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IMAGING AND NEUROCIRCUITRY OF OCD

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The history of the living world can be summarized as an elaboration of ever more perfect eyes, within a cosmos in which there is always something more to be seen. (Pierre Teihlard de Chardin, *The Phenomenon of Man*)

Once considered a rare condition, obsessive-compulsive disorder (OCD) is now recognized as a severe and often chronically disabling illness that affects 1% to 3% of the world's population (1–5). The condition is characterized by intrusive ritualistic thoughts, ideas, and behaviors (obsessions and compulsions, respectively) over which the person has little if any control. Recent investigation further suggests that the illness has its onset in childhood and adolescence in at least 80% of all cases, although it often goes undiagnosed until adulthood (6).

In recent years, neuroimaging studies have begun to bridge the gap between our understanding of the neurobiologic underpinnings of OCD and the development of effective clinical assessment measures and treatments for the illness. This is critical because even as use of the selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) has become routine in the treatment of OCD, at least one-third of OCD patients do not respond at all to currently available treatments (7). Many patients who respond to treatment do so only partially; continued functional impairment is the rule. It is the rare patient who experiences complete remission of his or her symptoms. A clearer understanding of the neuropathophysiologic mediation and expression of OCD may result in the identification of new and more effective treatments for this chronic and often crippling illness.

Indeed, this view is supported by many other neurologic and medical conditions for which treatment includes psychosocial and medication interventions acting on specific somatic substrates. Up until the 1930s, epilepsy was considered more a psychiatric than neurologic condition (8,9). Indeed, in the Middle Ages, persons with epilepsy were often believed to be possessed by the devil. Epilepsy carried considerable stigmata and was often a cause for shame; its victims were often considered to be "crazy" and in need of psychiatric treatment. This reflected, in part, a lack of knowledge about the neurobiologic substrates underlying epilepsy. With the advent of the EEG, it became evident that electrical abnormalities in the brain underlie various epileptiform conditions. The EEG also helps guide choice of treatment intervention (10); for example, different medications are used for persons suffering from temporal lobe epilepsy (e.g., carbamazepine) versus those suffering from grand mal seizures (e.g., phenobarbital). Treatment for other medical conditions such as diabetes, rheumatoid arthritis, and asthma also includes psychosocial and medication interventions acting on specific somatic substrates. Although we have not achieved comparable understanding of neuropsychiatric disorders such as OCD, 10 years from now we may have identified 10 different subtypes of OCD characterized by specific neurobiologic abnormalities that may, in turn, necessitate individualized treatment interventions (11). Neuroimaging allows for precise measurement of brain structure, chemistry and function, which can be correlated with both baseline and clinical outcome measures (e.g., Yale-Brown-Obsessive-Compulsive Scale, SSRI, CBT treatment) (12). This very powerful approach is answering hypothesis-driven investigations regarding pathophysiology, psychobiology, and treatment response in psychiatric disorders such as OCD. Brain imaging techniques in conjunction with advances in neuroscience and neuropsychopharmacology can contribute a great deal to the outstanding questions in child psychiatry relevant to enhanced diagnostic rigor and treatment development (13).

In this chapter, the authors review: (a) current neurocircuitry models of OCD that have converged to implicate abnormalities in cortical-striatal-thalamic-cortical circuits (14–20); (b) the relevant neuroimaging techniques utilized in investigating the neurocircuitry of OCD; and (c) neuroimaging studies conducted in OCD patients. The devel-

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opmental implications of these investigations are then discussed and a new clinical neurodevelopmental model of OCD is described as it may relate to treatment development.

NEUROCIRCUITRY OF OCD: CORTICOSTRIATAL CIRCUIT THEORIES

Basal Ganglia

As early as 1931, von Economo (21) described postmortem globus pallidus abnormality in OCD associated with postencephalitic parkinsonism. OCD behaviors are also increased in other basal ganglia disorders, including Huntington disease, Tourette syndrome, pediatric autoimmune neuropsychiatric disorders associated with group A β -hemolytic Streptococcal infections (including Sydenham's chorea), neuroacanthocytosis, and progressive supranuclear palsy (17,22–29). Aberrations in basal ganglia–frontal cortical networks may play an especially critical role in the emergence of OCD symptoms (14,16).

