Further Reading)

- ◆ **Recent Advances in the Genetics of Obsessive-Compulsive Disorder.** Jack F. Samuels in *Current Psychiatry Reports*, Vol. 11, No. 4, pages 277–282; August 2009.
- ◆ **Obsessive-Compulsive Disorder and Its Related Disorders: A Reappraisal of Obsessive-Compulsive Spectrum Concepts.** D. L. Murphy et al. in *Dialogues in Clinical Neuroscience*, Vol. 12, No. 2, pages 131–148; 2010.
- ◆ **OCD? Your Immune System Could Be to Blame.** Mitch Leslie in *ScienceNow*; May 27, 2010. Available at <http://news.sciencemag.org/sciencenow>
- ◆ **Should an Obsessive-Compulsive Spectrum Grouping of Disorders Be Included in DSM-V?** Katharine A. Phillips et al. in *Depression and Anxiety*, Vol. 27, No. 6, pages 528–555; 2010.