CHAPTER 27

The Role of Cingulate Cortex Dysfunction in Obsessive–Compulsive Disorder

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Chapter contents

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Obsessive-compulsive disorder (OCD) is a common neuropsychiatric illness that affects 2–3% of the population worldwide (Weissman *et al*., 1994). It can cause significant disability and functional impairment (Murray & Lopez, 1996) and is characterized by intrusive, repetitive thoughts and ritualistic behaviors that cause marked distress. Although standard diagnostic classifications consider OCD to be a single entity, it has become clear that several different OCD symptom factors exist (Baer, 1994; Leckman *et al*., 1997). Large factor analyses of OCD symptoms (Cavallini *et al*., 2002; Leckman *et al*., 1997; Summerfeldt *et al*., 1999) have usually 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, the vast majority of prior neurobiological and treatment studies of OCD have grouped patients with diverse symptom patterns together. Effective treatments for OCD include serotonin reuptake inhibitor (SRI) medications (Greist *et al*., 1995) and cognitive–behavioral therapy (CBT) (Marks, 1997). 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 to determine how the brain mediates their expression (Silbersweig & Stern, 1997).

The cingulate gyrus has been frequently implicated in the etiology of OCD and this serves as the context for the present chapter. For example, neurosurgical intervention with cingulotomy ablation can alleviate OCD symptoms. In one case, the cingulate seizures of a young girl evolved into OCD symptoms that achieved remission post-cingulotomy (Levin & Duchowny, 1991). Recently, resting-state neuroimaging studies examined the neural correlates of specific OCD symptom factors and they revealed important associations between activity in discrete subregions of the cingulate gyrus and specific OCD symptom domains. Rauch *et al*. (1998) found that the severity of contamination/washing correlated with regional cerebral blood flow (rCBF) in bilateral pregenual anterior cingulate cortex (pACC), midcingulate cortex (MCC), and other cortical areas. Saxena *et al*. (2004) found that the severity of hoarding and saving was negatively correlated with activity in the anterior MCC in OCD. Although both of these studies were preliminary in nature, they suggest that different OCD symptom clusters are mediated by different patterns of baseline activity in the cingulate gyrus.

From a neurochemical and treatment perspective, the serotonin and dopamine systems have been assessed in OCD. Although changes associated with drug treatments are still somewhat contradictory as indicated by pre- and post-treatment imaging, it appears that decreasing cingulate activity is sometimes associated with improvement in OCD symptoms. It also appears that OCD patients with higher baseline activity in posterior cingulate cortex (PCC) and a smaller increase in PCC activity with symptom provocation may be more likely to respond to SRIs.

Goals of This Chapter

This chapter provides a review and analysis of neuroimaging studies in OCD that have examined the structure or functions of the cingulate gyrus. It first considers studies of brain structure in OCD using magnetic resonance imaging (MRI). Studies of brain function using positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) are reviewed. Although the findings conflict to some extent, there is substantial evidence that ACC and MCC are involved early in OCD. As functional imaging studies have provided the most consistent and informative data about the pathophysiology of OCD, they are examined in greater detail. A section on electrophysiological studies of OCD using electroencephalography (EEG), evoked potentials (EPs), and magnetoencephalography (MEG) follows. Finally, hypotheses as to the role of cingulate dysfunction in OCD are presented, as well as a cingulate-circuit model of the pathophysiology of OCD that is supported both by neuroimaging findings and basic neuroanatomical research. This model describes how the symptomatic expression of OCD may be mediated by abnormally elevated activity along specific cingulate-subcortical brain circuits (Baxter *et al*., 1996; Saxena *et al*., 1998, 2001a; Saxena & Rauch, 2000), and how functional abnormalities in discrete subregions of the cingulate gyrus may be associated with specific OCD symptom factors.

Structural Brain Imaging

Postmortem anatomical data on OCD are non-existent. Therefore, our knowledge of brain structure in OCD derives almost entirely from *in vivo*, non-invasive neuroimaging. Structural neuroimaging identifies specific structures and tissues in the brain and quantifies their sizes (volumetry), shapes (morphometry), microstructure, or internal properties (MR diffusion imaging, MR relaxometry, and others). Each of these structural and tissue characteristics may be altered by abnormal development, pathology, and/or treatment. A challenge neuroimaging research on OCD is currently aiming to meet is to identify reliable structural abnormalities in

OCD, their selectivity and specificity with respect to other disorders and within subtypes of OCD, and their etiology.

Structural MRI studies

Since the mid-1990s, MRI has become standard for structural studies of the brain in OCD. As of this writing, over 20 volumetric MRI studies of OCD (Table 27.1) and two MR relaxometry investigations (Weilburg *et al.*, 1989; Garber *et al.*, 1989) have been published. Most volumetric MRI studies have used a region-of-interest (ROI) approach, but a few recent studies have employed voxel-based morphometry (VBM) to assess gray matter density or volume. The potential for morphometric MRI, diffusion-weighted MRI, perfusion-weighted MRI, and magnetization transfer MRI to study OCD remains largely untapped.

Noteworthy, MRI findings in OCD include abnormal volumes of orbitofrontal cortex (OFC) (Choi *et al.*, 2004; Kang *et al.*, 2004; Kim *et al.*, 2001; Szeszko *et al.*, 1999), striatum (Hanson *et al.*, 1989; Pujol *et al.*, 2004; Rosenberg *et al.*, 1997a,b; Scarone *et al.*, 1992; Weilburg *et al.*, 1989), thalamus (Gilbert *et al.*, 2000; Kim *et al.*, 2001; Rosenberg *et al.*, 2000a,b), and amygdala (Kwon *et al.*, 2003a,b; Szeszko *et al.*, 1999, 2004). These same structures are also implicated in the pathophysiology of OCD by functional neuroimaging studies. However, structural neuroimaging findings in OCD are not uniform across studies, possibly due to heterogeneity of OCD patient populations. More advanced morphometric MRI methods are beginning to be used to investigate OCD. Ha *et al.* (2005) calculated the fractal dimension (roughly a measure of the degree of complexity, such as the propensity to sulcal bifurcation) of the cerebral cortex in OCD patients from high-resolution MRI and found it to be highly significantly lower than that of healthy controls. These interesting results were derived from the gray matter–CSF interface and therefore may be sensitive to the exact MRI acquisition parameters.

Nine MRI studies of OCD published to date (Table 27.1) have measured cingulate gyrus volumes – six using ROI methods and three using VBM. Of these, only two studies have found abnormal cingulate volume. Szeszko *et al.* (2004) found significantly greater gray matter volume in a large ROI, corresponding to the anterior cingulate cortex (ACC) plus the anterior portion of the MCC (aMCC; Vogt *et al.*, 2003, 2005; Chapter 3), in drug-naïve children with OCD than in age-matched healthy controls. However, a recent VBM study (Valente *et al.*, 2005) reported lower gray matter volume in the left aMCC in adult OCD patients than normal controls. This volume difference was found in a sample that included OCD patients with comorbid major depression but became even stronger when the latter patients were removed from the analysis. In addition, there was a negative correlation between Factor 1 (aggressive obsessions and checking compulsions) and left ventral PCC (vPCC; Vogt *et al.*, 2005; Chapter 13), and a positive correlation between the severity of Factor 2 (symmetry/ordering) symptoms and volume of the left posterior MCC (pMCC; Vogt *et al.*, 2003). The other studies (Grachev *et al.*, 1998; Kang *et al.*, 2004; Kellner *et al.*, 1991; Kim *et al.*, 2001; Pujol *et al.*, 2004; Riffkin *et al.*, 2005; Szeszko *et al.*, 1999) showed no significant differences between OCD patients and controls in cingulate volumes or gray matter density.

One study employed diffusion tensor imaging (DTI) to examine white matter in OCD, reporting lower fractional anisotropy (FA) in three clusters in the midcingulate gyrus and one in the dorsal posterior cingulate gyrus (Szeszko *et al.*, 2005). However, all four of these clusters actually were centered on or adjacent to cortical gray matter in Talairach space suggesting that the results may have been influenced by volumetric or morphological abnormalities of the cingulate cortex in OCD, such as those described above. Cannistraro *et al.* (2006), in contrast, detected *above*-normal FA in the cingulum bundle in OCD patients. This is interesting, as DTI studies of a wide range of brain disorders to date have typically reported reduced, rather than elevated white matter FA. Nonetheless, the notion of fiber tract hypertrophy or hyperplasia associated with chronic over-activation in OCD of cerebral network node structures connected by the cingulum and other bundles is intuitively appealing and consistent with observations of clinical improvement following lesions of these tracts. Further DTI studies are called for to help elucidate the role of white matter in OCD.

Other MRI findings involving the cingulate cortex in OCD patients include elevated T1 relaxation times in the cingulum bundle (Garber *et al.*, 1989) and a post-surgical decrease in bilateral caudate body volumes following bilateral anterior cingulotomy for the treatment of intractable OCD (Rauch *et al.*, 2000). The latter result is due to the projections of cingulate cortex to the caudate nucleus as discussed in Chapter 28, and that surgical lesions of the cingulate gyrus can produce structural changes in the size of remote brain structures. However, the result is ambiguous as to whether post-surgical alleviation of OCD symptoms was directly mediated by removal of anterior cingulate tissue or a decrease of caudate volume.