Frontal Cortex

Fronto-striatal abnormalities have been hypothesized to represent the core pathology in OCD (15,16,30-34). Ventral prefrontal cortical regions, particularly anterior cingulate and medial orbital frontal cortex and their striatal target fields, have been most consistently implicated in the pathogenesis and maintenance of OCD (16,31,35-42). This may, in part, reflect the critical role of anterior cingulate and medial orbital frontal cortex in regulation of affect and motivation (31,35-37). Lesions to these brain regions results in the inability to inhibit context inappropriate responses and inappropriate impulse modulation and behavior. Indeed, neuropsychological studies suggest that a deficit in response inhibition abilities may represent a core deficit in OCD (43-48). Neurosurgical lesions (e.g., cingulotomy) have also been demonstrated to be effective in reducing OCD symptoms in treatment-refractory patients (49). In contrast, evidence for abnormalities in other frontal lobe regions (e.g., dorsolateral prefrontal cortex) are much less compelling.

The anterior cingulate and medial orbital frontal cortex and their striatal target fields in ventral striatum receive dense projections from mesiotemporal lobe, particularly the amygdala and hippocampus (31,50). Mesiotemporal structures including the amygdala and hippocampus play an especially important role in processing and responding to the emotional valence of affective stimuli (30,51–55). In fact, animal studies have demonstrated that serotonin reuptake inhibitors known to be effective in the treatment of OCD have particularly potent effects on receptors in the amygdala (56–59). Wise and Rapoport (60) have hypothesized that excess activity in mesial temporal-orbitofrontal and anterior cingulate regions and their striatal target fields could disinhibit particular regions of the thalamus leading to OCD behaviors.

Thalamus

The thalamus is a highly evolved sensory and motor gateway to the cortex that serves as the final subcortical input to frontal cortex and plays a critical role in consciousness, perception, and integration of information (32,61). The thalamus is an important component of frontal and limbic circuits; thalamic lesions result in neuropsychological and behavioral disturbances similar to deficits observed in OCD patients (17,31,62). In fact, "frontal lobe"-type syndromes frequently appear indistinguishable from vascular and degenerative disorders of the thalamus (17). The thalamus serves as a filter in integrating information before it reaches the cortex—a task facilitated by its many cortical and subcortical connections.

When released from the inhibitory influence of the striatum, the thalamus stimulates cortical output. This has led to descriptions of "direct" and "indirect" pathways modulating frontal cortical output to ensure context-appropriate responses (31-33). Although the "direct" pathway releases the inhibitory tonic influence of the striatum, thereby stimulating thalamic stimulation of the cortex so that instinctual and protective hard-wired behaviors are enhanced, the "indirect" pathway facilitates the cortex in shifting sets and responding to new situations on the basis of the particular circumstance and prior stored information by inhibiting the thalamus. Baxter and associates (32) have hypothesized neural hyperactivity in the direct versus indirect pathways and that this imbalance may result in obsessive and compulsive behaviors characteristic of the illness.

Preclinical investigation has demonstrated that compulsive behaviors can be provoked by altering thalamic function (63,64), whereas thalamic stimulation can result in compulsive behaviors in humans (65). This is particularly intriguing because neurosurgical lesion of the thalamus (e.g., partial thalamotomy) has actually been reported to reduce OCD symptoms in treatment-refractory OCD patients (49).

In summary, neurobiologic studies from preclinical and clinical laboratories have consistently implicated a corticostriato-thalamo-cortical network in the pathogenesis of OCD (15,16,32,60,66). Advances in neuroimaging (discussed in the following) provide an unprecedented opportunity for developing a mechanistic understanding of the developmental neurobiology of OCD as it relates to the behaviors that characterize the illness. These methods allow for the direct, *in vivo* and noninvasive "biopsy" of the brain at levels of spatial and temporal resolution heretofore possible only in animal or postmortem human studies. Neuroimaging studies also facilitate our taking advantage of advances in neuroscience and applying them directly to clinical neuropsychiatric conditions such as OCD. Such an approach may ultimately result in new diagnostic and therapeutic approaches with the identification of surrogate neurobiological markers predicting treatment response (or lack, thereof) (66–68). Although a detailed review of brain imaging methodology is beyond the scope of this chapter, a brief review is presented in the following. For more detailed descriptions, the reviewer is referred to relevant textbooks on brain imaging (69,70).

