7. Neuroimaging and the Pathophysiology of Obsessive-Compulsive Disorder (OCD)

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Introduction

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric illness characterized by intrusive, repetitive thoughts and ritualistic behaviors that cause marked distress. Common symptoms include harm-related fears with checking compulsions; contamination fears with cleaning compulsions; symmetry obsessions with arranging and repeating compulsions; and hoarding and saving compulsions. OCD affects 2–3% of the population worldwide[1] and can cause significant disability and functional impairment.[2] Effective treatments for OCD include serotonin reuptake inhibitor (SRI) medications[3] and cognitive–behavioral therapy (CBT).[4] Because OCD symptoms tend to be chronic, relatively consistent over time, and reliably reproducible, it has been possible to study them with a variety of neuroimaging techniques in an effort to determine how the brain mediates their expression.[5]

This chapter provides an updated review and analysis of the neuroimaging studies in OCD published to date. It first reviews studies of brain structure in OCD using computerized tomography (CT) and magnetic resonance imaging (MRI), then moves to studies of brain function using single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS). As functional imaging studies have provided the most consistent and informative data about the pathophysiology of OCD, they are examined in greater detail. Then follows a discussion of the functional neuroanatomy of frontal–subcortical brain circuits elucidated by basic research. Finally, a theoretical model of the pathophysiology of OCD that is supported both by neuroimaging findings and basic research is presented. This model describes

how the symptomatic expression of OCD may be mediated by abnormally elevated activity along specific frontal–subcortical brain circuits,[6] and how successful treatments may ameliorate symptoms. Of necessity, this review repeats much from earlier reviews.[7–12]

Studies of brain structure in obsessive-compulsive disorder (OCD) patients

CT studies of OCD

CT studies were the first to suggest brain abnormalities in OCD but did not provide consistent findings (see Table 7.1). Two CT studies[13,14] found that OCD patients had a significantly larger ventricle: brain matter ratio (VBR) – an index of brain atrophy – than controls, while one study found no differences in ventricular volumes between groups.[15] Another CT study found that the volume of the caudate nucleus was significantly smaller in male adolescents with childhood-onset OCD subjects than in male controls,[16] a finding that would later be replicated by some, but not all, MRI studies of OCD.

MRI studies of OCD

Compared with CT, MRI provides superior spatial resolution, distinction between gray and white matter, and visualization of neuroanatomical structures in multiple planes. As with CT, few consistent findings have emerged from MRI studies of OCD (see Table 7.1 for summary), although several studies have found abnormalities in the basal ganglia, orbitofrontal cortex (OFC), anterior cingulate gyrus (AC), and thalamus, structures also implicated in the pathophysiology of OCD by functional neuroimaging studies.

Several MRI studies have found abnormal volumes of basal ganglia structures in OCD patients compared with normal controls, including greater volumes of the right caudate nucleus and a loss of the normal left–right caudate asymmetry,[17] smaller caudate nucleus volumes and enlarged ventricles,[18] and smaller putamen volumes and larger third ventricles.[19] Decreased striatal volumes have been found to correlate with OCD symptom severity.[19] However, two other MRI studies found no differences in caudate volumes between OCD subjects and controls.[20,21]

The heterogeneity of structural neuroimaging findings in OCD may reflect heterogeneity in the disorder itself. Recent studies suggest that the discrepant basal ganglia volume findings in OCD may be due to different

Table 7.1 Structural imaging studies in obsessive-compulsive disorder (OCD)

Author and year (ref)	*Technique*	*Subjects*	*Results*
Insel et al 1983 (13)	CT	10 OCD patients 10 normal controls	OCD = controls
Behar et al 1984 (14)	CT	17 OCD patients 16 controls	VBR larger in OCD subjects
Luxenberg et al 1988 (16)	CT	10 male OCD adolescents 10 male control adolescents	Decreased caudate volume in OCD
Stein et al 1993 (15)	CT	24 patients	Increased ventricular volume in OCD
Garber et al 1989 (27)	MRI	32 treated OCD patients 14 normal controls	T1 abnormalities in anterior cingulate gyrus
Kellner et al 1991 (20)	MRI	12 OCD subjects 12 matched controls	Caudate volume in OCD = controls
Scarone et al 1992 (17)	MRI	20 treated OCD patients 16 normal controls	Increased right caudate volume in OCD
Robinson et al 1995 (18)	MRI	26 OCD patients 26 healthy controls	Decreased caudate volume in OCD
Aylward et al 1996 (21)	MRI	24 OCD patients 21 controls	OCD = controls for all structures
Jenike et al 1996 (28); and Grachev et al 1998 (29)	MRI	10 female OCD patients 10 female controls	Increased total cortex volume and decreased white matter in OCD Right frontal cortex volumes negatively correlated with non-verbal recall
Rosenberg et al 1997 (34)	MRI	19 children with OCD 19 healthy controls	Decreased striatal volume and larger third ventricles in OCD
Rosenberg et al 1997 (34); MacMaster et al 1999 (35)	MRI	21 children with OCD 21 healthy controls	Enlarged corpus callosum in OCD Decreased signal intensity in anterior corpus callosum

Table 7.1 Structural imaging studies in obsessive-compulsive disorder (OCD) – *Continued*

Author and year (ref)	*Technique*	*Subjects*	*Results*
Szezko et al 2000 (31)	MRI	26 OCD patients 26 healthy controls	Decreased orbitofrontal cortex and right amygdala volumes in OCD
Giedd et al 2000 (23)	MRI	34 children with streptococcus-related OCD and/or tics 82 healthy children	Larger caudate, putamen, and globus pallidus in streptococcus-related OCD/tics
Peterson et al 2000 (24)	MRI	113 patients with OCD, ADHD, or tic disorder 34 healthy controls	Anti-streptococcal antibody titers predicted higher putamen and globus pallidus volumes in OCD and ADHD
Gilbert et al 2000 (33)	MRI	21 never-treated children with OCD 10 OCD after paroxetine treatment 21 healthy controls	Larger thalamic volume in OCD; decreased after paroxetine treatment
Rosenberg et al 2000 (36)	MRI	11 children with OCD, before and after CBT	No change in thalamic volumes with treatment
Kim et al 2001 (32)	MRI	25 OCD patients 25 healthy controls	Increased gray matter density in left orbitofrontal cortex, thalamus, hypothalamus, and right insula in OCD

ADHD, Attention deficit hyperactivity disorder; CBT, cognitive–behavioral therapy; CT, computerized tomography; MRI, magnetic resonance imaging; VBR, ventricle: brain matter ratio.

etiologies in different subgroups of OCD patients. It has been suggested that there is a distinct subgroup of patients whose OCD is a pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS),[22] and that this subgroup has basal ganglia enlargement due to antibody-mediated inflammation. Enlarged caudate, putamen, and globus pallidus volumes have been seen in children with streptococcus-related OCD,[23] and larger volumes of putamen and globus pallidus have been

associated with higher antistreptolysin O antibody titers in subjects with OCD and/or attention deficit hyperactivity disorder (ADHD).[24] Conversely, those structural imaging studies of OCD patients that found *decreased* caudate volumes might have included more patients with comorbid tic disorders such as Tourette's syndrome (TS) or childhood-onset OCD, who may have more developmental brain abnormalities than other OCD patients. Some studies have found reduced caudate volumes in patients with TS,[25,26]and since patients with tic disorders have not always been excluded from imaging studies of OCD, they may have skewed their findings.

