Available online at www.sciencedirect.com
SCIENCE DIRECT®
Clinical Psychology Review 26 (2006) 32–49
CLINICAL PSYCHOLOGY REVIEW

Neuroimaging studies of obsessive–compulsive disorder in adults and children

Laura Friedlander *, Mary Desrocher

Department of Psychology, York University, 4700 Keele St., Toronto, ON, Canada M3J 1P3

Received 22 July 2004; received in revised form 22 January 2005; accepted 16 June 2005

Abstract

Obsessive–compulsive disorder (OCD) is a severe, highly prevalent and chronically disabling disorder that usually emerges during childhood or adolescence. Neuroimaging studies play an important role in advancing our understanding of the pathophysiology of OCD and in developing neurocircuitry models of this psychiatric illness. This paper provided an updated, comprehensive review and analysis of the relevant literature on baseline functional and structural neuroimaging studies of OCD in both paediatric and adult patients. The neuroanatomical findings were presented in the context of two models: executive dysfunction, which implicates the dorsolateral prefrontal cortex, caudate nucleus, thalamus, and striatum; and modulatory control, which implicates the orbitofrontal and medial prefrontal cortex and the cingulate gyrus. Neuroanatomical findings were not consistent across all studies, and limitations were examined. Recommendations for future research directions and the implications of the results for improved treatment were explored.

Keywords: Neuroimaging; OCD; Review

Obsessive–compulsive disorder (OCD) is defined by the presence of obsessive thoughts or acts and/or compulsive behaviours. This is a disorder that may begin in either childhood or adulthood, and may manifest in a number of different ways. One of the critical issues in research on OCD is examining the neurological correlates of the disorder. Like most psychiatric disorders, the literature shows that various structures in the brain may be abnormal in appearance or function in patients with OCD symptomatology. Many of the extant studies simply note the correlation of OCD symptoms with some neural correlate, without placing these findings in a theoretical context. This review paper will attempt to discuss the neurobiology of OCD in children and adults in the context of two key theoretical perspectives, those of executive dysfunction and modulatory control. We will first outline the diagnostic criteria of OCD, prevalence of the disorder, comparisons of symptoms across age and gender groups, issues of comorbidity, and clinical presentation to provide a review of what is known about the presentation of OCD. We will then provide a discussion of the neurobiology of OCD in the context of two models: executive dysfunction and modulatory control. We will conclude with limitations of the current research and proposed future directions.

* Corresponding author. Tel.: +1 416 736 2100x33111; fax: +1 416 736 5814.
E-mail address: lfriedla@yorku.ca (L. Friedlander).

0272-7358/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cpr.2005.06.010

1. Diagnostic criteria

According to the diagnostic criteria for OCD outlined by DSM-IV (American Psychiatric Association, 1994), obsessions are characterized as recurrent, persistent and irrational impulses, thoughts or images that cause marked anxiety or distress and are not just excessive worries of real-life problems. On the other hand, compulsions can be defined as ritualistic, repetitive and purposeful behaviours (e.g., checking) or mental acts (e.g., counting) that an individual feels obliged to perform in response to an obsession. The purpose of ritualistic behaviours or mental acts is to prevent or reduce marked distress, to neutralize obsessional thoughts or to prevent some dreaded event or situation. These compulsive behaviours or mental acts are considered to be excessive or are not connected in a realistic way to the obsessions they are supposed to neutralize or prevent. With the exception of children, individuals with OCD are able to recognize that their obsessive thoughts are senseless, unreasonable, excessive and irrational and come to the realization that their obsessions are a product of their mind. As well, individuals with OCD recognize that their compulsive behaviours are not absolutely necessary.

Rettew, Swedo, Leonard, Lenane, and Rapoport (1992) report that OCD symptoms frequently change over time, often with no clear pattern of progression. At any one time, most children will present with more than one OCD symptom, and many will have experienced almost all the classic OCD symptoms by the end of adolescence. Although the pattern or type of symptoms may change over time, the absolute number of symptoms typically remains constant (Piacentini & Bergman, 2000). The specific symptoms are virtually identical in both children and adults with no age related trends found with any one type of symptom (Rettew et al., 1992).

2. Prevalence

Recent research indicates that OCD is a common disorder in both adults and children. Until recently, childhood-onset OCD was considered to be rare and was unfamiliar to most professionals even though classic descriptions of the disorder featured cases with OCD symptoms originating in childhood (Swedo, Leonard, & Rapoport, 1992). Multiple epidemiologic studies conducted throughout the world consistently demonstrate an average lifetime prevalence of 1–3% in adults, with similar prevalence estimates for adolescents and children. The recognition that OCD was more common in childhood than once believed and retrospective reports that approximately 80% of OCD adult patients experience the onset of symptoms before the age of 18 (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995) focused the attention of researchers to the area of paediatric OCD.

3. Age of onset and gender distribution

Clinically based studies suggest that the average age of onset for childhood OCD ranges from 6 to 11 (Piacentini & Bergman, 2000) with a mean of 10.3 years (Shafran, 2001). Moreover, several studies suggest that the age of onset is earlier for boys (prepubertal onset) than for girls (begins during adolescence), with younger boys experiencing more severe symptoms than younger girls (Flament et al., 1988). The age of onset has been documented as having a bimodal distribution with peaks in early adolescence (12 to 14 years) and in early adulthood (20–22 years) (Robinson, 1998; Shafran, 2001; Snider & Swedo, 2000). It has been found that children with early onset (before age 7) are more likely to be males and to have a family member will OCD than those with OCD of a later onset. This suggests that biological factors (e.g., genetics) may play a prominent role in the development of the early-onset subtype (Piacentini & Bergman, 2000).

The majority of studies of childhood OCD find an average of 2 : 1 to 3 : 2 male–female ratio (Shafran, 2001). Although most clinic-based studies of primarily younger children suggest a male preponderance, epidemiologic surveys of adolescent samples report equivalent gender ratios and in adults equal gender representation or a slight female preponderance. It remains to be determined whether this discrepancy between gender distribution ratios for young children and adolescents is a function of age or caused by a referral bias (Piacentini & Bergman, 2000).

4. Comorbidity

OCD is highly comorbid with a variety of other psychiatric disorders. In contrast to adult studies that have well documented high rates of comorbidity with affective and anxiety disorders (Pigott, L' Heureux, Dubbert, Bernstein, &

Murphy, 1994), studies of children have included a diverse list of comorbid psychiatric disorders. Although comorbidity rates do vary across studies, the relative ranking of comorbid disorders in children is generally constant. The most common comorbid disorders are anxiety disorders (26–75%), depressive disorders (25–62%), tic disorders (20–30%), and disruptive behavioural disorders, (18–33%) (Piacentini & Bergman, 2000) with anxiety and affective disorders being reported the most frequently (Shafran, 2001). Other frequently reported disorders include learning disorders and developmental disorders (Robinson, 1998). It is not unusual for OCD patients to be diagnosed with multiple disorders (Swedo, Rapoport, Leonard, Lenane, & Cheslow, 1989). It has been reported that as many as 80% of children with OCD meet the diagnostic criteria for an additional AXIS I disorder and as many as 50% may experience multiple comorbid conditions.

5. Neuroimaging techniques used to study OCD

In the past decade, advances in non-invasive, in vivo brain imaging techniques have led to a greater understanding of the pathophysiology of OCD (Rosenberg, MacMillan, & Moore, 2001). Various techniques have been utilized to determine the brain regions that may be implicated in the neurological basis of the disorder. In terms of structural techniques, Computerized Tomography (CT) has been used to provide a picture of the gross neuropathology, and Magnetic Resonance Imaging (MRI) has provided greater resolution in examining the neuropathology that may occur in various brain structures. Functional techniques, which allow exploration of structures that become activated during specific cognitive or emotion-induction tasks, include Positron Emission Tomography (PET) and Single Positron Emission Computerized Tomography (SPECT), both of which measure changes in metabolism of radioactively labelled isotopes, such as oxygen, or metabolism of glucose; and Functional Magnetic Resonance Imaging (fMRI), which measures hemodynamic (blood flow) changes. A recent addition to the tools that have been used to study OCD is magnetic resonance spectroscopy (MRS), which measures the concentration of particular metabolites in key areas of the brain. These techniques have been used to explore a number of states of patients with OCD, namely: (1) comparison of OCD patients with healthy controls in baseline studies; (2) changes in the brain of OCD patients before and after treatment; and (3) OCD patients both in the resting state and during symptom provocation (Saxena, Brody, Schwartz, & Baxter, 1998). This paper will present the findings of baseline comparison studies, to outline the structural neuropathology of OCD.