Overall, structural MRI studies to date have not consistently demonstrated cingulate abnormalities in OCD but suggest two important changes and avenues for future research. First, MCC and dPCC are likely more vulnerable to OCD psychopathology than other parts of the cingulate gyrus. Second, white matter and volumetric studies following neurosurgical intervention

TABLE 27.1 Structural imaging studies in OCD

Authors	Technique	Subjects	Cingulate findings
Garber *et al.* (1989)	MRI	32 treated OCD patients 14 normal controls	Unmedicated patients had signif. correlation between right-left T1 asymmetry in ACC and OCD severity
Kellner *et al.* (1991)	MRI	12 OCD subjects 12 matched controls	No differences OCD versus controls
Scarone *et al.* (1992)	MRI	20 treated OCD patients 16 normal controls	N/A
Robinson *et al.* (1995)	MRI	26 OCD patients 26 healthy controls	N/A
Aylward *et al.* (1996)	MRI	24 OCD patients 21 controls	N/A
Jenike *et al.* (1996) and Grachev *et al.* (1998)	MRI	10 female OCD patients 10 female controls	Higher total cortex volume and lower white matter in OCD. **No cingulate differences.**
Rosenberg *et al.* (1997a,b)	MRI	19 children with OCD 19 healthy controls	N/A
Rosenberg *et al.* (1997a,b) and Macmaster *et al.* (1999)	MRI	21 children with OCD 21 healthy controls Corpus Callosum	N/A
Szeszko *et al.* (1999)	MRI	26 OCD patients 26 healthy controls	**No cingulate differences.**
Giedd *et al.* (2000)	MRI	34 children with streptococcus-related OCD and/or tics 82 healthy children	N/A
Peterson *et al.* (2000)	MRI	113 patients with OCD, ADHD, or Tic Disorder 34 healthy controls	N/A
Gilbert *et al.* (2000)	MRI	21 never-treated children with OCD; 10 after paroxetine; 21 healthy controls	N/A
Rosenberg *et al.* (2000)	MRI	11 children with OCD, before and after CBT	N/A
Kim *et al.* (2001)	MRI VBM	25 OCD patients 25 healthy controls	**No cingulate differences.**
Kwon *et al.* (2003a,b)	MRI	22 OCD patients 22 controls	N/A
Szeszko *et al.* (2004)	MRI	23 drug-naive OCD children 27 control children	**Greater ACC grey matter volume in OCD**
Kang *et al.* (2004)	MRI	36 OCD 36 Controls	**No cingulate differences.**
Pujol *et al.* (2004)	MRI VBM	72 OCD 72 Controls	None
Choi *et al.* (2004)	MRI	34 OCD 34 Controls	N/A
Riffkin *et al.* (2005	MRI	18 OCD 18 Schizophrenia 18 Controls	**No cingulate differences.**

MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; VBM, voxel-based morphometry; CBT, cognitive-behavioral therapy.

suggest that cingulate projections to the caudate nucleus may be pivotal to alleviating the symptoms of OCD.

Magnetic Resonance Spectroscopy

MRS is performed in a conventional MRI scanner to measure the concentrations of multiple metabolite species safely and non-invasively *in vivo*. Concentration is assayed from the response of the atomic nuclei in the brain to radio-frequency excitation pulses transmitted by the scanner head coil, while the subject is in the powerful magnetic field. As a rule, the nuclear isotope most commonly studied is the proton. Major neurometabolites detected by proton MRS include *N*-acetyl, glutamatergic, creatine, choline, and inositol compounds (Birken & Oldendorf, 1989; Maier, 1995), although the structural and physiological correlates of these compounds are not completely certain. Imprecisely, the levels of these major metabolites are thought to reflect nervous tissue composition (e.g., relative densities of neurons and glia), membrane metabolism, and cellular energetics (O'Neill & Schwartz, 2004; Rauch, 2003; Rosenberg *et al*., 2001a,b).

Table 27.2 summarizes the 10 published MRS studies of OCD. Findings include below-normal ratio of *N*-acetylaspartate to creatine+phosphocreatine ratio (NAA/Cr) in the striatum (Bartha *et al*., 1998; Ebert *et al*., 1997), above-normal glutamate and glutamine (Glx) in left head of the caudate nucleus that diminished in response to paroxetine (Bolton *et al*., 2001; Moore *et al*., 1998; Rosenberg *et al*., 2000a,b) but not to CBT (Benazon *et al*., 2003), above-normal choline compounds (Cho) and Cr (Mirza *et al*., 2006; Rosenberg *et al*., 2001a,b) and below-normal NAA/Cho and NAA/(Cho + Cr) in medial thalamus, and abnormal NAA and Cr in dorsolateral prefrontal cortex (DLPFC; Russell *et al*., 2003). Many of these findings are for pediatric OCD cases, and it is unknown if they also apply in adult OCD. Nevertheless, MRS studies have found neurochemical abnormalities in some of the same brain structures found to have structural and functional alterations in OCD. Only two MRS studies have examined the ACC in OCD patients and controls, finding below-normal NAA/Cr in adults (Ebert *et al*., 1997) and above-normal Glx in the pACC, with a trend towards above-normal Cr in children and adolescents with OCD (Rosenberg *et al*., 2004). NAA/Cr in the ACC (Ebert *et al*., 1997) correlated negatively with Yale-Brown Obsessive–Compulsive Scale (YBOCS, Goodman *et al*., 1989) score. Thus, early findings show greater neurochemical involvement of the ACC in OCD than shown with structural studies discussed above in posterior cingulate regions. Symptom provocation studies discussed below further suggest impairments of ACC and MCC functions.

TABLE 27.2 MR spectroscopy studies of OCD patients versus normal controls

Authors	Subjects/Treatment	Technique	Cingulate findings
Ebert *et al*. (1997)	12 OCD 6 controls	MRS	**Lower NAA in right ACC**
Bartha *et al*. (1998)	13 OCD 13 controls	MRS	N/A
Ohara *et al*. (1999)	12 OCD 12 controls	MRS	N/A
Fitzgerald *et al*. (2000) and Rosenberg *et al*. (2001)	11 OCD children 11 control children	MRSI	N/A
Bolton *et al*. (2001) Moore *et al*. (1998)	1 OCD child (case study) treated with paroxetine	MRS	N/A
Benazon *et al*. (2003)	21 OCD children pre-/post-CBT	MRS	N/A
Russell *et al*. (2003)	15 OCD children 15 healthy children	MRSI	N/A
Rosenberg *et al*. (2004)	20 OCD children 14 MDD children 14 Healthy children	MRS	**Lower GLX in bilateral ACC in OCD and MDD** Trend toward lower ACC Cr in OCD and MDD
Mizra *et al*. (2006)			

OCD, obsessive–compulsive disorder; MRS, magnetic resonance spectroscopy.

Functional Imaging Techniques for OCD

Four 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 or emotional 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) to measure glucose uptake and metabolism and ^{15}O-labeled CO_2 or H_2O to measure 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 ^{99}m-Technetium-D,L-hexamethyl-propyleneamine-oxime (HMPAO), ^{99}m-Technetium-ethyl-cisteinate-dimer (ECD), and the inhaled gas ^{133}Xenon. 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 (Rubin *et al.*, 1992). Readers interested in more detail are referred elsewhere (Sorenson & Phelps, 1987; Andreasen, 1989). Recent functional neuroimaging studies of OCD have employed magnetic resonance techniques such as functional MRI (fMRI), which measures correlates of regional brain activation by detecting changes in blood oxygenation level in different clinical states or cognitive tasks.

Functional Imaging Comparing OCD Patients with Normal Controls at Baseline

Eleven PET studies have compared resting brain activity in subjects with OCD versus controls (Table 27.3a). Nine of these measured activity in the cingulate gyrus in OCD, but only three found abnormalities. Swedo *et al.* (1989) found significantly higher glucose metabolism in multiple cerebral cortical regions, including bilateral ACC, in patients with childhood-onset OCD compared with controls. Perani *et al.* (1995) found higher glucose metabolic rates in ACC, MCC, and PCC in OCD patients than in normal controls. Saxena *et al.* (2004), however, found significantly *lower* dPCC metabolism in OCD patients with the compulsive hoarding syndrome, compared with normal controls, and lower aMCC and medial thalamic metabolism in compulsive hoarders compared with non-hoarding OCD patients. In contrast, non-hoarding OCD patients had significantly higher glucose metabolism in bilateral thalamus and caudate nucleus than controls. In fact, the majority of baseline PET studies of OCD have found no cingulate abnormalities, but rather, elevated activity in the OFC, striatum, and thalamus (Baxter *et al.*, 1987, 1988; Kwon *et al.*, 2003a,b; Nordahl *et al.*, 1989; Perani *et al.*, 1995; Sawle *et al.*, 1991; Swedo *et al.*, 1989; Saxena *et al.*, 2001b). As statistical significance for changes in the cingulate gyrus has been achieved in one-third of these studies, it is likely that there are differences in the OCD patient populations.

Of the 10 SPECT studies that compared OCD patients with normal controls at baseline (Table 27.3b), only three have found abnormal cingulate activity in OCD. Machlin *et al.* (1991) found a significantly higher ratio of the medial frontal cortex including ACC to whole cortex HMPAO concentration in medication-free OCD subjects compared with matched control subjects. A recent study found higher rCBF in the cingulate gyri of children and adolescents with OCD than in control children (Diler *et al.*, 2004). However, Busatto *et al.* (2001) found significantly lower left aMCC blood flow in patients with early-onset OCD, as compared with those with later-onset OCD and normal controls. The seven other baseline SPECT studies found no difference in cingulate activity between OCD patients and controls (Alptekin *et al.*, 2001; Crespo-Facorro *et al.*, 1999; Edmonstone *et al.*, 1994; Lacerda *et al.*, 2003; Lucey *et al.*, 1995, 1997; Rubin *et al.*, 1992).

Some of the variability in the results of the SPECT studies of OCD may be due to differences in rates of comorbid disorders between studies. Several of the studies included patients with major depression (Baxter *et al.*, 1987; Martinot *et al.*, 1990), which is known to strongly influence regional cingulate activity (Saxena *et al.*, 2001b). Caution must also be exercised before equating HMPAO uptake with rCBF or abnormal glucose metabolism in a pathological state such as OCD, in which the blood–brain barrier may be abnormal, and radiolabeled tracers could leak out of cells, causing dissociation of perfusion and retained tracer concentrations.