MRI studies have also found various abnormalities in cerebral cortical structures, the thalamus, and limbic structures in OCD patients, including T1-mapping abnormalities in the AC,[27] greater total cerebral cortical volumes,[28,29] enlarged AC volumes,[30] reduced OFC (including gray and white matter) and right amygdala volumes,[31] reduction in the normal right–left asymmetry in amygdala volumes,[31] increased gray matter density in multiple cortical regions,[32] and enlarged thalami.[33] These abnormalities might indicate widespread alteration of the programmed neuronal death that normally occurs during brain development, or reduced myelination in the brains of patients with OCD.[28] Abnormalities have also been found in white matter structures, including significantly lower volumes of total cerebral and cerebellar white matter,[28] but enlarged volumes[28,34] and decreased signal intensities in the corpus callosum (CC),[35] indicating increased myelination and greater concentration of white matter in the CC of OCD patients.

A few recent studies have investigated whether structural abnormalities seen in OCD patients change with successful treatment. In children with OCD, thalamic volumes have been found to decline significantly after 12 weeks of paroxetine treatment,[33] but not after treatment with CBT.[36] In patients with refractory OCD treated with anterior cingulotomy, caudate volumes decreased after surgery.[37] These results suggest that even short-term medication and surgical treatment can produce structural changes in the size of brain structures.

Functional imaging techniques

Four different functional neuroimaging study designs have been used to investigate the pathophysiology of OCD: (1) measuring cerebral activity in OCD patients versus normal controls with functional brain imaging scans done in neutral or baseline states; (2) scanning OCD patients before and after treatment to measure cerebral activity changes that correspond to treatment

response; (3) scanning patients while actively provoking their OCD symptoms; and (4) scanning OCD patients while they perform a cognitive activation task.

Most early functional neuroimaging studies of OCD used PET or SPECT, which employ radioisotope-labeled tracers to measure glucose metabolism or blood flow. PET, which offers better spatial resolution than SPECT, employs the radiolabeled tracers [^{18}F]fluorodeoxyglucose (FDG) and [^{11}C]deoxyglucose to measure glucose uptake and metabolism, and ^{15}O CO_2 or H_2O for regional cerebral blood flow (rCBF). In non-starvation conditions, glucose is by far the predominant energy substrate in the human brain, and its uptake has been shown to be a highly sensitive indicator of cerebral function. Under most circumstances, rCBF is highly correlated with glucose metabolism. SPECT uses tracers to estimate rCBF, including technetium-99m (Tc-99m)-*d,l*-hexamethylpropyleneamineoxime (HMPAO), Tc-99m-ethylcisteinate dimer (ECD), and the inhaled gas xenon-133 (^{133}Xe). Although HMPAO uptake usually is interpreted as a valid method of estimating the blood flow of one brain structure relative to that of another, HMPAO uptake is not consistently correlated with rCBF, especially in the basal ganglia.[38] Readers interested in more detail are referred to Chapter 1 and elsewhere.[39,40] Recent functional neuroimaging studies of OCD have employed magnetic resonance techniques such as MRS and fMRI. MRS measures concentrations of large molecules, such as *N*-acetylaspartate (NAA), glutamate, myoinositol, and choline in brain tissue by acquiring proton (^{1}H) spectra from these molecules following a magnetic resonance pulse.[41] fMRI measures correlates of regional brain activation by detecting changes in the blood oxygen-level dependent (BOLD) signal in the brain during different clinical states or cognitive tasks.

Functional neuroimaging studies comparing obsessive-compulsive disorder (OCD) patients to normal controls at baseline

Nine PET studies to date have compared subjects with OCD to controls (see Table 7.2 for details). Five of the nine studies found elevated metabolism or rCBF in the OFC (Figure 7.1),[42–46] while three found elevated activity in the basal ganglia,[42,43,47] three found increased thalamic activity,[45,47,48] and two found elevated metabolism in the AC.[45,47] Elevated activity has also been found in other parts of the prefrontal cortex.[42–46] One study had results at

Table 7.2 Baseline functional neuroimaging studies of obsessive-compulsive disorder (OCD) patients versus normal controls

Author and year (ref)	*Subjects*	*Technique*	*Results in OCD*
Baxter et al 1985 (42)	14 OCD (nine with depression) 14 depressed 14 controls	FDG-PET	Increased orbital gyri and caudate in OCD
Baxter et al 1988 (43)	10 non-depressed OCD 10 controls	FDG-PET	Increased orbital gyri and caudate in OCD
Nordahl et al 1989 (44)	Eight OCD 30 controls	FDG-PET	Increased orbitofrontal, decreased parietal cortex
Swedo et al 1989 (45)	18 OCD childhood onset 18 controls	FDG-PET	Increased orbitofrontal, prefrontal, anterior cingulate right thalamus, cerebellum
Martinot et al 1990 (49)	16 OCD Eight controls	FDG-PET	Decreased lateral prefrontal cortex in OCD
Sawle et al 1991 (46)	Six with obsessional slowness Six controls	^{15}O H_2O-PET	Increased orbitofrontal, and premotor cortex
Perani et al 1995 (47)	11 OCD 15 controls	FDG-PET	Increased cingulate, lenticular nuclei, and thalamus in OCD
Saxena et al 2001 (48)	27 OCD alone 17 OCD + depression 27 depression alone 17 controls	FDG-PET	Increased thalamus in OCD alone; decreased left hippocampus in depression alone and OCD + depression
Machlin et al 1991 (57)	10 OCD Eight controls	HMPAO-SPECT	Increased medial frontal cortex in OCD
Rubin et al 1992 (38)	10 OCD 10 controls	^{133}Xe-SPECT and HMPAO-SPECT	Xe: OCD = control HMPAO: increased parietal and frontal cortex, decreased caudate

Table 7.2 Baseline functional neuroimaging studies of obsessive-compulsive disorder (OCD) patients versus normal controls – *Continued*

Author and year (ref)	*Subjects*	*Technique*	*Results in OCD*
Adams et al 1989 (53)	11 OCD	HMPAO-SPECT	Decreased left basal ganglia
Edmonstone et al 1994 (52)	12 OCD 12 depressed 12 controls	HMPAO-SPECT	Decreased basal ganglia in OCD
Lucey et al 1995 (54)	30 OCD 30 controls	HMPAO-SPECT	Decreased superior frontal, inferior frontal, temporal, parietal cortex, right caudate, and right thalamus in OCD
Lucey et al 1995 (54) and 1997 (55)	15 OCD 16 PTSD 15 panic 15 controls	HMPAO-SPECT	Decreased right caudate and bilateral superior frontal cortex in OCD and PTSD
Crespo-Facorro et al 1999 (56)	27 OCD (seven with tics) 16 controls	HMPAO-SPECT	Decreased right OFC in OCD without tics
Busatto et al 2000 (59)	26 OCD (13 early onset, 13 later onset) 22 controls	ECD-SPECT	Decreased right OFC and left DLPFC, but OFC activity correlated with OCD severity. Decreased left AC, right OFC, and right thalamus in early onset OCD
Alptekin et al 2001 (58)	Nine OCD Six controls	HMPAO-SPECT	Increased right thalamus, left frontotemporal cortex, and bilateral OFC
Ebert et al 1996 (67)	12 OCD Six controls	MRS	Decreased NAA in right striatum and right AC
Bartha et al 1998 (68)	13 OCD 13 controls	MRS	Decreased NAA in left striatum
Ohara et al 1999	12 OCD 12 controls	MRS	OCD = control in lenticular nuclei NAA