6. Neuroimaging findings

In general, the results of neuroimaging studies have been presented in the absence of framing models, which may explain the relationship of OCD symptomatology to the functions of areas that may be dysfunctional. We will present the findings of the studies on neuroimaging in the context of two models that have been suggested to explain the neurobiology of OCD. The first is an executive dysfunction model, which proposes that the main dysfunction occurs in impulse control and inhibition of behaviours (e.g., Rapoport, 1991; Rauch et al., 1994). The second is a modulatory control model, in which the dysfunction may be one of inability to regulate socially appropriate behaviours (e.g. Saxena et. al., 1998). Neuroimaging findings which do not fit into either of these models will be presented with potential explanations for the implication of relevant brain areas.

7. Executive dysfunction

The model of executive dysfunction in OCD states that the main dysfunction in persons with the disorder is one of impulse control (e.g., Rapoport, 1991; Rauch et al., 1994). The main problem is the inability to inhibit responses that are not adaptive to a particular situation, which is sometimes termed perseveration, particularly when these responses are repeatedly exhibited despite feedback that they are not adaptive. Such executive dysfunction has been shown in patients with brain injuries (Ward, 1988), children with Attention Deficit Hyperactivity Disorder (Barkley, 1997), and in Parkinson's disease (Wolfe, Linn, Babikian, Knoefel, & Albert, 1990). In patients with OCD, this perseverative behaviour is seen particularly in the completion of compulsions. Neuropsychological evidence has typically implicated the dorsolateral regions of the prefrontal cortex in perseverative, disinhibited behaviours (Cummings & Mega, 2003).

Although dorsolateral areas are often implicated, this region of the prefrontal cortex acts in concert with the basal ganglia and thalamus, via frontostriatal circuits. In particular, the caudate nucleus has been shown to be highly

connected to the dorsolateral prefrontal cortex, via the striatum (Cummings, 1993). This circuitry has been implicated in the gating and inhibition of limbic system activity, typically in the completion of behaviours. One explanation is that patients may show an inability to extinguish certain thoughts and actions, even in the absence of an underlying emotional problem. The outcome would be that patients would perseverate on a single thought or action, which in turn may interfere with their capability to engage in alternative responses. Evidence for the role of this executive dysfunction circuit in OCD is presented below, and in Table 1.

8. Dorsolateral frontal cortex

The dorsolateral frontal cortex has been shown to have decreased volume (Lucey et al., 1997; Martinot et al., 1990) in baseline imaging of adults with OCD relative to controls. In a more recent adult study, Lacerda and colleagues (2003) found increased volume compared to the controls. No other studies have shown differences in the dorsolateral prefrontal cortex (e.g., Rosenberg & Keshavan, 1998; Szeszko et al., 2004), but have focused instead on a structure in the basal ganglia to which it is highly connected, the caudate nucleus. It is of interest to note that the two studies in which differences were not found in the dorsolateral prefrontal cortex were both conducted with children and adolescents, rather than with adults.

9. Basal ganglia

The area which has been implicated most consistently in the neurological basis of OCD is the caudate nucleus, one of the key structures of the basal ganglia. However, the findings have been mixed as to whether the structural and metabolic integrity of the caudate is different in those with and without OCD. Three studies have found decreased volume of the caudate nucleus bilaterally (Luxenberg et al., 1988; Robinson et al., 1995; Rubin, Villanueva-Meyer, Ananth, Trajmar, & Mena, 1992), while two studies found increased volume bilaterally (Baxter et al., 1987, 1988). Others have found only unilateral involvement of the caudate. One study has found increased volume of the right caudate (Scarone et al., 1992), with one study finding decreased right caudate volume (Lucey et al., 1997).

Other studies have not found significant differences between the size of the caudate nucleus in those with or without OCD (e.g. Aylward et al., 1996; Bartha et al., 1998; Insel, Donnelly, Lalakea, Alterman, & Murphy, 1983; Jenike et al., 1996; Kellner et al., 1991; Szeszeko et al., 2004). One way in which these studies differ from those in which findings of changes in the caudate were present is a longer duration of drug-free time when the neuroimaging scans were conducted. This raises the question as to whether it is OCD alone that affects the caudate, or the combination of OCD and medications that lead to caudate changes.

A few studies have also implicated other structures within the basal ganglia. The globus pallidus/putamen increased in volume in adults (Perani et al., 1995). Studies with children found decreased volumes in the putamen (Rosenberg, Keshavan, O' Hearn et al., 1997) and globus pallidus (Szeszeko et al., 2004). No differences were found in volumes of the putamen by Szeszeko and colleagues (2004), thus calling into question how reliable these findings are in children, and calls for further study in this age range.

10. Striatum

The striatum has also been shown to be related to OCD diagnosis. Lowered metabolism in the left striatum has been shown by Bartha et al. (1998), while lowered metabolism in the right has been found by Ebert et al., 1997. In the paediatric OCD literature, Behar et al. (1984) noted increased ventricular brain ratios observed in adolescent OCD patients compared to controls, which would be predicted with decreased striatal volumes. However, these researchers did not specifically measure striatal volumes in their report.

11. Thalamus

As a site of relay and integration of incoming sensory information with higher cortical functioning, the thalamus, and the dorsomedial nucleus in particular, is believed to play an important role in the etiology of OCD. A number of studies have explored the thalamic nuclei and their role in the neuropathology of OCD. Three adult studies have found

Table 1
Neuroimaging findings supporting the executive dysfunction model of obsessive–compulsive disorder

Brain area	Study	Technique	Age Group	Participants	Medication	Comorbidity	General findings
Dorsolateral frontal cortex	Martinot et al., 1990	PET	Adults	—16 OCD patients: 9M, 7F —Mean age: 44 years —Adults with mixed childhood/adult onset —8 healthy controls: 5M, 3F	—10 on meds —5 had no meds for at least 2 weeks before study —1 was drug-free	—No major depressive episode	—Decreased metabolism in lateral prefrontal cortex
	Lucey et al., 1997	SPECT	Adults	—15 OCD: 8M, 7F —Average duration: 14 years —Mean age: 36 years —16 with post-traumatic stress disorder: 14M, 2F —15 with panic disorder with agoraphobia: 8M, 7F —15 healthy controls: 8M, 7F	N/A	—No other Axis I disorders	—Decreased superior frontal cortex bilaterally in OCD
	Lacerda et al., 2003	SPECT	Adults	—16 OCD patients: 8M, 8F —Mean age: 29.5 years —Age at onset: 15.8 years —Length of illness: 13.7 years —17 healthy controls: 10M, 8F	—Drug-free for at least 30 days before the study —10 patients were drug-naïve	N/A	—Increased right superior frontal cortex in OCD patients
	Rosenberg and Keshavan, 1998	MRI	Children and/or adolescents	—21 OCD patients: 13M, 8F —Mean age: 12.7 years —Age of onset: 8.1 years —Duration of illness: 4.5 years —21 healthy controls	—Treatment-naïve	—10 had an anxiety disorder —1 had ADHD —3 had dysthymia —3 had oppositional or conduct disorder —Only 7 with OCD as sole diagnosis	—No difference in dorsolateral prefrontal cortex
	Szeszeko et al., 2004	MRI	Children and/or adolescents	—23 OCD patients: 7M, 16F —Mean age: 12.3 years —Mean age at illness onset: 9.1 years —27 healthy controls: 12M, 15F	—Drug-naïve patients	—8 had an anxiety disorder —3 dysthymia —1 ADD —1 ODD —2 trichotillomania —11 had OCD as sole diagnosis	—OCD patients=healthy controls for superior frontal gyrus
Basal ganglia	Insel et al., 1983	CT	Adults	—OCD patients: 6M, 4F —Mean age: 33.3 years —Mixed childhood/adult onset —10 normal control participants	—CT performed during a drug-free period	N/A	—OCD patients' caudate nucleus volume=control participants' caudate nucleus volume
	Baxter et al., 1987	PET	Adults	—14 OCD patients: 9M, 5F —Mean age: 31.6 years —14 with unipolar depression: 5M, 9F —14 controls: 7M, 7F	—5 on meds	—9 of OCD patients met criteria for major depression	—Increased bilateral head of caudate in OCD patients
	Baxter et al., 1988	PET	Adults	—10 OCD patients: 5M, 5F —Mean age: 35.5 years —Had illness for at least 1 year —10 control patients: 5M, 5F	—Drug-free for at least 2 weeks before study	—8 had major depression —3 met criteria for social phobia; 2 of which met criteria for simple phobia	—Increased heads of bilateral caudate nuclei in OCD patients

