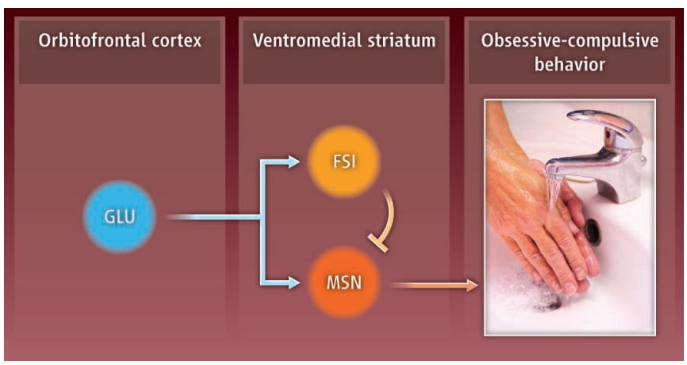
NEUROSCIENCE

Illuminating the Neural Circuitry of Compulsive Behaviors

Optogenetics is used to delineate and control a brain circuit that drives repetitive behavior in an animal model, opening up new possibilities for the treatment of compulsive disorders.

Scott L. Rauch and William A. Carlezon Jr.

Obsessive-compulsive disorder (OCD) is characterized by unwanted intrusive thoughts (obsessions) and ritualized repetitive behaviors (compulsions) that are often unpleasant and time-consuming; those afflicted feel tormented and can be functionally disabled. Classic examples include obsessions about contamination, which are associated with anxiety and lead to washing compulsions. Compulsive behaviors are not unique to OCD but are a feature of numerous neuropsychiatric disorders, including autism, substance use disorders, and Tourette's disorder (*1*). The complexity of OCD is emblematic of the challenges inherent in developing animal models of psychiatric disorders, in that repetitive behavior is readily measured, whereas intrusive thoughts are exceedingly difficult to quantify. On pages 1234 and 1243 of this issue, Ahmari *et al.* (*2*) and Burguière *et al.* (*3*) describe, respectively, the use of optogenetics (*4*) to produce and relieve compulsive-like behaviors in animal models. Their pioneering work highlights how models that link genetics, neuroanatomy, physiology, and behavior in ways that cut across disorders (*5*) can provide promising opportunities for developing diagnostics and treatments in the field.



Brain circuitry for repetitive behavior. Hyperactivation (by optogenetic stimulation) of a glutamatergic (GLU) pathway between the orbitofrontal cortex and ventromedial striatum can produce repetitive behavior (extensive grooming) in wild-type mice, presumably by elevating the activity of medium spiny neurons (MSNs). A genetic mouse model of OCD that exhibits repetitive behavior (grooming) shows deficits in the suppression of MSN activity; both can be normalized by activating (through optogenetic stimulation) fast-spiking striatal interneurons (FSIs) that inhibit MSN neurons. A classic example of OCD in humans is an obsession about contamination, which is associated with anxiety and leads to washing compulsions.

There are essentially no biomarkers or assays that serve as diagnostic tests in psychiatry (*6*). Findings from people with OCD support a circuitry model focused on a network of brain regions comprising the orbitofrontal and anterior cingulate cortex, striatum, and thalamus (*7*). Decades of functional brain imaging data indicate that in OCD, the nodes of this network exhibit hyperactivity at rest that is exacerbated during symptom induction and attenuated by successful treatment (*8*). These are, however, correlations; we lack the ability to induce the signs and symptoms of the disorder by manipulating activity within specific circuits. Moreover, the imaging data were obtained at modest spatial resolution, making it impossible to test hypotheses regarding specific microcircuitry of interest.

There are corresponding limitations in OCD therapeutics. Although treatments, including pharmacotherapy with selective serotonergic reuptake inhibitors, have modest efficacy, many patients are refractory, and responders are often left with residual symptoms (*9*). OCD is a prime example of how advances in circuitry models are fueling interest in regional neurostimulation, such as by deep brain stimulation (*10*) and transcranial magnetic stimulation (*11*). Unfortunately, these methods of gross regional stimulation to modulate circuits lack specificity at the cellular level. Although some efforts have enabled differential modulation of cells and neuronal fibers according to scale, size, orientation, direction, and myelination status (*12*), they pale in comparison to the neuroanatomic and cellular specificity possible with optogenetics (*2*–*4*). Optogenetics combines genetics and optics to allow temporally and spatially precise manipulation of electrical and biochemical events using fiber-optic light in living organisms.

Ahmari *et al.* and Burguière *et al.* use optogenetics to identify the specific circuits involved in regulating repetitive behavior (excessive grooming) in mice. Ahmari *et al.* found that hyperstimulation of an excitatory circuit between glutamatergic neurons in the orbitofrontal cortex and the ventromedial striatum triggers compulsive behavior (see the figure). Burguière *et al.* discovered that in a genetic mouse model of OCD, excessive grooming was caused by an impaired pathway in the ventromedial striatum (the inhibition of medium spiny neurons by fast-spiking striatal interneurons) within this same neural circuit. This delineation has broad implications for understanding the neural basis of OCD and other disorders that include compulsivity as a clinical feature. For example, repetitive behavior is a core feature of autism spectrum disorders, and studies in rodents (*13*) have used animal models similar to those used by Ahmari *et al.* and Burguière *et al.* The striatal regions identified by Ahmari *et al.* and Burguière *et al.* have also been implicated in repetitive behaviors seen with addiction that, through drug-induced neuroplasticity, become habits (*14*). These "transdiagnostic" behaviors may have common underlying circuitry, and therapeutics that target this circuitry may have broad indications that cut across conditions previously conceptualized as unrelated.