Neural Correlates of OCD Symptom Factors at Baseline

Few resting-state neuroimaging studies have examined the neural correlates of specific OCD symptom factors,

TABLE 27.3A Baseline PET studies of OCD patients versus normal controls

Authors	Subjects	Technique	Cingulate findings
Baxter *et al.* (1987)	14 OCD (9 with depression) 14 Depression; 14 controls	FDG-PET	None
Baxter *et al.* (1988)	10 non-depressed OCD 10 controls	FDG-PET	None
Nordahl *et al.* (1989)	8 OCD 30 controls	FDG-PET	None
Swedo *et al.* (1989)	18 OCD-childhood onset 18 controls	FDG-PET	**Higher bilateral ACC activity in OCD**
Martinot *et al.* (1990)	16 OCD 8 controls	FDG-PET	N/A
Sawle *et al.* (1991)	6 with obsessional slowness 6 controls	^{15}O-H_2O-PET	None
Perani *et al.* (1995)	11 OCD 15 controls	FDG-PET	**Higher anterior, middle, and posterior cingulate activity in OCD**
Cottraux *et al.* (1996)	10 OCD 10 controls	^{15}O-H_2O-PET	None
Saxena *et al.* (2001a,b)	27 OCD alone 17 OCD+Depression 27 Depression alone 17 controls	FDG-PET	None
Kwon *et al.* (2003a,b)	14 OCD 14 controls	FDG-PET	None
Saxena *et al.* (2004)	12 Compulsive hoarders 33 Non-hoarding OCD 17 controls	FDG-PET	**Hoarders versus Controls: lower dPCC** **Hoarders versus N-H OCD: lower aMCC**

but they have revealed some interesting associations between activity in subregions of cingulate cortex and specific OCD symptom domains. Rauch *et al.* (1998) found that the severity of Factor 3 (contamination/washing) symptoms correlated with rCBF in bilateral pACC, MCC, left OFC, and other cortical areas. Saxena *et al.* (2004) found that, across 45 OCD subjects, the severity of Factor 4 (hoarding and saving symptoms) was negatively correlated with activity in the aMCC (see Fig. 27.1). Although both of these studies were preliminary in nature, their results suggest that different OCD symptom clusters are mediated by quite different patterns of baseline cingulate activity.

Neurotransmitter and Receptor System Imaging

Recent PET and SPECT studies have measured binding to specific neurotransmitter receptors and transporters in OCD patients to identify neurochemical abnormalities. Four studies measured serotonin transporter (5-HTT) availability in OCD patients and controls. Two studies found significantly *lower* 5-HTT availability in the midbrain and brainstem in OCD patients (Stengler-Wenzke *et al.*, 2004; Hesse *et al.*, 2005), one significantly *lower* 5-HTT availability in the same regions in OCD patients than controls (Pogarell *et al.*, 2003), and one found no differences between groups (Simpson *et al.*, 2003). One PET study reported elevated serotonin 2a (5-HT2a) receptor binding density in the caudate nuclei of OCD patients, compared with controls, but no differences in the ACC (Adams *et al.*, 2005).

Findings concerning the dopamine system have been contradictory, although none examined the cingulate gyrus. Two studies found significantly higher dopamine transporter (DAT) density in the basal ganglia of OCD patients than controls (Kim *et al.*, 2003a,b; van der Wee *et al.*, 2004), but one found *lower* striatal DAT availability (Hesse *et al.*, 2005), and one study found *lower* dopamine D2 receptor binding in the left caudate nucleus in OCD (Denys *et al.*, 2004). More comprehensive studies will be required to better characterize neurotransmitter and

TABLE 27.3B Baseline SPECT studies of OCD patients versus normal controls

Authors	Subjects	Technique	Cingulate findings
Machlin *et al.* (1991)	10 OCD 8 controls	HMPAO-SPECT	**Higher medial frontal cortex rCBF in OCD**
Rubin *et al.* (1992)	10 OCD 10 controls	^{133}Xe- SPECT and HMPAO-SPECT	N/A
Edmonstone *et al.* (1994)	12 OCD, 12 Depressed, 12 controls	HMPAO-SPECT	None
Lucey *et al.* (1995)	30 OCD 30 controls	HMPAO-SPECT	None
Lucey *et al.* (1997)	15 OCD, 16 PTSD 15 Panic, 15 controls	HMPAO-SPECT	None
Crespo-Facorro *et al.* (1999)	27 OCD (7 with tics) 16 controls	HMPAO-SPECT	None
Busatto *et al.* (2000) and Busatto *et al.* (2001)	26 OCD (13 early-onset, 13 later-onset) 22 controls	ECD-SPECT	**Lower left aMCC rCBF in early-onset OCD**
Alptekin *et al.* (2001)	9 OCD 6 controls	HMPAO-SPECT	None
Lacerda *et al.* (2003)	16 OCD 17 healthy controls	HMPAO-SPECT	None
Diler *et al.* (2004)	18 OCD children 12 control children	HMPAO-SPECT	**Higher rCBF in cingulate in OCD**

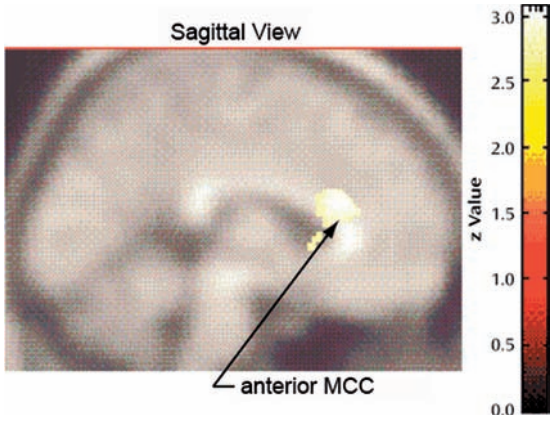

Fig. 27.1 Regions with lower glucose metabolism in compulsive hoarders than in non-hoarding OCD patients. Compared with non-hoarding OCD patients, compulsive hoarders had significantly lower glucose metabolism in bilateral aMCC (Talairach coordinates: $x = 2$, $y = 22$, $z = 20$; z-score=3.85, $p<0.001$, uncorrected) (reprinted with permission from Saxena *et al.*, 2004).

receptor dysfunctions that might underlie OCD, and whether they involve the cingulate gyrus.

Taken together, the various baseline functional neuroimaging studies of OCD patients compared with normal controls suggest inconsistent abnormalities in the cingulate gyrus. Most studies have not shown differences in baseline cingulate activity between OCD patients and controls, but a minority found abnormally high cingulate rCBF or glucose metabolism in OCD. Heterogeneity in the findings of these functional imaging studies of OCD could be accounted for by phenotypic variations between their subject samples. It is possible that the few studies that found higher baseline ACC or aMCC activity in OCD may have included a predominance of patients with contamination obsessions and washing/cleaning compulsions (Factor 3), whereas those that found lower cingulate activity may have included more compulsive hoarders or patients with early-onset OCD. Larger studies that control for variance in age of onset and the severity of different symptom factors will be required to further delineate the neural mediation of specific symptom factors and subtypes of OCD, and determine more precisely the role of cingulate abnormalities in OCD.

Functional Neuroimaging of OCD before and after Treatment

Functional neuroimaging studies before and after treatment test hypotheses about how the brain mediates psychiatric symptoms by determining what changes in regional activity occur when patients respond to treatment, and which changes correlate best with

symptomatic improvement. Such studies can also reveal differences in cerebral mechanisms of action between treatments. PET and SPECT have been used to evaluate OCD patients before and after treatment with SRIs, CBT, and neurosurgery.

Of the nine pre- and post-treatment PET studies of OCD, three found decreases in activity in the cingulate gyrus (Table 27.4). Baxter *et al.* (1992) found significant, pre- to post-treatment decreases in ACC metabolism in OCD responders to fluoxetine but not in responders to CBT, Perani *et al.* (1995) found significant declines in ACC, MCC, and PCC after SRI treatment, and Hansen *et al.* (2002) found a trend towards a decrease in left pACC metabolism after paroxetine treatment. These changes have not been seen in non-responders to treatment. Similarly, three of the eight pre- to post-treatment SPECT studies of OCD found significant pre- to post-treatment decreases in cingulate perfusion in responders to SRI treatment (Diler *et al.*, 2004; Hoehn-Saric *et al.*, 1991, 2001). Thus, decreasing cingulate activity may be associated with improvement in OCD symptoms but does not appear to be a necessary mechanism of action for treatment response.

The functional changes most strongly associated with OCD treatment response are decreases in activity in the right caudate nucleus (Baxter *et al.*, 1992; Diler *et al.*, 2004; Hansen *et al.*, 2002; Mindus *et al.*, 1991; Saxena *et al.*, 1999, 2002; Schwartz *et al.*, 1996), right OFC (Benkelfat *et al.*, 1990; Mindus *et al.*, 1991; Rubin *et al.*, 1995; Saxena *et al.*, 1999; Swedo *et al.*, 1992), and thalamus (Baxter *et al.*, 1992; Ho Pian *et al.*, 2005; Saxena *et al.*, 2002). These changes are specific to OCD and do not occur in patients with major depression (Saxena *et al.*, 2002) or other disorders treated with similar medications.