Table 7.2 Baseline functional neuroimaging studies of obsessive-compulsive disorder (OCD) patients versus normal controls – *Continued*

Author and year (ref)	*Subjects*	*Technique*	*Results in OCD*
Fitzgerald et al 2000 (70); Rosenberg et al 2001 (69)	11 OCD children 11 control children	MRS	Increased choline (Cho) and decreased NAA/Cho in bilateral medial thalamus

AC, Anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; ECD, Tc-99m-ethylcisteinate dimer; FDG, [^{18}F]-fluorodeoxyglucose; HMPAO, *d,l*-hexamethylpropyleneamineoxime; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; OFC, orbitofrontal cortex; PET position emission tomography; PTSD, post-traumatic stress disorder; SPECT, single photon emission computed tomography; ^{133}Xe, xenon-133.

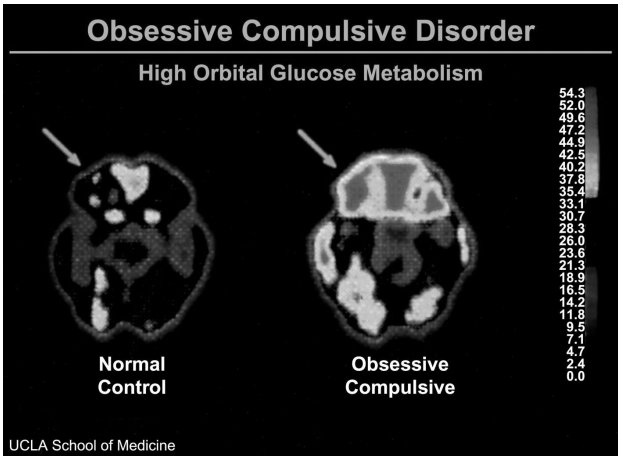


Figure 7.1 *Positron emission tomography (PET) images showing significantly elevated glucose metabolism in the orbitofrontal cortex in OCD patients, compared with normal controls.*

odds with those of the above PET studies, finding *lower* absolute metabolic rates in OCD subjects than in controls in all brain regions examined, including the lateral prefrontal cortex.[49] These results resemble PET findings in depressed OCD subjects[48,50] and may have been due to significant depressive symptoms in their patient sample.[51] Depressive symptoms strongly influence cerebral activity in OCD patients and are associated with *reduced* metabolism in caudate, thalamus, and limbic structures.[48]

SPECT studies of OCD have been less consistent than PET studies in finding increased activity compared to normal controls (Table 7.2). In the SPECT studies published to date that have compared OCD patients to normal controls at baseline, the most common finding has been *decreased* HMPAO uptake in the basal ganglia.[38,52–56] Comparisons of prefrontal cortical and thalamic perfusion have shown both increased[38,57,58] and decreased[56,57,59] HMPAO uptake. Some of the variability in the results of the SPECT studies of OCD may be due to differences in rates of comorbid depression between studies. Several of the studies included patients with major depression,[56,59] and depression severity was significantly negatively correlated with caudate activity.[48,55] Another important factor contributing to findings of caudate hypoperfusion in SPECT studies may be the presence of TS, other tic disorders, or comorbid ADHD in OCD subjects, since ventral striatal hypometabolism, hypoperfusion, and low HMPAO uptake have been found in several SPECT studies of TS and ADHD.[60–65] Caution must be exercised before equating HMPAO uptake with rCBF or abnormal glucose metabolism in a pathologic state such as OCD, in which the blood–brain barrier could be abnormal, causing dissociation of perfusion and metabolism.

Most MRS studies of OCD have measured NAA, thought to be a marker of neuronal density that is reduced in disease states that involve neuronal loss or dysfunction.[66] Low relative levels of NAA have been found in the striatum[67,68] and AC[68] in OCD patients compared with normal control subjects, while elevated choline concentrations[69] and reduced NAA/choline ratios[70] correlating with OCD severity have been found in the medial thalami of children with OCD. Elevated glutamate concentrations have also been found in the caudate nuclei of pediatric OCD patients.[71] Thus, MRS studies have found neurochemical abnormalities in the very same brain structures found to have structural and functional alterations in OCD.

The various baseline studies of OCD patients compared to normal controls consistently indicate elevated activity in the OFC, with less consistent abnormalities in the caudate nuclei, thalamus, and AC, which also show neurochemical alterations suggestive of neuronal dysfunction.

Cerebral correlates of obsessive-compulsive disorder (OCD) symptom factors

Although standard diagnostic classifications consider OCD to be a single diagnostic entity, it has become clear that several different OCD symptom factors

exist.[72,73] Large factor analyses of OCD symptoms[73] have yielded four principal symptom factors: (1) aggressive, sexual, and religious obsessions with checking compulsions; (2) symmetry obsessions with ordering, arranging, and repeating compulsions; (3) contamination obsessions with washing and cleaning compulsions; and (4) hoarding, saving, and collecting symptoms. These symptom factors appear to show different inheritance patterns. Despite this phenotypic heterogeneity, virtually all prior neurobiological and treatment studies of OCD have grouped patients with diverse symptom patterns together.

Very few neuroimaging studies have examined the neural correlates of specific OCD symptom factors. Rauch et al[74] found that the severity of factor 1 symptoms correlated significantly with rCBF in the bilateral striatum, while factor 2 symptoms had a trend toward *negative* correlation with rCBF in the right striatum. Factor 3 symptoms correlated with rCBF in the bilateral AC, left OFC, and other cortical areas. Saxena et al (unpublished data) found decreased cingulate gyrus metabolism in OCD patients with the compulsive hoarding syndrome, and found that AC metabolism was negatively correlated with the severity of factor 4 symptoms. Although these were preliminary results, they suggest that different OCD symptom clusters are mediated by quite different patterns of brain activity, raising the question of whether the heterogeneity in the findings of previous functional imaging studies of OCD could be accounted for by phenotypic variations between their subject pools. Moreover, patients with primary hoarding/saving symptoms have been underrepresented in most studies of OCD,[75] potentially skewing their results.