Kellner et al., 1991	MRI	Adults	—19 OCD patients: 12F, 7M —Mean age: 40 years —19 controls: 12F, 7M	N/A	N/A	—OCD patients' caudate nucleus volume=control participants' caudate nucleus volume
Rubin et al., 1992	SPECT	Adults	—10M OCD patients —Mean age: 34.9 years —10 control participants	—Drug-free for at least 4 weeks before study	—No one met criteria for other Axis I disorders	—Decreased head of caudate nucleus bilaterally in OCD patients
Scarone et al., 1992	MRI	Adults	—20 OCD patients: 8M, 12F —Mean age: 32.5 years —16 healthy controls: 10M, 6F	—Meds (SRI)	N/A	—Increased right caudate volume in OCD patients
Perani et al., 1995	PET	Adults	—11 OCD patients: 8F, 3M —Mean age: 26.1 years —7 checkers, 4 washers —Illness duration: 7.5 years —15 healthy controls: 11M, 4F	—Free from benzodiazepines and other psychotropic drugs for at least 2 weeks before study	—No Axis I comorbid disorders	—Increased pallidum/putamen complex in OCD patients
Robinson et al., 1995	MRI	Adults	—26 patients: 14 M, 12 F —Mean age: 32.2 years —Age at onset: 18.4 years —Duration of illness: 13.6 years —Symptoms of moderate severity —26 controls: 16 M, 10 F	—Clomipramine-hydrochloride —Benzodiazepines	—Major depression —Dysthymic disorder —Trichotillomania —Simple phobia	—Decreased bilateral caudate volume in OCD patients
Aylward et al., 1996	MRI	Adults	—24 OCD patients: 17M, 7F —Mean age: 34.4 years —Age at onset: 21.9 years —Moderate symptom severity —21 control participants: 14M, 7F	—Free of medications for 4 weeks to 2 years	—14 with general anxiety disorder —Panic disorder —Social phobias —Simple phobias	—OCD patients' caudate nucleus volume=control participants' caudate nucleus volume
Jenike et al., 1996	MRI	Adults	—10F with OCD —Mean age: 31.6 years —Mean age: 31.6 years —10F control participants	N/A	—No other psychiatric illnesses	—OCD patients' caudate nucleus volume=control participants' caudate nucleus volume
Lucey et al., 1997	SPECT	Adults	—15 OCD: 8M, 7F —Average duration: 14 years —Mean age: 36 years —16 with post-traumatic stress disorder: 14M, 2F —15 panic disorder with agoraphobia: 8M, 7F —15 healthy controls: 8M, 7F	N/A	—No other Axis I disorders	—Decreased right caudate volume in OCD patients compared with controls
Bartha et al., 1998	^{1}H MRS	Adults	—13 OCD patients: 7M, 6F —13 healthy control participants	—Med-free for 6 weeks	—1 had depression	—OCD patients' caudate nucleus volume=control participants' caudate nucleus volume
Luxenberg et al., 1988	CT	Children and/or adolescents	—10 male OCD patients —Mean age: 20.7 years —Severe OCD —Age of onset: <18 years —10 healthy male controls	N/A	—None of the patients were depressed at time of assessment	—Bilaterally smaller caudate nuclei in patients with OCD

(continued on next page)

Table 1 (*continued*)

Brain area	Study	Technique	Age Group	Participants	Medication	Comorbidity	General findings
Basal ganglia	Rosenberg, Keshavan, O'Hearn, et al., 1997	MRI	Children and/or adolescents	—19 children patients: 13M, 6F —Mean age: 12 years —Age of onset: 10 years —Duration of illness: 2.7 years —19 controls patients: 13M, 6F	—Treatment naive	—8 of 19 had anxiety disorders, 1 had ADHD, 2 had dysthymia, 3 had oppositional/conduct disorders —Only 5 had OCD as sole diagnosis	—Smaller putamen in OCD patients
	Szeszeko et al., 2004	MRI	Children and/or adolescents	—23 OCD patients: 7M, 16F —Mean age: 12.3 years —Mean age at illness onset: 9.1 years —27 healthy controls: 12M, 15F	—Drug-naïve patients	—(n = 8) anxiety disorder —(n = 3) dysthymia —(n = 1) ADD —(n = 1) ODD —(n = 2) Trichotillomania —(n = 11) OCD as sole diagnosis	—OCD patients had smaller volumes of the globus pallidus —OCD patients and healthy control did not differ in volumes of caudate nucleus and putamen
Striatum	Ebert et al., 1997	^{1}H MRS	Adults	—12 OCD patients: 8 M, 4F —Mean age: 27 years —Duration of illness: 11 years —6 controls: 5M, 1F	—10 were never medicated or had been med free for at least 6 months —2 receiving meds: —Clomipramine —Fluvoxamine	N/A	—Lowered metabolism in right striatum for OCD patients
	Bartha et al., 1998	^{1}H MRS	Adults	—13 OCD patients: 7M, 6F —13 healthy controls	—Med-free for 6 weeks	—1 had depression	—Lowered metabolism in the left corpus striatum in OCD patients
	Behar et al., 1984	CT	Children and/or adolescents	—17 OCD patients: 14M, 3F —Mean age: 13.7 years	N/A	—16 had 1 or more episodes of major depression in lifetime	—Increased ventricular brain ratios in OCD patients, predicted by decreased striatal volumes
Thalamus	Swedo, Schapiro et al., 1989	PET	Adults	—18 OCD patients: 9M, 9F —Severe OCD symptoms —Mean age: 27.8 years —Mean onset: 8.9 years —Duration of illness:19 years —Adults with childhood-onset OCD —18 healthy controls: 9M, 9F	—No psychotropic medication for 4 weeks before study	—Major depression —Anxiety disorder	—Increased right thalamus in OCD patients
	Perani et al., 1995	PET	Adults	—11 OCD patients: 8F, 3M —Mean age: 26.1 years —7 checkers, 4 washers —Illness duration: 7.5 years —15 healthy controls: 11M, 4F	—Free from benzodiazepines and other psychotropic drugs for at least 2 weeks before study	—No Axis I comorbid disorders	—Increased thalamus in OCD patients
	Alptekin et al., 2001	SPECT	Adults	—9 OCD patients: 3M, 6F —Mean age: 30.8 years —6 healthy controls: 2M, 4F	—5 were never medicated —4 drug-free for at least 6 months	N/A	—Increased right thalamus in OCD patients

Kim et al., 2001	MRI	Adults	—25 OCD patients: 17M, 8F —Mean age: 27.4 years —Mean duration of illness: 8.4 years —25 healthy controls: 17M, 8F	—3 had MDD, 1 had MDD and bulimia —21 had OCD as dole diagnosis	—8 were drug-naïve —Remainder were drug-free for at least 4 weeks	—Increased grey matter density in the thalamus in OCD patients
Lacerda et al., 2003	SPECT	Adults	—16 OCD patients: 8M, 8F —Mean age: 29.5 years —Age of onset: 15.8 years —Length of illness: 13.7 years —17 healthy controls: 10M, 8F	—Drug-free for at least 30 days before the study —10 patients were drug-naïve	N/A	—Increases in right and left thalamus in OCD patients
Rosenberg, Keshavan, O' Hearn et al., 1997	MRI	Children and/or adolescents	—19 OCD patients: 13M, 6F —Mean age: 12 years —Age of onset: 10 years —Duration of illness: 2.7 years —19 healthy controls: 13M, 6F	—Treatment-naïve	—8 of 19 had anxiety disorders, 1 had ADHD, 2 had dysthymia, 3 had oppositional/conduct disorders —Only 5 had OCD as sole diagnosis	—Larger third ventricle in OCD patients
Fitzgerald et al., 2000	^{1}H MRS	Children and/or adolescents	—11 OCD patients: 4M, 7F —Mean age: 11.2 years —Age of onset: 8.6 years —Mean duration of illness: 2.6 years —11 healthy control s: 4M, 7F	—Treatment-naïve	—5 had an anxiety disorder —6 had OCD as sole diagnosis —No one had major depression, but several reported depressive symptoms	—Reduction in NAA levels in right and left medial thalamus for OCD patients
Smith et al., 2003	^{1}H MRS	Children and/or adolescents	—27 OCD patients without MDD: 13M, 14F —Mean age: 10.3 years —Duration of illness: 2.63 years —MDD patients without OCD: 9M, 9F —18 healthy controls: 9M, 9F	—All psychotropic-naïve patients	—OCD patients: ($n=6$) anxiety disorder, ($n=2$) ODD, ($n=18$) OCD as sole diagnosis —MDD patients: ($n=6$) MDD as sole diagnosis	—Increased left and right medial thalamic choline concentrations in OCD patients compared to MDD patients and healthy controls

