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Toward a Neurobiology of Obsessive-Compulsive Disorder

Review

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OCD and OC-Spectrum Disorders

We all have habits and mannerisms, and some of these are strong and urgent. But for the most part, these are not intrusive behaviors; they are blended into our lives, give us personality, and form a background on which we build the much larger part of our cognitive activities. Even when we engage in rituals, they can be like games, as when children avoid stepping on cracks in the sidewalk. In people who suffer from obsessive-compulsive disorder (OCD), such "habits," "mannerisms," and "rituals" are out of control.

The name, OCD, comes from the hallmark signs and symptoms of the disease, which affect both cognition and motor behavior: *obsessions*, thoughts that repeat over and over again, unwanted but insistent; and *compulsions* to act, to repeat fragments of behavior over and over in ritualistic, stereotyped succession. Typically, particular compulsive acts are carried out in response to a particular obsession, as if to neutralize the anxiety and negative affect associated with that obsession. The most common of these obsessions and compulsions involve checking (going back over a behavior repeatedly in response to obsessive self-doubts whether it was done, and done just right), washing (for example, washing the hands until they bleed in response to the "obsession" that they are dirty), ordering (straightening up, like a child having to line up the shoes in his closet over and over, or having to put them in sets of three), and fears of performing aggressive or untoward behaviors and repeated attempts to prevent this.

For the neurobiologist, key observations about these symptoms include the following:

(1) People with OCD are usually aware that the obsessions and compulsions are nonsensical, but, despite great effort, they cannot control them.
(2) The obsessions and compulsions usually are not bizarre. They typically have possible or even ordinary content.
(3) There is marked cross-cultural consistency in the themes of the obsessions and compulsions, despite heterogeneity in specific symptoms.
(4) Some patients suffer mainly obsessions, others mainly compulsions, and still others both. Thus OCD can express itself as primarily a cognitive-affective disorder or primarily an executive-behavioral disorder.
(5) The obsessions and compulsions can go on for hours. For example, a "checker" checks, but cannot be *sure* and has to check again and again. The question "what if?" dominates, and there is no behavioral closure.

These observations suggest that, in OCD, neural circuits can trigger repetitive behaviors and thoughts that coexist with others in conscious awareness, and suggest that the triggering can be set off by what otherwise would often be innocuous events.

Two other cardinal features of OCD are that it typically has an early age of onset and that it very often is associated with comorbid conditions. Childhood onset OCD, emerging before puberty, tends to affect males more than females, tends to be related to motor tic disorders, and may be severe and refractory to standard therapies. Adult onset OCD peaks in the 20s, is more likely to affect females, and tends to be more sensitive to treatment. Worldwide, OCD is estimated to affect 1%–3% of the population. Patients with OCD often suffer from other anxiety disorders, including major depressive disorder, which has a lifetime prevalence of 60%–70% in OCD patients. It is the relationship between OCD and other so-called OC-spectrum disorders, however, that has had the greatest impact on ideas about the neurobiology of OCD. Estimates of the rate of OCD (or "OC behavior") in patients with Tourette syndrome (TS) are as high as 90%. This high cooccurrence, together with the phenomenologic similarities between OCD and TS, has prompted the hypothesis that these disorders may be closely linked in terms of genetics and pathophysiology. Other so-called OC-spectrum disorders include trichotillomania (characterized by compulsive hair-pulling behavior) and body dysmorphic disorder (characterized by obsessions with specific aspects of one's own appearance and ritualistic attempts to modify it). Little is known about the neurobiology of these disorders.

Evidence for Cortico-Basal Ganglia Circuit Dysfunction in OCD

There is no known overt locus of neuronal degeneration in OCD as there is, for example, in Parkinson's disease or Huntington's disease. However, functional imaging studies suggest that in OCD patients, there is abnormal metabolic activity in the orbitofrontal cortex, the anterior cingulate/caudal medial prefrontal cortex, and the caudate nucleus (the anterior part of the striatum) (Rauch and Baxter, 1998; Saxena et al., 1998). Activity within this cortico-basal ganglia network (sometimes called the "OCD circuit") is increased at rest relative to that in controls, is accentuated during provocation of symptoms, and is attenuated following successful treatment. This neuroimaging evidence supports earlier suggestions of basal ganglia involvement in OCD based on the fact that focal lesions in the striatum or in its target structure, the pallidum, can produce striking OCD-like behavior (Laplane et al., 1989).