Functional neuroimaging studies of obsessive-compulsive disorder (OCD) patients before and after treatment

Functional neuroimaging studies done before and after treatment test hypotheses about the brain mediation of psychiatric symptoms by determining what changes in regional brain activity occur when patients respond to treatment, and what regional changes correlate best with symptomatic improvement. Such studies can also reveal differences in cerebral mechanisms of action between treatments. PET has been used to study OCD patients before and after treatment with SRIs, CBT, and neurosurgery. Of the 10 pre- and post-treatment PET studies of OCD published to date, eight have found pre- to post-treatment decreases in the OFC and/or caudate nuclei in responders to treatment,[76–83] while a few have found decreases in the AC[47,83] and thalamus[82]

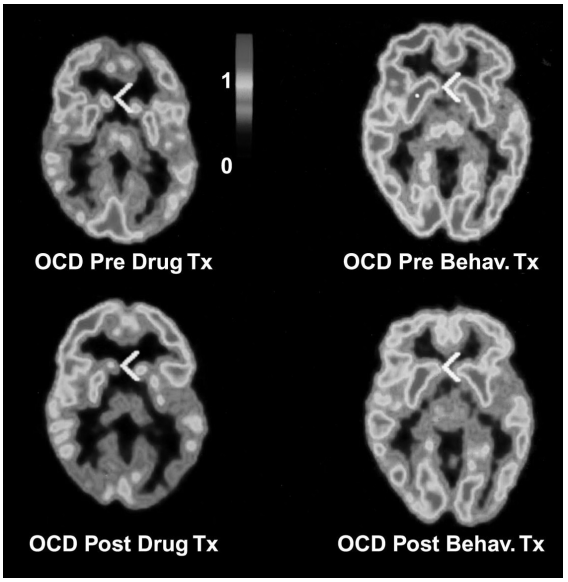


Figure 7.2 *Pre- and post-treatment positron emission tomography (PET) images of OCD patients treated with fluoxetine (left), and OCD patients treated with cognitive-behavioral therapy (right). Both patient groups showed similar significant decreases in right caudate metabolism with response to treatment.*

(Table 7.3). These changes have generally not been seen in non-responders to treatment. SPECT studies of OCD patients before and after treatment have also shown significant decreases in frontal cortex activity after treatment with SRI medications.[84–86] The changes most strongly associated with OCD treatment response are decreases in the right caudate nucleus[80–83] and right anterolateral OFC.[76,78] Moreover, these changes are specific to OCD and do not occur in patients with major depression[82] or other disorders treated with similar medications. MRS studies[71,87] found striking drops in glutamate resonance in the left caudate in 11 children with OCD after successful treatment with paroxetine. These changes are consistent with the glucose metabolic decreases seen with paroxetine treatment in FDG-PET studies of OCD,[82,83] and suggest that glutamate–serotonin interactions in the caudate may play a role in the pathophysiology and treatment of OCD. Thus, regardless of the type of imaging modality or the type of treatment used, pre- to post-treatment studies of OCD have consistently shown that OFC and caudate activity decreases with effective treatment.

A seminal study by Baxter et al[80] compared brain metabolic changes in OCD patients before and after treatment with either fluoxetine or CBT. In

Table 7.3 Pre- and post-treatment imaging studies in obsessive-compulsive disorder (OCD)

Author and year (ref)	*Subjects/treatment*	*Technique*	*Results with treatment*
Benkelfat et al 1990 (76)	Eight treated with clomipramine	FDG-PET	Decreased left caudate and OFC areas
Mindus et al 1991 (79)	Five treated with anterior capsulotomy	^{11}C-Glc-PET	Decreased caudate and OFC
Swedo et al 1992 (77)	13 subjects (eight on clomipramine, two on fluoxetine and three off medicine)	FDG-PET	Decreased bilateral OFC
Baxter et al 1992 (80)	Nine with fluoxetine, Nine with behavior therapy	FDG-PET	Decreased right caudate in responders to either treatment; loss of pathological correlations between OFC, caudate and thalamus
Perani et al 1995 (47)	Four with fluvoxamine, Two with fluoxetine Three with clomipramine	FDG-PET	Decreased cingulate
Schwartz et al 1996 (81)	18 treated with behavior therapy	FDG-PET	Decreased bilateral caudate in responders; loss of correlations between OFC, caudate, and thalamus
Saxena et al 1999 (78)	20 with paroxetine	FDG-PET	Decreased right caudate and right anterolateral OFC in responders
Saxena et al 2002 (82)	25 OCD 25 depression 16 OCD + depression (all treated with paroxetine) 16 controls	FDG-PET	OCD: decreased OFC, thalamus, right caudate Depress decreased VLPFC OCD + Depression increased caudate and putamen

Table 7.3 Pre- and post-treatment imaging studies in obsessive-compulsive disorder (OCD) – *Continued*

Author and year (ref)	*Subjects/treatment*	*Technique*	*Results with treatment*
Hansen et al 2002 (83)	20 OCD with paroxetine	FDG-PET	Decreased right caudate
Hoehn-Saric et al 1991 (84)	Six with fluoxetine	HMPAO-SPECT	Decreased medial frontal to whole cortex ratio
Rubin et al 1995 (85)	10 with clomipramine	^{133}Xe-SPECT and HMPAO-SPECT	Decreased cortical HMPAO uptake
Hoehn-Saric et al 2001 (86)	16 OCD + depression (nine with sertraline, seven with desipramine)	HMPAO-SPECT	Diffuse prefrontal decreases in responders
Rosenberg et al 2000 (71)	11 children with paroxetine	MRS	Decreased glutamate in left caudate

FDG, [^{18}F]-fluorodeoxyglucose; Glc, glucose; HMPAO, *d,l*-hexamethylpropyleneamineoxime; MRS, magnetic resonance spectroscopy; OFC, orbitofrontal cortex; PET, positron emission tomography; SPECT, single photon emission computed tomography; VLPFC, ventrolateral prefrontal cortex; ^{133}Xe, xenon-133.

both treatment groups, right caudate metabolic rates decreased significantly in responders but not in non-responders (Figure 7.2), showing that both pharmacological and non-pharmacological treatments can have significant effects on brain activity patterns that mediate neuropsychiatric disorders. When all responders to treatment were lumped together, significant correlations between metabolism in the right OFC, AC, caudate nucleus, and thalamus were found *before, but not after, treatment*. These correlations were not found in patients with unipolar depression or normal control subjects, suggesting that treatment-responsive OCD is characterized by abnormal, disease-specific, functional relationships between these brain regions only in the symptomatic state.[80] Successful treatment appears to disrupt the linkage of regional activity that existed before treatment.[76,80,81]

Pretreatment PET predictors of response to treatment

Functional imaging data has also been examined to determine if pretreatment regional brain metabolism predicts treatment response. Lower pretreatment glucose metabolism in the OFC has been associated with

better responses to the SRI clomipramine,[77] fluoxetine,[88] and paroxetine.[78] Response to paroxetine has also been correlated with higher pretreatment metabolism[89] and elevated glutamate concentrations[71] in the caudate nuclei. In contrast, higher pretreatment left OFC metabolism has been correlated with a response to CBT,[88] while higher pretreatment glucose metabolism in the right posterior cingulate cortex was associated with eventual improvement of OCD symptoms in patients who underwent anterior cingulotomy.[90] Taken together, these results suggest that OCD patients with different patterns of brain metabolism respond differentially to specific types of treatment (SRI versus CBT versus neurosurgery).

