

Unshackling the Slaves of Obsession and Compulsion: A Brain Science Success Story

For more than a century, scientists sought the explanation of a disorder affecting millions—obsessive-compulsive disorder (OCD)—in child-rearing practices or personality conflicts and prescribed psychiatric therapy, largely without success. Then, in the 1970s and 1980s, scientists began to view OCD as a biological problem. The resulting revolution in understanding and treating OCD drew not only from clinicians, but also from several lines of neuroscientific work and other disciplines, including genetics and immunology. Judith Rapoport, chief of the Child Psychiatry Branch at the National Institute of Mental Health, and her colleague, Gale Inoff-Germain, explore the OCD success story—and its current limitations—for its lessons for research on other neuropsychiatric diseases and for public policy.



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*by Judith L. Rapoport, M.D.,
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Samuel Johnson, one of the literary giants of the 18th century, leapt in and out of doorways before finally entering them and repeatedly touched buildings he passed while he walked the streets of London. Johnson suffered from what we now recognize as a severe case of obsessive-compulsive disorder (OCD) and complex motor tics. Among other famous figures who probably had OCD were the religious leaders John Bunyan, who was plagued by blasphemous thoughts damning God during his sermons, and Martin Luther, who continually feared that he had left out some important part of a prayer or sermon—an omission that would be a terrible sin. Both men had obsessions, that is, repetitive and unwanted thoughts that they could not control.

OCD is a common, often chronic illness that affects 2 to 3 percent of the population, according to many studies. People severely affected with OCD

are imprisoned by sterile and frustrating self-imposed rituals (compulsions) and ruminations (obsessions). Some spend many hours every day washing themselves or checking something. For example, one woman never left home because of her compulsive need to check and recheck that the doors and

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windows of her house were locked. A teenage boy developed hypothermia and was taken to the hospital after his endless showering used up the household's hot water. Even when the water became cold, he could not leave the shower because he did not "feel clean enough." A successful newspaper reporter could no longer entertain anyone in her home because her inability to throw out newspapers and magazines had turned it into a virtual ware-

house for old paper. She came to treatment only after her house was condemned as a fire hazard. These are examples of extreme OCD, but the quality of life for most people with the disorder is compromised by boring and endless preoccupations with unlikely dangers or fears of contamination.

Although OCD has been recognized for more than 100 years, the past 25 years have seen an explosion of new information, new treatments, scientific excitement, and optimism among physicians. Once viewed as a quintessentially psychological disorder, OCD is now a model for how brain research can lead to understanding and treating a common, long-standing neuropsychiatric disorder. Inspired in part by this work, other anxiety disorders such as separation anxiety and specific phobias are increasingly being characterized in terms of specific brain pathways that do not function normally. Effective treatments are documented for most (although not all) adults and children with OCD, and today this disorder is seen as a classic success story of neuroscience and neuropharmacology. The principal challenges that remain are to find new means to help the significant minority of patients who do not respond to known treatments and to make all forms of treatment more widely available. Also an issue is the tendency of both researchers and physicians to label too many disorders "OCD" or "OCD spectrum," which helps neither patients nor the direction of research. But first, the OCD story.

OCD BASICS

People with OCD are usually as sane and rational as the rest of us, but their very normalcy can make them want to keep their "crazy" symptoms

a secret—one reason OCD was long believed to be rare. Even people with OCD who are in treatment for, say, depression, may not mention their OCD symptoms to their therapist. Who would want to reveal a compulsive need to count and recount the number of tiles on the floor, to tie and retie shoe laces to make them symmetrical and “just right,” or to confess endlessly to nonexistent sins?

Although science now has a far better understanding of OCD, that understanding has not reached the lay public. When people (particularly children) first experience symptoms of OCD, they are bewildered by what they find themselves doing and thinking. One bright and imaginative boy wondered whether he was being used by Martians to carry out their orders and thought the Martians were looking for a sign that he had received their “message.” He simply could not explain his symptoms (repeatedly entering and reentering each room) to himself any other way, so he was relieved to meet other children with similar behaviors, which scientists call motor rituals. Each new generation of patients needs to be educated that OCD is fairly common, related to brain abnormalities, and treatable.