Dysfunction of the basal ganglia and associated cor-

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tico-basal ganglia circuits may be a common neural feature of OCD and OC-spectrum disorders including TS. For example, in TS, activity in the prefrontal cortex and the caudate nucleus is increased, and activity in the putamen and the pallidum is decreased when active efforts are made to suppress tics (Peterson et al., 1998).

Neurobiology of the OCD Circuit

What features of the cortico-basal ganglia circuits linking the orbitofrontal and anterior cingulate cortex to the caudate nucleus might account for the cardinal features of OCD? Based on the effects of lesions in humans and experimental animals and on the results of single-unit electrophysiological recordings, all three of these structures have been implicated in the evaluation of the significance of stimuli as positive or negative (rewarding or punishing). All three have also been linked to aspects of executive function. Finally, cortico-basal ganglia circuits have been suggested to form a neural system critical for habit learning and for the routine performance of habits, and structures of the OCD circuit have specifically been implicated in the acquisition of stereotyped behaviors.

Orbitofrontal Cortex

Lesions involving the orbitofrontal cortex in humans lead to deficits in behavioral planning and decision making based on estimates of the positive or negative consequences of particular actions (Damasio et al., 1990). In monkeys, neurons in the orbitofrontal cortex modulate their activity in relation to the motivational value of stimuli and the reward preferences of the animal, and orbitofrontal lesions result in selective abnormalities in reward expectancy and preferences (Rolls, 1996; Tremblay and Schultz, 1999). In what has come to be called the somatic marker hypothesis, Damasio and his colleagues suggest that exposure to particular stimuli or contexts reactivate somatic states (autonomic responses, as indicated in their experiments by galvanic skin responses) that, through experience, have become associated with the stimuli. They propose that in OCD, this reactivation of somatic markers in response to expected outcomes becomes excessive, driving the behavioral repetition.

Support for this general view of orbitofrontal cortex function comes from studies by the Damasio group on the behavior of patients with restricted ventromedial frontal cortex lesions in gambling tasks. Even knowing the "odds," these patients were unable to make the winning response. Elliott and colleagues (Elliott et al., 1999) have shown with functional magnetic resonance imaging that in such gambling tasks, activity in the orbitofrontal cortex is unique in being proportional to the uncertainty of outcomes.

Anterior Cingulate Cortex

The anterior cingulate cortex and adjoining medial prefrontal cortex are strongly interconnected with the orbitofrontal cortex and structures of the limbic system and, like the orbitofrontal cortex, have been implicated by lesion, recording and imaging studies in motivation and affective behavior, and in major depression as well as OCD (Price et al., 1996; Weeks et al., 1996). There is a fairly direct route from the anterior cingulate cortex to the motor cortex. The anterior cingulate cortex sends direct anatomical connections to the rostral cingulate motor area, and this cortical area in turn projects to the motor cortex (Picard and Strick, 1997). Restricted chemical lesions of the rostral cingulate motor area render monkeys incapable of selecting an action based on the reward contingencies associated with it (Shima and Tanji, 1998). As part of a cortical network, then, the orbitofrontal cortex and anterior cingulate cortex could together exert a powerful influence both on the perceived emotional value of stimuli and on the selection of behavioral responses based on these experience-based expectancies and perceived outcomes.

The Basal Ganglia

How could the basal ganglia influence this network? The neocortex and basal ganglia are connected by parallel loops or families of cortico-basal ganglia connections. The basal ganglia are thought to exert control over action release through antagonistic "push–pull" output pathways, which serve to select intended actions. These functions are disrupted in hypokinetic disorders such as Parkinson's disease, in which action is diminished, and in hyperkinetic disorders such as Huntington's disease, in which action is excessive. It has been suggested that, by analogy, dysfunction of these cortico-basal ganglia pathways may also occur in some neuropsychiatric disorders, including OCD and TS (Swerdlow and Koob, 1987).

Different sets of cortico-basal ganglia loops are thought to have specialized functions depending on the cortical areas participating in the loops (Alexander et al., 1990). This organization may account for the symptom specificity of OCD and OC-spectrum disorders. For example, in TS, in which repetitive tics or actions are the predominant symptoms, the "motor loop" through the putamen is more affected than it is in OCD according to neuroimaging data. In OCD, which typically involves obsessions as well as compulsive actions, the neural circuits interconnecting the orbitofrontal and anterior cingulate cortex with the basal ganglia are involved.