Neuroimaging studies of obsessive-compulsive disorder (OCD) symptom provocation

Perhaps the most direct information about brain–behavior relationships in OCD comes from symptom provocation studies that reveal patterns of brain activation occurring in real time, while patients are actively experiencing obsessions, anxiety, and urges to perform compulsive rituals. Symptom provocation studies have been conducted using two main methods: (1) comparing functional brain imaging scans acquired during exposure to a stimulus tailored specifically to induce each patient's OCD symptoms to scans acquired during exposure to an innocuous control stimulus, and (2) measuring changes in brain activity after exacerbating OCD symptoms with pharmacological challenges.

Exposure-based symptom provocation studies with PET[91–93] and fMRI[94,95] have consistently found increases in glucose metabolism or rCBF in the OFC, caudate, AC, and thalamus during the provoked state (Figure 7.3), more in patients than in controls, with less consistent activation of other cerebral cortical regions and limbic structures such as the amygdala,[94] hippocampus,[92,95] and insula[94] (see Table 7.4 for details). In some studies, OCD symptom severity correlated with activation of the OFC,[91,93,95] but different directions of correlation were found in different subregions of the OFC, suggesting that different subregions might play opposing roles in mediating and suppressing OCD symptoms, respectively.[91]

Symptom provocation studies using SPECT have yielded less consistent findings. One found that rCBF was somewhat increased during imaginal flooding, but decreased significantly during *in vivo* exposure to stimuli that induced OCD symptoms in superior cortical regions.[96] Two SPECT studies have measured changes in brain activity after exacerbating OCD symptoms

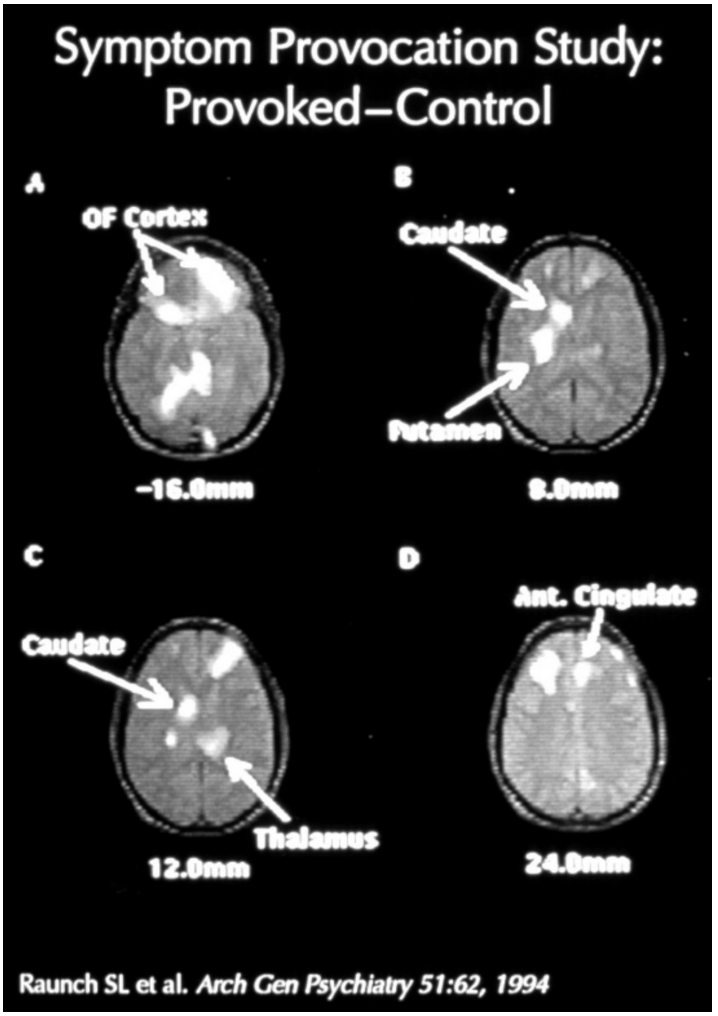


Figure 7.3 *Positron emission tomography (PET) images showing areas of significant activation of orbitofrontal cortex, caudate, putamen, thalamus, and enterior cingulate gyrus during OCD symptom provocation, compared to the control (resting) state.*

with pharmacological challenges with variable results: one used oral *m*-chlorophenylpiperazine (m-CPP)[97] (a serotonin receptor agonist), and the other used sumatriptan[98] (a serotonin 1d agonist). Again, the results of these SPECT studies are difficult to interpret because of the inherent limitations of the SPECT techniques used.

Taken together, the studies of OCD symptom provocation strongly link the expression of OCD symptoms with activation of the same brain areas

Table 7.4 Obsessive-compulsive disorder (OCD) symptom provocation studies

Author and year (ref)	*Subjects*	*Technique*	*Results*
Zohar et al 1989 (96)	10 OCD	^{133}Xe-SPECT	Increased rCBF in cortex with imaginal flooding, and decreased with *in vivo* exposure
McGuire et al 1994 (92)	Four OCD	^{15}O CO_2-PET	OCD symptoms correlated with increased inferior frontal, posterior cingulate, striatum, GP, thalamus, hippocampus; decreased dorsal prefrontal and parietal-temporal cortex
Cottraux et al 1996 (93)	10 OCD 10 controls	^{15}O H_2O-PET	Greater increases in bilateral OFC in OCD than normals Greater increases in thalamus and putamen in normals
Breiter et al 1996 (94)	13 OCD Six Controls	fMRI	Activation of bilateral OFC, anterior cingulate, frontal, and temporal cortex, amygdala, insula, lenticular nuclei, and right caudate
Adler et al 2000 (95)	Seven OCD	fMRI	Activation of OFC, DLPFC, temporal cortex, amygdala, hippocampus, and right AC
Hollander et al 1995 (97)	14 OCD challenged with m-CPP	^{133}Xe-SPECT	Increased global cortical perfusion
Stein et al 1999 (98)	14 OCD challenged with sumatriptan	HMPAO-SPECT	Increased right thalamus and putamen, decreased right caudate; symptom exacerbation associated with increased right cerebellum and decreased left inferior frontal and mid-frontal areas

AC, Anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GP, globus pallidus; m-CPP, *m*-chlorophenylpiperazine; OFC, orbitofrontal cortex; PET, positron emission tomography; rCBF, regional cerebral blood flow; SPECT, single positron emission computed tomography; ^{133}Xe, xenon-133.

found to be overactive at baseline. These studies strengthen the hypothesis that OCD symptoms are mediated by increased activity in the frontal–subcortical circuits connecting these structures to one another.

