The causes of this syndrome have long been controversial. Now research is unearthing both genetic and environmental triggers and pointing the way to better treatments

Making Sense of Tourette's

When Purdue University neurobiologist Peter Hollenbeck lectures in front of his 400-student cell biology class, the symptoms of his Tourette syndrome—the up-and-down movements of one arm, the twists of his head, the barely audible sounds—virtually disappear. But, by the time the lecture is finished, the urge to move is unbearable. He quickly retreats to his office to "tic, tic, tic," he says, "until the need subsides."

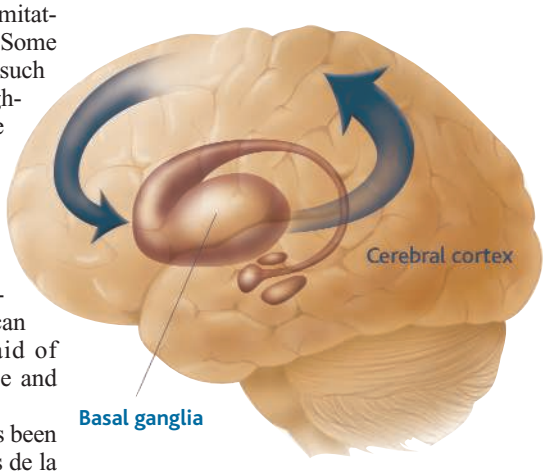
Hollenbeck has a mild case of Tourette syndrome, whose effects he chooses to endure rather than experience the slight sedation he feels when medicated. Other people are more harshly affected. A small minority exhibits complex behaviors such as imitating others or blurting out profanities. Some are tormented by obsessive thoughts, such as the scientist who had to give up high-energy physics because every time he saw a "Danger—High Voltage" sign, he felt compelled to touch the equipment. Many cases of Tourette's are socially inconspicuous, and people with the syndrome deride the stereotyped depictions that occasionally appear in the media. But severe cases can still provoke, as James Boswell said of Samuel Johnson's Tourette's, "surprise and ridicule."

The cause of Tourette syndrome has been controversial ever since Georges Gilles de la Tourette, a neurologist who shared a mentor with Sigmund Freud at the Salpêtrière Hospital in Paris, first described the condition in 1885. Is the syndrome the result of hysteria (Tourette's hypothesis), repressed sexual conflicts, or oppressive mothers, which were the favored explanations for much of the 20th century? Or is it an organic defect of the brain, as many neuroscientists and physicians now hold? The ability of neuroleptic drugs, beginning with haloperidol in the 1960s, to reduce tics supported the neurologic position. But why then are people with severe cases sometimes drawn toward socially proscribed behaviors?

New findings are beginning to resolve old controversies. Researchers are identifying parts of the brain affected by the syndrome. They are teasing out the genetic and environmental factors that help produce it. New behavioral and pharmacological treatments are improving the quality of life for Tourette's sufferers. Although many features of the syndrome remain baffling, researchers say that the intensified research of recent years has begun to pay off.

Defining the phenotype

The wide range of Tourette's symptoms makes it tough to figure out how many people have the syndrome. Many children exhibit tics such as blinking or shrugging. When researchers observed first- through sixth-grade classrooms in Montgomery County, Maryland, in 1999–2000, they saw single or occasional tics in 18% of children and persistent tics in 6%. But just a fraction of these children would be diagnosed as having Tourette syndrome. Current diagnostic criteria require the presence of multiple motor tics and one or more vocal tics that persist for more than 1 year. Typically, the tics wax and wane over the course of weeks and months, with old tics disappearing and new ones taking their place. Children often show the initial signs of tics at ages 6 or 7, and in many cases the tics diminish significantly in the mid- to late teen years.



Faulty wiring? Tourette syndrome appears to arise from defects in neural circuits (shown schematically by arrows) passing from the cerebral cortex through the structures constituting the basal ganglia and back to the cerebrum.

"When I'm asked how many people have it," says John Walkup, a child and adolescent psychiatrist at Johns Hopkins University (JHU) School of Medicine in Baltimore, "my response is, 'Have what: mild tics or a severe case?' " According to Lawrence Scahill, who studies neuropsychiatric disorders at the Yale Child Study Center, a plausible lower bound for the syndrome is 1 in 1000 people and a plausible upper bound is 1 in 100. But because many people who would meet the diagnostic criteria for Tourette syndrome never seek treatment, better estimates are elusive.

