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The neural bases of obsessive–compulsive disorder in children and adults

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Abstract

Functional imaging studies have reported with remarkable consistency hyperactivity in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and caudate nucleus of patients with obsessive–compulsive disorder (OCD). These findings have often been interpreted as evidence that abnormalities in cortico–basal ganglia–thalamo–cortical loops involving the OFC and ACC are causally related to OCD. This interpretation remains controversial, however, because such hyperactivity may represent either a cause or a consequence of the symptoms. This article analyzes the evidence for a causal role of these loops in producing OCD in children and adults. The article first reviews the strong evidence for anatomical abnormalities in these loops in patients with OCD. These findings are not sufficient to establish causality, however, because anatomical alterations may themselves be a consequence rather than a cause of the symptoms. The article then reviews three lines of evidence that, despite their own limitations, permit stronger causal inferences: the development of OCD following brain injury, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, and neurosurgical lesions that attenuate OCD. Converging evidence from these various lines of research supports a causal role for the cortico–basal ganglia–thalamo–cortical loops that involve the OFC and ACC in the pathogenesis of OCD in children and adults.

Obsessive–compulsive disorder (OCD) is a debilitating illness (Koran, 2000; Koran, Thienemann, & Davenport, 1996) that has a lifetime prevalence of 2–3% in nearly every country for which epidemiological data are available (Bland, Newman, & Orn, 1988; Horwath & Weissman, 2000; Karno, Golding, Sorenson, & Burnam, 1988; Robins et al., 1984; Sasson et al., 1997; Weissman et al., 1994). It affects an estimated 50 million people worldwide (Sasson et al., 1997). OCD is typically characterized by the presence of both obsessions and compulsions, although the presence of either obsessions or compulsions alone is sufficient to make the diagnosis of OCD (American Psychiatric Association, 2000). Obsessions are recurrent, persistent, and intrusive ego-dystonic thoughts, impulses, or images; compulsions are repetitive behaviors or mental acts that are executed with the goal of preventing or reducing distress or preventing some dreaded event or situation (American Psychiatric Association, 2000).

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Childhood- Versus Adult-Onset OCD

The age of onset of OCD seems to have a bimodal distribution, with a peak in childhood (at approximately 10 years of age) and another in early adulthood (Geller, 2006; Geller, Biederman, Jones, Shapiro, et al., 1998). Estimates of the prevalence of OCD among adolescents are of approximately 2–3.5% (Flament et al., 1988; Valleni-Basile et al., 1994; Zohar et al., 1992). Approximately 40% of cases of childhood-onset OCD continue into adulthood, and

that number increases to 60% when subthreshold presentations of OCD are also considered (Stewart et al., 2004). Conversely, one-third to one-half of adults with OCD have the onset of their symptoms in childhood or adolescence (Eichstedt & Arnold, 2001).

Childhood- and adult-onset OCD differ in several ways. Compared to adult-onset OCD, childhood-onset OCD is more prevalent among males (Eichstedt & Arnold, 2001; Geller, Biederman, Jones, Shapiro, et al., 1998); is more familial (Bellodi, Sciuto, Diaferia, Ronchi, & Smeraldi, 1992; do Rosario-Campos et al., 2005; Nestadt et al., 2000; Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995); and is associated with a higher prevalence of tic disorders, both in the patients with OCD themselves and in their first-degree relatives (Chabane et al., 2005; Grados et al., 2001; Pauls et al., 1995). These findings have led some authors to suggest that childhood-onset OCD is a distinct, "tic-related" subtype of OCD (Eichstedt & Arnold, 2001; Taylor, 2005). The distinction between childhood- and adult-onset OCD may also have treatment implications: adults with childhood-onset OCD respond less to treatment with clomipramine than do adults with adult-onset OCD, independent of illness duration or severity (Ackerman, Greenland, Bystritsky, Morgenstern, & Katz, 1994).

Most brain imaging studies that include adults with OCD use mixed samples that include adults with childhood- and adult-onset OCD. Given the evidence that brain activity differs in adults with childhood- versus adult-onset OCD (Busatto et al., 2001), such heterogeneous samples may compromise statistical power and confound findings. In addition, many studies report only the mean and standard deviation of age of illness onset, which are inadequate to characterize what are likely to be bimodal distributions. Consequently, knowing whether findings apply to all adults with OCD or only to those with childhood- or adult-onset OCD is impossible for most existing studies that include adults with OCD.

In addition, few studies have compared the neural correlates of OCD across children and adults, severely limiting our knowledge of their similarities and differences. One of the aims of this review is to begin to redress this gap by systematically evaluating the similarities and differences in findings from studies of the neural bases of pediatric and adult OCD. We should note, however, that differences in findings across these age groups may be due to several factors. We list four, nonexhaustive possibilities. First, any such differences may be a consequence of comparing children with OCD with mixed samples that include adults with childhood-onset OCD and adults with adult-onset OCD. If childhood-onset OCD is a distinct biological subtype, this comparison confounds age or developmental effects with the effects of illness subtype. Second, such differences may be a consequence of compensatory behavioral, cognitive, or affective responses, which may be more developed, or simply different, in adults. Third, such differences may reflect the differences in phenomenology between pediatric and adult OCD (Geller, Biederman, Jones, Park, et al., 1998). Fourth, such differences may be a consequence of brain development, affecting either the neural systems directly involved in the symptoms of OCD or closely related systems.

Functional Neuroimaging of OCD

Much of our understanding of the pathophysiology of OCD has been derived from functional neuroimaging studies. Broadly speaking, these can be divided into four categories, according to the experimental paradigm used (Saxena & Rauch, 2000): (a) resting studies, which compare some measure of brain activity at rest in patients with OCD and controls; (b) symptom provocation studies, which compare brain activity before and after the provocation of symptoms (e.g., through contact with something dirty in patients with obsessions about germs and cleanliness); (c) treatment studies, which compare brain activity at rest before and after treatment with medication or psychotherapy; and (d) cognitive activation studies, which compare brain activity in patients with OCD and controls as they perform a cognitive task. Combinations of these categories are also possible: one can, for example, image cognitive activation or symptom provocation before and after treatment (Lázaro et al., 2008;

Nakao et al., 2005b), or image cognitive activation before and after symptom provocation.

Three brain areas—the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the head of the caudate nucleus—have been consistently implicated in a large number of resting, symptom provocation, and treatment studies of adults with OCD. These areas (a) are hyperactive at rest in adults with OCD relative to healthy controls, (b) become more active with symptom provocation, and (c) no longer show hyperactivity at rest following successful treatment with either medication or cognitive–behavioral therapy (Baxter, Clark, Iqbal, & Ackermann, 2001; Saxena, Bota, & Brody, 2001; Saxena, Brody, Schwartz, & Baxter, 1998; Saxena & Rauch, 2000; Schwartz, 1998; Whiteside, Port, & Abramowitz, 2004). These findings have generally been interpreted as evidence that abnormalities in these or closely related areas cause OCD (e.g., Baxter et al., 2001; Saxena et al., 1998, 2001; Saxena & Rauch, 2000).

Two studies have compared resting blood flow before and after pharmacological treatment in children with OCD (Castillo et al., 2005; Diler, Kibar, & Avci, 2004). One of these studies (Diler et al., 2004) also compared resting blood flow in the children with OCD before treatment with resting blood flow in a group of healthy controls. The findings of this study were largely consistent with the findings in adults, including hyperactivity at rest in the caudate and ACC of treatment-naive children, which declined following treatment. The other study (Castillo et al., 2005) failed to detect any differences between pre- and posttreatment scans. We are not aware of any symptom provocation studies in children with OCD.

The vast majority of functional imaging studies of OCD through the end of the 1990s used resting, symptom provocation, or pre- versus posttreatment designs. A comprehensive review of imaging studies of OCD that was published in 2001 listed 17 resting studies, 7 symptom provocation studies, 10 pre- versus posttreatment studies, and only 4 cognitive activation studies (Saxena et al., 2001). The situation has shifted in recent years, with the publication of a large number of cognitive activation studies in adults with OCD, using a wide variety of cognitive tasks (with an emphasis on executive function tasks). The tasks used have included the go/no-go (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Roth et al., 2007), Stroop (Harrison et al., 2006; Nakao et al., 2005a; van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005), Eriksen flanker (Fitzgerald et al., 2005), multisource interference (Yucel et al., 2007), stop signal (Woolley et al., 2008), numeric conflict (Viard et al., 2005), reversal learning (Remijnse et al., 2006), tower of London (van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005), spatial N-back (van der Wee et al., 2003), continuous performance (Ursu, Stenger, Shear, Jones, & Carter, 2003), task switching (Gu et al., 2008), word generation (Pujol et al., 1999), and serial reaction time (Rauch et al., 1997, 2001, 2007) tasks. The findings of these studies have generally been consistent with the findings of resting, symptom provocation, and treatment studies, highlighting functional disturbances in the OFC, ACC, basal ganglia, and related areas (Menzies et al., 2008). Rather than attempting to survey this large and varied literature, though, we wish to highlight a general difficulty with interpreting cognitive activation studies that applies across tasks.

Typically, a given cognitive task only activates those areas involved in the cognitive processes required to perform the task. Whether and how the cognitive processes involved in the tasks that have been used to study OCD may relate to the symptoms of OCD is not always obvious. Cognitive activation studies therefore often have less face validity than resting, symptom provocation, or treatment studies for addressing the neural bases of obsessive–compulsive symptoms. For example, most cognitive activation studies of OCD have used inhibitory control tasks. Patients with OCD exhibit behavioral deficits in at least some inhibitory control tasks (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005), and imaging studies that employ those tasks are useful to determine the neural correlates of those deficits. However, the relevance of those studies to understanding the symptoms of OCD depends on the unproven assumption that those symptoms relate directly to a deficit in inhibitory control. The symptoms of OCD have indeed been suggested to be a consequence of deficient inhibitory control, with obsessions arising from a failure to inhibit intrusive thoughts, and

compulsions arising from a failure to inhibit certain behaviors (Chamberlain et al., 2005). Deficits in inhibitory control have, however, been reported for several psychiatric disorders, including attention-deficit/hyperactivity disorder (Barkley, 1997; Nigg, 2001), bipolar disorder (Larson, Shear, Krikorian, Welge, & Strakowski, 2005; Quraishi & Frangou, 2002; Robinson et al., 2006), schizophrenia (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000), and addiction (Li & Sinha, 2008; Yucel & Lubman, 2007). The presence of deficits in inhibitory control in so many disorders with such widely varying phenotypes suggests caution in interpreting such deficits as the root cause of OCD.