TABLE 27.4 Pre- and post-treatment imaging studies in OCD

Authors	Subjects/treatment	Technique	Cingulate changes
Benkelfat *et al.* (1990)	8 treated with clomipramine	FDG-PET	None
Swedo *et al.* (1992)	13 subjects - 8 on clomipramine, 2 on fluoxetine and 3 off meds	FDG-PET	None
Baxter *et al.* (1992)	9 with fluoxetine, 9 with behavior therapy	FDG-PET	**Decreased right ACC in fluoxetine responders**
Perani *et al.* (1995)	4 with fluvoxamine, 2 with fluoxetine, and 3 with clomipramine	FDG-PET	**Decreased anterior, middle, and posterior cingulate metabolism**
Schwartz *et al.* (1996)	18 treated with behavior therapy	FDG-PET	None
Saxena *et al.* (1999)	20 with paroxetine	FDG-PET	None
Saxena *et al.* (2002)	25 OCD, 25 Depression, 16 OCD+Depression, all treated with paroxetine, 16 Controls	FDG-PET	None
Hansen *et al.* (2002)	20 OCD with paroxetine	FDG-PET	**Trend toward decreased left ACC**
Kang *et al.* (2003)	10 OCD with various SSRI's	FDG-PET	None
Hoehn-Saric *et al.* (1990)	6 with fluoxetine	HMPAO-SPECT	**Decreased medial frontal rCBF**
Rubin *et al.* (1995)	10 with clomipramine	^{133}Xe-SPECT and HMPAO-SPECT	N/A
Molina *et al.* (1995a,b)	1 with clomipramine	HMPAO-SPECT	None
Rosenberg *et al.* (1998)	11 OCD children with paroxetine	MRS	None
Hoehn-Saric *et al.* (2001)	16 OCD+Depression (9 with sertraline, 7 with desipramine)	HMPAO-SPECT	**Diffuse prefrontal and ACC decreases in responders**
Benazon *et al.* (2003)	21 OCD children with CBT	MRS	N/A.
Diler *et al.* (2004)	18 children treated with paroxetine	HMPAO-SPECT	**Decreased cingulate rCBF in responders**
Carey *et al.* (2004)	14 with inositol	HMPAO-SPECT	None
Ho Pian *et al.* (2005)	15 OCD with Fluvoxamine	HMPAO-SPECT	N/A
Castillo *et al.* (2005)	10 OCD children with clomipramine	ECD-SPECT	None

Pre-treatment Functional Neuroimaging: Predictors of Treatment Response in OCD

Functional imaging data have also been examined to determine if pre-treatment regional activity predicts treatment response. Lower pre-treatment glucose metabolism in the OFC has been associated with better response to the SRIs clomipramine (Swedo *et al.*, 1992), fluoxetine (Brody *et al.*, 1998), paroxetine (Saxena *et al.*, 1999), and fluvoxamine (Rauch *et al.*, 2002). Response to paroxetine has also been correlated with higher pre-treatment metabolism (Saxena *et al.*, 2003) and elevated glutamate concentrations in the caudate nuclei (Rosenberg *et al.*, 2000a,b). In contrast, response to CBT was correlated with higher pre-treatment left OFC metabolism (Brody *et al.*, 1998). In two studies, higher pre-treatment glucose metabolism in the right PCC was associated with eventual improvement of OCD symptoms in patients treated with fluvoxamine (Rauch *et al.*, 2002), and also in patients who underwent anterior cingulotomy (Rauch *et al.*, 2001). Hendler *et al.* (2003) found that eventual responders to the SRI sertraline showed less activation of the pMCC and dPCC during OCD symptom provocation than did non-responders. However, that study did not compare baseline rCBF between groups.

Taken together, these studies suggest that OCD patients with different patterns of pre-treatment brain activity respond differentially to specific types of treatment (SRIs, CBT, neurosurgery). With regard to the cingulate gyrus, OCD patients with higher baseline PCC activity and less increase in PCC activity with symptom provocation are more likely to respond to SRIs.

Neuroimaging During 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; that is, while patients are actively experiencing obsessions, anxiety, and urges to perform compulsive rituals. Symptom provocation studies have been conducted using three main methods: (1) comparing functional 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, (2) measuring changes in activity after exacerbating OCD symptoms with pharmacological challenges, and (3) using visual stimuli, such as photographs, to induce obsessional anxiety or urges to perform compulsions during imaging.

Exposure stimuli-based symptom provocation studies with PET, SPECT, and fMRI have consistently found increases in glucose metabolism or rCBF in the OFC, caudate nucleus, and thalamus during the provoked state (Adler *et al.*, 2000; Breiter *et al.*, 1996; Chen *et al.*, 2004; Mataix-Cols *et al.*, 2004; McGuire *et al.*, 1994; Nakao *et al.*, 2005a; Rauch *et al.*, 1994); usually more in patients than in controls, with less consistent activation of the cingulate gyrus, other cortical regions, and the amygdala, hippocampus, and insula. Seven of 14 exposure-based symptom provocation studies found increases in cingulate activity in OCD patients during the provoked state (Table 27.5). Four of these studies showed localized activation of the aMCC (Breiter *et al.*, 1996; Mataix-Cols *et al.*, 2004; Phillips *et al.*, 2000; Rauch *et al.*, 1994), one found activation of the right ACC with no further localization (Adler *et al.*, 2000), and two observed activation of the PCC (McGuire *et al.*, 1994; Nakao *et al.*, 2005a). Only six studies to date have compared the brain activation patterns of OCD patients with those of normal controls during provocation of OCD symptoms. Two of these studies found greater cingulate activation in OCD patients than in controls (Breiter *et al.*, 1996; Mataix-Cols *et al.*, 2004), but four found no differences in cingulate activation between groups (Chen *et al.*, 2004; Cottraux *et al.*, 1996; Phillips *et al.*, 2000; Schienle *et al.*, 2005).

It is an interesting fact that most studies reporting ACC activation in OCD patients during symptom provocation used patients who were on medications at the time of the study (Breiter *et al.*, 1996; Mataix-Cols *et al.*, 2004; Phillips *et al.*, 2000). Those studies that scanned unmedicated patients have generally not found ACC activation during symptom provocation (Chen *et al.*, 2004; Cottraux *et al.*, 1996; McGuire *et al.*, 1994; Nakao *et al.*, 2005a; Rauch *et al.*, 2002; van den Heuvel *et al.*, 2004). This suggests that the ACC may be less responsive to OCD symptom provocation in the untreated state than when patients are on medications.

Several neuroimaging studies provoked symptoms in subpopulations of OCD patients who had the same primary symptom factor. Of the five studies that provoked symptoms in patients with primary contamination/washing OCD, two found cingulate activation. One activated the left dPCC (McGuire *et al.*, 1994) and one the right aMCC (Phillips *et al.*, 2000), but none found a significant difference in cingulate activation between OCD patients and normal controls. The two provocation studies of compulsive checkers also did not find differences from controls in cingulate activation (Cottraux *et al.*, 1996; Phillips *et al.*, 2000), although Phillips *et al.* (2000) observed greater activation of the right aMCC by washing-related pictures in checkers than in washers.

Mataix-Cols *et al.* (2004) studied a heterogeneous group of OCD patients and provoked three specific

TABLE 27.5 OCD symptom provocation studies

Authors	Subjects	Technique	Results in cingulate
Zohar *et al.* (1989)	10 OCD	^{133}Xe-SPECT	Increased cerebral cortex rCBF with imaginal flooding; decreased rCBF with ***in vivo*** exposure.
Rauch *et al.* (1994)	8 OCD	^{15}O-CO_2-PET	**Increased rCBF in left aMCC**
McGuire *et al.* (1994)	4 contamination OCD	^{15}O-CO_2-PET	**OCD symptoms correlated with rCBF in left dPCC**
Cottraux *et al.* (1996)	10 OCD checkers 10 controls	^{15}O-H_2O-PET	None
Breiter *et al.* (1996)	13 OCD 6 controls	fMRI	**Activation of bilateral aMCC in OCD only**
Adler *et al.* (2000)	7 OCD	fMRI	**Activation of right ACC**
Phillips *et al.* (2000)	7 OCD washers, 7 OCD checkers 8 controls	fMRI Washing pictures	**Greater activation of right aMCC in checkers than washers; no diff. from controls**
Rauch *et al.* (2002)	9 contamination OCD	^{15}O-CO_2-PET	None
Hendler *et al.* (2003)	26 OCD before treatment with sertraline	ECD-SPECT	**Less activation of right pMCC and dPCC in responders than non-responders during provocation**
Mataix-Cols *et al.* (2004)	16 OCD 17 controls	fMRI pictures	**Activation of bilateral pACC and right sACC/ OFC by washing pictures; right aMCC and bilateral sACC/OFC/ gyri recti with checking pictures; in OCD > Controls**
Chen *et al.* (2004)	10 females with contamination OCD	Perfusion-weighted MRI	None
van den Heuvel *et al.* (2004)	11 contamination OCD 10 controls	^{15}O-H_2O-PET	None
Nakao *et al.* (2005b)	10 OCD	fMRI before and after treatment	Pre-Tx: PCC activated Post-Tx versus pre-Tx: **less activation of left aMCC by symptom provocation**
Schienle *et al.* (2005)	10 OCD 10 controls	fMRI trigger photos	None

symptom factors in all, as well as controls, finding that provocation of harm obsessions and checking compulsions (Factor 1) activated the right aMCC and an area spanning bilateral subgenual ACC (sACC), OFC, and gyrus rectus, more in OCD patients than in controls (Fig. 27.2), while provocation of contamination/washing symptoms (Factor 3) activated bilateral pACC and right sACC/OFC significantly more in OCD patients than in controls. Provocation of compulsive hoarding/saving symptoms (Factor 4) also activated bilateral pACC and left aMCC, but there was no difference between OCD patients and controls. This research group found similar symptom-factor-specific patterns of activation in normal controls, but to a lesser extent (Mataix-Cols *et al.*, 2003). However, they did not study Factor 2 (symmetry and order obsessions with arranging, counting, and repeating compulsions) and did not use individually tailored or *in vivo* exposures, but rather, photographs and instructions to imagine obsessional situations to provoke symptoms.