Abbreviations: M—male, F—female, MDD—Major Depressive Disorder, CT—Computed Tomography, MRI—Magnetic Resonance Imaging, SPECT—Single Photon Emission Computed Tomography, PET—Positron Emission Tomography, ^{1} H MRS—Hydrogen Proton Magnetic Resonance Spectroscopy.

increased metabolism in the thalamus of persons with OCD (Lacerda et al., 2003; Perani et al., 1995; Kim et al., 2001), while two studies have found increased metabolism in the right thalamus (Alptekin et al., 2001; Swedo, Schapiro et al., 1989). The most direct evidence for its critical role comes from neuroimaging studies in adult OCD patients that have demonstrated abnormalities in the thalamus that have been linked with symptom severity and treatment response (e.g., Perani et al., 1995).

To date, three studies have been conducted on children examining the thalamus. Fitzgerald, Moore, Paulson, Stewart, and Rosenberg (2000), utilizing ^{1}H MRS, which allows for non-invasive measurement of brain biochemistry, found decreased NAA levels (*N*-acetyl-aspartate, a measure of neuronal integrity) in the medial thalamus in treatment-naïve paediatric patients, and no differences in NAA levels in the lateral thalamus between controls and OCD patients. Smith and colleagues (2003) found increased bilateral medial thalamic choline concentrations. Medial thalamic regions are thought to be involved in affective and motivational processes, whereas the lateral thalamus has been implicated in motor functioning. Changes in medial thalamic NAA levels may be linked with obsessive and not compulsive symptoms. These researchers speculate that the medial thalamic regions may be more involved with limbic circuitry which is thought to play an important role in neurocognitive-emotion dysfunction represented by increased obsessive symptomatology. On the other hand, researchers hypothesize that the lateral thalamic region may be more involved in motorized compulsive behaviours.

One study by Rosenberg, Keshavan, O' Hearn, et al. (1997) observed larger third ventricle volumes (which could be related to the thalamus), in juvenile patients compared to control subjects. This is only one study and more research is needed to replicate this finding.

12. Summary

Neuroimaging studies show that the frontostriatal circuitry of the dorsolateral–caudate–striatum–thalamus, have been implicated in the neurological basis of OCD. One of the key differences in examining the studies in adults versus children is that the frontal lobes and caudate have been implicated in more studies in adults, whereas the striatum and thalamus are more likely to be implicated in children. This may be due to differences in brain maturation and early consolidation of neuroanatomical functions.

13. Modulatory control

A second model of the neuropathology of OCD states that this disorder is caused by damage to the orbitofrontal cortex, medial cortex, and associated areas (Saxena et al., 1998). Orbitofrontal cortex is involved in modulating socially appropriate behaviours. When its functioning is impaired, a patient may show tactless, impulsive, disinhibited behaviour. When the medial cortex is impaired in function, a person may show deficits in motivation, with a focus on one aspect of their environment, and ignoring all others, in addition to persistence in this one area of function (Cummings, 1993). In OCD, dysfunction in these areas may underlie the nature of the obsessions, which typically focus on themes of danger, sexuality, or cleanliness, and the persistence of the obsessions in leading to compulsions. Associated areas of the brain, which show high connectivity to orbital and medial portions of the prefrontal cortex, include the cingulate gyrus and amygdala. It is important to note, in extant research that none of these areas have been shown to be abnormal in children with OCD (Saxena et al., 1998). Table 2 provides a summary of neuroimaging findings supporting the modulatory control model of OCD.

14. Orbitofrontal and medial cortex

Increased metabolism has been the most common finding in patients with OCD, particularly in the orbitofrontal cortex (e.g. Baxter et al., 1987, 1988; Sawle, Hymas, Lees, & Frackowiak, 1991; Swedo, Schapiro et al., 1989), and the medial frontal cortex (Machlin et al., 1991; Sawle et al., 1991). The study by Szeszko et al. (1999) was one of the few structural studies to show decreased volume bilaterally in the orbitofrontal cortex using MRI scans. Only one study has been published with negative findings in the orbitofrontal cortex (Machlin et al., 1991). The implication of these findings is that increased metabolism may underlie the persistence of the obsessive thoughts in the maintenance of the disorder. The question is whether this overactivity is pathological, in that it may lead to cell death and decreased volume.

Table 2
Neuroimaging findings supporting the modulatory control model of obsessive–compulsive disorder

Brain area	Study	Technique	Age group	Participants	Medication	Comorbidity	General findings
Orbitofrontal and medial cortex	Baxter et al., 1987	PET	Adults	—14 OCD patients: 9M, 5F —Mean age: 31.6 years —14 with unipolar depression patients: 5M, 9F —14 controls: 7M, 7F	—5 on meds	—9 of the OCD patients met criteria for major depression	—Increased left orbitofrontal gyrus
	Baxter et al., 1988	PET	Adults	—10 OCD patients: 5M, 5F —Mean age: 35.5 years —10 control patients: 5M, 5F —Had illness for at least 1 year	—Drug-free for at least 2 weeks before study	—8 had major depression in past —3 met criteria for social phobia; 2 of which met criteria for simple phobia	—Increased bilateral orbital gyri
	Swedo, Schapiro et al., 1989	PET	Adults	—18 OCD patients: 9M, 9F —Severe OCD symptoms —Mean age: 27.8 years —Onset: mean 8.9 years —Duration: 19 years —Adults with childhood-onset —18 healthy controls: 9M, 9F	—No psychotropic medication for 4 weeks before study	—Major depression —Anxiety disorder	—Increased left orbito frontal and bilateral prefrontal
	Machlin et al., 1991	SPECT	Adults	—10 OCD patients —Mean age: 34.1 years —Varying severity —Age of onset: 15.8 years —Mixed childhood/adult onset —8 healthy controls	—Med-free for 4 weeks to 2 years before study	—No one had major depression	—Increased medial frontal cortex in OCD —Negative findings for orbital–frontal glucose metabolism in OCD
	Sawle et al., 1991	PET	Adults	—6 OCD patients —Mean age: 34.3 years —Duration: 15.8 years —Mixed childhood/adult onset —6 healthy controls	—3 on meds	—Depression	—Hypermetabolism in bilateral orbital frontal, premotor, and midfrontal cortices
	Rubin et al., 1992	SPECT	Adults	—10M OCD patients —Mean age: 34.9 years —10 control participants	—Drug-free for at least 4 weeks before study	—No one met criteria for other Axis I disorders	—Increased left posterofrontal cortex in OCD patients —Increased orbitofrontal cortex bilaterally in OCD patients
	Crespo-Facorro et al., 1999	SPECT	Adults	—21 OCD patients without motor tics: 14M, 7F —Mean age: 32 years —8 OCD patients with motor tics: 7M, 1F —Mean age: 26 years —In these cases, obsessive–compulsive symptoms were predominant presenting complaint —16 healthy controls: 10M, 6F	—Patients were either withdrawn from all medications for a 2 week period, a 4 week period if they were using fluoxetine, or had never been treated	—Current or past history of Gilles de la Tourette syndrome was ruled out —($n=7$) Had chronic tic disorder	—Decrease in the right orbitofrontal cortex in the OCD group without chronic tic disorder compared to healthy controls —No difference for OCD patients with and without motor tics
	Szeszeko et al., 1999	MRI	Adults	—26 OCD patients: 14M, 12F —Mean age: 32.2 years —Mean onset of illness: 13.8 years —26 healthy controls: 16M, 10F	—8 patients had a history of major depression	—20 had received prior treatment including SSRIs or clomipramine hydrochloride, for 4 or more weeks	—Reduced bilateral orbitofrontal volumes in OCD patients

(continued on next page)

Table 2 (*continued*)