Optogenetics provides a glimpse of highly selective means to control brain circuits, but there are obstacles for its use in nonhuman primate models of disease or clinical settings (*15*). These include logistical issues (an optical fiber that tethers the subject to the stimulator), ethical and pragmatic concerns (use of viral vectors to express proteins in target cells that create neural sensitivity to light stimulation), and—given that these disorders often arise in childhood and adolescence (*1*)—the largely unaddressed

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question about how this type of intervention affects the developing brain. A lesson of the Ahmari *et al*. study is that acute stimulation does not produce repetitive behaviors; multiple exposures to stimulation are needed for the phenotype to develop, which suggests that signs of compulsive disorders can be acquired through neuroplasticity. More work is needed to examine how optogenetic manipulation of key circuits early in life affects developmental trajectories to ensure no unintended effects. These current limitations notwithstanding, the cutting-edge and insightful research of Ahmari *et al*. and Burguière *et al*. illuminates the neurocircuitry of compulsive behavior with unprecedented clarity. Although there is still far to go, these discoveries represent a major leap forward toward eventual methods for "flipping the off-switch" on pathological compulsive behaviors.

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PHYSICS

Interfacing Atoms and Light—The Smaller the Stronger

The strong interaction of neutral atoms with photons in a waveguide cavity may provide a way to create quantum information networks.

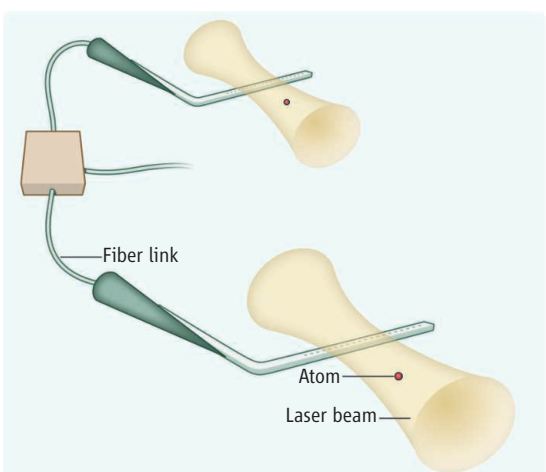
Matthias Keller

Most of us use the Internet to exchange information in everyday life. The ever-increasing rate at which Internet connections transmit data requires faster and faster conversion of local information into signals that can be easily transmitted over long distances. For example, the information sent by your computer is converted from electronic signals into optical signals, which are then sent through a network of optical fibers. Without the reliable and high-speed conversion of information from electronic to optical form, modern communication would not be possible. With the emergence of quantum technologies, most notably quantum information technology, the way we communicate is about to change fundamentally. On page 1202 of this issue, Thompson *et al*. (*1*) describe a system that has the potential to become an interface between atoms and optical signals and provide local information storage and transmission in the quantum domain.

In recent years, the processing of quantum information, where quantum-mechanical effects are used to potentially speed up computations, has been demonstrated in several systems (*2*–*6*). With these achievements, the question of long-distance communication in the quantum realm arises (*7*). As in the classical communication domain, a crucial building block consists of converters that can transform quantum information from one form into another, so-called quantum hybrid systems or quantum interfaces. Currently, the most successful implementation for such quantum interfaces for long-distance quantum communication is cavity quantum electrodynamics, where atoms interact with light in a cavity.

Recently, the transfer of information between atomic states by single light particles (photons) or the entanglement of their states has been demonstrated (*8*–*10*). However, a technological challenge is still the fast, efficient, and faithful transfer of information between atoms and photons. To enhance the interaction between photons and atoms, both need to be tightly confined at the same location, and trapped for a sufficiently long time to allow the information transfer. The smaller the space in which both are confined, the stronger the interaction is, and the faster the interface operates.

In 1999, Ye *et al*. (*11*) trapped atoms in an optical cavity and demonstrated the control of the interaction between atoms and single photons. This technique was later used by Stute *et al*. (*8*) to demonstrate a quantum network. In a quest to increase the coupling strength between atoms and photons, Colombe *et al*. (*12*) combined a cavity, formed by laser-machined optical fiber ends with high reflective coating, with magnetically trapped atoms on a chip. Because of the small volume of such a cavity,



Toward quantum networks. Thompson *et al*. trapped atoms with laser beams in the vicinity of photonic waveguide cavities, as shown in the expanded view. The coupling interaction was determined by measuring the emission of photons that escaped the trap through the tip of a tapered optical fiber. These photons, guided by optical fibers, could potentially interact with other trapped atoms. The interactions in these quantum networks could provide a way to store and send quantum information.

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