BRAIN IMAGING TECHNIQUES

Neuromorphometry

Newer noninvasive neuroimaging procedures permit measurement of changes in regional brain anatomy, chemistry, and function. Pioneering work in psychiatric neuroimaging has already resulted in findings of critical relevance to psychiatric disorders despite the brief period during which these techniques have been in use (71). For example, less than 15 years ago, measurement of structural abnormalities in neuropsychiatric disorders was limited to postmortem brain studies (70). Understandably, many were (and some remain) skeptical about applying brain imaging to neuropsychiatric disorders such as OCD. This may, in part, reflect the lack of sensitivity of earlier neuroimaging techniques (e.g., skull x-ray and ventriculogram) (70). The emergence of computerized tomography (CT) ushered in a new era of brain research during which evaluation of living tissue would become routine.

Moreover, although many discounted Johnstone and colleagues' (72) CT finding of cerebral ventricular abnormalities in schizophrenia, these currently represent some of the most replicated and best-established findings in psychiatry (69).

Quantitative CT and the more recent emergence of magnetic resonance imaging (MRI), which allows for enhanced three-dimensional (3D) acquisitions, tissue differentiation without putative ionizing radiation risks have revolutionized our ability to conduct precise, in vivo and noninvasive quantitative neuromorphometric studies of regional brain anatomy. These studies are critical because the volume of a brain region of interest in neuropsychiatric disorders has been demonstrated to reflect that region's function (73,74). Volumetric neuroimaging studies are also critical to guide functional, metabolic, and neurochemical studies and can also help characterize neurodevelopmental and degenerative effects of neuropsychiatric disorders (75). Interpretation of functional neuroimaging studies is, therefore, predicated on controlling for volumetric differences between patients and controls as well as psychotropic medication-induced volumetric changes (76-78).

Functional Neuroimaging

Although quantitative measures of brain volume are critical, newer and more sophisticated functional neuroimaging

techniques may be more sensitive in identifying subtle brain abnormalities in neuropsychiatric disorders (79). Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) permit measurement of cerebral blood flow, metabolism, neurochemistry, and receptor function. These techniques have been instrumental in elucidating the pathophysiology of OCD. Both SPECT and PET techniques use ligands labeled with radiation. These putative radiation risks limit their viability in pediatric populations and in longitudinal repeated studies assessing neurodevelopment and neurodegenerative effects. For example, many institutional review boards preclude PET studies in healthy control children. This may, however, become more feasible with advances in methodology including 3D PET, which may reduce radiation exposure significantly. Although radiation risks associated with SPECT are considerably lower than PET, the decreased resolution of SPECT limits its usefulness.

The recent advent of magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) represent powerful approaches for the direct, in vivo and noninvasive measurement of brain chemistry and function without ionizing radiation risks. Recent investigation in OCD suggests that these techniques are very sensitive in identifying brain abnormalities not evident even with sophisticated morphometric MRI (79). In contrast to PET, fMRI allows for enhanced temporal resolution of brain function rather than focusing on measurement of brain activity during a single brief time interval (67). Event-related fMRI allows for second-to-second temporal resolution (80). Newer techniques including magnetoelectroencephalography (MEG) or electroencephalography (EEG) with fMRI studies allow acquisition and analysis brain activity in real-time with a spatial resolution in millimeters and a temporal resolution of milliseconds (81). Although not currently available, this is an active area of investigation and expected to be available in the very near future.