Brain area	Study	Technique	Age group	Participants	Medication	Comorbidity	General findings
Orbitofrontal and medial cortex	Busatto et al., 2000	SPECT	Adults	—26 OCD patients: 15M, 11F —Mean age: 32.1 years —Mean age of onset: 15.2 years —Mean duration: 16.9 years —22 healthy controls: 12M, 10F	—11 drug-naïve —15 had no medication for 3 weeks (or 6 weeks in case of fluoxetine)	—($n=5$) Current motor/vocal tics	—Reduction in right orbitofrontal cortex in OCD patients
	Alptekin et al., 2001	SPECT	Adults	—9 OCD patients: 3M, 6F —Mean age: 30.8 years —6 healthy controls: 2M, 4F	—5 were never medicated —4 drug-free for at least 6 months	N/A	—Increased bilateral orbitofrontal cortex in OCD patients
	Kim et al., 2001	MRI	Adults	—25 OCD patients: 17M, 8F —Mean age: 27.4 years —Mean duration of illness: 8.4 years —25 healthy controls: 17M, 8F	—3 had MDD, 1 had MDD and bulimia —21 had OCD as sole diagnosis	—8 were drug-naïve —Remainder were drug-free for at least 4 weeks	—Increased grey matter density in left orbitofrontal cortex
	Lacerda et al., 2003	SPECT	Adults	—16 OCD patients: 8M, 8F —Mean age: 29.5 years —Age at onset: 15.8 years —Length of illness: 13.7 years —17 healthy controls: 10M, 8F	—Drug-free for at least 30 days before the study —10 patients were drug-naïve	N/A	—Increased inferior frontal cortex
	Kang et al., 2004	MRI	Adults	—36 OCD patients: 28M, 8F —Mean age: 26.3 years —Mean illness duration: 8.9 years —36 healthy controls: 28M, 8F —Matched for age and sex	—11 were drug-naïve —All previously treated remained psychotropic-free for at least 4 weeks	—No major psychiatric disorder such as: schizophrenia and bipolar disorder —4 had major depressive disorder	—Reduction in left orbitofrontal cortex in OCD patients
	Rosenberg and Keshavan, 1998	MRI	Children and/or adolescents	—21 OCD patients: 13M, 8F —Mean age: 12.7 years —Age of onset: 8.05 years —Duration of illness: 4.45 years —21 healthy controls	—Treatment-naïve —Only 7 with OCD as sole diagnosis	—Anxiety disorders ($n=10$) —ADHD ($n=1$) —Dysthymia ($n=3$) —Oppositional or conduct disorder ($n=3$)	—Increased ventral prefrontal cortex volumes in OCD patients

Cingulate gyrus	Garber, Ananth, Chiu, Griswold, & Oldendorf, 1989	MRI	Adults	—32 OCD patients: 20M, 12F —Mean age: 35 years —Had OCD for at least 2 years —Mean age at onset: 18 years —Mixed childhood/adult onset —14 controls: 9M, 5F	—19 patients were on clomipramine	—Free of other psychiatric illnesses including depression, panic disorder	—Patients with a positive family history of OCD had more abnormalities in the anterior cingulate gyrus than did patients with a negative family history or normal controls
	Swedo, Schapiro et al., 1989	PET	Adults	—18 adult OCD patients: 9M, 9F —Severe OCD symptoms —Mean age: 27.8 years —Onset: mean 8.9 years —Duration of illness:19 years —Adults with childhood-onset OCD —18 healthy controls: 9M, 9F	—No psychotropic medication for 4 weeks before study	—Major depression —Anxiety disorder	—Increased bilateral anterior cingulate gyri
	Perani et al., 1995	PET	Adults	—11 OCD patients: 8F, 3M —Mean age: 26.1 years —7 checkers, 4 washers —Illness duration: 7.5 years —15 healthy controls: 11M, 4F	—Free from benzodiazepines and other psychotropic drugs for at least 2 weeks before study	—No Axis I comorbid disorders	—A bilateral increase anterior, middle and posterior cingulate cortex
	Ebert et al., 1997	^{1}H MRS	Adults	—12 OCD patients: 8M, 4F —Mean age: 27 years —Duration of illness: 11 years —Moderate to severe symptoms —6 control participants: 5M, 1F	—10 were never medicated or had been med free for at least 6 months — 2 receiving meds: —Fluvoxamine	N/A	—Decreased volume of cingulate cortex
	Busatto et al., 2000	SPECT	Adults	—26 OCD patients: 15M, 11F —Mean age: 32.1 years —Mean age of onset: 15.2 years —Mean duration: 16.9 years —22 healthy controls: 12M, 10F	—(n = 11) drug-naïve —(n = 15) No medication for 3 weeks (or 6 weeks in case of fluoxetine)	—5 had current motor/vocal tics	—Reduction in left anterior cingulate cortex in OCD patients
	Szeszeko et al., 2004	MRI	Children and/or adolescents	—23 OCD patients: 7M, 16F —Mean age: 12.3 years —Mean age at illness onset: 9.1 years —27 healthy controls: 12M, 15F	—Drug-naïve patients	—8 had an anxiety disorder —3 had dysthymia —1 had ADD —1 had ODD —2 had trichotillomania —11 had OCD as sole diagnosis	—OCD patients had more total gray matter in the anterior cingulate gyrus

Abbreviations: M—male, F—female, MDD—Major Depressive Disorder, CT—Computed Tomography, MRI—Magnetic Resonance Imaging, SPECT—Single Photon Emission Computed Tomography, PET—Positron Emission Tomography, ^{1} H MRS—Hydrogen Proton Magnetic Resonance Spectroscopy.

15. Cingulate gyrus

Another area of the brain that is implicated in the neuropathology of OCD is the cingulate cortex, which has connections to the frontal cortex and basal ganglia. Several studies have shown changes in this area of the brain. Two adult studies have shown increased volume of the cingulate in those with OCD relative to controls (Perani et al., 1995; Swedo, Schapiro et al., 1989), while two studies have showed decreased volume (Busatto et al., 2000; Ebert et al., 1997). In the pediatric literature, Szeszeko et al. (2004) found greater gray matter in the anterior cingulate gyrus relative to the controls. This is only one study and further research with paediatric populations is needed to replicate Szeszeko and colleagues' finding. The cingulate gyrus has been implicated in a number of paradigms where modulation of behaviour has been assessed (Cummings & Mega, 2003).

16. Summary

Evidence suggests a strong role for the orbitofrontal and medial prefrontal cortices in the pathology of OCD, in concert with the function of the cingulate gyrus. The generation and maintenance of underlying obsessions may be the role of this circuitry.

17. Findings outside of these models

Evidence in paediatric populations show that another brain structure may be implicated in the onset and maintenance of OCD symptoms: the corpus callosum. Generally, the role of the brain structure is to integrate functions of the right and left hemispheres; as such it is uncertain what role this structure may play in OCD. The findings of its relevance are presented here to allow for completeness of the literature review and to stimulate speculation as to the functions the corpus callosum may play.

18. Corpus callosum

The study by Rosenberg, Keshavan, Dick, et al. (1997) is one of the first studies to examine regional morphology of the corpus callosum (CC) in treatment-naïve, non-depressed paediatric patients. The CC connects the cerebral hemispheres and each area of the CC projects to specific brain regions. For example, the genu connects the prefrontal and premotor cortices, whereas the splenium connects the inferior temporal lobes. These researchers reported abnormal total CC area, as well as abnormal genu and splenium sizes in paediatric OCD patients. These results suggest that abnormalities in frontal and temporal association cortices may be intricately linked with the symptom presentation of OCD. Another important finding from this study is that CC length and area (including the genu, anterior and posterior body, isthmus, and anterior splenium) of OCD patients was significantly correlated with OCD compulsive, but not obsessive symptomatology.

An age-related increase in corpus callosal area in healthy control children and not in OCD patients was found. To get an idea of the developmental difference in age-related increase between OCD patients and controls, researchers calculated the approximate age at which the CC region in patients were comparable in size to controls. For example, the anterior and middle splenium of a 7-year-old OCD patient were comparable in size to those of a 14-year-old control child. The researchers speculate that the larger CC area in OCD may be the result of an exaggeration of myelination of colossal fibres, with myelination in earlier onset OCD producing larger CC areas, while myelination occurring in healthy controls is more gradual, catching up by late adolescence or early adulthood. This hypothesis may offer an explanation as to why Jenike et al. (1996) found no differences in total CC area between adult OCD patients and controls.