Early theories about the causes of OCD focused on psychosocial influences, such as parenting styles, and the role of psychological defense mechanisms. Even traditional analysts, however, noted that psychoanalysis was seldom an effective treatment, and Sigmund Freud presciently maintained that OCD was a brain disorder.

In the 1970s, several independent studies launched a revolution in the understanding of OCD. First, a five-city epidemiologic study in the United States—a kind of psychiatric “census”—showed that OCD occurred in 2 to 3 percent of the population, or about 7 million people according to the population of the United States today. Second, both anecdotal evidence and pilot studies suggested that the new group of antidepressants known as serotonin reuptake inhibitors (SRIs) might be helpful not only for depression but also for OCD. This led to large groups of patients with OCD being sought for double-blind, placebo-controlled trials to make sure that the drugs actually worked on obsessions and compulsions, not just on depression.

For those of us involved in running the trials, the results were unforgettable. At first, the change in the patients we were studying was gradual, but by the end of the eight-week trials, it was clear that the drug that increased brain serotonin helped and that the placebo and other antidepressants that did not affect serotonin did not help. People who

had OCD for years described how they could now “shrug it off” or how the unwanted thoughts and impulses were somehow fading. We saw people reclaim their lives, go back to work. One man who had lived in

isolation for years emerged and married his high school sweetheart. A young girl who had previously avoided playmates because of her contamination fears was able to stand in front of her sixth-grade science class and explain how she overcame her OCD.

Once researchers began seeing significant numbers of people with OCD, often along with their families, some striking patterns appeared. Although relatively rare cases of OCD are induced by trauma (for example, rape or other violent assault), most cases are not. About 20 percent of the patients had one

or more other family members with OCD, and about 50 percent of the adult patients said the disorder had started before they were 15 years old. That discovery has led to increased study of children with OCD. In a few important ways, childhood OCD differs clinically from the adult pattern. Childhood-onset OCD is more likely to run in families (that is, it may be more genetic), and it is more likely to be present together with motor tics (for example, excessive eye blinking or shrugging of the shoulders) or Tourette’s syndrome (a combination of motor and vocal tics). A subgroup of children may develop OCD as a result of an autoimmune reaction to streptococcal infection.

THE NEW NEUROBIOLOGY OF OCD

On the basis of the initial epidemiologic and pharmaceutical studies, and brain imaging studies that followed beginning in the 1980s, the brain circuitry of OCD has become one of the most clearly and meaningfully delineated brain dysfunction patterns known.

As scientists had seen, the first important class of drugs discovered to dramatically benefit people with OCD involved the neurotransmitter serotonin. Although many lay people assume that drugs are developed from a biological understanding of a disorder, the converse is often true. For example, the effectiveness of antipsychotics was discovered accidentally, but subsequent studies of the action of these drugs led to the recognition that the dopamine system was important in understanding

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psychosis. The discovery that the serotonin reuptake inhibiting drug clomipramine, as well as the selective serotonin reuptake inhibitors (SSRIs) such as Prozac, were useful for OCD provided the clue that brain serotonin might not be normal in OCD. The study of the biology of OCD has also broadened to include other neurotransmitters and compounds, such as those that affect dopamine and, more recently, glutamate.