In summary, previous *in vivo* investigation of neuropsychiatric disorders such as OCD was limited by measures that provided only a peripheral index of brain function. Direct assessment of brain was limited to postmortem neuropathologic study or *in vivo* study in animal models. The aforementioned neuroimaging techniques provide an unprecedented opportunity to measure brain anatomy, chemistry, and function to elucidate the neurobiologic underpinnings of neuropsychiatric disorders such as OCD, which may translate into the development of new assessment procedures and treatments. In the following section, we discuss a series of neuroimaging studies that have consistently implicated regional changes in cortico-striatal-thalamic-cortical neural circuitry (66) being involved in the pathogenesis and maintenance of OCD.

NEUROMORPHOMETRY OF OCD (TABLE 113.1)

Global Changes of Ventricles, Cerebral Volume, and Atrophy

Although total brain volume has not been found to differ between OCD patients and controls (76,82–88), Behar and

associates (89) reported significantly increased ventricular brain ratio (VBR) in adolescent OCD patients compared to controls. Rosenberg and co-workers (87) observed significantly increased third ventricular volumes in 19 treatmentnaive, pediatric OCD patients compared to 19 age- and sexmatched controls but no differences in lateral ventricular volume as measured by volumetric MRI. In contrast, Insel

TABLE 113.1. STRUCTURAL NEUROIMAGING STUDIES IN OBSESSIVE-COMPULSIVE DISORDER

	Volumetric Findings						
Structure	Decreased	Increased	No Difference				
Total cerebral volume/ intracranial volume			Giedd et al., 2000 ^a Rosenberg et al., 1997 Gilbert et al., 2000 Aylward et al., 1991 Breiter et al., 1994 Jenike et al., 1996				
Ventricular brain ratios Lateral ventricles		<i>Behar et al., 1984</i> Stein et al., 1993	Robinson et al., 1995 Stein et al., 1997 Insel et al., 1983 <i>Rosenberg et al., 1997 Luxenberg et al., 1998</i> Insel et al., 1983 Kellner et al., 1991 Robinson et al., 1995 Jenike et al., 1996				
Third ventricle		Rosenberg et al., 1997	Aylward et al., 1996 Stein et al., 1997				
Total prefrontal cortex		Grachev et al., 1998 (in 10 PU subregions)	<i>Rosenberg et al., 1997</i> Robinson et al., 1995 Jenike et al., 1996				
Orbital frontal cortex Dorsolateral prefrontal cortex Anterior cingulate cortex	Szeszko et al., 1999	Rosenberg and	Grachev et al., 1998 Rosenberg and Keshavan, 1998 Szeszko et al., 1999				
Posterior cingulate cortex Basal ganglia caudate	<i>Luxenberg et al., 1988</i> Robinson et al., 1995	Keshavan, 1998 Scarone et al., 1992 Giedd et al., 2000ª	Grachev et al., 1998 Rosenberg and Keshavan, 1998 Rosenberg et al., 1997 Kellner et al., 1991				
			Stein et al., 1993, 1997 Aylward et al., 1991, 1996 Jenike et al., 1996 <i>Peterson et al., 2000^b</i>				
Putamen	Rosenberg et al., 1997	Giedd et al., 1995, 2000 ^a Peterson et al., 2000 ^b	Jenike et al., 1996 Aylward et al., 1996				
Globus pallidus		Giedd et al., 2000 ^a Peterson et al., 2000 ^b	Jenike et al., 1996				
Thalamus		Gilbert et al., 2000	Jenike et al., 1996 Giedd et al., 2000ª				
Amygdala	Szeszko et al., 1999		Rosenberg and Keshavan, 1998				
Hippocampus			Rosenberg and Keshavan, 1998 Szeszko et al., 1999 Jenike et al., 1999				
Superior temporal gyrus			Rosenberg and Keshavan, 1998				

Italics indicate studies in the pediatric age-range.

 $^{\circ}$ Studied patients with pediatric autoimmune neuropsychiatric disorders associated with Group A β -hemolytic streptococcal infection.

^bStudy by Peterson et al. included both pediatric and adult subjects. Putamen and globus pallidus were increased in patients with obsessive-compulsive disorder and attention deficit hyperactivity disorder who had increased antistreptolysin O and antideoxyribonuclease B antibody titers.

and colleagues (90) observed no significant differences in VBR between adult OCD patients and healthy comparison subjects. Examination of cortical gray and white matter has, however, demonstrated increased gray-white matter ratios in adult OCD patients (83,84). Such abnormalities could be owing to aberrations in prenatal programmed cell death or postnatal reductions or delays in myelination (84). Recent investigation has suggested abnormalities of postnatal myelination in pediatric OCD patients (91,92).