Despite these limitations, cognitive activation studies can certainly be informative. Early cognitive activation studies, for example, found that healthy controls recruited the striatum during performance of an implicit (habit) learning task, whereas patients with OCD recruited the hippocampus, despite similar behavioral performances across the groups (Rauch et al., 1997, 2001).[1] These findings suggested that patients with OCD might use hippocampus-dependent (declarative) learning to overcome deficits in striatum-dependent (implicit) learning. If so, the performance of patients with OCD should suffer more than that of healthy controls when a secondary task that taxes working memory is introduced, and this was confirmed experimentally (Deckersbach et al., 2002). These studies show that even in the absence of obvious differences in behavioral performance, cognitive activation studies may highlight differences in neural activity that reflect compensatory strategies. The pathogenic relation, if any, of deficits in implicit (habit) learning and the symptoms of OCD remains unclear however. Even if compulsions are maladaptive, exaggerated habits (Graybiel & Rauch, 2000), why patients with OCD would have difficulty using the striatal habit-learning system (Packard & Knowlton, 2002) to learn other habits remains unclear. Post hoc, one can speculate that in patients with OCD the striatal habit-learning system is "overloaded" by compulsions, making it impossible for them to learn other habits. However, from the idea that OCD prominently involves exaggerated habits (the compulsions), one could equally plausibly have predicted the opposite pattern of findings: that the habit learning system in OCD should be especially powerful and effective. This highlights again the difficulties with interpreting the relevance of cognitive tasks and cognitive activation studies for the pathogenesis of OCD.

1. A more recent study using the same paradigm confirmed abnormal recruitment of the hippocampus in patients with OCD, even though it failed to detect differences in activation of the striatum between patients with OCD and healthy controls (Rauch et al., 2007).

Cortico–Basal Ganglia–Thalamo–Cortical (CBGTC) Loops and the Pathophysiology of OCD

The OFC and ACC are intimately connected to the basal ganglia via CBGTC loops (Alexander, DeLong, & Strick, 1986; Mega & Cummings, 2001; Middleton & Strick, 2001b). Several CBGTC loops exist, and they seem to run largely parallel courses through the basal ganglia (Alexander et al., 1986; Mega & Cummings, 2001; Middleton & Strick, 2001b). Each of these loops receives inputs from multiple cortical areas and then projects back to one of its cortical areas of origin, thereby partly closing the loop (Alexander et al., 1986). No consensus exists in the literature about exactly how many such loops there are, but a particularly influential formulation proposes the existence of five loops, whose target areas are (a) the supplementary motor area, (b) the frontal eye fields, (c) the dorsolateral prefrontal cortex (DLPFC), (d) the lateral OFC, and (e) the ACC (Alexander et al., 1986). A more recent formulation adds two additional loops with target areas in the medial OFC and in the inferotemporal/posterior parietal cortex, and suggests that each of the loops may actually be further subdivided into multiple parallel loops (Middleton & Strick, 2001b). The main site in the striatum through which the CBGTC loops involving the OFC and ACC run is the head of the caudate nucleus (Alexander et al., 1986; Mega & Cummings, 2001; Middleton & Strick, 2001b). The findings from the resting, symptom provocation, and treatment studies described above may therefore be interpreted as implicating the

CBGTC loops involving the OFC and ACC (henceforward referred to as OFC/ACC CBGTC loops) in OCD.

An influential idea based on these observations is that OCD results from an imbalance between the so-called "direct" and "indirect" pathways through the basal ganglia (Figure 1; Baxter et al., 2001; Saxena et al., 1998, 2001; Saxena & Rauch, 2000). The net effect of the direct pathway is excitatory, and the net effect of the indirect pathway is inhibitory (Figure 1), so these pathways are sometimes said to form positive and negative feedback loops, respectively. This simple model of opposing direct and indirect pathways has proven extremely useful in understanding hyperkinetic and hypokinetic movement disorders, such as Huntington and Parkinson diseases, respectively (Wichmann & DeLong, 1996). The idea is that excessive relative activity in the direct pathway disinhibits cortical motor programs, producing hyperkinetic symptoms, such as the chorea in Huntington disease. Conversely, excessive relative activity in the indirect pathway inhibits cortical motor programs, producing hypokinetic symptoms, such as the difficulty initiating movement in Parkinson disease.

These symptoms are in the motor domain, but different symptoms may occur if the balance of the direct and indirect pathways is compromised in nonmotor CBGTC loops. In particular, excessive relative activity in the direct pathway in OFC/ACC CBGTC loops has been suggested to result in a positive feedback loop in which obsessive thoughts become "trapped" (Baxter et al., 2001; Saxena et al., 1998, 2001; Saxena & Rauch, 2000). Consistent with this idea, the prevalence of obsessive–compulsive symptoms is significantly greater in Huntington disease than in the general population (Anderson, Louis, Stern, & Marder, 2001; Beglinger et al., 2007; De Marchi & Mennella, 2000), and some case reports describe onset of OCD following the onset of Huntington disease (Cummings & Cunningham, 1992; Scicutella, 2000).

This theory of OCD is not without difficulties. In particular, it does not explain why patients with OCD should have *specific* obsessions, as opposed to obsessing about everything. This can be unpacked into two, related questions.

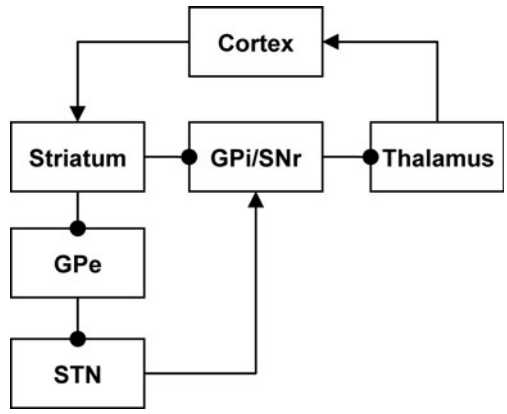

Figure 1. The classical conceptualization of the anatomy of CBGTC loops in terms of direct and indirect pathways (Albin, Young, & Penney, 1989; DeLong, 1990). The direct pathway runs from the cortex to the striatum, then directly to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr), then to the thalamus, and finally back to the cortex. The indirect pathway runs from the cortex to the striatum, then to the globus pallidus external segment (GPe), the subthalamic nucleus (STN), the GPi/SNr, the thalamus, and finally back to the cortex. Arrows represent excitatory (glutamatergic) connections and filled circles represent inhibitory (GABAergic) connections. The direct pathway contains an even number of inhibitory connections (2), so its net effect from the cortex back to the cortex is excitatory. The indirect pathway contains an odd number of inhibitory connections (3), so its net effect from the cortex back to the cortex is inhibitory.

The first is why one finds great similarity in the contents of obsessions cross-culturally (Sasson et al., 1997); the second is why each individual patient tends to obsess only about a small subset of the larger set of common obsessions. One suggestion has been that "in persons with OCD, a response bias exists toward stimuli relating to socioterritorial concerns about danger, violence, hygiene, order, and sex—the themes of most obsessions in patients with OCD—mediated by orbitofrontal circuits" (Saxena & Rauch, 2000). However, the OFC responds to a variety of both positive and negative emotional stimuli, as well as to neutral stimuli that have been previously paired with positive or negative outcomes (Elliott & Deakin, 2005; Elliott, Dolan, & Frith, 2000; Kringelbach & Rolls, 2004; O'Doherty, 2007; Rolls, 1996, 1999, 2004; Schultz, Tremblay, & Hollerman, 2000; Zald & Kim, 2001). Why, then, "socioterritorial concerns" in particular should become locked in

the OCD positive feedback loop is unclear. This suggestion also fails to explain why some patients with OCD will obsess about germs and wash compulsively, whereas others may obsess about whether they have locked the doors to their house and check the locks compulsively.

Searching for the Pathogenesis of OCD

As noted above, the findings that in patients with OCD the OFC, ACC, and caudate nucleus are hyperactive at rest, become more active under symptom provocation, and show less activity following treatment have generally been interpreted as evidence that hyperactivity in these areas generates the symptoms of OCD (e.g., Baxter et al., 2001; Saxena et al., 1998, 2001; Saxena & Rauch, 2000). However, several alternative interpretations of these findings are equally plausible. We know, for example, that when healthy controls are exposed to pictures depicting OCD-relevant scenes (specifically, pictures that are washing relevant, checking relevant, and hoarding relevant) and are asked to imagine related scenarios (e.g., "imagine that you must come into contact with what's shown in the following pictures without washing yourself afterward"), they activate regions similar to those that are hyperactive in OCD (Mataix-Cols et al., 2003). One possible interpretation of these findings is that rather than being the origin of obsessional content, these regions become hyperactive as a normal *consequence* of the obsessional content (Shafran & Speckens, 2005). We also know that the OFC and ACC are involved in emotion regulation (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross, 2005). Thus, again hyperactivity in these areas may be a *consequence* of an attempt by patients with OCD to regulate their anxiety, rather than being the cause of their symptoms.

A related, although slightly different idea is that hyperactivation of the OFC, ACC, and caudate nucleus simply reflects the need to inhibit compulsive behavior during the scan (Peterson, 2003). This idea is supported by the finding that the ACC and the head of the caudate nucleus are activated when patients with Tourette syndrome (TS) voluntarily inhibit their tics (Peterson et al., 1998). The genetic, phenomenological, and pathophysiological similarities between TS and OCD (Fineberg, Saxena, Zohar, & Craig, 2007; Marsh, Leckman, Bloch, Yazgan, & Peterson, 2008) suggest that excessive activity in these areas in patients with OCD might reflect the inhibition of compulsions. Further support for this idea comes from the findings that the OFC, ACC, and caudate are activated in a variety of tasks that require the suppression of a prepotent response (Peterson, 2003). Weighing against this thesis are human lesion studies suggesting that response inhibition may be localized to the right inferior frontal cortex, rather than in the OFC, ACC, or caudate (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004). The evidence from functional imaging for an involvement of the OFC in response inhibition, as studied using the go/no-go task, also remains inconclusive, with block designs typically showing OFC activation, but event-related designs failing to show such activation (Elliott & Deakin, 2005).

Other authors have similarly suggested that OFC hyperactivation may reflect patients' efforts to inhibit their symptoms during the scanning procedure (Adler et al., 2000; Roth et al., 2007), remaining agnostic as to whether that inhibition is targeted specifically at obsessions, compulsions, anxiety, or possibly all of them. Consistent with the idea that OFC activity plays an inhibitory role, keeping the obsessions, compulsions, or anxiety in check, greater activation of the OFC during symptom provocation is associated with a *smaller* increase in reported symptoms with the provocation (Adler et al., 2000; Rauch et al., 1994). If OFC hyperactivity played a role in *causing*, rather than in inhibiting symptoms, then greater activation of the OFC during symptom provocation should be associated with a *greater*, not a lesser, increase in symptoms.