Neuroimaging studies of cognitive activation in obsessive-compulsive disorder (OCD)

Cognitive activation studies attempt to delineate the pathophysiology of a disorder by finding abnormalities in regional brain activation during specific cognitive tasks. All cognitive activation studies comparing OCD patients to controls published thus far have shown abnormal brain activation patterns in OCD patients (Table 7.5). PET[99] and fMRI[100] studies of OCD patients

Table 7.5 Cognitive activation studies in obsessive-compulsive disorder (OCD)

Author and year (ref)	*Subjects/task*	*Tracer*	*Results*
Rauch et al 1997 (99) and 2001 (100)	Nine females with OCD Nine female controls Implicit sequence learning	^{15}O CO_2-PET and fMRI	Controls activated inferior striatum; but OCD patients activated medial temporal lobe
Lucey et al 1997 (102)	19 OCD 19 controls	HMPAO-SPECT	Null sorts correlated with rCBF in left inferior frontal cortex and caudate
Pujol et al 1999 (103)	20 OCD 20 controls	fMRI	Greater left inferior frontal cortex activation and defective suppression of activation in OCD
Rauch et al 2001 (100)	Six females with OCD 10 female controls	fMRI	Controls activated inferior striatum; OCD patients activated medial temporal lobe

fMRI, Functional magnetic resonance imaging; HMPAO, *d*, *l*-hexamethylpropyleneamineoxime; PET, positron emission tomography; rCBF, regional cerebral blood flow; SPECT, single positron emission computed tomography.

versus control subjects performing an implicit (procedural) sequence learning task have found that controls activated the bilateral inferior striatum and deactivated the thalamus, whereas OCD patients showed no changes in either the inferior striatum or thalamus, but instead showed bilateral mesial temporal activation. These results suggest that OCD patients have cortico–striatal–thalamic dysfunction, and so access brain systems involved in explicit memory[101] for tasks that normal controls would process implicitly, without conscious awareness. Another study showed that OCD patients made more errors than controls during performance of the Wisconsin Card Sort Task (WCST), which tests the ability to shift cognitive set and executive functions. The number of errors was significantly correlated with the rCBF in the left inferior frontal cortex and left caudate.[102] OCD patients were also found to have significantly greater frontal cortical activation than controls during a phonologically guided word-generation task, and a defective suppression of this activation during the following rest period.[103] This area of investigation into OCD is in its infancy and much more research will be required to reveal consistent links between symptoms, cognitive deficits, and brain activity abnormalities in OCD.

Summary of functional neuroimaging findings in obsessive-compulsive disorder (OCD)

Although not all studies agree, review of the OCD functional brain imaging literature reveals a remarkable amount of data suggesting abnormalities in OFC, caudate nuclei, and thalamus, linked by well-described neuroanatomical circuits.[104] The great majority of studies provide evidence for elevated activity in these structures in the untreated state that consistently decreases with response to treatment but is increased with symptom provocation. Several studies suggest a preferential role for the right caudate nucleus in mediating OCD symptoms and/or the response to pharmacotherapy. The caudate nucleus has been found to have baseline structural, neurochemical, and functional abnormalities in OCD. Caudate activity decreased after treatment of OCD with CMI (clomipramine), fluoxetine, paroxetine, CBT, and neurosurgery, but increased with symptom provocation. Further, recent studies have shown a failure of caudate activation during implicit sequence learning in OCD. Pathological correlations of glucose metabolic rates (or rCBF rates) in the caudate, OFC and thalamus characterize the symptomatic state of OCD,

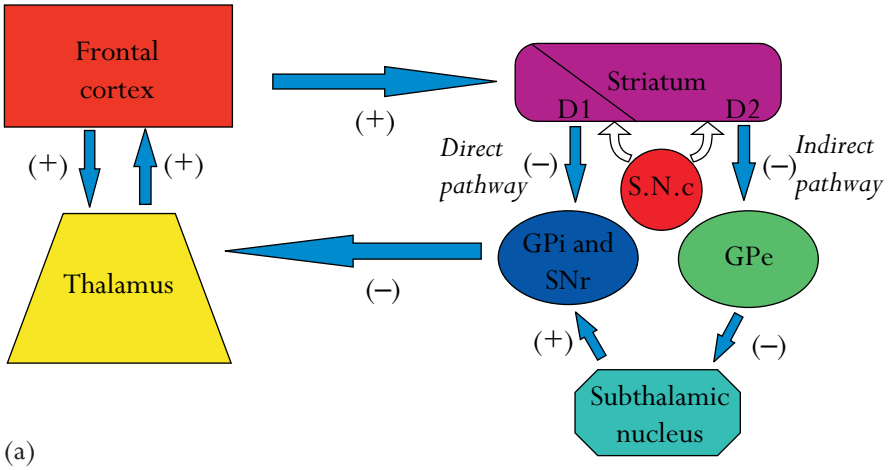
and are abolished by successful treatment. Although less consistently, functional neuroimaging data also support the involvement of the AC, amygdala, and related limbic structures in OCD. Differences between studies may be due to symptomatic differences between subject pools, differences between the treatments used, different duration of treatment, different scanning conditions, and different methods of localizing brain regions.

Neuroanatomy of frontal–subcortical brain circuits

Alexander et al[104] described a series of discrete, parallel, neuroanatomical circuits connecting the prefrontal cortex, basal ganglia, and thalamus. Many frontal–subcortical circuits exist, originating in nearly every part of the cerebral cortex and projecting through different subcompartments of the basal ganglia and thalamus. The various frontal–subcortical circuits subserve different behavioral functions and appear to mediate the symptomatic expression of several neuropsychiatric syndromes.[6,7]

Figure 7.4(a) presents a diagram of the classical conceptualization of frontal–subcortical circuitry. Classically, each of these circuits was described as having two loops: a direct pathway and an indirect pathway. In primates, the direct pathway projects from the cerebral cortex to the striatum to the internal segment of the globus pallidus/substantia nigra, [the pars reticulata complex (GPi/SNr)] – the main output station of the basal ganglia – then to the thalamus, and back to the cortex. The indirect pathway has a similar origin from the cortex to the striatum, but then projects from the striatum to the external segment of the globus pallidus (GPe) and then to the subthalamic nucleus before projecting to the GPi/SNr complex, where it rejoins the common pathway to the thalamus and back to the cortex. The prefrontal cortex and thalamus also reciprocally activate each other. Impulses along the direct pathway (with two inhibitory connections) 'disinhibit' the thalamus and activate the system in a positive feedback loop, while activity along the indirect pathway (with three inhibitory connections) would provide negative feedback, inhibiting the thalamus. Thus, the direct and indirect pathways appear to balance each other, allowing for both facilitation and suppression of complex motor programs, via their opposite effects on thalamo-cortical activation.[105]

Recent evidence suggests that the indirect pathway has interactions with the direct pathway that are much more complex than those envisioned in the classic model.[106] Researchers agree, however, that whatever the exact cir-

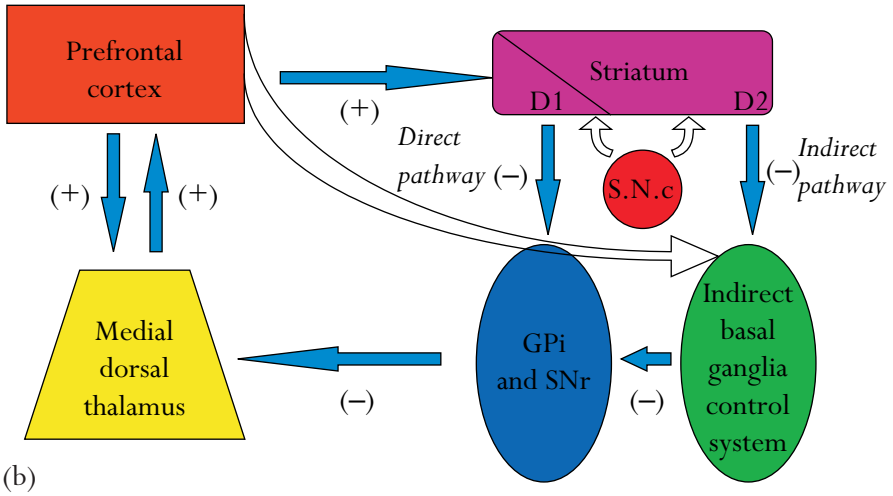


(a)