Striatum

Despite the striatum being posited as a primary site of pathology in OCD (30), structural neuroimaging studies of the caudate nucleus in adult OCD patients have revealed contradictory findings. Scarone and colleagues (93) reported increased right caudate size in OCD patients compared to controls, whereas Robinson and co-workers (85) found bilateral reductions in caudate volume in OCD patients. Four MRI studies have reported no significant differences in caudate size between OCD patients and controls (79,82,94,95). Investigation of the other components of the basal ganglia, including the putamen and globus pallidus, has not demonstrated volumetric differences between adult OCD patients and controls (84,94,96,97). These studies were potentially confounded by several factors including illness chronicity, past treatments, heterogeneity of OCD, and differences in imaging methodology used. Structural imaging studies in children may prove especially instructive because they allow for examination of neurodevelopmental factors and repeated studies for longitudinal assessment.

Nonetheless, structural neuroimaging studies in pediatric OCD patients have not been entirely consistent. Behar and associates' (89) observation of increased VBR in adolescent OCD patients is consistent with reductions in striatal volume (information on striatal volumes was not provided).

More recently, Luxenberg and co-workers (96) reported bilateral reductions in caudate volume in adolescent men with OCD compared to controls using quantitative CT. Using volumetric MRI, two recent investigations (87,98) found no significant differences in caudate volume between treatment-naive pediatric OCD patients and age- and sex-case matched controls. Localized reductions in putamen volume associated with OCD symptom severity but not illness duration, however, were observed in pediatric OCD patients compared to controls (Fig. 113.1). Reduced putamen volumes have been reported in Tourette syndrome (99), a condition frequently associated with OCD symptoms. Putaminal lesions associated with OCD also have been reported in isolated case reports (100,101) and pediatric OCD patients have antibodies directed at the putamen at rates significantly greater than in healthy pediatric comparison subjects (102).

In this regard, it is important to point out that Giedd and associates (24,26) have reported increased volumes in caudate, putamen, and globus pallidus in children with OCD or tics associated with group A β hemolytic streptococcal (GABHS) infections and pediatric patients with Sydenham chorea and associated OCD and tic behaviors compared to healthy children. These conditions are now referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) (103,104) and may represent discrete subtypes of OCD and tic disorders. Increased basal ganglia volumes may be consistent with hypothesized antibody-mediated inflammation of the basal ganglia in poststreptococcal or OCD or tic disorders (103,104). Giedd and colleagues (24,26), however, did not observe an association between basal ganglia size and symptom severity of OCD or tics, suggesting an indirect relationship between basal ganglia size and the pathophysiology of the condition. Allen and associates (104) observed plasmapheresis to be dramatically effective in PANDAS patients in reducing OCD and tic symptom se-



FIGURE 113.1. Measurement of putamen in the axial plane using a manual tracing technique (*left*). Putamen volume by group (*right*). OCD, obsessive-compulsive disorder. Adapted from Rosenberg DR, Keshavan MS, O'Hearn KM, et al. Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. *Arch Gen Psychiatry* 1997;54: 824–830.



FIGURE 113.2. Sequential magnetic resonance imaging of basal ganglia volumes in a male adolescent undergoing plasma exchange for infection-related obsessive-compulsive disorder. Reprinted from Giedd JN, Rapoport JL, Leonard HL, et al. Case study: acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. J Am Acad Child Adolesc Psychiatry 1996;35(7): 913–915.