Our goal is not to suggest that one of these various interpretations is the correct one. Instead, we wish to emphasize that all are consistent with the findings that the OFC, ACC, and caudate nucleus are hyperactive at rest, become more active under symptom provocation, and show less activity following treatment. For example, if the activation of these areas reflects an attempt to inhibit symptoms, such activation could be

expected to be higher at rest in patients with OCD than in healthy controls, to increase with symptom provocation, when such inhibition becomes more necessary, and to decrease after treatment, when such inhibition becomes less necessary.

The problem with interpreting these activations as the cause of the symptoms is that these functional imaging findings are inherently correlational: they demonstrate only that activity in these areas correlates with a symptomatic state in OCD. One might hope that anatomical imaging studies would resolve the difficulties in establishing a causal role for these areas in OCD. However, much evidence suggests that repeatedly engaging in a class of behaviors or cognitive processes can change brain structure (Lazar et al., 2005; Mechelli et al., 2004; Pascual-Leone, 2001; Schlaug, 2001; Schlaug, Norton, Overy, & Winner, 2005). Thus, even anatomical differences in the brains of patients with OCD may be a consequence rather than a cause of the disorder. This highlights the usefulness of studying patients with OCD as close to symptom onset as possible, when such epiphenomenal changes may be less prominent. OCD is, however, often diagnosed long after the onset of symptoms, making this strategy relatively impractical. Furthermore, subclinical patterns of thinking and behavior that may long precede clinically significant symptoms (Rasmussen & Eisen, 2002) may also conceivably produce epiphenomenal changes in brain structure that could be apparent by the time of symptom onset.

The problem is that, like functional imaging studies, anatomical studies only provide information about the correlates of the disorder. Several valuable animal models of OCD have been developed in efforts to study causal mechanisms in OCD more directly (Joel, 2006; Korff & Harvey, 2006). These have, however, been criticized because they only model repetitive behaviors; compulsive behaviors in OCD are intimately tied to obsessions, and we have no way of assessing whether animals have obsessions (Shafran & Speckens, 2005).

Other lines of evidence may, however, help establish causality in humans. We will explore three such lines of evidence. First, certain brain lesions due to accidents, stroke, and other naturalistic causes seem to cause OCD. Second, some cases of OCD and of related psychiatric disorders, such as TS, seem to develop as a consequence of an autoimmune reaction in which antibodies to Group A beta-hemolytic streptococcus attack and damage the basal ganglia (Hoekstra & Minderaa, 2005; Leonard & Swedo, 2001; Murphy, Husted, & Edge, 2006; Snider & Swedo, 2004); these are usually termed pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Third, several neurosurgical procedures make localized lesions in attempts to provide symptom relief in severe, treatment-refractory cases of OCD.

Each of these lines of evidence has important limitations in establishing a causal role for abnormalities in specific brain regions in producing OCD. First, studies of OCD as a consequence of brain injury typically involve a small number of subjects who have diffuse lesions that vary greatly across subjects. Furthermore, demonstrating that lesions that affect certain brain circuits result in OCD does not prove a pathogenic role for those circuits in most cases of OCD. Second, the validity of the PANDAS construct remains controversial (Harris & Singer, 2006; Kurlan, 2004; Kurlan & Kaplan, 2004; Singer & Loiselle, 2003), with substantial difficulties involved in establishing a causal relation between infection with Group A beta-hemolytic streptococcus and the development of neuropsychiatric disorders (and additional difficulties in proving that the possible autoimmune reaction affects the basal ganglia). Third, neurosurgical studies lack appropriate controls, and the mechanisms by which they attenuate OCD symptoms are not fully understood. Moreover, an improvement in symptoms following certain neurosurgical lesions does not prove that the circuits that were lesioned caused the symptoms (just as having gastric bypass surgery and losing weight as a result does not prove that the cause of excess weight was an enlarged stomach).

Although each of the aforementioned lines of evidence (anatomical imaging, OCD as a consequence of brain injury, PANDAS, and neurosurgery) in isolation is insufficient to establish causality, their convergence with functional imaging studies in implicating OFC/ACC CBGTC loops in OCD would provide some reassurance that those loops may indeed

play a causal role in OCD. We will therefore review each of these lines of evidence in turn.

Anatomical and Spectroscopy Studies in Adults With OCD

Studies based on regions of interest (ROIs)

Volumetric studies measure the volumes of specific ROIs in the brain. Proton magnetic resonance spectroscopy (^{1}H-MRS) studies measure the concentrations of certain metabolites in ROIs. *N*-Acetyl-aspartate (NAA), one of those metabolites, has been of particular interest in studies of disease processes because decreases in NAA levels may indicate neuronal loss or dysfunction (Barker, 2001; Dager & Steen, 1992; Maier, 1995). NAA levels may be more sensitive than volumetric measures to detect neuronal abnormalities (Bartha et al., 1998; Cendes, Andermann, Preul, & Arnold, 1994; Ebisu, Rooney, Graham, Weiner, & Maudsley, 1994).

The vast majority of anatomical imaging studies of OCD have been conducted after the early functional imaging findings implicated the OFC, ACC, and caudate nucleus in the pathophysiology of OCD. Those studies were therefore strongly influenced by the theory that OFC/ACC CBGTC loops are centrally involved in the pathogenesis of OCD, and have therefore tended to look specifically at brain regions that are part of those loops: the OFC, ACC, caudate nucleus or striatum, and thalamus. Fewer studies have focused specifically on the globus pallidus, another key component of those loops.

OFC. Several studies have reported bilateral reductions in OFC volumes in adults with OCD (Atmaca et al., 2006; Atmaca, Yildirim, Ozdemir, Tezcan, & Poyraz, 2007; Szeszko et al., 1999); one study reported a volume reduction only in the left OFC (Kang et al., 2004). A study that measured specifically the volume of the medial OFC also found it to be reduced bilaterally in adults with OCD (Cardoner et al., 2007). Another study that divided the OFC into anterior and posterior regions reported a volume reduction in the left anterior OFC, but not in the left posterior or right anterior or posterior OFC (Choi et al., 2004). Both left and right OFC volumes have been found to correlate inversely with the severity of OCD symptoms (Atmaca et al., 2007; Kang et al., 2004) and to be larger posttreatment in patients who responded to a trial of selective serotonin reuptake inhibitors than in treatment-naive or treatment-refractory patients (Atmaca et al., 2006). In summary, considerable evidence suggests that OFC volumes are significantly reduced in adults with OCD, with greater reductions accompanying more severe symptoms.

ACC. Several ^{1}H-MRS studies have reported decreased levels of NAA in the ACC of adults with OCD (Ebert et al., 1997; Jang et al., 2006; Sumitani, Harada, Kubo, & Ohmori, 2007; Yucel et al., 2007). Furthermore, treatment with the selective serotonin reuptake inhibitor citalopram increases levels of NAA in the ACC (and other regions of the prefrontal cortex [PFC]) in adults with OCD (Jang et al., 2006), although no significant correlation was detected between increases in NAA and decreases in symptom severity. Several studies have compared ACC volumes in adults with OCD and normal controls, but have generally failed to detect significant differences (Atmaca et al., 2006, 2007; Grachev et al., 1998; Kellner et al., 1991; Riffkin et al., 2005; Szeszko et al., 1999), even when the ACC has been subdivided into anterior and posterior regions (Kang et al., 2004).

To the extent that decreased levels of NAA are a more sensitive indicator of neuronal loss or dysfunction than traditional volumetric measurements (Bartha et al., 1998; Cendes et al., 1994; Ebisu et al., 1994), these findings may indicate the presence of subtle neuronal abnormalities in the ACC of adults with OCD. The fact that the reductions in NAA are reversible with administration of citalopram (Jang et al., 2006) suggests that those reductions may reflect reversible abnormalities either in metabolic processes or in neuropil (axonal or dendritic arbors and synapses), rather than reductions in the number of neurons (Barker, 2001).

Striatum. Studies comparing caudate volumes in adults with OCD and healthy controls have yielded highly variable findings. Although

most studies have not detected significant differences (Atmaca et al., 2006, 2007; Aylward et al., 1996; Kang et al., 2004; Kellner et al., 1991; Riffkin et al., 2005), two studies have reported decreased caudate volumes in OCD (Luxenberg et al., 1988; Robinson et al., 1995). One study reported increases in the volume of the head of the right caudate in adults with OCD (Scarone et al., 1992), but two studies failed to detect significant differences in volumes of the head of the caudate between adults with OCD and healthy controls (Bartha et al., 1998; Kellner et al., 1991). One study reported increased ventral striatum volumes in adults with OCD (Cardoner et al., 2007). Studies using ^{1}H-MRS have been slightly more consistent, with two studies reporting decreased levels of NAA in the striatum of adults with OCD (Bartha et al., 1998; Ebert et al., 1997), but a third study failing to detect such differences (Sumitani et al., 2007).

The variability in findings for the caudate may be, in part, a consequence of the heterogeneous nature of the circuits that traverse it. Different portions of the caudate participate in different CBGTC loops, and disturbances in only one or two of those loops (e.g., the ones involving the OFC and ACC) may not be of sufficient magnitude to yield differences in overall caudate volume. In fact, different portions of the caudate could differ from healthy controls both in the direction and magnitude of the effect. Thus, the overall volume of the caudate could be normal (Atmaca et al., 2006, 2007; Aylward et al., 1996; Kang et al., 2004; Kellner et al., 1991; Riffkin et al., 2005) or even reduced (Luxenberg et al., 1988; Robinson et al., 1995) in adults with OCD, whereas the volumes of the head of the caudate (Scarone et al., 1992) and ventral striatum (Cardoner et al., 2007) could be increased. Volume increases in the head of the caudate and ventral striatum, if confirmed, would provide additional evidence for the involvement of OFC/ACC CBGTC loops in OCD, because these are the regions of the striatum through which such loops run.

Globus pallidus. Most components of the OFC/ACC CBGTC loops—the OFC, ACC, striatum, and thalamus—have been relatively well investigated in ROI studies. However, two other key components of these loops—the subthalamic nucleus and the globus pallidus—remain largely unstudied. Volumes of the subthalamic nucleus have not been assessed because this is a small, poorly demarcated structure that is exceedingly difficult to measure. The few studies that have measured volumes of the globus pallidus or overall volumes of the lenticular nuclei in adults with OCD generally failed to detect differences from healthy controls (Choi et al., 2007; Jenike et al., 1996; Luxenberg et al., 1988).