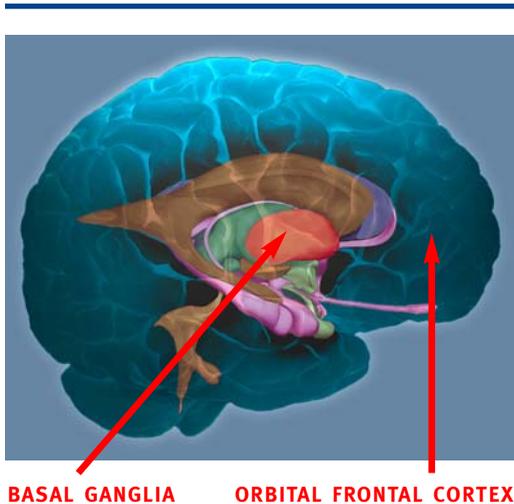
Neuroimaging techniques—including computer-assisted tomography (CT), positron emission tomography (PET), and, most recently, functional magnetic resonance imaging (fMRI)—were critical to understanding OCD. Studies have shown smaller brain volumes and abnormal patterns of brain activation in several regions, including the orbital frontal cortex and the basal ganglia, in people with OCD. These discoveries were supplemented by magnetic resonance spectroscopy studies suggesting that OCD may involve brain abnormalities in the neurotransmitter glutamate.

Hypotheses about possible abnormalities in the part of the brain called the basal ganglia in people with OCD have come not only from noting the frequent connection between OCD and motor or vocal tics

but also from case reports of sudden onset of OCD after local damage to this brain region. Literally, basal ganglia means “lower nerve knots,” and the ganglia are indeed buried deep within the brain. Animal studies have shown this part of the brain to be important for planning complicated motor movements and for making decisions about these movements. These reports of OCD associated with basal ganglia damage were followed by the fascinating observation that several neurological problems thought to be related to basal ganglia damage (such as Sydenham’s chorea, tics, or Tourette’s syndrome) are also associated with OCD. That is, children and adults with basal ganglia disorders are likely to also have OCD.

The observation that Sydenham’s chorea is associated with OCD provides support

for an autoimmune response model of OCD, because, in this chorea, an autoimmune response to streptococcal infection leads to antibodies that attack selective regions of the patient’s brain.



This composite 3D MRI and CT scan image shows two parts of the brain that have been shown to be abnormal in people with OCD: the orbitofrontal cortex and, deep within the brain, the basal ganglia.

Brain imaging studies have also shown that a part of the cerebral cortex, the orbital frontal cortex, appears to be overactive in people with OCD. This region, too, is involved in complex planning and is also connected to systems in the temporal lobe that modulate emotions. Thus, many clinical aspects of OCD, such as the overfocus on planning and extreme anxiety, are now coming together with the neurobiological research.

A FAR FROM UNIFORM DISORDER

Although commonalities exist, several subgroups of people with OCD have been definitively or tentatively identified. For example, treating abnormalities in the dopamine system seems important in people with both OCD and a tic disorder, making up one possible subgroup. This subgroup appears to overlap considerably with childhood-onset OCD. Determining characteristics that are common to all people with OCD, compared with those that are distinctive to subgroups, will help scientists better understand what causes OCD and will also allow more

individualized treatment planning.

Another possible subgroup, which appears to involve an autoimmune dysfunction, was defined in children and labeled with the acronym PANDAS, for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. The

PANDAS syndrome is diagnosed by specific criteria, including the presence of OCD or a tic disorder and two or more episodes with abrupt onset or sudden worsening of symptoms after streptococcal infection.

Some controversy has long been part of the scientific debate about the role of immune processes in neuropsychiatric disorders. For example, non-steroidal anti-inflammatory drugs appear to be of some benefit to people with Alzheimer's disease, and studies of the brains of people who died of the disease have found indications of inflammation. Consequently, inflammation is suspected to play a role in causing Alzheimer's, although this has not yet been proved. Because both streptococcal infection and obsessive compulsive symptoms are commonly found in children, it is difficult to be sure that the streptococcal infection is actually involved in causing the OCD. Figuring out cause and effect is also complicated because, in general, OCD and tics may come and go. But support for the role of antibodies in OCD and similar disorders comes from a variety of research, including initial studies of treatments based on an autoimmune approach that we discuss later.