verity. In fact, Giedd and colleagues (25) conducted serial MRI scans and observed a striking relationship among basal ganglia volume, OCD symptom severity, and treatment with plasmapheresis in an adolescent with autoimmune OCD (PANDAS) (Fig. 113.2). Recently, Peterson and colleagues (27) reported that higher antistreptolysin O antibody titers were associated with larger basal ganglia volumes in OCD patients with chronic or recurrent streptococcal infections. This finding was not specific to OCD; however, as higher antibody titers were also associated with enlarged basal ganglia volumes in attention deficit hyperactivity disorder (ADHD) patients with chronic or recurrent streptococcal infections (Fig. 113.3; Table 113.2). In fact, Peterson and colleagues (27) found robust associations between diagnosis of ADHD and titers of antistreptolysin O and antideoxyribonuclease B titers, whereas no such association was seen between antibody titers and a diagnosis of OCD or chronic tic disorders. We also do not know the impact of chronic recurrent or streptococcal infections on basal ganglia volume in children who do not develop OCD, tic disorders, or ADHD. Further study is clearly warranted.

Taken together, these findings underscore the need for standardization of research studies in patients with OCD and controlling for potential confounds of comorbidity, treatment effects, and illness duration. It also illustrates how brain imaging is exploiting advances in developmental neurobiology with important implications for neurodiagnostic assessment and treatment development. A neurodevelopmental perspective is equally critical as illustrated in the following.

Prefrontal Cortex

Morphometric MRI measurement of the prefrontal cortex has also yielded conflicting findings. Total prefrontal cortical volumes have not been found to differ between adult OCD patients and controls (84,85,105). Jenike and associates (84) did observe increased opercular volumes in OCD patients. Grachev and co-workers (105) reanalyzed the 10 adult female OCD patients and matched controls studied by Jenike and associates (84) using a sophisticated topographic parcellation method (106) and found an increase in six right frontal and four left parcellation units in OCD patients. Anterior cingulate, orbitofrontal, and opercular cortical volumes did not differ significantly between OCD patients and controls. Grachev and associates (105) also noted a significant correlation between increased volume of right inferior frontal pars triangularis and right midfrontal cortical volumes and poor cognitive performance on nonverbal immediate recall testing. More recent investigation (107) found localized reduced bilateral orbital frontal volumes in OCD patients versus healthy comparison subjects. Superior frontal gyrus and anterior cingulate volumes did not differ between OCD patients and controls.

Consistent with findings in adults, Rosenberg and colleagues (87) reported no significant differences between treatment-naive pediatric OCD patients and controls in total prefrontal cortical volume; however, a neurocognitive study of a similar sample of pediatric OCD patients (44) revealed a selective deficit in the core prefrontal cognitive function, neurobehavioral response inhibition, with no abnormalities in working memory (delayed response) or preparatory set (Fig. 113.4). Monkey studies and human clinical studies suggest that ventral prefrontal cortex plays a critical role in mediating the suppression of context inappropriate responses (17,108-116), whereas dorsal prefrontal cortex may play a more specific role in mediating delayed response and preparatory set (117,118). Subsequent investigation demonstrated increased corpus callosal area in treatment-naive pediatric OCD patients compared to controls,



particularly in the regions of the genu and splenium (91). The corpus callosum connects the cerebral hemispheres so that the genu connects ventral prefrontal cortex and the striatum, whereas the splenium connects temporal lobe regions (119,120).

Rosenberg and associates (91) also noted that the agerelated increase in corpus callosal area in healthy children and adolescents was absent in OCD patients (Fig. 113.5A). Controls achieved comparable corpus callosal areas to their age-matched OCD counterparts between 16 and 18 years of age, which is consistent with prior findings of no significant differences in corpus callosal area between adult OCD patients and controls (83,84). Postnatal reduction or delay in myelination in OCD has been hypothesized to be involved

FIGURE 113.3. Association of titers, diagnoses, and basal ganglia volumes. The interaction of antistreptolysin 0 titers with attention-deficit/hyperactivity disorder and obsessive-compulsive disorder diagnoses are presented graphically. Basal ganglia volumes are adjusted for the effects of all independent variables in the multivariate analysis of covariance (Table 113.2); hence, the residuals of the volumes after the adjustment can be positive or negative. These volume residuals are plotted against the raw antistreptolysin 0 values for each of the relevant diagnostic groups. Titers are plotted in dark circles for the noted diagnostic group and in lighter diamonds for all other subjects. Reprinted from Peterson BS, Leckman JF, Tucker D, et al. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. Arch Gen Psychiatry 2000;57:364–372.