Thalamus. Volumes of the thalamus have been reported to be larger in treatment-naive adults with OCD than in healthy controls (Atmaca et al., 2006, 2007). Patients who responded to medication treatment had smaller thalami post-treatment than either treatment-naive or treatment-refractory patients, with no differences detected between the latter two groups (Atmaca et al., 2006). Patients were not scanned before and after treatment, so whether treatment responders had smaller thalami to begin with or as a consequence of treatment is unclear. Nevertheless, a study that scanned children with OCD before and after medication treatment did detect medication-induced reductions in thalamic volume that moreover correlated with symptom improvement (Gilbert et al., 2000), suggesting that the findings of smaller thalami in treatment-responding adults may also have been a consequence of treatment. Thalamic volumes were found to correlate positively with symptom severity in both treatment-naive and treatment-refractory patients (Atmaca et al., 2006, 2007).

Two studies failed to detect differences in volumes of the thalamus between adults with OCD and healthy controls (Kang et al., 2004; Kwon et al., 2003). However, approximately 70% of the patients in one of these studies (Kang et al., 2004) had previously been treated with medication (although all were medication free for at least 4 weeks at the time of study), and the medication history and medication status of patients in the other study (Kwon et al., 2003) were not reported. Given the evidence that medication treatment may reduce thalamic volumes in patients with OCD, the failure of

these studies to detect differences between adults with OCD and controls could conceivably be due to the effects of medication.

Other areas. Other areas that strongly influence the OFC/ACC CBGTC loops, by virtue of their projections to the same regions of the striatum as the OFC or ACC, include the superior temporal gyrus and hippocampus (Alexander et al., 1986; Middleton & Strick, 2001b). These areas have received less attention in studies of OCD. Nevertheless, volume reductions have been reported for both the superior temporal gyrus (Choi et al., 2006) and hippocampus (Kwon et al., 2003) in adults with OCD. Two studies failed to detect volumetric abnormalities in the hippocampus of adults with OCD (Jenike et al., 1996; Szeszko et al., 1999), but one of these (Jenike et al., 1996) had a small sample and failed to find differences in most areas, and the other (Szeszko et al., 1999) found a trend for less asymmetry in hippocampus volumes in adults with OCD.

An area that is closely related, anatomically and functionally, to the OFC and ACC is the amygdala (Amaral, Price, Pitkanen, & Carmichael, 1992; Carmichael & Price, 1995; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Rolls, 1999; Zald & Kim, 2001). The amygdala also projects strongly to the mediodorsal nucleus of the thalamus (Amaral et al., 1992), the final relay station before the OFC/ACC CBGTC loops project back to the cortex (Alexander et al., 1986; Middleton & Strick, 2001b), and it is therefore critically positioned to influence the output of these loops. The amygdala's key role in mediating normal fear and anxiety (LeDoux, 2000, 2007; Phelps & LeDoux, 2005) and its prominent involvement in anxiety disorders (Bremner, 2004; Miller, Taber, Gabbard, & Hurley, 2005; Rauch, Shin, & Wright, 2003) highlight its potential relevance for understanding the pathophysiology of OCD, a disorder in which anxiety plays a crucial role (Foa, Steketee, & Ozarow, 1985; Rachman & Hodgson, 1980). The few studies that have examined volumes of the amygdala in adults with OCD have, however, yielded inconsistent findings, with one study reporting bilateral reductions in amygdala volume (Szeszko et al., 1999) and another reporting an increase in left amygdala volume (Kwon et al., 2003).

Summary. Volumetric studies in adults with OCD provide convincing evidence for reduced OFC volumes, suggestive evidence for increased thalamic and normal ACC volumes, and inconsistent evidence for caudate or striatum volumes. ^{1}H-MRS studies in adults with OCD provide convincing evidence for decreased NAA levels in the ACC and suggestive evidence for decreased NAA levels in the striatum. Together, these findings point to abnormalities in volumes or NAA levels in all components of the OFC/ACC CBGTC loops that have been studied in detail. Abnormalities in closely related areas, such as the hippocampus, amygdala, and superior temporal gyrus, have also been reported. The findings from volumetric and ^{1}H-MRS studies of adults with OCD are summarized in Table 1.

Limitations of ROI approaches

ROI approaches suffer from two serious limitations. First, because manual delimitation of ROIs is laborious, ROI studies often analyze only a small number of regions for which there are prior suspicions of abnormality, which limits the opportunity to find abnormalities in unanticipated regions. Automated methods to delimit ROIs partly alleviate this problem, but they are significantly less accurate than manual methods. Second, anatomical ROIs may not correspond to functionally meaningful units because gross anatomical structures or landmarks do not always reflect anatomical connectivity or cytoarchitecture. For example, several CBGTC loops run through the caudate nucleus (Alexander et al., 1986; Middleton & Strick, 2001b) and each of those loops also partly seems to run through the putamen (Haber, 2003). Considering each nucleus (caudate or putamen) as a whole misses both the distinctions between different loops within the nucleus and the fact that portions of one nucleus should be considered together with portions of the other. A meta-analysis of positron emission tomography (PET) and single-photon emission computed tomography studies of OCD that found reliable differences between patients with OCD and normal controls in the

Table 1. *Summary of volumetric, VBM, and ^{1}H-MRS findings in children and adults with OCD*

	Children	Adults
ROI volumes		
OFC		− − − − −[a] −[b]
ACC	+ +	= = = = = = = =
Striatum[c]	= −[d]	= = = = = = =[e] =[e] +[e] +[f] − −
GP	−	= = =[g]
Thalamus	+	= = + +
STG	=	−
Amygdala	= =	+ −
Hippocampus	=	= = −
VBM		
OFC		+ − ±[h]
ACC[i]	−	− − −
Striatum		+[f] +[j] +[j]
Thalamus		+ +
STG		+ −
Amygdala		+
Insula		+ + − −
Cerebellum		+ −
^{1}H-MRS		
ACC		* * * *
Striatum		* * =
Thalamus[k]	* * * *	

Note: In a given cell, each symbol represents one study. Symbols in different cells may refer to the same study. ACC, anterior cingulate cortex; GP, globus pallidus; ^{1}H-MRS, proton magnetic resonance spectroscopy; OCD, obsessive–compulsive disorder; OFC, orbitofrontal cortex; ROI, region of interest; STG, superior temporal gyrus; VBM, voxel-based morphometry; (+) increased volumes or increased gray matter density in patients; (−) decreased volumes or decreased gray matter density in patients; (=) no significant differences between patients and healthy controls; (*) abnormal concentrations of neurometabolites (*N*-acetyl-aspartate, choline, or creatine/phosphocreatine) in patients.
[a]Medial OFC.
[b]Left anterior OFC.
[c]Studies refer to the caudate unless otherwise noted.
[d]Decreased putamen but not caudate volumes.
[e]Head of the caudate.
[f]Ventral striatum.
[g]Lenticular nuclei.
[h]Gray matter increases and decreases were reported for differing regions of OFC.
[i]All gray matter decreases were reported for both the ACC and the medial frontal gyrus.
[j]Putamen.
[k]All studies refer to the medial thalamus.

orbital gyrus and the head of the caudate nucleus, but not in the OFC or caudate nucleus as a whole (Whiteside et al., 2004), illustrates the importance of moving toward finer anatomical distinctions in the study of OCD.

These limitations are addressed by two techniques: voxel-based morphometry (VBM) and tensor-based morphometry. VBM is a popular whole-brain approach that gives voxel-by-voxel measurements (Ashburner & Friston, 2000). It remains controversial, however, because errors in spatial normalization may confound all subsequent computations, resulting in unreliable findings (Bookstein, 2001). Tensor-based morphometry is used to analyze local morphological changes on the surface of cortical or subcortical structures (a procedure often termed "surface analysis") or to measure cortical thickness. This approach gives highly localized, point-by-point measurements. Surface analyses, however, still require the prior delimitation of ROIs, as it is within a previously delimited

ROI that surface analysis gives detailed, point-by-point measurements.

Cortical thickness

The findings from the only extant study of cortical thickness in OCD (Shin et al., 2007) are consistent with a pathophysiological model that emphasizes disturbances in the OFC, but also suggest abnormalities in a number of areas that are not traditionally considered involved in the pathophysiology of OCD. This study found cortical thinning in several areas of the left hemisphere of adults with OCD, including not only the OFC but also the ventrolateral prefrontal, middle frontal, precentral, superior temporal, parahippocampal, and lingual cortices. No abnormalities were detected in the ACC or anywhere in the right hemisphere. The findings from this study should be interpreted with care because most patients were medicated. Nevertheless, the finding of thinning in the superior temporal cortex is consistent with the volume reductions that have been reported for the superior temporal gyrus (Choi et al., 2006), and the finding of thinning in the parahippocampal cortex may point to broader abnormalities in the tissue surrounding the hippocampus that would be consistent with the volume reductions that have been reported for the hippocampus proper (Kwon et al., 2003).

Surface analysis

Only two studies, both conducted by the same group and with adults, have used surface analysis to analyze subcortical structures in OCD. One of these studies focused on the hippocampus and reported shape changes concentrated on the hippocampus head (Hong et al., 2007). These results are consistent with the previous report by the same group of volumetric abnormalities in the hippocampus of adults with OCD (Kwon et al., 2003). The other study focused on the basal ganglia and found outward deformities concentrated in the dorsal anterior caudate nucleus bilaterally and, to a lesser extent, in the ventral lateral part of the left putamen (Choi et al., 2007). These results are surprising, given that these are not the striatal regions through which the OFC/ACC CBGTC loops run (Alexander et al., 1986; Haber, 2003; Lehericy et al., 2004; Middleton & Strick, 2001b). The results of these surface analysis studies need to be interpreted with care because neither study corrected for multiple comparisons, and in both studies the majority of patients had a history of medication (although all were medication free for at least 4 weeks prior to scanning). Surface analysis techniques are also sufficiently new that replication by other laboratories would be important.

VBM

Several studies have used VBM to compare gray matter in adults with OCD and healthy controls (Kim et al., 2001; Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008). Findings from these studies have been generally consistent with the pathophysiological model of OCD that emphasizes the OFC and ACC and their loops through the basal ganglia. Both increases (Kim et al., 2001; Valente et al., 2005) and decreases (Pujol et al., 2004; Valente et al., 2005) in gray matter have been reported for differing subregions of the OFC, highlighting the potential value of a finer level of morphological analysis than is typically achieved in ROI-based studies. Decreases in gray matter have been consistently reported in the ACC and surrounding medial frontal gyrus (Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008). Increases in gray matter have generally been reported in the striatum (Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008). These increases have included the ventral striatum (Pujol et al., 2004), which is consistent with the known neuroanatomy of OFC/ACC CBGTC loops, but also the putamen (Valente et al., 2005; Yoo et al., 2008), which is less clearly consistent with the standard pathophysiological model of OCD. Increases in gray matter have also been reported in the thalamus (Kim et al., 2001; Yoo et al., 2008). VBM studies have also reported abnormalities in other areas that have been found abnormal in volumetric studies or in the only study of cortical thickness in OCD to date (Shin et al., 2007) and that relate closely to OFC/ACC CBGTC loops. For example, VBM studies have reported both increases (Kim et al., 2001) and decreases (Yoo et al., 2008) in gray matter in the superior temporal

gyrus, as well as increases in gray matter in the parahippocampal gyrus, extending to the amygdala (Valente et al., 2005).