Taken together, the studies of OCD symptom provocation strongly link the expression of OCD symptoms with activation of the same brain areas found to be overactive at baseline, primarily the OFC, basal ganglia, and thalamus, with variable activation of the cingulate gyrus. A few studies found greater cingulate activation in OCD patients than controls during symptom provocation (Breiter *et al.*, 1996; Mataix-Cols *et al.*, 2004) and the aMCC is the cingulate subregion most often associated with provoked OCD symptoms. As with baseline cingulate abnormalities, abnormal cingulate activation during symptom provocation may only be found in subsets of OCD patients and exaggerated activation of the aMCC may only be seen in medication-treated patients. It is possible that OCD patients with prominent Factor 3 symptoms may not show much cingulate

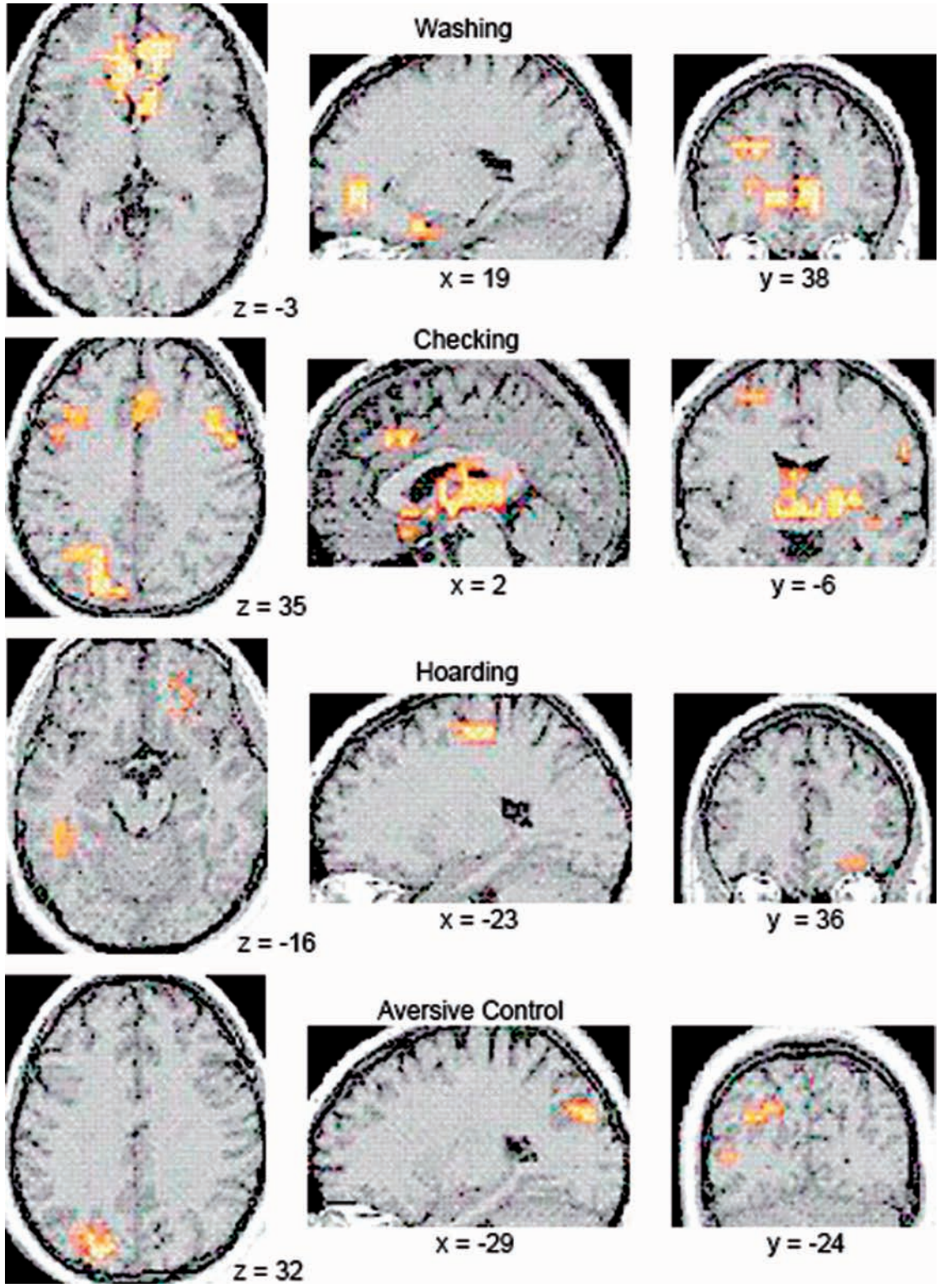

Fig. 27.2 Regions activated in OCD patients more than controls during symptom provocation. During provocation of contamination obsessions, OCD patients showed significantly more activation than controls in bilateral pACC, right sACC/OFC, right caudate nucleus, ventrolateral prefrontal cortex (VLPFC), amygdala, and left middle frontal gyrus. During provocation of harm obsessions and urges to check, OCD patients showed significantly greater activation than controls in the right aMCC and an area spanning bilateral sACC, OFC, and gyrus rectus, right putamen/globus pallidus, right thalamus, right hippocampus, right inferior frontal gyrus, bilateral DLPFC, and left parieto-occipital cortex. During provocation of hoarding/saving obsessions, OCD patients activated right OFC, left fusiform gyrus, and left superior frontal gyrus significantly more than controls.

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activation because they may already have high baseline activity in the cingulate cortex (Rauch *et al.*, 1998), creating a 'ceiling effect.' The PCC appears to only rarely mediate the expression of OCD symptoms (McGuire *et al.*, 1994; Nakao *et al.*, 2005a). Thus, variability of cingulate activation between studies may result from heterogeneity in subject samples, medication effects, and differences in symptom provocation methods.

Neuroimaging During Cognitive Tasks

Cognitive activation studies attempt to delineate the pathophysiology of a disorder by finding abnormalities in a regional activation pattern during specific cognitive tasks. Typically, such an approach targets a specific region or circuit of interest and/or a particular cognitive domain of interest, such as learning, memory, or response inhibition. Almost all cognitive activation studies comparing OCD patients to controls have shown abnormal activation patterns in OCD and most have demonstrated abnormal cingulate activation and they are summarized in Table 27.6.

Several fMRI cognitive activation studies of OCD employed interference and response inhibition tasks to probe the error detection and conflict monitoring functions associated with MCC. Ursu *et al.* (2003) used a

TABLE 27.6 Cognitive sctivation studies in OCD

Authors	Subjects	Tracer/task	Results in cingulate
Rauch *et al.*(1997)	9 females with OCD 9 female controls	^{15}O-CO_2-PET Implicit sequence learning	None
Pujol *et al.* (1999)	20 OCD 20 controls	fMRI Word generation	N/A
Rauch *et al.* (2001)	6 OCD 12 controls	fMRI Implicit sequence learning	None
van der Wee *et al.* (2003)	11 OCD 11 controls	fMRI spatial n-back task	**Greater activation of aMCC & pMCC in OCD**
Ursu *et al.* (2003)	11 OCD 13 controls	Event-related fMRI CPT with graded response conflict	**Greater aMCC activation in OCD** than controls during errors and some high conflict conditions
Maltby *et al.*, (2005)	14 OCD 14 controls	Event-related fMRI Go/No Go task	**Greater activation of pACC, aMCC, vPCC, in OCD during both errors and high- conflict correct responses.**
Fitzgerald *et al.* (2005)	8 OCD 7 controls	Event-related fMRI interference task	**Both groups activated aMCC/SMA during errors. Activation of sACC only in OCD. Only controls activated aMCC/SMA during correct responses.**
van den Heuvel *et al.* (2005a,b)	22 OCD 22 controls	Event-related fMRI Tower of London task	**Less activation of aMCC, DLPFC, striatum in OCD than controls. Greater correlation of task load with bilateral aMCC activation in OCD than controls.**
Nakao *et al.* (2005a, b)	24 OCD 14 controls	fMRI with Stroop before and after treatment	**Pre-Tx: Both groups activated right aMCC, but OCD < Controls Post-Tx: right aMCC and left pMCC/SMA activated. Post versus pre-Tx: less activation in bilateral dPCC and left pMCC**
van den Heuval *et al.* (2005)	16 OCD 15 panic disorder 13 hypochondriasis 19 controls	fMRI color/emotional Stroop	No difference in AC activation between groups during color naming. **In OCD versus controls, emotional interference correlated with dorsal ACC activation**.
Viard *et al.* (2005)	12 childhood-onset OCD (11/12 on meds) 15 controls	Event-related fMRI number comparison task	**Greater activation of aMCC in OCD during non-repeated trials; non-symptom resistant patients had greater activation of vPCC than symptom- resistant patients.**

MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; **aMCC,** anterior midcingulate cortex; **VBM,** voxel-based morphometry, fMRI, functional MRI, MRS, magnetic resonance spectroscopy; vPCC, ventral posterior cingulate cortex, **PET,** positron emission tomography; SPECT, single photon emission computed tomography; CBT, cognitive-behavioral therapy.

continuous performance task with graded levels of response conflict and found that OCD patients had greater activation of the aMCC than controls during errors, as well as some high-conflict trials, suggesting they have an 'overactive action-monitoring system' that signals potential for errors even when none were made. These may mediate the OCD patients' exaggerated doubts, critical self-evaluation, and need for repetitive corrective behaviors.

Maltby *et al*. (2005) reasoned that if the action-monitoring system is dysfunctional in OCD and that exaggerated activity in the MCC should be demonstrable during high-conflict trials, even in the absence of actual errors. To test this hypothesis, they employed a version of a Go/No-go task and found that, in comparison with controls, OCD subjects exhibited exaggerated activation in pACC, aMCC, supplementary motor area (SMA), and vPCC during both commission of errors and high conflict, 'correct reject' trials. Only OCD patients activated inferior frontal cortex, striatum, and thalamus during high-conflict correct responses. Fitzgerald *et al*. (2005) used a version of the Erikson flanker task and found that, while both OCD and normal control subjects exhibited aMCC activation during commission of errors, only OCD subjects showed error-related activation of sACC, which was positively correlated with OCD symptom severity (Fig. 27.3). Again, only OCD subjects showed activation of the striatum during non-error conflict processing. Using a number comparison task, Viard *et al*. (2005) found that medicated, adult patients with childhood-onset OCD showed greater activation of aMCC during visual presentation of non-repeated numbers than repeated numbers, compared with controls, suggesting that the patients had a greater neural response to task-irrelevant incongruities (conflict) between numerical stimuli.

Taken together, these studies provide strong evidence that hyperactivation of the aMCC in OCD patients is associated with detection of errors and difficult, high-conflict tasks that involve incongruity of responses. This is consistent with an overactive conflict monitoring system described by Carter *et al*. (Botvinick *et al*., 2004; Carter *et al*., 1999). In contrast, striatal hyperactivation occurs in OCD patients during high conflict, 'correct reject' responses, not during errors.