Comorbid conditions complicate many diagnoses. As many as half of the patients who come to clinics with the symptoms of Tourette syndrome also have other disorders. Obsessive-compulsive disorder (OCD) and attention deficit–hyperactivity disorder (ADHD) are the most common, but Tourette's patients also have elevated rates of depression, anxiety disorders, and social and emotional difficulties. A clinician might have to decide, for example, whether repeatedly lining up a finger with a corner of a room constitutes a tic or a compulsion.

Some researchers see Tourette syndrome as a single discrete disorder that may be accompanied by other syndromes such as OCD or ADHD. Others see Tourette's as part of a spectrum of disorders with common causes and varying manifestations. The distinction is critical when designing studies of Tourette's, says Mary Robertson, a neuropsychiatrist at Royal Free and University College London Medical School. If patients with Tourette's symptoms alone have a different disorder from that of patients with Tourette's and OCD, researchers need to distinguish between the two groups to search for causes. "Unless you define what the phenotype is, studies of Tourette syndrome are nonsense," Robertson says.

Investigators who image the brain have made some progress in detecting patterns of neural activity that might help in making diagnoses. For example, imaging studies show that when ticcing or suppressing tics, people with Tourette syndrome differ from controls in localized brain activity.

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Published by AAAS

But the patterns of activity vary from person to person, so observing and describing tics remains the best way to arrive at a diagnosis.

From phenotypes to causes

Brain imaging has also helped focus attention on the parts of the brain that seem to give rise to the symptoms of Tourette syndrome: the basal ganglia. These are a set of interconnected brain structures positioned beneath the cerebral cortex. Neural circuits run from the cerebrum through the basal ganglia and then back to the cerebral cortex, providing a feedback loop that helps integrate brain functioning. In some ways, the basal ganglia act as an operating system, linking volitional acts initiated in the cerebrum with the nerves and muscles that carry out our wishes.

In Tourette syndrome, that operating system appears to be somewhat buggy, says Jonathan Mink, a neuroscientist at the University of Rochester Medical Center in New York. One function of the basal ganglia is to learn and regulate the expression of discrete chunks of behavior, such as particular movements or thoughts. In this way, says Mink, the basal ganglia help the other parts of the brain perform, combine, and suppress behaviors. "A lot of learning involves enabling the behaviors you want and inhibiting the ones you don't," he says.

Mink suspects that, in Tourette syndrome, groups of neurons in the basal ganglia fail to inhibit particular movements or other unwanted behaviors. As a result, these behaviors surface as tics. Furthermore, circuits from all parts of the cerebral cortex—including those involved in motion, sensation, and emotion—pass through the basal ganglia. Disinhibiting specific parts of the basal ganglia may trigger different manifestations of Tourette's and related disorders. Also, although circuits largely run in parallel through the basal ganglia, some neurons spread across circuits, allowing for crosstalk. This might explain, for example, why tics get stronger when someone is stressed or tired.

Researchers don't know why parts of the basal ganglia may be malfunctioning. But the neurotransmitter dopamine appears to be involved, because many of the drugs that are effective against Tourette syndrome block dopamine receptors. Researchers have looked at dopamine release, dopamine reception, and secondary pathways within postsynaptic neurons, but no obvious culprit has emerged. However, a recent imaging study has revealed an elevated number of dopamine-containing neurons in one part of the basal ganglia of Tourette's patients, and another has shown that abnormal brain function during a memory test can be restored to normal by manipulating dopamine.

Advocates. These athletes and artists with Tourette's are trying to change the image of the syndrome.

Genetic origins?

Several lines of evidence point toward a genetic cause of Tourette syndrome. The disorder tends to run in families and is several times more common in boys than girls. In some families, parents pass the syndrome on to their children as if it were a dominant trait. Even when Tourette's arises anew in a generation, relatives are often more likely to suffer from associated conditions such as OCD or ADHD.