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THE GENETICS BEHIND OCD

Evidence from family and twin studies points to a genetic component of OCD, especially when it begins in childhood. Family studies let scientists see what disorders appear together in families. A key issue in these genetic studies is deciding what to count as OCD. Some family members may have tics, but no OCD symptoms. Other family members may have trichotillomania, a disorder involving hair-pulling that is sometimes viewed as related to OCD. Studying entire families, therefore, helps researchers see what might be part of a whole “OCD spectrum,” and looking at the genetic information using these broad or spectrum definitions as well as narrow ones (just classic OCD) is essential in modern genetic studies.

An outpouring of technological advances in genetic research has begun to transform the study of OCD. Newer methods will soon enable even faster and less expensive acquisition of genetic information, but

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promising results are already emerging.

Candidate genes, selected so far on the basis of which drugs work best for OCD and on the brain circuitry discovered through imaging studies, are being examined to see whether they are associated with OCD. Studies that compare people with OCD and those without the disorder focus on whether particular chromosomal markers are more frequent in the first group. Probably most important is that two studies of families

with multiple members who have OCD have pointed toward the same region on chromosome 9.

Another kind of research called cytogenetic study (involving the study of physical duplication, deletion, or disruption of chromosomes) has also yielded an intriguing result. In several such studies, a chromosome deletion known as the 22q11 deletion (which results in a disorder called velocardial facial syndrome) was found to be associated with OCD, particularly in children.

As yet, these advances in genetics are too preliminary to benefit people with OCD or their families, but scientists know that at a certain point an understanding of genetics leads to, or combines with, an understanding of physiology to make huge gains possible. In schizophrenia research, for example, studies of the gene *COMT* (which regulates neurotransmitter metabolism) have shown different brain responses in people

with schizophrenia who have the risk form of the gene (the “risk” allele) when they perform certain cognitive tests and in normal control subjects. Other studies of risk genes involved in depression have shown different brain patterns in response to faces expressing emotion in people with the risk form of those genes.

TREATMENTS, PROVEN AND POTENTIAL

Cognitive Behavior Therapy

Pharmaceuticals are only one approach to treating OCD. Cognitive behavior therapy (CBT) was shown to be effective for both children and adults with OCD, and for many people it will be the first and only treatment that they will need. The most effective part of behavior therapy is usually the repeated and voluntary exposure to something that triggers the OCD, for example, touching something “contaminated” and then not washing for a certain period of time. Each symptom is addressed in turn, and it usually takes several weeks to see results. Nevertheless, CBT has a great advantage over drugs: it continues to work when the therapy has stopped, but drugs typically are effective only while they are taken.

Many kinds of behavior therapy exist. For example, the commercial Weight Watchers plan uses behavior therapy, and the physiological training method called biofeedback is also a kind of behavior therapy. But these techniques are different and will not help people with OCD. For these people, it is important not only to have a trained behavior therapist but also one experienced with OCD and with what is called exposure with response prevention (ERP). CBT/ERP has been studied for decades, but only recently have the studies begun to include large sample groups of subjects and appropriate control subjects (comparison groups) so that firm conclusions may be drawn. The consensus, though, is that, if CBT/ERP is available, it should be tried first, before drugs. Moreover, recent studies in both adults and children show that the combination of medication and CBT can be more effective than either approach used alone.

SRIIs

Initial research on treating OCD focused on the SRIIs, drugs that increase serotonin availability at the nerve endings. What is particularly helpful in treatment is that, although one SRII or SSRI may not be sufficiently effective or may produce unpleasant side effects for a particular patient,

a different drug may be both effective and without unwanted side effects for that person. Drugs approved for the treatment of OCD are listed in the box at left.

Drugs Approved for Treatment of OCD:

clomipramine (Anafranil)

fluoxetine (Prozac)

fluvoxamine (Luvox)

paroxetine (Paxil)

sertraline (Zoloft)

Note: Red text indicates those drugs approved by the Food and Drug Administration for children and adults.