The Stroop task is another classical paradigm for studying interference effects and action monitoring in conjunction with functional imaging. Performance of this task requires the subject to attend to one stimulus feature (e.g., color) while inhibiting responses to other features (e.g., semantic meaning or emotional content). Two recent imaging studies have used the Stroop task to study action monitoring in OCD. Nakao *et al*. (2005a, b) found that, prior to treatment, OCD patients had significantly less activation of bilateral aMCC than controls during a Chinese version of the Stroop task. After treatment with fluvoxamine or CBT, OCD patients activated the right aMCC and left pMCC/SMA but had *decreased* activation of bilateral dPCC and left pMCC. However, this study's results may be suspect because of low significance thresholds, small sample sizes, and failure to correct for multiple comparisons in the statistical analyses. van den Heuvel *et al*. (2005a) used emotional and color Stroop tasks and found that, while color naming interference was associated with comparable ACC activation in OCD patients and controls, the OCD group exhibited exaggerated amygdala and

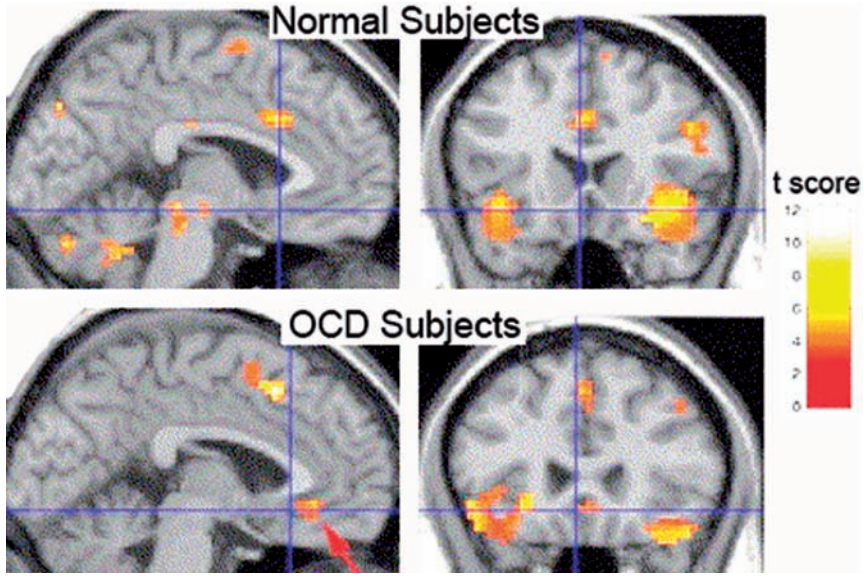

Fig. 27.3 Activation in OCD patients and controls during commission. OCD patients and controls showed similar activation of aMCC and SMA when making errors on the Erikson flanker interference task, but only OCD patients activated sACC (red arrow) during errors (Talairach coordinates: $x = -3$, $y = 30$, $z = -6$; z-score=3.89, $p < 0.01$, corrected) (reprinted with permission from Fitzgerald *et al*., 2005).

hypothalamic activation when contrasting naming the color of OCD-related words versus neutral words. Greater emotional interference by OCD-related words was correlated with increasing activation of bilateral dorsal ACC in OCD patients versus controls. The precise location of these effects within the cingulate gyrus was not reported, but, based on prior findings; it would be expected to be in the pACC. In previous Stroop imaging studies of normal subjects, emotional interference activated the pACC (Whalen *et al*., 1998), whereas cognitive interference activates the aMCC and it increases with increased task difficulty (Bush *et al*., 1998; Chapter 12).

OCD patients also have abnormal brain activity during learning and memory tasks. Rauch *et al*. adapted an implicit sequence learning task, the serial reaction time (SRT) task, for use in conjunction with functional imaging, in an effort to probe cortico-striato-thalamic function in the context of non-conscious information processing (Rauch *et al*., 1995, 1997b). Using ^{15}O-PET and fMRI with the SRT task, they demonstrated that, while OCD patients exhibited a normal magnitude of implicit learning, they did not show normal striatal recruitment and instead activated hippocampus and parahippocampal cortex in an aberrant fashion (Rauch *et al*., 1997, 2001). Similarly, Fernandez *et al*. (2003) found that OCD patients failed to activate the left caudate during performance of the Tower of Hanoi task, which assesses planning, working memory, and inhibition, compared with controls.

van den Heuvel *et al*. (2005b) recently employed a higher-level procedural learning task, the Tower of London, to probe frontal-striatal function during planning. They found that, in comparison with normal controls, OCD subjects exhibited less activation of left aMCC, right DLPFC, and striatum during planning. However, increasing task load correlated with increased activation in bilateral aMCC, parahippocampal cortex, ventrolateral prefrontal cortex (VLPFC), and brainstem in OCD patients, compared with controls. These probes indicate that patients with OCD have deficient striatal activation during procedural and implicit learning/memory tasks and appear to activate explicit memory regions such as the parahippocampal cortex instead of the striatum in a manner that may be compensatory. Van der Wee *et al*. (2003) used an fMRI spatial working memory task and found that, in comparison with normal controls, OCD subjects exhibited impaired performance at the highest working memory load. Although both groups showed activation of medial prefrontal cortex extending into dorsal aMCC, DLPFC, and parietal cortex, the OCD group exhibited exaggerated activation in a region spanning dorsal aMCC and pMCC, in a load-independent fashion.

The heterogeneity of ACC activation in OCD patients versus controls in these studies may be related to the specific cognitive tasks used. OCD patients show hyperactivation of the aMCC during tasks that involve conflict monitoring, error detection, incongruity, and spatial working memory. The ACC appears to be hyperactivated in OCD patients by cognitive tasks that involve affective response to errors, suggesting that OCD patients have exaggerated emotional responses to errors. In contrast, OCD patients may show aMCC *hypo*activation during planning and response inhibition tasks. The cingulate cortex is not activated by implicit learning tasks or test paradigms that do not involve conflicts or errors. The OFC, striatum, and thalamus are activated in OCD patients by cognitive tasks that involve suppression of prepotent responses, and by symptom provocation paradigms, which also require response inhibition while the patient is in the scanner.

Neuroimaging During Emotion

Several imaging studies have examined response to emotion-inducing stimuli, such as disgusting or threatening pictures in OCD and they are summarized in Table 27.7. Phillips *et al*. (2000) found that both OCD washers and checkers activated right aMCC and bilateral PCC while viewing disgusting images, but there was no difference between OCD patients and controls in cingulate activation. Two recent fMRI studies compared brain responses with fear- and disgust-inducing pictures in OCD patients and healthy controls. Shapira *et al*. (2003) found less activation of the left sACC in OCD patients than controls while viewing disgust-inducing pictures, but no differences between groups when viewing threat-inducing stimuli. Schienle *et al*. (2005) found greater activation of the insula in OCD than controls with both threatening and disgusting pictures, but no activation of the cingulate cortex in either group. Another fMRI study of response to general threat-related stimuli, that is, fearful versus neutral or happy faces, also found no cingulate activation in OCD (Cannistraro *et al*., 2004).

OCD patients do not appear to show exaggerated cingulate responses to threat-related or disgust-inducing visual stimuli. This indicates that the increased cingulate activation in many symptom provocation studies in OCD patients is not merely due to a generally elevated threat perception or hypersensitivity to disgusting stimuli during passive viewing, but rather to specific activation of cognitive processes related to monitoring for errors and, perhaps, compulsive urges during active tasks. This area of investigation into OCD is in its infancy, and more research will be required to reveal consistent links between symptoms, cognitive deficits, emotional processing, and cingulate cortex activity abnormalities.

TABLE 27.7 Emotional activiation studies in OCD

Authors	Subjects	Imaging modality/task	Results in cingulate
Phillips *et al.* (2000)	7 OCD washers, 7 OCD checkers, 14 controls	fMRI Disgust images	**Activation of right aMCC and bilateral PCC in washers & checkers; no diff. from controls.**
Shapira *et al.* (2003)	8 contamination OCD 8 controls	fMRI threat and disgust pictures	**Similar activation of ACC in both groups for threat; diff. for disgust: less sACC activation in OCD than controls.**
Cannistraro *et al.* (2004)	10 OCD 10 controls	fMRI emotional faces	None
Schienle *et al.* (2005)	10 OCD 10 controls	fMRI fear-inducing and disgusting scenes	None

Electrical and Magnetic Evoked Responses

EEG samples volume-conducted spontaneous rhythmic electrical activity. This activity is generated by large ensembles of neurons and reflects brain states that endure for seconds to hours, including stages of somnolence and levels of consciousness. Electric evoked potentials (EPs), also known as event-related potentials, sample transient or steady-state electrical activity transpiring across milliseconds to seconds. This activity is phase-locked to an eliciting exogenous or endogenous stimulus (e.g., flashing light) or event such as a voluntary finger lifting. MEG and magnetic evoked potentials (MEPs) are analogous to EEG and EPs, respectively, for central nervous magnetic activity.

Several early studies noted diffuse or focal slow-wave or epileptiform EEG features in a subset of OCD patients. Both elevated and diminished levels of absolute and relative EEG power have been reported for each EEG frequency band in patients with OCD (reviewed by Bucci *et al.*, 2004; Fontenelle *et al.*, 2000; Locatelli *et al.*, 1996). These power shifts may be related to anxiety in OCD patients, possibly associated with cingulate dysfunction or expressed through abnormal cingulate activity. Some OCD patients are surmised to exhibit hyperexcitability of the cortex related to decreased intra-cortical inhibition and overactivity in paralimbic frontal-subcortical circuits, including those involving the cingulate cortex (Greenberg *et al.*, 2000). Flor-Henry *et al.* (1979) postulated that EEG abnormalities in OCD patients arose from perturbed cingulate–orbitofrontal connections. A recent retrospective study (Sherlin & Congedo, 2005) of eight OCD patients and eight controls used the popular and successful low-resolution electromagnetic tomography source-localization technique (Pascual-Marqui *et al.*, 1999) to estimate the generators of waking EEG power in each major frequency band and multiple sub-bands. The principal finding was that OCD patients generated excess β power relative to controls. Excess power in the β1 sub-band (12–16 Hz) localized to caudal aMCC and pMCC, in the β2 sub-band (16–20 Hz) it localized to caudal pMCC and dPCC, in the β3 (20–24 Hz), and β4 (24–28 Hz) sub-bands it localized to dPCC. For each sub-band, the β-source zone comprised not just the indicated cingulate subregion, but also suprajacent mesial cortex extending to the cerebral convexity. Otherwise, it is difficult to tie these disparate early findings to the cingulate gyrus in any direct way.