To determine whether abnormal CC area is the result of atypical myelination, a study was conducted by Mac Master, Keshavan, Dick, and Rosenberg (1999) investigating CC signal intensity, which has been noted to be a reliable indicator of myelination in this area. These researchers found altered signal intensity that was localized in the anterior genu of the CC, with no abnormalities observed in the middle or posterior genu regions. The anterior genu region connects the ventral prefrontal cortex to the striatum, areas that been suspected to be involved in the pathophysiology of OCD. The researchers suggest that the significant increase in CC size is due to increased genu myelination, changing the signal intensity in the anterior genu, resulting in abnormal activity in the ventral prefrontal cortex and striatal circuit.

19. Summary

Two models of OCD have been presented, executive dysfunction, and modulatory control. Evidence currently seems to be divided between these two models, and it may be that they are somewhat complementary.

20. Proposed integration of models

The most recent working model has modified and extended earlier theories of OCD put forth by several groups of researchers in the field (e.g., Alexander, DeLong, & Strick, 1986; Modell, Mountz, Curtis, & Greden, 1989). Saxena et al. (1998) contend that the OCD circuit has two loops namely a direct and indirect pathway. In primates, the direct pathway has its origin in the frontal cortex which then stimulates the D1 receptors of the striatum. The striatum then projects to the internal portion of the globus pallidus/substantia nigra, pars reticulata complex (GPi/SNr), which is considered to be the main output station of the basal ganglia. From there, the GPi/SNr projects to the thalamus which has direct connections with the frontal cortex. The direct pathway consists of two excitatory and two inhibitory projections, and thus disinhibits the thalamus and activates the system in a self-perpetuating positive feedback loop. The indirect pathway leading from the frontal cortex activates the D2 receptor in the striatum, which in turn inhibits the indirect basal ganglia control system. This control system consists of the globus pallidus external and the subthalamic nucleus. It should be noted that much of the input to the subthalamic nucleus does not go through the striatum but rather directly from the frontal cortex to the indirect basal ganglia control system. The control system then projects to the GPi/SNr, where it rejoins the common pathway to the thalamus and back to the frontal cortex. The indirect pathway has three inhibitory connections, and thus provides negative feedback that inhibits the thalamus. It would appear that the direct and indirect feedback loops balance each other out and allow for both activation and inhibition of complex motor behaviours, via their opposite effects on the thalamo-cortical circuit. However, Saxena et al. (1998) propose that a model of OCD pathophysiology would have an imbalance of the direct and indirect pathways, with the direct pathway having a greater influence, leading to greater thalamo-cortical activation. Hyperactivity in this pathway may result in greater concern for such things as danger, and hygiene (the themes of most obsessions), compelling the patient to respond with compulsive behaviours, making it difficult to switch to other more adaptive behaviours. The question is whether the orbitofrontal-medial-cingulate circuitry is part of the frontal circuitry noted in this model. If so, this may be an addition which is in need of future research.

The executive dysfunction model, as summarized by Saxena and colleagues, may be a reasonable attempt to explain compulsions, whereas the modulatory control model may better explain the onset and maintenance of obsessions. It would be of interest in future studies involving symptom provocation to note what areas of the brain seem more active during obsessions and compulsions.

21. Limitations

As can be seen in the tables, differences between studies can be the result of many factors. One factor may be small sample size (e.g., Kellner et al., 1991) that may result in insufficient statistical power to detect differences between the control group and OCD patients, or to make these differences less consistent. Moreover, many studies included clinical patients that had other comorbid disorders (e.g., anxiety disorders, affective disorders), as well as patients on medications, making it difficult to elucidate abnormalities in neuroanatomical structures that may be specific to OCD. For example, in the study by Baxter et al. (1987) most of the subjects had concurrent major depression, and although nine of them were drug-free for at least 2 weeks, five were taking an assortment of antidepressants, benzodiazepines, and neuroleptics. Medication status at the time of scanning might also explain the discrepant findings by Scarone et al. (1992) who found increased activity in the right caudate volume in OCD patients who were taking serotonin reuptake inhibitors (SRIs), while Aylward et al. (1996) found no differences in caudate size between the control subjects and the OCD patients who were drug-free. At this time, the brain volumetric effects of ongoing therapy with SRIs or different classes of drugs are not known. Many studies report that patients are medication-free for only a short period of time before scanning (e.g., Rubin et al., 1992).

Another critical factor that may lead to mixed results is related to the issue of matching clinical patients with the controls. Specifically, gender composition differed among studies both in terms of male to female ratios and with respect to how close gender was matched between the comparison groups within each study. Research by Filipek,

Richelme, Kennedy, and Caviness (1994) suggest that there may be a gender-related effect on brain structure volume, when looking at the ratios of specific brain structures to total cerebral volume. For instance, in the healthy population the caudate volume has been found to be larger in female brains than in male brains. Thus, it may not be sensible to compare the results of the study by Jenike et al. (1996) who used only female OCD patients to the findings by Rubin et al. (1992) who recruited only adult males.

Although standard diagnostic classifications regard OCD to be a single diagnostic entity, patients with OCD are part of a heterogeneous group with a diverse set of symptoms that vary in terms of severity (e.g., Machlin et al., 1991), age of onset (e.g., adult and childhood onset), and duration of their illness. Despite this phenotypic heterogeneity, most prior neuroimaging studies have classified these patients into one group. For example, within the PET studies section, Swedo, Schapiro et al. (1989) examined adults with childhood-onset OCD, while Martinot et al. (1990) selected adults with mixed childhood/adult onset. It may be possible that the underlying pathology of patients whose illness began in childhood may differ from those with adult onset (e.g., Busatto et al., 2001).

To date, only one neuroimaging study has examined the neural correlates of specific OCD symptom factors. Rauch et al. (1998) found a factor consisting of aggressive, religious, and sexual obsessions and checking compulsions that correlated significantly with regional cerebral blood flow (rCBF) in bilateral anterior cingulate and left orbitofrontal cortex. Symmetry related and order related OCD symptoms were found to be negatively correlated with rCBF in the right striatum. Although these results are considered to be preliminary, this raises the question as to whether discrepant findings among the neuroimaging studies presented in the two tables could be accounted for by phenotypic variations among the subjects participating in these studies.

Other important factors to consider relate more specifically to the imaging techniques and analyses employed in the studies. As can be seen in the tables, a variety of scanning techniques have been used including CT, MRI, SPECT, PET and ^{1}H MRS. Compared with CT, MRI offers superior spatial resolution, distinction between gray and white matter, and the ability to visualize neuroanatomical structures in multiple planes. Moreover, in contrast to the single photon emitters that are utilized in SPECT imaging, the double signal in PET imaging studies allows for PET techniques to have higher spatial resolution than SPECT (Saxena et al., 1998). Differences in imaging techniques may make it difficult to compare studies and this may be another factor that may account for inconsistent findings.

22. Conclusions and future directions

At this time, a relatively cohesive working model of OCD pathophysiology exists with room for alternative interpretations, different model designs, hypotheses, and conclusions (Modell et al., 1989). Thus, with further research this current model will continue to be modified and refined into the years to come. There are several avenues that future studies may consider exploring. First, many neuroimaging studies have examined only a limited number of brain regions, generating a bias toward verification of well established models. Neuroimaging techniques should more thoroughly examine the brain to determine whether abnormalities associated with OCD are limited to the components of the cortico–striato–thalamo-cortical circuitry. For example, several recent studies have begun to implicate the amygdala (Szeszko et al., 1999), prompting researchers to rethink their current conceptualization of their theories of the pathophysiology of OCD. Models involving the amygdala would be quite relevant given that it is involved in emotional appraisal of external stimuli and acquiring and consolidating reactions to conditioned fear and anxiety, factors which are evident in OCD symptomatology (Rauch, 2000).

Second, future studies should also examine the circuitry of disorders that are highly comorbid with OCD such as ADHD, for similarities and differences. Interestingly, Casey et al. (1997) implicate the frontostriatal circuitry in ADHD. While Saxena et al. (1998) propose that overactivation of the direct pathway would result in intrusive thoughts and repetitive behaviours as seen in OCD, Casey and colleagues propose that underactivation of the direct pathway would lead to constantly interrupted behaviours as seen in ADHD. Examining interconnections between OCD and other disorders may provide researchers with further insight into the etiology of OCD. On a related note, neuroimaging studies have not adequately tested for specificity by diagnosis. That is, imaging studies generally compare OCD patients to psychiatrically healthy control subjects. In order to establish specificity of results in OCD, imaging studies should compare OCD to other anxiety disorders and depression, disorders that are commonly comorbid with OCD (Rauch, 2000).