Augmenting Drugs

Complete remission of OCD symptoms in response to a single drug (typically an SSRI) is rare. Physicians will, therefore, try several different drugs with patients and experiment with dosage. But after that, a combination of an SSRI with another drug may be used for those who are still severely affected (sometimes called “treatment resistant” or “treatment refractory”). These secondary

drugs are used to “potentiate” or “augment” the effects of the first.

Drugs that affect the dopamine system were among the first to be shown (in a double-blind, placebo-controlled trial) to be effective as augmenting agents for OCD. Many of those currently used are atypical antipsychotics, such as risperidone or olanzapine. But their long-term effects when used in OCD are still largely unexplored, and information describing use with children and adolescents is limited. These drugs may also cause weight gain and have other negative effects on the endocrine system, so patients need to be followed carefully by a physician.

Autoimmune Treatments for PANDAS

A notable treatment success is based on the autoimmune model of PANDAS. For example, a double-blind, placebo-controlled study of intravenous immunoglobulin (IVIG) showed improvement for the patients who received the IVIG and not for the placebo group. An open trial (that is, a trial without a placebo control) of plasmapheresis (plasma exchange) also looked encouraging. For several reasons, these “immunomodulatory” treatments are not currently being considered for general use, but they are prompting sufficient interest to encourage continued research.

The only published double-blind study of penicillin treatment with a placebo control group did not show an improvement in symptoms from the antibiotic. Despite this finding, some physicians are using penicillin prophylaxis for children whose OCD appears to spike repeatedly in relation to streptococcal infections. Clearly, this study should be replicated, perhaps with a more carefully chosen group of subjects.

New Drug Treatments

Although the same particular biological processes and pathways may be disturbed in most people with OCD, it is not clear which biological systems are the main sources of the problem. This complexity compounds

Other brain-based approaches being explored in an attempt to help those unresponsive to available treatment are at the same time clarifying how the brain works and how various treatments achieve their results.

the difficulty of developing treatments, but new approaches are continually being explored on the basis of increased knowledge about OCD.

For example, although it is still early in the research, some open trials and limited results suggest that opiates such as oral morphine sulphate or glutamate antagonists (drugs such as riluzole that block or limit effects on glutamate) may be helpful. The positive results

of using these drugs in people with OCD support the suspicion that signaling pathways in the brain for neurotransmitters other than serotonin may be involved in some kinds of OCD.

New Nondrug Treatments

Surgical efforts to treat psychiatric disorders during the first half of the 20th century appropriately resulted in a public skepticism that persists to this day, but over the past decade neurosurgery has been revolutionized. Although still used only for the most severely incapacitated and “intractable” patients, and only after approval by formal medical and ethics boards, surgical treatments use dramatically improved techniques. One such technique is radiosurgery, which involves lesions produced by controlled cross-fired irradiation at localized sites in the brain. Still, this and other neurosurgical procedures must be considered experimental, at this stage, and are unlikely to be studied in children.

Other brain-based approaches being explored in an attempt to help those unresponsive to available treatments are at the same time clarifying how the brain works and how various treatments achieve their results. The most noninvasive technique of this type is transcranial magnetic stimulation (TMS). TMS is used with awake patients, requires no anesthesia, and produces direct cortical brain stimulation by creating a transient magnetic field that induces electric currents in the brain. So far, the technique is not particularly promising as therapy for OCD, but TMS has yielded information about OCD brain circuitry and may have a role in guiding or screening for more invasive procedures.

Another new area is deep brain stimulation (DBS), which appears to produce some of the outcomes previously obtained by neurosurgeons when they made lesions in the brain. Initial evidence of its effectiveness came in treatment of movement disorders, particularly tremors and Parkinson's disease. DBS is a flexible and reversible technique that involves high-frequency stimulation of neurons at sites important for movement disorders. Although DBS is still a new tool, some preliminary evidence for its effectiveness exists, and a few severely ill patients with OCD are being studied.