Several EP components and desynchronizations have been reported as abnormal in OCD (Asahi *et al.*, 1993; Leocani *et al.*, 2001; Molina *et al.*, 1995a,b; Morault *et al.*, 1997; Nolfe *et al.*, 1998; Savage *et al.*, 1994). Many studies focused on late cognitive EPs, especially the N200/P300/slow-wave complex, particularly in the auditory modality. fMRI studies indicate that one intracranial P300 (P3) generator lies in ACC (McCarthy *et al.*, 1997). Recent source analyses of scalp data (Dien *et al.*, 2003; Mulert *et al.*, 2004) locate P3-like activity in MCC. Depth recordings in epileptics identify intracranial correlates of the scalp P3, principally its P3a subcomponent linked to the orienting response with likely generation in pACC (Baudena *et al.*, 1995; Halgren *et al.*, 1994b; Smith *et al.*, 1990) and PCC (Halgren *et al.*, 1994a, 1995; Smith *et al.*, 1990).

For the N200 potential, shortened latency (Herrmann *et al.*, 2003; Morault *et al.*, 1997) and enhanced (de Groot *et al.*, 1997; Towey *et al.*, 1990), diminished (Morault *et al.*, 1997), or normal (Herrmann *et al.*, 2003) amplitude have been measured in OCD. For the slow wave, both shortened (de Groot *et al.*, 1997) and lengthened (Morault *et al.*, 1997) latency and enhanced amplitude (Towey *et al.*, 1990) have been recorded in OCD.

For the P3, most studies (de Groot *et al*., 1997; Herrmann *et al*., 2003; Morault *et al*., 1997; Towey *et al*., 1990) found shortened latency in OCD. Several found diminished (Kim *et al*., 2003a,b; Malloy *et al*., 1989; Sanz *et al*., 2001; Towey *et al*., 1994), though some found enhanced (Di Russo *et al*., 2000; Herrmann *et al*., 2003) P3 amplitude in OCD. The combination of decreased latency and decreased amplitude of P3 is unusual; increased latency and decreased amplitude is seen in most brain disorders. P3 effects are thought to reflect inadequate frontal inhibition in OCD. It is possible that aberrant electrical responses of cingulate regions contribute to P3 abnormalities observed in OCD, through direct volume propagation or interactions with P3 sources in other cortices. Meanwhile, multiple other, non-cingulate P3 sources are firmly established. Thus, it will require further detailed EP investigations to determine the precise role of cingulate function or dysfunction in producing aberrant P3 signals in OCD.

The most interesting EP results from a cingulate perspective concern the event-related negativity (ERN). The ERN (Falkenstein *et al*., 1991, 1995; Gehring *et al*., 1990, 1993, 1995) is a negative-electrical deflection that is demonstrated in experimental paradigms where the subject can commit task-related errors and recognize them as such. The ERN typically appears only during error trials and, unlike most EP waves, is time-locked not to the stimulus, but to the response. ERN onset occurs 50–100 ms after the response. Peak amplitude increases with the certainty of error (Falkenstein *et al*., 1991; Gehring *et al*., 1993). Gehring *et al*. (2000) discovered that the amplitude of the ERN was enhanced in OCD patients and correlated with the severity of their OCD symptoms.

The enhanced ERN in OCD has been attributed to hyperactivity of a medial frontal cortex, including cingulate cortex, action-monitoring system that generates exaggerated error signals, producing doubt, and displacement behaviors (compulsions) in OCD patients (Pitman, 1987; Schwartz, 1997). Alternative interpretations suggest that the ERN represents error detection (Scheffers *et al*., 1996) or detection of response conflict in which error is more likely to occur (Carter *et al*., 1998). Johannes *et al*. (2001) replicated above-normal amplitude of the ERN in OCD, as well as delayed latency and caudally displaced scalp distribution. They attributed the larger, later, more posterior ERN in OCD patients to prolonged error monitoring due to altered error processing function of the MCC (Kiehl *et al*., 2000). Hajcak *et al*. (Hajcak & Simons, 2002; Hajcak *et al*., 2003) subsequently found elevated ERN amplitudes in high obsessive-character relative to low obsessive-character normal subjects, and in high-worrying relative to low-worrying normals. These results suggest that ERN aberrations may be present even in sub-clinical OCD and in other conditions associated with anxiety.

The cingulate cortex has long been suggested as a candidate generator of the ERN (Dehæne *et al*., 1994; Gehring *et al*., 1993; Holroyd *et al*. 1998; Luu *et al*., 2000; Miltner *et al*. 1997). Using dipole-source analysis of densely recorded scalp EPs in normal subjects, several investigators have localized an ERN source in the aMCC, in some cases bordering on neighboring brain regions. Miltner *et al*., (1997, 2003) derived a dipole within aMCC for the visual ERN, on the dorsal aspect of aMCC for the auditory ERN, and on dorsal aMCC bordering into SMA for the somatosensory ERN. Holroyd *et al*. (1998) derived an ERN dipole in the caudal portion of aMCC for hand movements and on dorsal aMCC bordering into SMA for foot movements. Using similar methods, Luu *et al*. (2003) identified multiple medial cortical regions active during error monitoring. A generator for the ERN was located in pACC and a generator for a kindred 'feedback-related negativity' component centered in SMA and extended into the dorsal aspect of pMCC. Luu *et al*. (2003) conceive of the ERN as a manifestation of a cingulate-based action-learning system, representing activity of the cingulate cortex during the early stages of discrimination learning in which rapid changes of behavior adapt to emergent demands.

MEG and MEP have been used sparingly in the study of OCD. Using sophisticated methods of cortical surface modeling and source localization, Ciesielski *et al*. (2005) examined MEP during a delayed matching-to-sample task. MEP activation for OCD patients differed highly significantly from that of healthy controls in multiple association cortices, but not in the cingulate gyrus. Unfortunately, data were reported for only four patients, one of whom did not meet diagnostic criteria for OCD. Novel MEG findings by Amo *et al*. (2004) included paroxysmal rhythmic activity in multiple cortical regions, including the cingulate gyrus in 12 OCD patients without comorbid seizure disorders, all of whom were taking SRI medications, but not in controls. This is an intriguing finding, but it must be reexamined in unmedicated OCD patients.

While investigations of EEG and other EP components have to date proven of limited value in unraveling the role of the cingulate cortex in OCD, the available ERN studies highlight an association of aMCC activity with conflict monitoring that relates in a natural way to the error-related anxiety and checking compulsions so prevalent in OCD. Further studies of the ERN and kindred EP components should examine subgroups of OCD patients, in particular those with and without checking symptoms. Paradigms should rate acute anxiety in each subject and verify acute anxiety responses by polygraphy. Analyses should localize functional effects to specific subregions of the cingulate cortex.

Cingulate Abnormalities in OCD

Although the neuroimaging and electrophysiological studies reviewed above have not fully elucidated the role of cingulate dysfunction in OCD, a few coherent patterns have emerged and different cingulate subregions play unique roles in OCD. Structural and resting-state functional neuroimaging studies have rarely found abnormal cingulate volume or baseline activity in OCD patients. Similarly, only a few of the many OCD treatment studies have shown pre- to post-treatment changes in cingulate activity. Given that only one-third of the symptom provocation studies that compared OCD patients with controls have found greater activation of cingulate cortex in OCD, cingulate hyperactivation does not appear to be associated with the expression of all OCD symptoms. It is also rarely found in unmedicated OCD patients. These studies suggest that only specific subgroups of OCD patients may have cingulate abnormalities. These abnormalities may, themselves, be heterogeneous, with Factor 3 (contamination/cleaning symptoms) perhaps associated with higher baseline pACC and MCC activity, Factor 4 (compulsive hoarding/saving) and early-onset OCD associated with lower baseline aMCC activity, and Factor 1 (obsessions about harm and aggression, pathological doubt, and checking compulsions) associated with hyperactivation of the aMCC during symptom provocation. Because so few baseline imaging studies have examined the neural correlates of specific OCD symptom factors, and no study to date has measured changes in brain activity associated with response of specific symptom factors to treatment, the role of the cingulate gyrus in the pathophysiology of specific OCD symptoms and their response to treatment is still unclear.

Dysfunction of Anterior Midcingulate Cortex in OCD

Cognitive activation and symptom provocation studies have provided the most specific information regarding the roles of cingulate subdivisions in OCD, especially the aMCC. In patients with OCD, the aMCC appears to be hyperactivated preferentially by cognitive tasks that involve conflict monitoring, incongruity, or risk for errors (Maltby *et al.*, 2005; Ursu *et al.*, 2003; van der Wee *et al.*, 2003; Viard *et al.*, 2005), as well as by increasing task load (van den Heuvel *et al.*, 2005b), indicating that OCD patients have exaggerated monitoring for conflict and errors. However, the aMCC may be insufficiently activated during high-level planning and cognitive interference tasks (Nakao *et al.*, 2005a; van den Heuvel *et al.*, 2005b). Treatment with medication or CBT may enhance aMCC activation in OCD patients during certain cognitive tasks (Nakao *et al.*, 2005b; Viard *et al.*, 2005).

The aMCC is also the cingulate subregion most commonly activated in OCD symptom provocation studies. Although their results are somewhat inconsistent, those paradigms that specifically elicited urges to check activated the aMCC more often than those that provoked contamination obsessions, urges to wash, or hoarding obsessions, either in OCD patients or in normal controls. Pathological doubt and obsessive fears of making mistakes can be understood as an exaggerated perception of the risk for errors, consistent with a hyper-responsive aMCC. Contamination obsessions and urges to wash and clean, however, usually do not involve error monitoring. Therefore, contamination-related symptom provocation paradigms would not be expected to activate the aMCC any more in OCD patients than in controls. Indeed, provocation of contamination obsessions and washing compulsions has rarely activated the cingulate, and most often activates the OFC, caudate, and thalamus.