The only other areas for which abnormalities have been found in at least two VBM studies in adults with OCD are the insula (Kim et al., 2001; Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008) and cerebellum (Kim et al., 2001; Pujol et al., 2004). The insula is contiguous with the posterior OFC and is heavily interconnected with both the OFC and the ACC (Mesulam & Mufson, 1982; Mufson & Mesulam, 1982; Ongur & Price, 2000). The cerebellum and frontal cortex are interconnected in parallel corticocerebellar loops (Kelly & Strick, 2003; Middleton & Strick, 1997, 2000, 2001a), and the cerebellum can also influence the striatum via a disynaptic connection through the thalamus (Hoshi, Tremblay, Feger, Carras, & Strick, 2005). The potential involvement of the insula and cerebellum in OCD may therefore be consistent with the pathophysiological model that emphasizes disturbances in the OFC/ACC CBGTC loops and related areas in OCD.

Although abnormalities in several other areas have been reported in single VBM studies, they have not been replicated across studies. Although this does not exclude the possible involvement of other areas, it does provide some measure of reassurance that the main structural abnormalities in adults with OCD are concentrated along the OFC/ACC CBGTC loops and related areas. The findings from VBM studies of adults with OCD are summarized in Table 1.

Anatomical and Spectroscopy Studies in Children With OCD

Studies based on ROIs

OFC. We are not aware of any volumetric studies of the OFC in pediatric OCD. This is a major gap in the literature, given that reduced volumes in the OFC are the most consistent finding in the volumetric literature on adult OCD.

ACC. One study reported larger volumes of the ACC in treatment-naive children with OCD than in matched controls, with larger ACC volumes accompanying more severe symptoms (Rosenberg & Keshavan, 1998). Another study reported increased volumes of gray matter, but not of white matter, in the ACC of medication-naive children with OCD (Szeszko, MacMillan, McMeniman, Chen, et al., 2004). These findings stand in contrast to those in adults with OCD, which have generally failed to detect volumetric abnormalities in the ACC. A possible explanation for this difference in findings across age groups is that the ACC may develop differently in patients with OCD and healthy controls. One cross-sectional study reported a nearly significant correlation between age and ACC volumes in healthy children but not in children with OCD (Rosenberg & Keshavan, 1998). If this finding is confirmed, ideally in a longitudinal study, it could mean that ACC volumes are larger in children with OCD but then stay relatively constant with advancing age, whereas ACC volumes in healthy children might be smaller but then increase with age, resulting in similar ACC volumes in patients with OCD and healthy controls by adulthood.

Striatum. Two studies detected no significant differences in caudate volumes between children with OCD and matched controls (Rosenberg et al., 1997; Szeszko, MacMillan, McMeniman, Chen, et al., 2004), although one of these studies reported smaller putamen volumes in children with OCD (Rosenberg et al., 1997). The finding of a putamen abnormality is somewhat surprising from the perspective of the pathophysiological model of OCD that emphasizes the OFC/ACC CBGTC loops, given that those loops run mostly (although not exclusively) through the caudate; replication of this finding would therefore be important. If confirmed, this finding would also emphasize the need for volumetric studies of the putamen in adults with OCD, because virtually all volumetric studies of the striatum in adults with OCD have focused on the caudate.

Globus pallidus. One study reported smaller globus pallidus volumes in medication-naive children with OCD compared with matched healthy controls (Szeszko, MacMillan, McMeniman, Chen, et al., 2004). This finding stands in contrast to those in adults with OCD, which have generally failed to detect volumetric abnormalities in the globus pallidus.

Thalamus. One study reported increased thalamic volumes in medication-naive children with OCD that decreased to normal levels following treatment with the selective serotonin reuptake inhibitor paroxetine (Gilbert et al., 2000). Furthermore, the reduction in thalamic volumes with treatment correlated with the improvement in OCD symptoms. The finding of increased thalamic volumes in children with OCD is consistent with similar findings in adults. The finding that paroxetine treatment in children with OCD reduces thalamic volumes is also consistent with the indirect evidence that medication reduces thalamic volumes in adults with OCD. Another study found no differences in volumes of the thalamus measured before and after successful cognitive–behavioral therapy (Rosenberg, Benazon, Gilbert, Sullivan, & Moore, 2000), suggesting that the reduction in volumes of the thalamus seen with paroxetine treatment is not necessary for symptom improvement. This study, however, did not include a control group, so the possibility that the children with OCD in this study might not have significantly enlarged thalami prior to treatment cannot be excluded.

Several studies by the same group using ^{1}H-MRS have reported abnormalities in the medial thalamus of treatment-naive children with OCD. The first such study detected reduced ratios of NAA to choline and NAA to creatine/phosphocreatine + choline levels in the medial but not the lateral thalami of treatment-naive children with OCD (Fitzgerald, Moore, Paulson, Stewart, & Rosenberg, 2000). The findings were interpreted as indicative of reduced NAA levels in the medial thalami in the patient group, with the caveat that an increase in choline could produce the same results. Indeed, subsequent studies from the same group did report increases in choline (Rosenberg, Amponsah, Sullivan, MacMillan, & Moore, 2001; Smith et al., 2003) and creatine/phosphocreatine levels (Mirza et al., 2006) in the medial thalami of children with OCD, suggesting that the earlier findings reflected elevated levels of choline and creatine/phosphocreatine rather than decreased levels of NAA. In fact, measurement of absolute NAA concentrations in the medial thalamus did not reveal differences between children with OCD and matched controls (Rosenberg et al., 2001). The significance of elevated choline and creatine/phosphocreatine levels in the medial thalamus remains to be fully elucidated. Nevertheless, it is noteworthy that these abnormalities occur in the medial thalamus, where the mediodorsal nucleus (the primary nucleus of the thalamus in OFC/ACC CBGTC loops) is located.

Other areas. The only study that measured volumes of the superior temporal gyrus and hippocampus in children with OCD did not detect significant differences from healthy controls (Rosenberg & Keshavan, 1998). This is in partial contrast to the findings in adults, which tentatively suggest that these structures may be abnormal in adults with OCD. Two studies failed to detect significant differences in amygdala volumes between children with OCD and healthy controls (Rosenberg & Keshavan, 1998; Szeszko, MacMillan, McMeniman, Lorch, et al., 2004), although one of these studies found that children with OCD, unlike healthy controls, had significantly larger left than right amygdalae (Szeszko, MacMillan, McMeniman, Lorch, et al., 2004). Abnormalities in other areas, for example, increased NAA levels in the left but not right DLPFC of children with OCD (Russell et al., 2003) and decreased pituitary volumes in boys but not girls with OCD (MacMaster et al., 2006), have been reported sporadically but need to be replicated.

Summary. Significantly fewer volumetric or ^{1}H-MRS studies exist for children than for adults with OCD. Nevertheless, two findings receive convergent support from more than one study of children with OCD: increased volumes of the ACC and abnormal metabolite concentrations in the thalamus. Findings that were obtained in only one study and require replication include reduced putamen and globus pallidus volumes and increased thalamus volume. The findings from volumetric and ^{1}H-MRS studies of children with OCD are summarized in Table 1.

The findings of increased thalamic volumes in children with OCD echo similar findings in adults. The findings of increased ACC volumes in children with OCD, however, are in contrast to the findings in adults with OCD, which have generally failed to detect volumetric

abnormalities in the ACC, although they are consistent with several ^{1}H-MRS studies that have reported decreased NAA levels in the ACC of adults with OCD. The finding of reduced globus pallidus volumes in children with OCD is also in contrast to the findings of the few existing volumetric studies of the globus pallidus in adults with OCD. Volumetric studies in adults with OCD have generally not measured the putamen, so whether reduced putamen volumes are found in adults with OCD remains unclear.

Most extant volumetric and ^{1}H-MRS studies of OCD have focused on comparing volumes or metabolite levels between patients with OCD and healthy controls, paying little to no attention to how the volumes or metabolite levels change with age in persons with and without OCD. This information is, however, vitally important for a developmental perspective on the pathogenesis of OCD, as well as to understand how the abnormalities reported in children with OCD ultimately evolve to the abnormalities reported in adults with OCD, at least for adults with childhood-onset OCD. Similarly, studies of adults with OCD should distinguish better whether their findings relate to adult- or childhood-onset OCD, or to both.

VBM

No cortical thickness or surface analysis studies of children with OCD have been reported in the literature. However, two VBM studies have been recently published (Carmona et al., 2007; Gilbert et al., 2008). One of these (Gilbert et al., 2008) reported decreased gray matter in the left ACC and in the medial frontal gyrus bilaterally in children with OCD, consistent with similar findings in adults (Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008) and with the hypothesized involvement of the ACC in OCD. The consistency of the findings of decreased gray matter in the medial frontal gyrus in children and adults underscores the need to consider not only the ACC proper, but also the surrounding medial frontal gyrus as a potential locus of abnormality in OCD.

The other VBM study in children with OCD (Carmona et al., 2007) also reported a large cluster of decreased gray matter in the cingulate cortex, although that finding did not remain significant after correcting for multiple comparisons. Other large clusters of decreased gray matter were found in the middle frontal gyrus, with the cluster in the right middle frontal gyrus remaining significant after correcting for multiple comparisons. Additional clusters were also reported, but they were substantially smaller and none remained significant after correcting for multiple comparisons. Additional studies are necessary to determine whether the finding in the middle frontal gyrus is reproducible, especially because of the 18 children with OCD, 11 had comorbid tic disorder and 10 were on medication.

The only consistent finding between the two existing VBM studies of children with OCD is reduced gray matter in the ACC. Although this is consistent with similar findings in VBM studies of adults with OCD, it contrasts with the findings of volumetric studies in children with OCD, which have generally found *increased* ACC volumes (Rosenberg & Keshavan, 1998; Szeszko, MacMillan, McMeniman, Chen, et al., 2004). A possible explanation for this discrepancy comes from the observation that, depending on the details of the VBM procedure used, VBM may characterize gray matter density rather than volume (Good et al., 2001). In fact, one of the studies (Gilbert et al., 2008) states precisely that its findings concern gray matter densities, not volumes, and that this may explain their discrepancy with prior volumetric studies. The findings from VBM studies of children with OCD are summarized in Table 1.