Because of the seemingly simple transmission of the disorder in some families, researchers in the 1990s expected to find a single, relatively rare genetic variant, as in Huntington's disease, that caused at least some cases. But that model proved to be too simple, says David Pauls, a geneticist at the Harvard School of Public Health and Massachusetts General Hospital in Boston. Instead, genetic studies suggested that several chromosomal regions were involved, with the genes in these regions having contrasting effects. According to Matthew State, a geneticist at the Yale Child Study Center and the Center for Genomics and Proteomics, "Studies have pointed to genes with dominant, recessive, and intermediate inheritance, which makes our lives very difficult."

Researchers are eagerly awaiting the fall release of results from an ongoing genetic study of 256 families being conducted by an international consortium. Meanwhile, other studies that can be done with far fewer research subjects are sharpening the focus on suspicious chromosomal regions and identifying new ones. Many geneticists now suspect that Tourette syndrome results from several genetic variants acting in concert. They also believe that, if enough research subjects can be recruited, future genetic studies will uncover the specific variants responsible for the absence or presence of comorbidities with Tourette's.

Environmental complications

But genes are only part of the story: As with other complex diseases, environmental factors influence the syndrome. Although identical twins tend to share Tourette syndrome, in about 20% of cases one has the syndrome and the other does not. And even when both have Tourette's, their experiences with the syndrome can differ markedly, with the lighter-weight twin at birth often having more severe symptoms. Possible environmental factors range from complications during pregnancy, to stressful early-life experiences, to random events during development. But suspicion has focused on an infectious agent.

Since the 18th century, physicians have known that rheumatic fever can lead to

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movement disorders in a subset of those afflicted. This observation led researchers to wonder whether streptococcal infections—the cause of rheumatic fever—might be behind some cases of Tourette syndrome. Some children first show signs of Tourette's after a strep infection, and subsequent infections often seem to exacerbate their tics. In addition, immunologic studies have suggested that in some children the antibodies generated to combat strep misidentify and damage neurons in the basal ganglia. "Parallel lines of research were coming together and showing the same thing: that strep is a factor," says Susan Swedo of the National Institute of Mental Health, who categorizes such cases of Tourette's and related conditions as pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS).

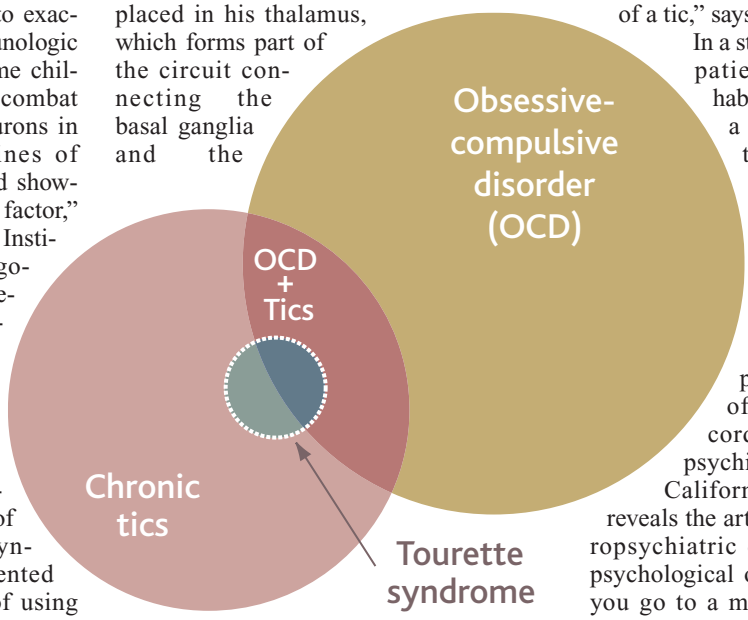
Swedo and her colleagues have conducted double-blind trials of penicillin and azithromycin prophylaxis to prevent exacerbations of tics in children with Tourette syndrome. They also have experimented with the more invasive process of using plasmaphoresis to remove anti–basal ganglia antibodies from the blood. Although the waxing and waning of the syndrome complicates the interpretation of results, Swedo is convinced that both approaches can significantly reduce the impairment caused by Tourette's and related disorders.