In addition to loop topography, special features of the OCD circuit may contribute to its effects on behavior. Both the orbitofrontal and anterior cingulate cortex project to the ventral part of the caudate nucleus and to the ventral striatum. In the monkey, these regions have been found to send outputs not only to the pallidum, but also to a large part of the dopamine-containing substantia nigra pars compacta, from which the nigrostriatal tract originates. Haber and colleagues suggest that these limbic system-related basal ganglia connections do not follow the segregated loop plan completely, with the result that limbic outflow can affect a wide part of the striatum (Lynd-Balta and Haber, 1994). Moreover, the caudal orbitofrontal and anterior cingulate/caudal medial prefrontal cortex are also the main source of input to the striosomal system in the head of the caudate nucleus (Eblen and Graybiel, 1995). Striosomes in this region have been linked to reward effects (Aosaki et al., 1995; White and Hiroi, 1998), and they appear to be differentially active under conditions in which the animals perform repetitive, stereotyped behaviors in response to dopamine receptor agonists (Canales and Graybiel, 2000).

These special features of orbitofrontal and anterior cingulate cortico-basal ganglia circuits could be important not only for understanding OCD and OC-spectrum

symptomatology, but also for understanding developmental aspects of these disorders. Striatal circuits develop according to gradients, and for a prolonged period the orbitofrontal/cingulate-linked striosomal system and ventral regions lead the rest of the caudate-putamen complex in their maturational state.

OCD and Chunking Functions of Cortico-Basal Ganglia Circuits

One hypothesis emerging from these findings is that the basal ganglia may influence both motor pattern generators in the brainstem and spinal cord and "cognitive pattern generators" in the cerebral cortex. By this view, the loops running from the neocortex to the basal ganglia and then to the thalamus and back to the neocortex may help to establish cognitive habits, just as they may influence the development of motor habits (Graybiel, 1997). If so, the cortico-basal ganglia loop dysfunction in OCD could reflect both sides of basal ganglia function, motor and cognitive, to bring about repetitive actions (compulsions) and repetitive thoughts (obsessions).

Another hypothesis proposed about the basal ganglia is that they help to recode cortical and other inputs into a form that allows actions to be released as "chunks" or sequences of behavior (Graybiel, 1998). This function, under normal conditions, could be important in forming coordinated, sequential motor actions and in developing streams of thought and motivation. The architecture of cortico-basal ganglia circuitry could support the smooth progression from a cognitive framework establishing priorities for potential behaviors to behavioral selection, which in turn would facilitate fluid and adaptive behavioral output. Conversely, dysfunction of this cortico-basal ganglia system could contribute to the symptoms of OCD patients: they become stuck in a conceptual framework, unable to shift from one priority set to the next, and thus remain locked into a specific behavioral output program. The "what if" doubts and anxiety suffered by the OCD patient may indicate a lack of loop closure between expected outcomes and the chunks of behavior that should generate them.

A large part of the frontal cortex receives inputs from the basal ganglia conveyed via the thalamus. These same cortical regions not only project to the basal ganglia (mainly to the striatum) but also project to other brain regions including the thalamus. Cortico-thalamic loops are thought to be critical for cortical functioning. If the basal ganglia form associations among cortical inputs on the basis of context and evaluative signals, and thereby promote automation of selected behaviors, they could relieve the frontal cortex of a substantial computational load in carrying out executive functions. With both corticothalamic and cortico-basal ganglia systems functioning under normal conditions, parallel processing could then occur with the corticothalamic circuits supporting conscious (explicit) information processing and cortico-basal ganglia supporting automatic (implicit) processing functions. If cortico-basal ganglia pathways become abnormal, as appears to be true in OCD, such parallel processing capabilities would be compromised. Information normally processed automatically could intrude into the conscious domain as obsessions, and behavioral selection could become narrowed to compulsive acts. Such dysfunction could contribute to the compelling nature of obsessions in OCD and to the stereotypic behaviors carried out as compulsions.

Toward a Neurobiology of OCD

To date, work on the neurobiology of OCD and OC-spectrum disorders has advanced to the point of suggesting that cortico-basal ganglia circuits are dysfunctional in OCD, but neither the mechanisms nor the genetics and epidemiology of these disorders are understood. There is a great opportunity for further research bringing together molecular and systems neuroscience with clinical studies of these disorders. We mention here important issues to be addressed.