PANDAS

Another potential line of evidence for the involvement of the basal ganglia in OCD comes from the study of PANDAS. This designation refers to childhood-onset OCD or tic disorders with abrupt onset or an episodic symptom course, in which symptom onset or exacerbation is temporally associated with infection with Group A beta-hemolytic streptococcus (GAS; Swedo et al., 1998). Several authors have suggested that PANDAS are autoimmune disorders caused by antibodies to GAS that interact with the basal ganglia, in particular the striatum (Hoekstra & Minderaa, 2005; Leonard & Swedo,

2001; Murphy, Husted, & Edge, 2006; Snider & Swedo, 2004). Controversy remains, however, regarding not only this causal hypothesis but the validity of the PANDAS construct itself (Harris & Singer, 2006; Kurlan, 2004; Kurlan & Kaplan, 2004; Singer & Loiselle, 2003).

GAS infection was first observed to produce Sydenham chorea, an illness associated with rheumatic fever and characterized primarily by involuntary rapid, jerky movements, which are often accompanied by other motor, behavioral, and emotional problems, including obsessive–compulsive symptoms and OCD (Swedo et al., 1989, 1993). Later observations identified putative cases of abrupt childhood-onset OCD or TS that followed GAS infections but did not meet criteria for Sydenham chorea (Allen, Leonard, & Swedo, 1995; Swedo et al., 1998). Establishing a clear and definitive causal role for GAS infections in these cases has proven difficult, however, in part because GAS infections are so common in childhood (Murphy, Sajid, & Goodman, 2006).

Experimental evidence suggests but does not prove a causal role for GAS in the onset or exacerbation of OCD or TS. Several studies have reported elevated anti basal ganglia antibodies in the sera of patients with TS or OCD (Dale, Heyman, Giovannoni, & Church, 2005; Kiessling, Marcotte, & Culpepper, 1994; Rizzo, Gulisano, Pavone, Fogliani, & Robertson, 2006; Singer et al., 1998; Wendlandt, Grus, Hansen, & Singer, 2001), although at least one study failed to detect differences in anti basal ganglia antibodies between patients with PANDAS and healthy controls (Singer et al., 2004). One study reported that immunomodulatory treatment of PANDAS led to improvements in both OCD and TS symptoms (Perlmutter et al., 1999), although this study has been criticized on multiple grounds (Singer, 1999). Two studies have reported that antibiotic prophylaxis and treatment was effective in reducing symptoms in PANDAS (Murphy & Pichichero, 2002; Snider, Lougee, Slattery, Grant, & Swedo, 2005), although these studies should be considered preliminary because neither of them included a placebo group. Finally, infusion of sera from TS patients who have elevated antineuronal antibodies into the striatum of rats has been reported to produce an increase in stereotypies (Hallett, Harling-Berg, Knopf, Stopa, & Kiessling, 2000; Taylor et al., 2002), although these findings have not always been replicated (Loiselle, Lee, Moran, & Singer, 2004; Singer et al., 2005).

The caudate, putamen, and globus pallidus are enlarged in patients with PANDAS (Giedd, Rapoport, Garvey, Perlmutter, & Swedo, 2000), just as they are in Sydenham chorea (Giedd et al., 1995). Changes in basal ganglia volumes are commonly found in OCD and TS, however, so the possibility that the volumetric changes found in patients with PANDAS simply reflect changes associated with TS or OCD, independently of an association with GAS infection, cannot be excluded. Stronger evidence for a causal link between an autoimmune reaction and enlarged basal ganglia volumes would be obtained if immunomodulatory treatment was shown to reduce the size of enlarged basal ganglia. A case study of an adolescent boy with exacerbation of OCD symptoms after a streptococcal pharyngitis showed precisely that, and the reduction in basal ganglia volumes was also accompanied by a reduction in symptom severity (Giedd, Rapoport, Leonard, Richter, & Swedo, 1996). However, larger controlled studies are needed to confirm these findings.

To summarize, the existing evidence suggests but does not prove that a GAS infection may, in some cases, trigger an autoimmune response that attacks the basal ganglia, leading to OCD, TS, Sydenham chorea, or a combination of these disorders. The specific CGBTC loops affected may determine the neuropsychiatric presentation, with disturbances in motor loops causing TS or Sydenham chorea and disturbances in OFC/ACC CBGTC loops causing OCD.

OCD as a Consequence of Brain Injury

The onset of OCD following focal brain lesions can provide valuable clues regarding the anatomical bases of OCD. In principle, simply because a lesion in a given brain region can produce OCD, that does not necessarily imply that all or even some cases of non-lesion-related OCD involve impairments in that region. Nevertheless, if lesion studies highlight the same general circuits that have been implicated in anatomical and functional imaging studies of OCD, the case

for a causal role for those circuits in the pathogenesis of OCD becomes stronger.

Multiple reports describe cases of OCD following lesions confined to the basal ganglia (Carmin, Wiegartz, Yunus, & Gillock, 2002; Chacko, Corbin, & Harper, 2000; Laplane et al., 1989; Lopez-Rodriguez, Gunay, & Glaser, 1997; Rodrigo Escalona, Adair, Roberts, & Graeber, 1997; Weilburg et al., 1989; Weiss & Jenike, 2000); two describe cases following lesions confined to the OFC (Kim & Lee, 2002; Ogai, Iyo, Mori, & Takei, 2005); a few describe cases following lesions involving broader expanses of frontal cortex (Swoboda & Jenike, 1995; Ward, 1988; Weiss & Jenike, 2000); and a few others describe cases following more widespread lesions, which nonetheless also involve the frontal lobes (typically including the OFC) or the basal ganglia (Berthier, Kulisevsky, Gironell, & Lopez, 2001; Gamazo-Garran, Soutullo, & Ortuno, 2002; Max et al., 1995). In addition, two case reports describe *improvements* in preexisting OCD after hemorrhage in the basal ganglia (Fujii, Otsuka, Suzuki, Endo, & Yamadori, 2005; Yaryura-Tobias & Neziroglu, 2003).

The consistency of the brain areas involved in these case reports with those implicated in anatomical and functional imaging studies of patients with OCD suggests a causal role for the frontal cortices (in particular, the OFC) and the basal ganglia in the pathogenesis of OCD. Some caution is warranted when interpreting the findings of case reports, however, for three main reasons. First, the number of subjects involved is relatively small, even when considering the findings of all available case reports. Second, the stress associated with having a brain lesion could, by itself, aggravate or even precipitate some cases of OCD. In fact, greater psychosocial adversity is associated with the development of obsessive–compulsive symptoms following traumatic brain injury (Grados et al., 2008). Third, the possibility of reporting bias cannot be excluded, given that several of the cases mentioned above were reported after theories of the involvement of the OFC and respective loops through the basal ganglia had appeared in the literature, and clinicians may have been more willing to report cases consistent with that theoretical framework. To the extent that childhood- and adult-onset OCD may have differing etiologies, these cases may also bear mostly on adult-onset illness, as the vast majority of them involve adults (often older adults).

A large, prospective study assessed new-onset obsessive–compulsive symptoms in 80 children and adolescents (ages 6–18) following severe traumatic brain injury (Grados et al., 2008). This study reported a high prevalence of new-onset obsessions or compulsions 1 year after injury, with 21 out of the 80 subjects reporting obsessions or compulsions at that time but not before the lesion. Conversely, five subjects who had obsessions or compulsions before the lesion no longer had them 1 year after the lesion. Medial prefrontal and temporal lobe lesions were associated with new-onset obsessions, but this effect disappeared when obsessions and compulsions were considered conjointly. OFC lesions seemed to be associated with *fewer* symptoms, suggesting that anatomical integrity of the OFC is required for the onset of OCD. This is consistent with neurosurgical treatments for OCD that disrupt the OFC or its connections, but it contrasts with the case reports that have implicated lesions of the OFC in the onset of OCD (Kim & Lee, 2002; Ogai et al., 2005). A possible explanation for this discrepancy is that lesions to certain subregions of the OFC may cause OCD, whereas lesions to other subregions may prevent its expression.

This study suffered from three important limitations. First, it used an ROI approach that examined only the areas that have traditionally been implicated in OCD (OFC, medial PFC, basal ganglia, and thalamus), plus the temporal lobe. Second, symptoms were assessed 1 year after injury, and their onset or disappearance could, at least in some cases, be due simply to the passing of time. The absence of a group of matched noninjured controls in the study precludes any inferences regarding the extent to which the changes in symptoms were caused by the injury. Third, scanning and symptom assessment occurred 9 months apart. In addition, the focus of the study was on obsessive–compulsive symptoms, not full-blown OCD. In fact, only 2 out of the 80 children had new-onset OCD following the lesion.

In summary, several reports describe cases of OCD following lesions of the basal ganglia or frontal cortex (with an emphasis on the OFC); two reports describe cases of improvement in OCD after lesions of the basal ganglia. A larger, prospective study (Grados et al., 2008) also suggests a role for the OFC in obsessive–compulsive symptoms following brain injury, although in that study lesions to the OFC were inversely related to symptom severity. The same study also reported an association between lesions to the medial PFC (which included the ACC) and obsessions. All of these findings are consistent with the hypothesis that the pathogenesis of OCD involves CBGTC loops, in particular, the loops involving the OFC and possibly the ACC.

Despite the convergence of findings from lesion studies with those from anatomical and functional imaging studies, the correct way to conceptualize the relation of lesion findings with functional imaging findings remains elusive. For example, we have seen above that the OFC is often hyperactive in OCD. Do we interpret this as evidence that activity of the OFC is somehow causally related to the symptoms of OCD and therefore expect a lesion of the OFC to improve symptoms, given that a lesioned OFC would not be active? Or do we interpret the imaging data as evidence that the OFC is working in overdrive to try to inhibit or control the expression of OCD symptoms and therefore expect a lesion of the OFC to worsen the symptoms? Or do we interpret the hyperactivity in OFC not as a sign of heightened function but rather of dysfunction in that region and therefore expect that lesions of the OFC might produce OCD, by making the OFC dysfunctional? Different versions of all of these hypotheses can be found implicitly or explicitly in the literature. Existing lesion studies do not, however, help us discriminate between these alternatives, given that lesions of the OFC have been associated with both increases and decreases in OCD symptoms. More research is needed to address these questions.

Another question, raised specifically by findings of the prospective study described above (Grados et al., 2008), is whether the temporal lobe may also be involved in the pathogenesis of OCD. In support of this possibility, temporal lobe epilepsy has been associated with OCD and obsessive–compulsive symptoms (Kroll & Drummond, 1993; Monaco et al., 2005). In addition, several studies have reported anatomical abnormalities in the superior temporal gyrus in patients with OCD (Choi et al., 2006; Kim et al., 2001; Shin et al., 2007; Yoo et al., 2008). One possibility, which we have already discussed, is that the temporal lobe, in particular the superior temporal gyrus, is involved in OCD via its connections with the regions of the striatum that are part of the OFC/ACC CBGTC loops (Alexander et al., 1986). However, additional research is needed to test this hypothesis.