DOES AN OCD SPECTRUM EXIST?

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been suggested as part of an OCD family, or spectrum, of disorders. Included are eating disorders such as anorexia nervosa, trichotillomania, body dysmorphic disorder (a preoccupation with an imagined physical defect in appearance or a vastly exaggerated concern about a minimal defect), autism, and Asperger's syndrome. For some of these disorders, however, including trichotillomania and anorexia, the SRI drugs are

not particularly beneficial. For others, such as autism, some help comes from these drugs, but the results are usually not dramatic.

For now, this particular spectrum grouping does not seem to be useful in terms of clinical treatment. The drugs used for OCD seem less helpful for these other disorders, and behavior therapy appears more difficult. Many psychiatric disorders, after all, involve excessive activity or overfocus in one sphere of life, and the proposed OCD grouping potentially could become ever-larger without providing more useful information. Until a specific brain abnormality or a clear and salient risk gene is identified for OCD, scientists may have little to gain by identifying such a spectrum. This lesson can be applied more widely. Broad definitions of the disorder were helpful for family research studies on schizotypal personality and other schizophrenia spectrum disorders but have not helped treatment.

CAVEATS TO THE SUCCESS STORY

Most success stories have limitations, and OCD is no exception. For at least 25 percent of people with OCD, treatment is not effective, even in

those people who have tried both behavior therapy and drugs. People with severe or debilitating OCD for whom drugs are effective face the expense of life-long treatment. Some types of OCD (for example, severe hoarding) are particularly difficult to treat. These are both problems and potential clues to new understanding.

Answers will come from additional research. For example, researchers still need to explore the relation of OCD to neuroendocrine changes. OCD exacerbations often occur in pregnancy, but scientists do not know why, nor do they understand whether a relation to diabetes mellitus exists, as has been suggested. Also, continuation of sophisticated magnetic resonance spectroscopy studies will undoubtedly lead to investigating processes in the brain such as the glutamate system.

As is the case with other chronic diseases, the cost of appropriate treatment can be beyond the reach of many people with OCD. Another concern is that outside large cities the availability of therapists trained in CBT/ERP is severely limited.

These daunting obstacles continue to limit the extent to which OCD can be treated, affecting patients, family members, and the health care professionals who put forth so much effort and determination in meeting the challenges of OCD. The results are considerable human and economic costs to these many patients, their families, and their communities.

Despite all the successes so far in research and treatment, the fruits of this neuroscience success story are not available to all who need them so desperately. It is particularly frustrating to have this problem now, when the research has never been so exciting and so ready to be translated into proven new treatments. An important first step would be parity in reimbursement for all psychiatric disorders, comparable to that for diseases labeled physical.

The OCD story is perhaps the most dramatic example yet of how a once purely “psychological” disorder is now understood in largely biological terms. This success also shows the importance of interdisciplinary research, because it took a combination of epidemiologic, pharmacologic, brain imaging, neurosurgical, and immunologic studies to work out the OCD puzzle. Scientists must find a way to train even more people who are knowledgeable about both clinical psychiatric

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syndromes and these synergistic fields of basic research so that what they have learned in understanding OCD will truly be a model for what modern neuroscience can achieve. ■

If you or someone you are trying to help may have OCD, an important step is professional diagnosis of the disorder. Psychology or psychiatry departments at universities and medical schools have lists of physicians, social workers, and behavior therapists. The Obsessive Compulsive Foundation, a nonprofit, national organization, has a Web site (www.ocfoundation.org) that offers up-to-date information and resources, including a referral list of mental health professionals for your geographic area and a low-cost newsletter. The National Association of Cognitive-Behavioral Therapists (www.nacbt.org) is another useful resource. These organizations can help you find qualified professionals, get reliable information, and connect with support groups.



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