Third, although neuroimaging studies have pointed to cortico–striato–thalamo-cortical circuitry as being dysfunctional in OCD, at this time, researchers have primarily focused their attention on models of OCD that are based

on non-human primates (Saxena et al., 1998). They have not yet begun to examine how this circuitry can be applied to the symptomatology of both adult and paediatric human patients with OCD. Such an explanatory model is still in its infancy with further research needed to detect specific functional abnormalities within this circuit. Once dysfunctional brain regions or aberrant connections between structures have been localized, the next step is to attempt to comprehend how the dysfunction(s) may contribute to the expression of both obsessive and compulsive symptoms. Utilizing neuroimaging methodology to look at component features of OCD, including anxiety, compulsions, and maladaptive thoughts, will help to formulate a model that is specific to the symptoms of the disorder in humans.

With improvements in spatial resolution of imaging techniques, we will be able to follow the unfolding of changes in neural activity that occurs as the symptoms of OCD evolve. That is, in the future it should be possible to identify particular brain regions that may be associated with the buildup of an obsession, the intensification of the urge, the performance of the compulsion, and the resolution of the obsession. Such an observation would allow us to detect the dynamics of activity occurring within this circuit, providing us with a more complete understanding of the pathophysiology of this disorder. Additionally, this information would be useful in determining the most appropriate timing for the application of treatment (Graybiel & Rauch, 2000). Such critical information should then be translated from the imaging laboratory to the clinic where it can directly benefit the patients. Early intervention and prevention strategies aided by longitudinal imaging studies that follow the course of OCD from childhood on, are the most promising methodologies for a more complete understanding of how we can treat and improve the well-being of adults and children with OCD.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381.

Alptekin, K., Degirmenci, B., Kivircik, B., Durak, H., Yemez, B., & Derebek, E., et al. (2001). Tc-99m HMPAO brain perfusion SPECT in drug-free obsessive–compulsive patients without depression. *Psychiatry Research. Neuroimaging*, *107*, 51–56.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Aylward, E. H., Harris, G. J., Hoehn-Saric, R., Barta, P. E., Machlin, S. R., & Pearlson, G. D. (1996). Normal caudate nucleus in obsessive–compulsive disorder assessed by quantitative neuroimaging. *Archives of General Psychiatry*, *53*(7), 577–584.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*, 65–94.

Bartha, R., Stein, M. B., Williamson, P. C., Drost, D. J., Neufeld, R. W. J., & Carr, T. J., et al. (1998). A short echo ^{1}H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive–compulsive disorder and comparison subjects. *American Journal of Psychiatry*, *155*(11), 1584–1591.

Baxter, L. R., Phelps, M. E., Mazziota, J. C., Guze, B. H., Schwartz, J. M., & Selin, C. E. (1987). Local cerebral glucose metabolic rates in obsessive–compulsive disorder: A comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry*, *44*, 211–218.

Baxter, L. R., Schwartz, J. M., Mazziota, J. C., Phelps, M. E., Pahl, J. J., & Guze, B. H., et al. (1988). Cerebral glucose metabolic rates in nondepressed patients with obsessive–compulsive disorder. *American Journal of Psychiatry*, *145*(12), 1560–1563.

Behar, D., Rapoport, J. L., Berg, C. J., Denckla, M. B., Mann, L., & Cox, C., et al. (1984). Computerized tomography and neuropsychological test measures in adolescents with obsessive–compulsive disorder. *American Journal of Psychiatry*, *141*, 363–369.

Busatto, G. F., Buchpiguel, C. A., Zamignani, D. R., Garrido, G. E. J., Glabus, M. F., & Rosario-Campos, M. C., et al. (2001). Regional cerebral blood flow abnormalities in early-onset obsessive–compulsive disorder: An exploratory SPECT study. *Journal of American Academy of Child and Adolescent Psychiatry*, *40*(3), 347–354.

Busatto, G. F., Zamignani, D. R., Buchpiguel, C. A., Garrido, G. E. J., Glabus, M. F., & Rocha, E. T., et al. (2000). A voxel-based investigation of regional cerebral blood flow abnormalities in obsessive–compulsive disorder using single photon emission computed tomography (SPECT). *Psychiatry Research. Neuroimaging*, *99*, 15–27.

Casey, B. J., Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., & Schubert, A. B., et al. (1997). Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(3), 374–383.

Crespo-Facorro, B., Cabranes, J. A., López-Ibor Alcocer, M. I., Payá, B., Fernández Pérez, C., & Encinas, M., et al. (1999). Regional cerebral blood flow in obsessive–compulsive patients with and without chronic tic disorder. A SPECT study. *European Archives of Psychiatry and Clinical Neuroscience*, *249*, 156–161.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*(8), 873–880.

Cummings, J. L., & Mega, M. S. (2003). *Neuropsychiatry and behavioural neuroscience*. New York: Oxford University Press.

Ebert, D., Speck, O., Konig, A., Berger, M., Hennig, J., & Hohagen, F. (1997). ^{1}H magnetic resonance spectroscopy for neuronal loss in the cingulate gyrus and the right striatum. *Psychiatry Research. Neuroimaging*, *74*, 173–176.

Filipek, P. A., Richelme, C., Kennedy, D. N., & Caviness, V. S. (1994). The young adult human brain: An MRI-based morphometric analysis. *Cerebral Cortex*, *4*(4), 344–360.

Fitzgerald, K. D., Moore, G. J., Paulson, L., Stewart, C. M., & Rosenberg, D. R. (2000). Proton spectroscopic imaging of the thalamus in treatment-naïve pediatric obsessive–compulsive disorder. *Biological Psychiatry*, *47*, 174–182.

Flament, M. F., Whitaker, A., Rapoport, J. L., Davies, M., Berg, C. Z., & Kalikow, K., et al. (1988). Obsessive compulsive disorder in adolescence: An epidemiological study. *Journal of American Academy of Child and Adolescent Psychiatry*, *27*(6), 764–771.

Garber, H. J., Ananth, J. V., Chiu, L. C., Griswold, V. J., & Oldendorf, W. H. (1989). Nuclear magnetic resonance study of obsessive–compulsive disorder. *American Journal of Psychiatry*, *146*(8), 1001–1005.

Graybiel, A. M., & Rauch, S. L. (2000). Toward a neurobiology of obsessive–compulsive disorder. *Neuron*, *28*, 343–347.

Insel, T. R., Donnelly, E. F., Lalakea, M. L., Alterman, I. S., & Murphy, D. L. (1983). Neurological and neuropsychological studies of patients with obsessive–compulsive disorder. *Biological Psychiatry*, *18*(7), 741–751.

Jenike, M. A., Breiter, H. C., Baer, L., Kennedy, D. N., Savage, C. R., & Olivares, M. J., et al. (1996). Cerebral structural abnormalities in obsessive–compulsive disorder. A quantitative morphometric magnetic resonance imaging study. *Archives of General Psychiatry*, *53*(7), 625–632.

Kang, D., Kim, J., Choi, J., Kim, Y., Kim, C., & Youn, T., et al. (2004). Volumetric investigation of the frontal–striatal circuitry in patients with obsessive–compulsive disorder. *Journal of Neuropsychiatry and Clinical Neurosciences*, *16*, 342–349.

Kellner, C. H., Jolley, R. R., Holgate, R. C., Austin, L., Lydiard, R. B., & Laraia, M., et al. (1991). Brain MRI in obsessive–compulsive disorder. *Psychiatry Research*, *36*(1), 45–49.

Kim, J., Lee, M. C., Kim, J., Kim, I. Y., Kim, S. I., & Han, M. H., et al. (2001). Grey matter abnormalities in obsessive–compulsive disorder: Statistical parametric mapping of segmented magnetic resonance images. *The British Journal of Psychiatry*, *179*, 330–334.

Lacerda, A. L. T., Dalgalarrondo, P., Caetano, D., Camargo, E. E., Etchebehere, E. C. S. C., & Soares, J. C. (2003). Elevated thalamic and prefrontal regional cerebral blood flow in obsessive–compulsive disorder: A SPECT study. *Psychiatry Research. Neuroimaging*, *123*, 125–134.