Neurosurgical Lesions

Neurosurgical lesions are sometimes made to attenuate symptoms in extremely severe cases of OCD that do not respond to psychotherapy and medication. Four types of neurosurgical lesions are used: anterior capsulotomy, subcaudate tractotomy, cingulotomy, and limbic leucotomy (for reviews, see, e.g., Greenberg, Murphy, & Rasmussen, 2000; Greenberg et al., 2003; Mindus, Rasmussen, Lindquist, & Noren, 2001). All are small bilateral lesions that interrupt white matter tracts that connect the OFC or ACC with subcortical structures involved in CBGTC loops. Their success, although modest, provides additional converging evidence for the involvement of the OFC, ACC, and their associated CBGTC loops in the pathophysiology of OCD.

The lesions in anterior capsulotomy are placed in the anterior limb of the internal capsule. Such lesions are believed to interrupt the connections between the OFC and the mediodorsal nucleus of the thalamus (Greenberg et al., 2000; Mindus et al., 2001), which is the thalamic nucleus with densest reciprocal connections with the OFC and the primary nucleus in the thalamus involved in CBGTC loops that connect to the OFC (Fuster, 1997; Ongur & Price, 2000). The lesions in subcaudate tractotomy are placed below and immediately anterior to the head of the caudate nucleus. They seem to be restricted to white matter, as they are anterior to the substantia innominata and rarely include the cortex (Malhi & Bartlett, 1998;

Newcombe, 1975). These lesions are believed to disconnect the OFC from the thalamus, basal ganglia, and limbic system (Feldman, Alterman, & Goodrich, 2001; Malhi & Bartlett, 1998). They have also been shown to produce degeneration in the anterior limb of the internal capsule, which can be traced back to the mediodorsal nucleus of the thalamus (Mindus et al., 2001). The lesions in cingulotomy are placed in the cingulate bundle (i.e., cingulum). The mechanisms by which cingulotomy reduces the severity of OCD symptoms are unknown, but may involve the fibers that connect the ACC and the caudate nucleus (Rauch et al., 2000). Limbic leucotomy refers simply to a combination of subcaudate tractotomy and cingulotomy.

Evaluating the success of these procedures is complicated by the small number of subjects in each study and the obvious ethical difficulties with conducting randomized double-blind studies involving neurosurgical lesions (Earp, 1979). In addition, different studies use different criteria (e.g., remission of symptoms, percent improvement over preoperative symptom severity) to evaluate the success of these procedures. Nevertheless, estimated success rates are generally approximately 50% or more for all procedures (Jenike, 1998; Mindus et al., 2001). Similar rates are, however, often seen in open trials of medication or psychotherapy and typically drop substantially in blinded, controlled treatment trials.

The fact that these procedures primarily target fiber bundles that connect the OFC or ACC with related subcortical structures, notably the thalamus and basal ganglia, provides additional evidence for the involvement of these circuits in the pathogenesis of OCD. Such evidence remains circumstantial, however, for three reasons. First, all of these procedures were developed largely empirically between 30 and 60 years ago (Bingley, Leksell, Meyerson, & Rylander, 1977; Kelly et al., 1973; Knight, 1964; Richardson, 1973; Talairach, Hecaen, David, Monnier, & Ajuriaguerra, 1949; Whitty, Duffield, Tov, & Cairns, 1952), often based on neuroanatomical theories that are now outdated. Consequently, in most cases we still do not fully know all of the neuroanatomical connections that they affect. Second, the improvement in symptoms is often gradual following surgery, occurring over a time span of weeks to months (Jenike, 1998). This suggests that the anatomical changes underlying such improvement may be a secondary consequence of the lesion, possibly involving retrograde degeneration or a neuroplastic response. Indeed, volume reductions in distant structures have been observed after localized neurosurgical lesions (Rauch et al., 2000; Taren, Curtis, & Gebarski, 1994). Third, the fact that a lesion in a given circuit improves symptoms does not necessarily imply that an abnormality at that lesion site or even in that circuit caused the symptoms. In fact, the same neurosurgical procedures used for the treatment of OCD are also used for a variety of other conditions, including other anxiety disorders (Cosgrove & Rauch, 2003), depression (Cosgrove & Rauch, 2003; Malhi & Bartlett, 2000), and intractable pain (Wilkinson, Davidson, & Davidson, 1999). For all of these reasons, whether these procedures target directly and specifically the circuits involved in the pathogenesis of OCD remains unclear.

Development of OFC/ACC CBGTC Circuits

Knowledge of the normal development of OFC/ACC CBGTC circuits may provide clues to the neurodevelopmental processes that go awry in patients with OCD. Although brain weight and volume nearly reach their adult values by 5–6 years of age (Courchesne et al., 2000; Dekaban & Sadowsky, 1978; Giedd, Snell, et al., 1996; Kretschmann, Kammradt, Krauthausen, Sauer, & Wingert, 1986; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sahni, Jit, & Sodhi, 1998), the brain continues to develop throughout childhood, adolescence, and early adulthood. The total volume of gray matter starts to decrease after around 5 years of age (Courchesne et al., 2000; Pfefferbaum et al., 1994; Reiss et al., 1996; Sowell et al., 2003), with cortical thickness and gray matter density decreasing in much of the cortex (Gogtay et al., 2004; Sowell et al., 2004). In contrast, white matter volume increases throughout childhood, adolescence, and early adulthood (Courchesne et al., 2000; Giedd et al., 1999; Matsuzawa et al., 2001; Pfefferbaum et al., 1994; Reiss et al., 1996; Sowell et al., 2003). In general, sensorimotor areas mature earlier and higher order areas, including the OFC, mature

later (Benes, 1989; Gogtay et al., 2004; Yakovlev & Lecours, 1967). During the years in which childhood-onset OCD typically starts, the PFC, basal ganglia, and thalamus are undergoing major developmental changes. Furthermore, some of those changes seem to affect primarily boys, which may explain the higher prevalence of OCD among boys than among girls. This section reviews these developmental changes and their possible relation to the pathogenesis of OCD.

Development of the PFC

The PFC grows markedly between 5 and 14 years of age (Kanemura, Aihara, Aoki, Araki, & Nakazawa, 2003; Sowell et al., 2004; Thompson et al., 2000). Such growth seems to include the most ventral aspects of the PFC (Sowell et al., 2004; Thompson et al., 2000), possibly including the OFC. However, the studies that have mapped the growth of the PFC did not include the ventral surface of the brain, so the growth patterns of the OFC remain to be elucidated. Some evidence suggests that the fastest growth in the PFC occurs between 8 and 14 years of age (Kanemura et al., 2003), the period during which most cases of childhood-onset OCD begin, raising the possibility that abnormalities in that growth could cause childhood-onset OCD—a hypothesis that is consistent with the findings of reduced OFC volume in patients with OCD. The PFC, including the OFC, continues to mature through adulthood (Gogtay et al., 2004), however, so abnormalities in later stages of maturation of the OFC could conceivably cause adult-onset OCD.

The growth of the PFC during childhood and adolescence may be largely driven by the development of white matter (Barnea-Goraly et al., 2005; Reiss et al., 1996). In fact, gray matter density and cortical thickness in PFC seem to *decrease* during childhood, adolescence, and young adulthood (Gogtay et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 2004). Furthermore, postmortem studies indicate that the density of synapses and the sizes of neuronal cell bodies and dendritic fields in PFC increase only until approximately 2 to 3 years of age (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Koenderink, Uylings, & Mrzljak, 1994; Petanjek, Judas, Kostovic, & Uylings, 2008). Whether this means that OCD is caused primarily by abnormalities in the development of white matter or in the regressive processes that fine-tune synaptic organization in OFC is unknown.

Future studies should address more directly the normal development of the OFC. Several of the magnetic resonance imaging (MRI) studies that have mapped cortical development did not map the inferior surface of the brain (Sowell et al., 2003, 2004; Thompson et al., 2000) and postmortem developmental studies have generally focused on the lateral PFC (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Koenderink et al., 1994; Petanjek et al., 2008). Our knowledge of the development of the OFC is therefore indirect, and the extent to which the OFC and the lateral and dorsal PFC share similar developmental trajectories is unknown. One study reported that while the volume of white matter in dorsal PFC increased throughout childhood and adolescence, the volume of white matter in the OFC decreased (Reiss et al., 1996), raising the possibility that these structures may develop differently. Even within the OFC, decreases in gray matter density throughout childhood and adolescence seem to follow medial–lateral and anterior–posterior gradients (Gogtay et al., 2004). A better understanding of the development of the OFC in healthy children and in children with OCD could substantially advance our understanding of the pathogenesis of this disorder.

Current knowledge of the development of the ACC is similarly limited. Volumes of the cingulate seem to change less during childhood and adolescence than do volumes of other regions such as the frontal or medial temporal lobes (Sowell, Trauner, Gamst, & Jernigan, 2002). Gray matter density also seems to change less across the life span in the ACC than in many other cortical regions (Sowell et al., 2003). Furthermore, cortical thickness and size of the dorsal ACC seem to change relatively little between 5 and 11 years of age, although cortical thickness and size of the ventral ACC may increase in that age range (Sowell et al., 2004). Together, these findings may suggest that anatomical development is less prominent in the ACC than in other portions of the OFC/ACC CBGTC loops during the years in which OCD typically begins. The

volume of the right ACC has, however, been reported to increase during childhood and adolescence (Casey et al., 1997; Marquardt et al., 2005). Furthermore, larger volumes of the right ACC have been associated with better performance on an attentional task in children and adolescents (Casey et al., 1997). Some authors have argued that development of the ACC during infancy, childhood, and adolescence may underlie the improvements in self-regulatory capacities that characterize these periods (Posner & Rothbart, 1998; Posner, Rothbart, Sheese, & Tang, 2007). Whether abnormalities in the development of the ACC may lead to deficits in the self-regulation of intrusive thoughts, images, or feelings, or to the well-documented deficits in inhibitory control in OCD (Chamberlain et al., 2005) is unknown.