in the pathogenesis of OCD (84). In support of this hypothesis, MacMaster and colleagues (92) reported increased signal intensity localized to the genu region of the corpus callosum in pediatric OCD patients compared to controls. Increased genu area in pediatric OCD patients could be related to excess myelin sheath thickness (92). An alternative explanation is abnormal pruning or reduction of neural elements within the corpus callosum. This may be less likely because neuronal apoptosis occurs very early in development (121), whereas myelinization takes place during the peak periods of onset of pediatric OCD (122).

Subsequent investigation has revealed significantly increased ventral prefrontal cortical volumes in anterior cingulate cortex in 21 treatment-naive pediatric OCD patients

Independent Variable	Basal Ganglia		Type 3 Sum of Squares	F ^a	P ^b	Independent Varible	Basal Ganglia		Type 3 Sm of Squares	F ^a	P ^b
Age	Caudate	R	185 622.2	0.70	.41	ASO titer	Caudate	R	77 976.8	0.29	.59
		L	329 784.1	1.16	.28			L	163 312.5	0.57	.45
	Putamen	R	403 527.5	1.82	.18		Putamen	R	719 418.1	3.25	.07
		L	1 949 333.2	9.24	.003			L	162 392.0	0.77	.38
	GP	R	68 399.0	1.80	.18		GP	R	124 003.6	3.27	.07
		L	1426.6	0.04	.85			L	311 963.2	7.78	.006
Sex Cauda Putam GP	Caudate	R	26 436.7	0.10	.75	$ASO \times CTD$	Caudate	R	14 529.1	0.05	.81
		L	20 262.5	0.07	.79			L	888.4	0.003	.96
	Putamen	R	41 336.3	0.19	.67		Putamen	R	479 307.9	2.16	.14
		L	3410.7	0.02	.90			L	564 780.3	2.68	.10
	GP	R	75 676.4	2.0	.16		GP	R	2594.2	0.07	.79
		L	3287.1	0.08	.77			L	6767.6	0.16	.69
Cerebral C volume F	Caudate	R	9 399 861.6	35.47	.0001	$ASO \times OCD$	Caudate	R	17 949.4	0.07	.79
		L	9 539 401.1	33.61	.0001			L	31 020.8	0.11	.74
	Putamen	R	14 425 018.5	65.15	.0001		Putamen	R	554 597.5	2.51	.12
		L	11 771 290.4	55.82	.0001			L	180 705.5	0.86	.36
	GP	R	2 509 899.4	66.13	.0001		GP	R	47 453.5	1.25	.27
		L	2 017 826.0	50.34	.0001			L	271 584.3	6.78	.01
CTD	Caudate	R	447 291.1	1.69	.20	ASO imes ADHD	Caudate	R	19 359.1	0.07	.79
		L	740 785.4	2.61	.11			L	44 599.2	0.16	.69
	Putamen	R	2 122 069.4	9.58	.003 ^c		Putamen	R	382 533.3	1.73	.19
		L	795 020.5	3.78	.05 ^c			L	1 284 129.5	6.10	.01
	GP	R	16 303.4	0.43	.51		GP	R	320 157.8	8.44	.005
		L	52 985.6	1.32	.25			L	121 207.3	3.02	.08
OCD	Caudate	R	2751.9	0.01	.92	ASO imes ADHD	Caudate	R	24 437.7	0.09	.76
		L	7.9	0.00	.99	imes OCD		L	7602.8	0.03	.87
	Putamen	R	154 842.7	0.70	.41		Putamen	R	713 789.6	3.22	.07
		L	34 663.3	0.16	.69			L	1 223 781.8	5.80	.01
	GP	R	43 768.0	1.15	.28		GP	R	272 664.1	7.18	.009
		L	73 499.1	1.83	.18			L	98 375.9	2.45	.12
ADHD	Caudate	R	2851.2	0.01	.92	Error	Caudate	R	26 502 840.2	_	_
		L	125.9	.000	.98			L	28 386 288.6	_	
	Putamen	R	37 475.8	0.17	.68		Putamen	R	22 140 347.0	_	_
		L	56 711.5	0.27	.61			L	21 087 448.1	_	_
	GP	R	179 236.2	4.72	.03 ^d		GP	R	3 795 193.9	_	
		L	103 525.9	2.58	.11			L	4 008 318.0	—	

TABLE 113.2. ANTIBODY AND DIAGNOSIS ASSOCIATIONS WITH BASAL GANGLIA VOLUMES

 a df = 1 for all except error, where df = 100.