Figure 7.4 *(a) Classic conception of direct and indirect frontal–basal ganglia–thalamo–cortical pathways. The frontal–subcortical circuit originates in the frontal cortex, which projects to striatum. The* ***direct*** *pathway projects from striatum to the globus pallidus interna (GPi) substantia nigra, pars reticulata (SNr) complex (the main output station of the basal ganglia), which projects to the thalamus, and which has reciprocal, excitatory projections to and from the cortical site of origin. This pathway contains two excitatory and two inhibitory projections, making it a net positive-feedback loop. The* ***indirect*** *pathway also originates in the frontal cortex and projects to the striatum, but then projects to the globus pallidus externa (GPe), then to the subthalamic nucleus, then back to the GPi/SNr complex, prior to returning to the thalamus and, finally, back to the frontal cortex. This indirect circuit has three inhibitory connections, making it a net negative-feedback loop.*

cuitry of the indirect pathway, activity through it results in increased activity in the GPi/SNr complex, thereby strengthening the inhibition of the thalamus.[107] Our current conceptualization of frontal–subcortical circuitry (Figure 7.4b) acknowledges the present uncertainties by referring to the indirect pathway elements as the indirect basal ganglia control system. In these frontal–subcortical circuits, excitatory projections predominantly use glutamate as a neurotransmitter, while inhibitory ones mainly employ gamma-aminobutyric acid (GABA). Several peptide transmitters also have important roles within these pathways.[108] Other neurotransmitters (dopamine, serotonin, acetylcholine, etc) modify the activity of projections between these structures.

The connections between cortex and striatum have been described as 'a common substrate for movement and thought'.[109] The striatum, and the caudate nucleus in particular, is involved in processing cortical information



(b)

Figure 7.4 *Continued (b) Current conceptualization of prefrontal–basal ganglia–thalamo–cortical circuitry. Recent anatomical studies have called into question previous views of basal ganglia circuitry. Here, we refer to an indirect basal ganglia control system that consists of the GPe and the subthalamic nucleus. Connections within these structures are more complex than previously thought. The prefrontal cortex has excitatory projections to indirect pathway structures. In addition, the GPe directly projects to the GPi/SNr complex. Nevertheless, the net effect of activity in the indirect circuit still appears to be inhibition of the thalamus, thereby decreasing thalamo-cortical drive. The frontal–subcortical circuits originating in the lateral prefrontal cortex, the orbitofrontal cortex, and the anterior cingulate gyrus, all pass through subcompartments of the medial dorsal nucleus of the thalamus.*

for the initiation of behavioral responses and also plays an important role in procedural learning – the acquisition of new habits and skills which require minimal conscious awareness.[110] Conventionally, the striatum is divided into the caudate nucleus, putamen, and nucleus accumbens (see Figure 7.5). Different regions of the striatum receive input from different cortical regions.[104] The OFC, a paralimbic isocortical area, projects to the ventromedial caudate nucleus, while the dorsolateral prefrontal cortex (an associative neocortical area) projects to the dorsolateral caudate, and the anterior cingulate gyrus and hippocampal formation (limbic areas) project to the nucleus accumbens (see Figure 7.5). Circuits involved in motor programming travel through the putamen. These topographical representations are maintained in a related, but distinct, topology through the globus pallidus, subthalamic nucleus, and thalamus, creating relatively segregated, closed loops.[104] Direct and indirect pathways are present in each of the loops – motor, associative, and limbic.[111–113] Several different thalamic nuclei are involved in these

circuits, but those originating in limbic and association cortex areas all pass through subregions of the medial dorsal nucleus of the thalamus.[114]

A function of the frontal–subcortical circuits passing through the striatum is the execution of pre-packaged, complex, sequence-critical, response behaviors (macros) that, to be adaptive, must be executed quickly in response to specific stimuli, to the exclusion of other responses dictated by interfering stimuli.[7,8] Naturally occurring activity along the direct pathway would tend to rivet behavior to the execution of the appropriate macros, until the need is judged to have passed. Conversely, activation of the indirect pathway may have as part of its function the suppression of direct pathway-driven behaviors when it is time to switch to another behavior – something OCD patients have difficulty doing.

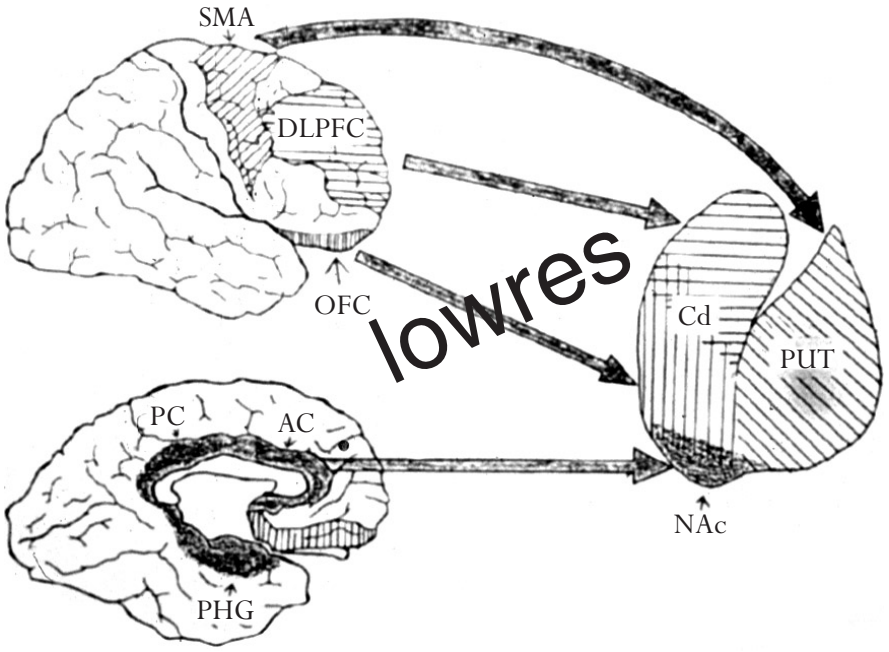


Figure 7.5 *Frontal–striatal projections. Illustration of regional distribution of cortical projections to separate striatal subcompartments. The supplementary motor areas (SMA; slanted lines) projects to the putamen (PUT), the dorsolateral prefrontal cortex (DLPFC; horizontal lines) projects to the dorsolateral head of the caudate nucleus (Cd), the orbitofrontal cortex (OFC; vertical lines) projects to the ventromedial head of the caudate, and the anterior cingulate gyrus (AC); posterior cingulate gyrus (PC), and parahippocampal gyrus (PHG) (all shaded areas) project to the nucleus accumbens (NAc). Though there may be slight overlap, cortical projection fields within the striatum are topographically distinct.*

A model of the pathophysiology of obsessive-compulsive disorder (OCD)

Imbalance of direct–indirect pathway tone in the orbitofrontal–subcortical circuit

Functional neuroimaging data clearly support pathophysiological theories put forward previously[115–119] regarding the role of the OFC, basal ganglia, and frontal–subcortical circuits in OCD. The present working model of the pathophysiology of OCD expands upon earlier theories and incorporates newer data regarding the neuroanatomy and function of frontal–subcortical brain circuits, as well as a proposed mechanism for symptom reduction with treatment.