Development of the basal ganglia and thalamus

The volume of the caudate nucleus has generally been reported to decrease during childhood and adolescence (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Giedd, Snell, et al., 1996; Jernigan, Trauner, Hesselink, & Tallal, 1991). Some evidence suggests that such decreases may be most pronounced between 4 and 12 years of age (Giedd, Snell, et al., 1996), and marked tissue loss has been reported in the head of the caudate between 7 and 13 years of age (Thompson et al., 2000). These age ranges are consistent with the ages during which childhood-onset OCD typically begins, raising the possibility that abnormal development of the caudate could cause childhood-onset OCD. Volumes of the lenticular nuclei (Giedd et al., 1997; Giedd, Snell, et al., 1996; Jernigan et al., 1991; Reiss et al., 1996; Sowell et al., 2002) and thalamus (Jernigan et al., 1991; Reiss et al., 1996; Sowell et al., 2002) also decrease throughout childhood and adolescence. In addition, white matter tracts within the basal ganglia and between the basal ganglia and thalamus also develop during childhood and adolescence (Barnea-Goraly et al., 2005). Together with the findings of maturation of frontal cortex during childhood and adolescence (Barnea-Goraly et al., 2005; Gogtay et al., 2004; Kanemura et al., 2003; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Reiss et al., 1996; Sowell et al., 1999, 2002, 2004; Thompson et al., 2000), these results may reflect the integrated development of CBGTC loops. OCD may be caused by abnormalities in the development of one or more of the key structures or white matter tracts in these loops.

Gender differences in the development of CBGTC circuits

Many studies have reported sexual dimorphisms in the human brain (Gilmore et al., 2007; Goldstein et al., 2001; Luders et al., 2005; Rabinowicz, Dean, Petetot, & de Courten-Myers, 1999; Sowell et al., 2007). These tend to occur in regions that have high concentrations of sex steroid receptors during brain development (Goldstein et al., 2001), suggesting a role for gonadal hormones in causing such dimorphisms. Gender differences in brain structure and development during childhood and adolescence may provide an explanation for the significantly higher prevalence of childhood-onset OCD in boys than in girls. In fact, existing evidence suggests that both the caudate and the OFC, two key components of the OFC/ACC CGBTC loops, differ markedly and develop differently in boys and girls.

On average, male brains are larger than female brains across all age groups (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Courchesne et al., 2000; Giedd et al., 1997; Giedd, Snell, et al., 1996; Goldstein et al., 2001; Lenroot et al., 2007; Reiss et al., 1996; Sowell et al., 2007). Comparisons of volumes of brain structures between males and females are therefore usually performed after adjusting for overall brain volume. When this is done, girls have greater caudate volumes than boys (Caviness et al., 1996; Giedd et al., 1997; Giedd, Snell, et al., 1996; Sowell et al., 2002). In addition, the decline in volumes of the caudate and lenticular nuclei during childhood and adolescence may be restricted to boys (Giedd et al., 1997; Giedd, Snell, et al., 1996; Sowell et al., 2002). Childhood and adolescence may therefore be particularly critical for the development of the basal ganglia in boys, which may explain why boys are more susceptible than girls to OCD and other

disorders of CBGTC circuitry such as TS and attention-deficit/hyperactivity disorder.

Potential sexual dimorphisms in the human OFC during childhood or adolescence remain to be studied. In adulthood, women have larger OFC volumes than men (Goldstein et al., 2001), and in a sample spanning childhood to old age, females had thicker OFC cortices than males (Sowell et al., 2007). These anatomical differences have functional implications, as males perform better on average than females on tasks that rely on OFC function (Overman, 2004). Such performance differences seem to apply across most age groups, and have been found even in children younger than 3 years of age (Overman, 2004). Similar findings have been reported in monkeys, with male infant monkeys performing better than female infant monkeys on an object discrimination reversal task, which is known to depend on the OFC (Clark & Goldman-Rakic, 1989). The OFC also appears to develop earlier in male monkeys than in female monkeys (Clark & Goldman-Rakic, 1989; Goldman, Crawford, Stokes, Galkin, & Rosvold, 1974). In short, the structure, function, and development of the OFC seem to differ between males and females. The contribution of these differences to the differing susceptibilities of boys and girls to OCD remains to be elucidated however.

Several lines of evidence suggest that these differences in OFC structure, function, and development in males and females are caused by the effects of gonadal hormones on the OFC during development. First, the OFC has high affinity for androgen binding (Clark, MacLusky, & Goldman-Rakic, 1988) and high aromatase activity (MacLusky, Clark, Naftolin, & Goldman-Rakic, 1987; MacLusky, Naftolin, & Goldman-Rakic, 1986) in the developing monkey, suggesting that it may be particularly susceptible to the influence of gonadal hormones. Second, treating female infant monkeys with androgen early in postnatal life abolishes the performance differences between male and female monkeys in the object discrimination reversal task (Clark & Goldman-Rakic, 1989). Third, female rats have more extensive dendritic fields in the OFC than do male rats, but those differences are abolished by neonatal gonadectomy (Kolb, Pellis, & Robinson, 2004). The finding of more extensive dendritic fields in the OFC of female rats may also help to explain the findings of larger volume (Goldstein et al., 2001) and thicker cortex (Sowell et al., 2007) in the OFC of women.

Conclusions

All of the lines of research reviewed herein—anatomical imaging, PANDAS, OCD as a consequence of brain injury, and neurosurgery for treatment-refractory OCD—suggest a role for OFC/ACC CBGTC loops in the pathogenesis of OCD, but each suffers from important limitations. Anatomical imaging findings point to abnormalities in the OFC/ACC CBGTC loops in both children and adults with OCD. However, these findings are inherently correlational and therefore do not license any conclusions regarding a causal role for those abnormalities in OCD. Studies of PANDAS and of OCD as a consequence of brain injury suggest that insults to OFC/ACC CBGTC loops may indeed cause OCD. Specifically, studies of PANDAS suggest that an autoimmune insult to the basal ganglia may cause OCD; however, controversy remains regarding this putative pathogenic mechanism and even the very existence of PANDAS. Studies of OCD as a consequence of brain injury suggest that lesions in key components of these loops may also cause OCD; however, much of this evidence is based on case reports. Finally, neurosurgical lesions used for treatment-refractory OCD suggest that lesions placed in key components of the OFC/ACC CBGTC loops can be effective in attenuating the symptoms of OCD; however, the improvement in symptoms is often gradual, raising the possibility that it may be due to degeneration or plasticity elsewhere in the brain, rather than an effect of the primary lesion itself. Despite the limitations when each of these lines of evidence is considered in isolation, the remarkable convergence of findings across all of them does suggest a causal role for the OFC/ACC CBGTC loops in OCD, in both children and adults.

Assuming that OCD is indeed caused by abnormalities in OFC/ACC CBGTC loops, do the findings reviewed above suggest a particular locus within those loops that may be responsible for OCD? In adults with OCD, anatomical imaging studies using ROI approaches point to volumetric or NAA abnormalities in all components

of the OFC/ACC CBGTC loops that have been studied in detail: the OFC, ACC, striatum, and thalamus. Whole-brain approaches such as VBM have also found gray matter abnormalities in all of these areas. Abnormalities in other areas closely related to the OFC/ACC CBGTC loops, including the superior temporal gyrus, hippocampus, and amygdala, have also been found in both ROI and whole-brain anatomical studies. Several VBM studies have also highlighted abnormalities in the insula, another area closely related to the OFC/ACC CBGTC loops (Mesulam & Mufson, 1982; Mufson & Mesulam, 1982; Ongur & Price, 2000).

The implications for the pathogenesis of OCD of such widespread abnormalities within OFC/ACC CBGTC loops and potentially also in related areas in adults with OCD can be interpreted in at least four ways. First, the etiology of OCD may involve some mechanism that causes widespread abnormalities in all of these structures. Second, the etiology of OCD may involve some mechanism that causes an abnormality in just one or a small number of these structures, with the abnormalities in the remaining structures being a consequence of dynamic changes prompted by that primary etiologic abnormality. As we have seen, anatomical imaging studies after neurosurgery have shown that localized lesions in one structure or fiber bundle of the OFC/ACC CBGTC loops can cause volume changes in remote, albeit related structures (Rauch et al., 2000; Taren et al., 1994). Thus, abnormalities in one or a few structures in these loops could translate into structural abnormalities in all of the structures within the loops and related structures elsewhere. Third, the etiology of OCD may, as in the second hypothesis, consist of an initial abnormality in just one or a few structures, with the abnormalities in the remaining structures following from that, but with different cases of OCD possibly arising from initial abnormalities in different structures. Lesion studies suggest that damage to any one of several components of the OFC/ACC CBGTC loops is sufficient to cause OCD, raising the possibility that even non-lesion-related cases of OCD may be a consequence of different initial abnormalities. Fourth, the widespread abnormalities may actually be an artifact of averaging across subjects, with individual subjects having more localized abnormalities that vary across subjects.

One way of trying to disentangle these possibilities would be to conduct longitudinal anatomical imaging studies that followed patients with OCD over extended period of time, starting as close to their diagnosis as possible. Such studies could determine whether the abnormalities start in only one or a few structures (with the initial site of the abnormality possibly varying by case) and then spread to other structures. A cruder and less conclusive alternative is to compare the findings from anatomical imaging studies across children and adults with OCD to determine whether the findings in children suggest abnormalities in a smaller subset of regions than do the findings in adults. If so, this could indicate that abnormalities in OCD start in a specific subset of the regions that have been found abnormal in adults with OCD. Differences between findings in children and adults with OCD could, however, be due to multiple factors, including a comparison across childhood- and adult-onset subtypes, differing types and rates of comorbidity, differing ascertainment biases, and differing durations of illness.

Unfortunately, the extant literature does not allow us to conclude with any certainty which areas are and are not affected in children with OCD. Existing studies clearly point to anatomical abnormalities in the ACC and metabolite abnormalities in the thalamus. No anatomical abnormalities have yet been reported in the other structures that are affected in adults with OCD, including the OFC and caudate, but that may be attributable either in whole or in part to the fact that those structures have not yet been properly studied in children with OCD. For example, even though the most consistently replicated volumetric finding in adults with OCD is a reduction in volume of the OFC, no ROI studies have analyzed the volume of the OFC in children with OCD. Similarly, even though the most consistent finding for the striatum of adults with OCD is a reduction in NAA levels, no studies have analyzed NAA levels in the striatum of children with OCD. In addition, of the two VBM studies of pediatric OCD, one had fairly small samples (Gilbert et al., 2008), and in the other the majority of children were on medication (Carmona et al., 2007).

A large-scale longitudinal study that followed children or adults with high familial risk for OCD from before their diagnosis through several years later would clearly provide a much richer and more dynamic view of the unfolding of pathology in the brain affected by OCD. Such a study should ideally be multimodal, including, for example, anatomical MRI, functional MRI, ^{1}H-MRS, investigation of white matter fiber tracts using diffusion tensor imaging, and investigation of neurotransmitter and receptor levels using PET. The results of such a study could then inform a more detailed search for the ultimate cause or causes of OCD: clearly, the focus of such a search would be vastly different if OCD were found to be a consequence of, say, an abnormality localized initially in the striatum, than if it were found to be a consequence of abnormalities affecting, from the very beginning, several structures of the OFC/ACC CBGTC loops and related structures elsewhere.

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