What Is the Lesion in OCD? When Does It Occur? And How Are Its Effects Counteracted by Treatment?

There is a clear need to understand more about the neuropathology of OCD. If lesions of the striatum can induce intense compulsive behaviors and stereotypies, does this mean that there are subtle lesions of the striatum in OCD that conventional methods have failed to pick up? Magnetic resonance spectroscopy is beginning to suggest reduced N-acetylaspartate within the striatum of persons with OCD, so that neuronal density there may actually be reduced (Fitzgerald et al., 2000). Short of cell death, abnormal brain chemistry in OCD could affect neurotransmission in cortico-basal ganglia circuits, leading to the abnormal metabolic activity seen in imaging studies. Very little is known about the neurochemistry of OCD, but a clue may come from the fact that the most successful pharmacologic therapy for OCD is treatment with inhibitors of serotonin reuptake sites (SRIs). Effective therapy with SRIs can in part reverse the abnormal metabolic activity seen in this OCD circuit, suggesting that the modulatory effects of serotonin can act on the cortico-basal ganglia circuit defined in scanning studies.

Despite this clinical result, strong evidence of a primary serotonergic or other neurotransmitter abnormality in OCD is lacking. One suggestion is that SRIs have their beneficial effects via downregulation of 5HT-1D autoreceptors within orbitofrontal cortex (El Mansari et al., 1995). In animal studies, these receptor changes have been shown to follow the time course of antiobsessional therapeutic effects (8 weeks) in the orbitofrontal cortex, but to follow the time course of antidepressant therapeutic effects (4 weeks) within dorsolateral prefrontal cortex. This temporal difference is interesting given that these two regions of the frontal cortex have been implicated by functional imaging studies in OCD and major depressive disorder, respectively. Although cortico-basal ganglia circuit dysfunction may be common to OCD and TS, however, different neurotransmitter systems in these circuits may be critical in modulating their different symptom complexes, at least as judged by pharmacotherapy. In contrast to OCD, in TS it is dopamine receptor antagonists (principally D2 class receptor antagonists) that appear to be the most effective agents for reducing tic frequency. In cases of OCD with comorbid tics also, but not in OCD cases without tics, the efficacy of SRIs may be boosted by the addition of dopamine receptor antagonist treatment (McDougle et al., 1994).

What Are the Genetics of OCD? Can Environmental Factors Induce OCD? Do Common Etiologic Mechanisms Underlie OCD and OC-Spectrum Disorders Such as TS?

OCD is familial and so is TS. Some studies have suggested that OCD and TS represent different phenotypic expressions of the same genetic vulnerability. The genetics of OCD is not yet understood, but there is now a coordinated international effort, by the Tourette Syndrome International Consortium for Genetics, to identify susceptibility genes for TS. Finding out about the genetics of TS should help at least to narrow the search for genetic factors in OCD and, given the frequent comorbidity of the two disorders, may yield candidate genes for OCD as well. If so, there would be the chance to identify the molecular basis for OCD dysfunction.

There are also potential etiologic links between OCD and OC-spectrum disorders based on the possibility that OCD and OC-spectrum disorders can occur as a result of infection. This idea was proposed by von Economo, who described patients suffering from obsessions and compulsions in the wake of the great 1917 epidemic of viral encephalitis in Europe. This proposal has received new impetus from the work of Swedo and colleagues (Swedo et al., 1998), who have studied disorders precipitated by rheumatic fever, caused by type A β-hemolytic streptococcal infection. Such infections can lead to Syndenham's chorea, itself characterized by symptoms including obsessions, compulsions, and tics, and to OCD-like syndromes. This group of disorders has been termed Pediatric Autoimmune Neuropsychiatric Disorders Associated with Strep (PANDAS). Their underlying pathology is thought to involve an autoimmune-mediated attack on the striatum precipitated by the streptococcal infection. Altogether, then, current evidence suggests that there may be susceptibility genes for OCD and OC-spectrum disorders as well as environmental factors precipitating these disorders—and that their interactions, when understood, may lead to new forms of successful therapy.

What Are the Dynamics of Cortico-Basal Ganglia Circuit Function during the Expression of OCD Symptoms?