This pathophysiological model posits that in persons with OCD there is a response bias toward stimuli relating to socio-territorial concerns about danger, violence, hygiene, order, sex, etc – the themes of most obsessions in patients with OCD – mediated by frontal–subcortical circuits involving the OFC.[7,80] There is much experimental and clinical evidence that the OFC is involved in the mediation of emotional responses to biologically significant stimuli, anticipatory anxiety, detection of errors, and social–affiliative behavior.[120] The orbitofrontal–subcortical circuit appears to mediate voluntary, prospective control of behavior influenced by affectively charged memories and internal information. In normal individuals, socio-territorial concerns and responses to stimuli perceived as dangerous may be mediated by activity through the orbitofrontal–subcortical direct pathway, with appropriate inhibition from the indirect pathway. OCD patients, however, may have a lower threshold for system activation by socio-territorial stimuli, as well as impaired inhibition of cortical–subcortical activity.[121] This could be due to excess tone in the direct relative to the indirect orbitofrontal–subcortical pathway (Figure 7.6), allowing concerns about danger, violence, hygiene, order, sex, etc, to rivet attention to themselves, compelling patients to respond with ritualistic behavior, and resulting in an inability to switch to other behaviors. Such an imbalance of direct–indirect pathway tone would produce the hyperactive circuit seen in functional neuroimaging studies of OCD that, in turn, mediates the repetitive, fixed behaviors relating to socio-territorial concerns in OCD.

It is unknown which brain structures may contain neuronal abnormalities that give rise to orbitofrontal–subcortical hyperactivity in OCD patients, but some evidence points to the striatum.[67,68,71] It is possible that, in patients with OCD, there may be dysfunction involving the intrinsic structure of the striatum, which is divided neurochemically into striosome and matrix

compartments.[122,123] Striosomes receive preferential input from the OFC and AC,[124] and are involved in negative feedback control of activity in the frontal–subcortical circuits.[123] Abnormal development, loss, or dysfunction involving striosomes in the ventromedial caudate might result in an imbalance between direct and indirect pathways in the orbitofrontal–subcortical circuit, resulting in the symptoms of OCD. Damage to striosomes or other areas of the striatum could potentially be produced by post-infectious anti-neuronal autoantibodies, thought to be implicated in at least a subset of patients with OCD.[125,126] Orbitofrontal–subcortical hyperactivity in OCD may also be the result of abnormal neuroanatomical development of these structures, or a failure of pruning of neuronal connections between them.[28,30]

Mechanism of action of SRI in OCD

Currently, drugs that strongly inhibit serotonin reuptake are the only medications consistently proven effective in the treatment of OCD. It has been hypothesized that SRI medications decrease activity in the orbitofrontal–subcortical circuit, possibly by changing the relative balance of

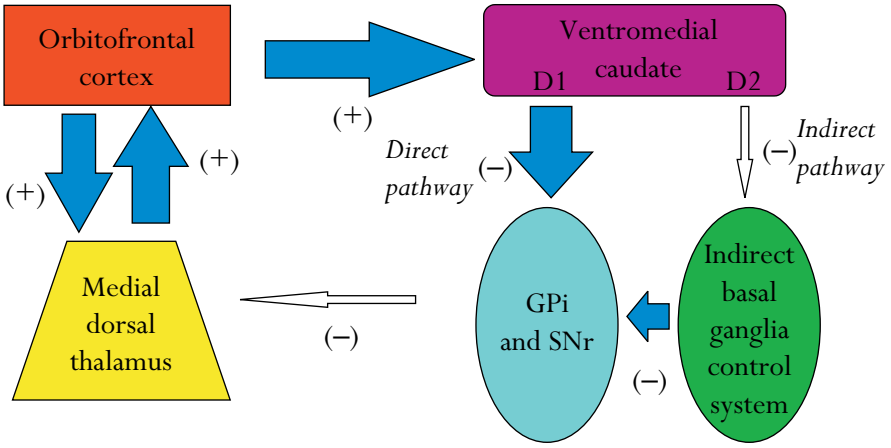


Figure 7.6 *Model of obsessive-compulsive disorder (OCD) pathophysiology. OCD symptomatology may be the result of a captured signal in the direct orbitofrontal–subcortical pathway, a positive-feedback loop. This could be due to excess tone in the direct (large arrows) relative to the indirect (small arrows) orbitofrontal–subcortical pathway, resulting in increased activity in the orbitofrontal cortex, the ventromedial caudate, and the medial dorsal thalamus. This orbitofrontal–subcortical hyperactivity would allow concerns about danger, violence, hygiene, order, sex, etc, to rivet attention to themselves, compelling patients to respond with ritualistic behavior, and resulting in an inability to switch to other behaviors.*

activity through the indirect versus direct frontal–subcortical pathways.[7–12,127] The serotonergic innervation of the striatum is heavily concentrated in the ventromedial caudate and nucleus accumbens, precisely those subcompartments that receive input from the OFC and AC.[127,128] Serotonergic pathways from the midbrain also project strongly to the subthalamic nucleus and globus pallidus,[129] key structures for the control of basal ganglia output.[107] Serotonergic drugs may also exert their effect in the OFC. Recent work has demonstrated differential effects of SRI drugs in OFC versus the dorsal prefrontal cortex, in a time course that corresponds to the effects of these medications on OCD symptoms versus depressive symptoms. SRIs have been found both to enhance serotonin release and to desensitize serotonin autoreceptors in the OFC after 8 weeks, but not 3 weeks, whereas effects in the dorsal prefrontal cortex occur after 3 weeks.[130,131] The glucose metabolic decreases in the OFC and caudate seen after successful treatment may reflect decreased release of excitatory neurotransmitters such as glutamate in these regions.[132]

Future directions

Functional neuroimaging studies have advanced our understanding of brain–behavior relationships with respect to OCD greatly, but much is still unknown. No post-mortem neuroanatomical studies of OCD exist to delineate its pathophysiology. The roles of various neurochemical systems in OCD are similarly unclear. Although there is some indirect evidence suggesting serotonergic abnormalities in OCD, there is no direct evidence demonstrating any such abnormalities, or whether they are primary or secondary phenomena in OCD. Phenotypic heterogeneity could account for many of the inconsistencies among previous neuroimaging studies of OCD. Current studies are seeking to find the neurobiological and genetic substrates of specific OCD symptom factors, as well as predictors of treatment response.

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