The aMCC, described as limbic motor cortex that governs response selection (see Chapter 1 of this volume), has also been shown to be involved in conscious regulation of emotion. This region is activated both during transient anxiety (Chua *et al.*, 1999; Kimbrell *et al.*, 1999) and during reappraisal and suppression of negative affect (Phan *et al.*, 2005). Efferent projections from the aMCC to the amygdala appear to modulate amygdala activity (Paus, 2001; Chapter 9). Activity in the aMCC is negatively correlated with left amygdala activity when subjects label threatening photographs (Hariri *et al.*, 2002) and was correlated with the magnitude of decrease in negative affect when subjects reappraised their emotional responses to negative photographs (Ochsner *et al.*, 2004; Phan *et al.*, 2005). Thus, in certain OCD patients, aMCC hyperactivity could represent an attempt to control exaggerated amygdala responses to stimuli perceived as threatening (Adler *et al.*, 2000; Breiter *et al.*, 1996; Cannistraro *et al.*, 2004; van den Heuvel *et al.*, 2004). Of course, functional neuroimaging studies cannot determine whether the observed cingulate hyperactivity is the cause or result of exaggerated action monitoring and error perception in OCD, or of OCD symptoms themselves. Hyperactivity of the aMCC in subgroups of OCD patients could be due either to intrinsic pathology within this region, such as deficient GABA-mediated intracortical inhibition (Greenberg *et al.*, 2000), deficient inhibitory input from remote regions, or excessive excitation by a remote area, such as thalamus, OFC, DLPFC, parahippocampal gyrus, or temporal polar cortex (Morecraft *et al.*, 1993).

In sharp contrast, Factor 4 (hoarding/saving symptoms) and early-onset OCD are associated with abnormally *low* baseline activity in the aMCC that correlates with hoarding severity (Busatto *et al.*, 2001; Saxena *et al.*, 2004). Our group has suggested that the

compulsive hoarding syndrome may be a neurobiologically distinct variant of OCD whose symptoms may be mediated by diminished activity in the aMCC (Saxena *et al*., 2004). Functions of the aMCC include monitoring response conflict, error detection, focused attention, executive control, and willed motivation (Awh & Gehring, 1999; Carter *et al*., 1998; Devinsky *et al*., 1995); all cognitive processes that appear to be impaired in compulsive hoarders (Frost & Gross, 1993; Frost *et al*., 2000; Saxena *et al*., 2002). The ACC also plays a key role in decision-making, especially in choosing between multiple conflicting options (Krawczyk, 2002). Thus, low aMCC activity may mediate the remarkable indecisiveness, attentional problems, and other cognitive deficits seen in compulsive hoarders (Frost & Gross, 1993; Frost *et al*., 2000; Hartl *et al*., 2004). In compulsive hoarders and patients with early-onset OCD, deficient aMCC activity could also be due to intrinsic pathology, like a lesion in this area, dysfunction of excitatory, glutamatergic pyramidal neurons, deficient excitation, or excessive inhibition of the aMCC by a remote site.

A Cingulate Circuit Model of the Pathophysiology of OCD

Functional neuroimaging data clearly support pathophysiological theories put forward previously (Baxter *et al*., 1992; Insel, 1988; Modell *et al*., 1989; Rapoport & Wise, 1988; Swerdlow & Koob, 1987) regarding the role of the cortico-striato-pallido-thalamo-cortical circuits in OCD. Alexander *et al*. (1986) described a series of discrete, parallel, neuroanatomical circuits connecting the prefrontal cortex, basal ganglia, and thalamus and this model has been updated by Middleton in Chapter 28 to include open-loop circuitry in the ACC in addition to previously proposed closed-loop circuits. Frontal-subcortical circuits exist and many originate in nearly every part of the cerebral cortex and project to different sub-compartments 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 (Cummings, 1993). The frontal-subcortical circuits involving the OFC, ACC, and MCC appear to mediate voluntary, prospective control of behavior influenced by affectively charged memories and internal information. The current working model of the pathophysiology of OCD 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—mediated by elevated activity along the limbic frontal-subcortical circuits (Baxter *et al*., 1996; Saxena *et al*., 1998, 2001a,b).

Different regions of the striatum receive input from different cortical regions (Alexander *et al*., 1986). The OFC, a limbic neocortical area (Zald & Kim, 1996), projects to the ventromedial caudate nucleus, while the DLPFC (an associative neocortical area) projects to the dorsolateral caudate, and the hippocampal formation projects to the nucleus accumbens. Other circuits involved in motor programming travel through the putamen. Different subregions of the cingulate cortex also send strong projections to different striatal structures. The ACC projects primarily to the limbic parts of the striatum, the anteromedial caudate nucleus, and nucleus accumbens (Eblen & Graybiel, 1995; Mega & Cummings, 1996; Chapter 28). The MCC, involved in response selection and regulation of motor behavior, projects heavily to putamen and only lightly to the caudate nucleus, whereas projections from the PCC, involved in memory and visuospatial functions, have the opposite distribution – heavy in the dorsal caudate and light in the putamen (Baleydier & Mauguiere, 1980). These topographical representations are maintained in a related, but distinct, topology through the globus pallidus, subthalamic nucleus, and thalamus, creating relatively segregated, closed loops for MCC and PCC (Alexander & Crutcher, 1990) and open-loops for ACC (Chapter 28). Direct and indirect pathways through the internal and external segments of the globus pallidus, respectively, are present in each of the loops – motor, associative, and limbic (Joel & Weiner, 1997; Smith *et al*., 1990). These direct and indirect pathways appear to balance each other and allow for both facilitation and suppression of complex motor programs, via their opposite effects on thalamo-cortical activation (Alexander & Crutcher, 1990). Several different thalamic nuclei are involved in these circuits, but those originating in limbic and association cortex pass through subnuclei of the mediodorsal thalamic nucleus (Mega & Cummings, 1994).

A function of these cingulate-subcortical circuits is the execution of 'pre-packaged,' complex, sequence-critical, response behaviors that, to be adaptive, must be executed quickly in response to specific stimuli, to the exclusion of other responses dictated by interfering stimuli (Baxter *et al*., 1996, 2000). Naturally occurring activity along the direct pathway would tend to rivet behavior to the execution of the appropriate responses, 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. Excess 'tone' in the direct relative to the indirect limbic cingulate-subcortical pathways would allow concerns about danger, violence, hygiene, order, sex, etc. to focus attention to themselves, compelling patients to respond

with ritualistic behavior, and result in an inability to switch to other behaviors. Such an imbalance of direct over indirect pathway tone would also produce the abnormally high glucose metabolism and rCBF seen in functional neuroimaging studies of OCD that, in turn, mediate the repetitive, fixed behaviors relating to socio-territorial concerns in OCD (Baxter *et al.*, 1996; Saxena *et al.*, 1998; Saxena & Rauch, 2000).

It is unknown which structures contain neuronal abnormalities that give rise to limbic cingulate-subcortical hyperactivity in OCD, but much evidence points to the striatum (Bartha *et al.*, 1998; Ebert *et al.*, 1996; Rosenberg *et al.*, 2000a,b), which is divided neurochemically into striosome and matrix compartments (Gerfen, 1992). Striosomes receive preferential input from the OFC, ACC, and MCC (Eblen & Graybiel, 1995) and are involved in negative feedback control of activity in the frontal-subcortical circuits (Gerfen, 1992). 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 (Murphy *et al.*, 1997; Snider & Swedo, 2004). Limbic circuit 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 (Jenike *et al.*, 1996; Rosenberg *et al.*, 1998).

The functional neuroimaging data reviewed above indicate that this model of frontal-subcortical circuit overactivity does not apply to all patients with OCD. There are certain subgroups of patients, such as compulsive hoarders and, possibly, patients with early-onset OCD, who do not show frontal-subcortical overactivity. In fact, the severity of OCD Factor 2 (symmetry and order obsessions with arranging, repeating, and counting compulsions) was found in one study to correlate with *lower*, rather than higher, striatal activity (Rauch *et al.*, 1998). Thus, subsets of OCD patients may have hyperactivity involving cingulate cortex circuitry; perhaps those with prominent Factors 1 or 3 symptoms.

Future Directions

Functional neuroimaging studies have advanced our understanding of brain–behavior relationships with respect to OCD greatly, but much is still unknown. No postmortem neuroanatomical studies of OCD exist to delineate its pathophysiology. The roles of various neurochemical systems in OCD are similarly unclear. Although there is some evidence suggesting serotonergic and dopaminergic abnormalities in OCD, there is no direct evidence demonstrating 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.

Future studies will be required to elucidate the role of specific subregions of the cingulate in OCD. One prerequisite is that future studies use standardized nomenclature and definitions for the functional subdivisions of cingulate cortex described in this volume. Another is that they distinguish these subregions in ROI analyses. MRS is one technique that is well suited to test some of the hypotheses about relationships between abnormalities in cingulate subregions and different subtypes of OCD put forth above. MRS studies that measure Glx and GABA should be able to identify localized abnormalities of these neurotransmitters in specific cingulate subregions that would be expected to correlate with the abnormalities of glucose metabolism and rCBF seen in PET and SPECT studies. We would hypothesize low baseline Glx in the aMCC of compulsive hoarders and patients with early-onset OCD, but high baseline aMCC Glx in patients with prominent Factor 3 symptoms.

Symptom provocation studies that target specific OCD symptom dimensions should help delineate the neural substrates of the major symptom factors of OCD, and would help determine which ones are mediated by cingulate dysfunctions. Future studies should use individually tailored, *in vivo* exposure paradigms that measure provoked obsessional distress and urges to perform compulsions separately during brain imaging. Such studies could potentially distinguish the neural mediation of obsessions, compulsions, and resistance of urges. They could also determine whether the findings of prior studies that used picture stimuli to provoke specific OCD symptoms in a broad sample of OCD patients (Mataix-Cols *et al.*, 2004) can be replicated, and whether brain activation patterns differ between different subgroups of patients. We would expect provocation of Factor 1 symptoms to activate the aMCC. Activation of the aMCC should correlate with pathological doubt and urges to check. Pre- and post-treatment PET and SPECT studies that measure the severity of specific OCD symptom factors can help clarify the neural mediation of specific symptom dimensions of OCD their response to treatment, and should be able to determine whether the cingulate mechanisms of response are the same or differ among symptom factors.

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