Even though neuroimaging studies have pointed to cortico-basal ganglia circuits as being dysfunctional in OCD, it is still not clear what the functional abnormality is in these circuits in OCD and how they contribute to the expression of OCD symptoms. Nor is it clear how these circuits work normally, or how the multiple loops of this system interconnecting the cortex, thalamus and basal ganglia actually operate. Improvements in the temporal and spatial resolution of imaging will soon make it possible to follow the cascade of neural activity changes that occur during the evolution of OCD symptoms. Then it should be possible to identify brain sites participating in the buildup of an obsession, the attendant anxiety, the escalation of an urge, the performance of a compulsion, and the resolution of the obsession and accompanying anxiety. This would for the first time allow detection of the dynamics of activity in circuits active in the expression of OCD symptoms. Advances in imaging with magnetic resonance spectroscopy and labeled receptor and other ligands should also help to clarify the neurochemistry of the disorder.

Are Some OCD Behaviors Learned or Conditioned?

There is no clear answer to this question, but what *is* known is that in some OCD patients, partial reversal of OCD symptoms and abnormal cortico-basal ganglia circuit activity can be achieved by behavioral therapy in which patients are exposed systematically and under supervision to the very stimuli that otherwise provoke obsessions and compulsions (Baxter et al., 1992). This evidence strongly suggests that studies of learning and memory mechanisms in relation to the development of repetitive behaviors may help in understanding the neurobiology of OCD. Interestingly, different levels of responsivity to either behavioral therapy or pharmacologic therapy have even been observed in groups of OCD patients, and these have been correlated with different levels of metabolic activity in the orbitofrontal cortex and anterior cingulate cortex (Brody et al., 1998). Such clinical data suggest that the OCD population may be heterogeneous and that experience-based plasticity may differentially affect the "OCD circuit" in some patients. More generally, these findings raise the possibility that, in addition to susceptibility genes for OCD, environmental factors may be important in determining the emergence of particular types of OCD symptoms in different patients.

Are the Obsessions and Compulsions in OCD Exaggerated Forms of Habits of Thought and Action?

Even if imaging studies identify the cascades of activity in cortico-basal ganglia circuits occurring during expression of OCD symptoms, it still will be unclear what form of neural encoding is responsible for the symptoms or for their resolution. One interesting possibility is that the neural circuits that normally mediate habits and automated behaviors become hyperactive or inaccessible to a stop signal in OCD and related disorders. Three recent models for studying what goes on in cortico-basal ganglia circuits when habits are formed are pertinent here. In the first, monkeys were taught a sensorimotor conditioning task in which light or sound cues were associated with reward, and recordings were made from the tonically active neurons of the striatum thought to be the cholinergic interneurons. As the monkeys learned the task, the neurons acquired responses to the conditioning stimuli, and they maintained those responses as long as dopamine was present in the striatum. Removal of dopamine reduced the acquired responses (Aosaki et al., 1994a, 1994b), and so did inactivation of the intralaminar thalamus (Matsumoto et al., 2000). In related work, removal of dopamine in the striatum before learning of a simple sequential push-button task prevented the task from being executed without cues as a unified behavioral sequence (Matsumoto et al., 1999). In the second set of experiments, the activity of projection neurons in the sensorimotor striatum of rats was monitored with chronically implanted tetrodes. The ensemble activity of these neurons was found to undergo large-scale and long-lasting changes as the rats learned the procedure and then performed it after learning (Jog et al., 1999; see also Carelli et al., 1997). These studies suggest that, with experience, striatal neurons can develop new responses to environmental stimuli. Given the activity changes in striatal projection neurons, this plasticity is likely to affect basal ganglia outputs and

thus cortico-basal ganglia loop function. In the third set of experiments, the expression of stereotypies induced in rats by repeated doses of psychomotor stimulant drugs was found to be closely correlated with heightened activation of the striosomal compartment of the striatum—the compartment preferentially interconnected with the anterior cingulate and orbitofrontal cortex (Canales and Graybiel, 2000). Such experiments highlight the potential for identifying the changes in neuronal activity that occur in cortico-basal ganglia circuits as repetitive action repertoires come to dominate behavior. A first step toward testing whether such striatal function could be affected in OCD has been carried out by testing people with OCD on implicit learning tasks that normally activate the striatum. Striatal activation was found to be deficient in the OCD subjects, but activation of the hippocampal system (normally recruited during explicit learning tasks) was abnormally high (Rauch et al., 1997). Coordination of human brain imaging of this sort with laboratory-based experiments holds great promise for uncovering the neurobiology of OCD.

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