Lucey, J. V., Costa, D. C., Adshead, G., Deahl, M., Busatto, G., & Gacinovic, S., et al. (1997). Brain blood flow in anxiety disorders. OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99m TcHMPAO single photon emission tomography (SPET). *The British Journal of Psychiatry*, *171*(10), 346–350.

Luxenberg, J. S., Swedo, S. E., Flament, M. F., Friedland, R. P., Rapoport, J., & Rapoport, S. I. (1988). Neuroanatomical abnormalities in obsessive–compulsive disorder detected with quantitative X-ray computed tomography. *American Journal of Psychiatry*, *145*(9), 1089–1093.

Machlin, S. R., Harris, G. J., Pearlson, G. D., Hoehn-Saric, R., Jeffery, P., & Camargo, E. E. (1991). Elevated medial–frontal cerebral blood flow in obsessive–compulsive patients: A SPECT study. *American Journal of Psychiatry*, *148*, 1240–1242.

Mac Master, F. P., Keshavan, M. S., Dick, E. L., & Rosenberg, D. R. (1999). Corpus callosal signal intensity in treatment-naïve pediatric obsessive–compulsive disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *23*, 601–612.

Martinot, J. L., Allilaire, J. F., Mazoyer, B. M., Hantouche, E., Huret, J. D., & Legaut-Demare, F., et al. (1990). Obsessive–compulsive disorder: A clinical, neuropsychological and positron emission tomography study. *Acta Psychiatrica Scandinavica*, *82*, 233–242.

Modell, J. G., Mountz, J. M., Curtis, G. C., & Greden, J. F. (1989). Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive–compulsive disorder. *Journal of Neuropsychiatry and Clinical Neurosciences*, *1*(3), 27–36.

Pauls, D. L., Alsobrook, J. P., Goodman, W., Rasmussen, S., & Leckman, J. F. (1995). A family study of obsessive–compulsive disorder. *American Journal of Psychiatry*, *152*, 76–84.

Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., & Scarone, S., et al. (1995). [18F] FDG PET study in obsessive–compulsive disorder: A clinical metabolic correlation study after treatment. *British Journal of Psychiatry*, *166*(2), 244–250.

Piacentini, J., & Bergman, L. (2000). Obsessive–compulsive disorder in children. *The Psychiatric Clinics of North America*, *23*(3), 519–533.

Pigott, T. A., L' Heureux, F., Dubbert, B., Bernstein, S., & Murphy, D. L. (1994). Obsessive–compulsive disorder: Comorbid conditions. *Journal of Clinical Psychiatry*, *55*, 15–27.

Rapoport, J. L. (1991). Recent advances in obsessive–compulsive disorder. *Neuropsychopharmacology*, *5*, 1–10.

Rauch, S. L. (2000). Neuroimaging research and the neurobiology of obsessive–compulsive disorder: Where do we go from here? *Biological Psychiatry*, *47*, 168–170.

Rauch, S. L., Dougherty, D. D., Shin, L. M., Alpert, N. M., Manzo, P., & Leahy, L., et al. (1998). Neural correlates of factor-analyzed OCD symptom dimensions: A PET study. *CNS Spectrums*, *3*(7), 37–43.

Rauch, S. L., Jenike, M. A., Alpert, N. M., Baer, L., Breiter, H. C., & Savage, C. R., et al. (1994). Regional cerebral blood flow measured during symptom provocation in obsessive–compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Archives of General Psychiatry*, *51*, 62–70.

Rettew, D. C., Swedo, S. E., Leonard, H. L., Leanne, M. C., & Rapoport, J. L. (1992). Obsessions and compulsions across time in 79 children and adolescents with obsessive–compulsive disorder. *Journal of American Academy of Child and Adolescent Psychiatry*, *31*(6), 1050–1056.

Robinson, R. (1998). Obsessive–compulsive disorder in children and adolescents. *Bulletin of the Meninger Clinic*, *62S*(4), A49–A64.

Robinson, D., Wu, H., Munne, R., Ashtari, M., Alvir, J. J., & Lerner, G., et al. (1995). Reduced caudate nucleus volume in obsessive–compulsive disorder. *Archives of General Psychiatry*, *52*(5), 393–398.

Rosenberg, D. R., & Keshavan, M. S. (1998). Toward a neurodevelopmental model of obsessive–compulsive disorder. *Biological Psychiatry*, *43*, 623–640.

Rosenberg, D. R., Keshavan, M. S., Dick, E. L., Bagwell, W. W., Mac Master, F. P., & Birmaher, B. (1997). Corpus callosum morphology in treatment-naïve pediatric obsessive compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *21*, 1269–1283.

Rosenberg, D. R., Keshavan, M. S., O'Hearn, K. M., Dick, E. L., Bagwell, W. W., & Seymour, A. B., et al. (1997). Frontostriatal measurement in treatment-naïve children with obsessive–compulsive disorder. *Archives of General Psychiatry*, *54*(9), 824–830.

Rosenberg, D. R., MacMillan, S. N., & Moore, G. J. (2001). Brain anatomy and chemistry may predict treatment response in paediatric obsessive–compulsive disorder. *International Journal of Neuropsychopharmacology*, *4*, 179–190.

Rubin, R. T., Villanueva-Meyer, J., Ananth, J., Trajmar, P. G., & Mena, I. (1992). Determination by high-resolution single-photon emission computed tomography. *Archives of General Psychiatry*, *49*, 695–702.

Sawle, G. V., Hymas, N. F., Lees, A. J., & Frackowiak, R. S. J. (1991). Obsessional slowness: Functional studies with positron emission tomography. *Brain*, *114*, 2191–2202.

Saxena, S., Brody, A. L., Schwartz, J. M., & Baxter, L. R. (1998). Neuroimaging and frontal–subcortical circuitry in obsessive–compulsive disorder. *British Journal of Psychiatry*, *173*(35S), 26–37.

Scarone, S., Colombo, C., Livian, S., Abbruzzese, M., Ronchi, P., & Locatelli, M. (1992). Increased right caudate nucleus size in obsessive–compulsive disorder: Detection with magnetic resonance imaging. *Psychiatry Research*, *45*(2), 115–121.

Shafran, R. (2001). Obsessive–compulsive disorder in children and adolescents. *Child Psychology and Psychiatry Review*, *6*(2), 50–58.

Smith, E. A., Russell, A., Lorch, E., Banerjee, P., Rose, M., & Ivey, J., et al. (2003). Increased medial thalamic choline found in pediatric patients with obsessive–compulsive disorder versus major depression or healthy control subjects: A magnetic resonance spectroscopy study. *Biological Psychiatry*, *54*, 1399–1405.

Snider, L. A., & Swedo, S. E. (2000). Pediatric obsessive–compulsive disorder. *Journal of American Medicine Association*, *284*(24), 3104–3106.

Swedo, S. E., Leonard, H. L., & Rapoport, J. L. (1992). Childhood-onset obsessive compulsive disorder. *Psychiatric Clinics of North America*, *15*(4), 767–775.

Swedo, S. E., Rapoport, J. L., Leonard, H., Lenane, M., & Cheslow, D. (1989). Obsessive–compulsive disorder in children and adolescents: Clinical phenomenology of 70 consecutive cases. *Archives of General Psychiatry*, *46*, 335–341.

Swedo, S. E., Schapiro, M. B., Grady, C. L., Cheslow, D. L., Leonard, H. L., & Kumar, A., et al. (1989). Cerebral glucose metabolism in childhood-onset obsessive–compulsive disorder. *Archives of General Psychiatry*, *46*, 518–523.

Szeszeko, P. R., MacMillan, S., McMeniman, M., Chen, S., Baribault, K., & Lim, K. O., et al. (2004). Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive–compulsive disorder. *American Journal of Psychiatry*, *161*, 1049–1056.

Szeszko, P. R., Robinson, D., Alvir, J. J., Bilder, R. M., Lenez, T., & Ashtari, M., et al. (1999). Orbitalfrontal and amygdala volume reductions in obsessive–compulsive disorder. *Archives of General Psychiatry*, *56*(10), 913–919.

Ward, C. D. (1988). Transient feelings of compulsion caused by hemispheric lesions: Three cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *51*, 266–268.

Wolfe, N., Linn, R., Babikian, V. L., Knoefel, J. E., & Albert, M. L. (1990). Frontal systems impairment following multiple lacunar infarcts. *Archives of Neurologies*, *47*(2), 129–132.