Many researchers are skeptical of the association and of pharmacological efforts to prevent strep infections in children with Tourette syndrome. "It's an intellectually compelling hypothesis that deserves further study, but the data are not all there," says Harvey Singer, a pediatric neurologist at JHU. Singer points out that most children contract multiple strep infections, so an association with tic exacerbations could be coincidental. Many researchers and physicians also worry about prescribing long-term use of antibiotics for children with neuropsychiatric disorders, because such widespread use would likely increase levels of drug resistance. An ongoing large-scale study of penicillin prophylaxis may provide some answers, but the strep connection is likely to remain controversial.

Treating the symptoms

For now, the most common treatment for Tourette syndrome remains what it has been for the past 4 decades: using drugs to alter the activity of dopamine and related neurotransmitters in the basal ganglia. Newer kinds of drugs, known as atypical neuroleptics, are thought to produce fewer unwanted side effects than did earlier treatments. Many physicians practice the "art of medicine," prescribing different drugs until they find one that works for a patient.

Earlier this year, a man suffering from a severe case of Tourette syndrome underwent an experimental procedure in which battery-powered electrodes were placed in his thalamus, which forms part of the circuit connecting the basal ganglia and the cerebral cortex. The electrical stimulation from the electrodes produced an almost complete cessation of his tics. Although the success has generated great excitement among patients, many researchers and physicians are cautious. "This is an experimental procedure that has significant risks," says JHU's Walkup. "We may not like all of the medications all of the time, but many patients find a way to get control of their tics with them."



Multifaceted. Not everyone with chronic tics has Tourette syndrome. Sometimes those with the syndrome also exhibit symptoms of obsessive-compulsive disorder (shown in this diagram) or other neuropsychiatric disorders, such as ADHD.

Other nonpharmaceutical interventions hold greater promise. Buoyed by the success of behavioral modification therapy in treating OCD, researchers have been examining similar approaches to Tourette syndrome. One problem with Tourette's, says John Piacentini, a specialist on childhood and teen neuropsychiatric disorders at the University of California, Los Angeles, is that it sets up a positive feedback loop. Patients feel the need to tic and then experience relief when they do, thus reinforcing the neural circuits involved in that behavior. To break the loop, Piacentini and his colleagues have been experimenting with behavioral techniques. People with Tourette syndrome are helped to be made aware of their tics—for example, by watching themselves in a mirror. They then are taught to replace the tic with a competing response. They might replace the tic with a movement that is less apparent, tense the muscle involved in the tic, or strengthen an antagonistic muscle. Such an approach "tries to disrupt the automatic chain of events underlying the expression of a tic," says Piacentini.

In a study conducted with his own patients, Piacentini has seen habit-reversal training produce a 30% reduction in tic severity. Now he is participating in a multicenter study to investigate the therapy more thoroughly.

Unifying mind and brain

The renewed emphasis on behavioral approaches is producing a broader view of Tourette syndrome. According to Neal Swerdlow, a psychiatrist at the University of California, San Diego, Tourette's reveals the artificiality of viewing a neuropsychiatric disorder as either purely psychological or purely neurological: "If you go to a meeting, single-cell neurophysiologists and people studying theories of the mind both have something to contribute to the discussion."

This unified view of Tourette syndrome has important implications in both the clinic and the lab, say physicians and researchers. The goal of treatment is not necessarily to eliminate tics, say clinicians; it is to enable someone with Tourette's to function effectively in society. The Tourette Syndrome Association Inc. (www.tsa-usa.org), an advocacy group founded in 1972 by some of the first patients to benefit from pharmacologic treatments, has worked hard to educate the public and the media about the syndrome. Especially for cases of Tourette's unaccompanied by severe comorbidities, understanding and accommodation can be as important as medications.

Similarly for the research community, an emphasis on the experiences and adaptations of individuals can suggest areas to explore that a narrow biomedical focus might overlook. For example, determining which patients could benefit most from behavioral approaches could provide physicians and their patients with badly needed guidance. Tourette syndrome has biological, psychological, and social dimensions, says Swerdlow, "and you can't separate out one of those without losing the disorder."

–STEVE OLSON

Steve Olson's most recent book is *Count Down: Six Kids Vie for Glory at the World's Toughest Math Competition.*

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