^bP values are Bonferroni, adjusted.

^cThe estimated marginal mean of the right and left putamen is smaller in subjects with CTD.

^dThe estimated marginal mean of the right globus pallidus in smaller in subjects with ADHD.

ADHD, attention-deficit/hyperactivity disorder;

ASO, antistreptolysin O; CTD, chronic tic disorder; ellipses, error terms; GP, globus pallidus; L, left; OCD, obsessive-compulsive disorder; R, right; x, statistical interaction of adjacent terms; lighter shading indicates P < .05; Overall, $R^2 = .34$.

Reprinted from Peterson BS, Leckman JF, Tucker D, et al. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch Gen Psychiatry* 2000;57:364–372. Multivariate analysis of variance assessing the strength of the association of diagnosis-by-antibody interactions with basal ganglia volumes.

compared to age and sex case-matched controls (88) (Fig. 113.5B). Increased anterior cingulate volumes were inversely correlated with reduced striatal volumes in OCD patients. Oculomotor response inhibition abnormalities also correlated with increased anterior cingulate volumes and reduced striatal volumes in pediatric OCD patients

(Fig. 113.5C). No significant differences were observed in posterior cingulate or dorsolateral prefrontal cortical volumes between pediatric OCD patients and controls (88). Thus, prefrontal cortical abnormalities in pediatric OCD may be localized to ventral prefrontal anterior cingulate circuits, particularly in younger patients.



FIGURE 113.4. Mean response suppression failures for nondepressed, psychotropic medication-naive pediatric patients with obsessive-compulsive disorder (OCD) and normal controls performing the antisaccadic task. Lines through distributions represent the mean value. Asterisks indicate P = .01; dagger, P = .02. Reprinted from Rosenberg DR, Averbach DH, O'Hearn KM, et al. Oculomotor response inhibition abnormalities in pediatric obsessive-compulsive disorder. Arch Gen Psychiatry 1997;54: 831–838.

Temporal Cortex

The temporal limbic structures, comprising the amygdala and hippocampi are critically involved in regulating emotion in both health and disease (123–125). This function undergoes striking changes throughout childhood, adolescence, and early adulthood (126,127). Medial orbital frontal cortex, anterior cingulate cortex, and ventral striatum receive dense afferent projections from limbic regions, including the amygdala and hippocampus (31,128).

Initial MRI investigation in adult OCD patients and healthy controls revealed no significant differences in mesiotemporal lobe brain structures (84,95,105). More recent investigation by Szesko and colleagues (107) using criteria from postmortem histologic analysis (129) with a semiautomated computerized system (130) demonstrated bilateral reductions in amygdala volume in OCD patients as compared to healthy controls. No significant differences between OCD patients and controls were observed in the hippocampus.

Recent investigation in pediatric OCD patients has also implicated the amygdala (87,91). Specifically, Rosenberg and associates (87) reported reduced putamen but not caudate volumes in treatment-naive pediatric OCD patients. The putamen receives more projections from the amygdala than the caudate and reduced putamen volumes are observed after temporal lobe lesions (131). In pediatric OCD patients, a positive correlation was observed between putamen and amygdala volumes but not amygdala and caudate volumes (87). Subsequent investigation also revealed significant differences between pediatric OCD patients and controls in the size of the splenium, the region of the corpus callosum that connects temporal-limbic regions (91). However, direct measurement of whole temporal lobe, amygdala, and hippocampal and superior temporal gyrus volumes failed to reveal any significant differences between pediatric OCD patients and age- and sex-matched controls (88). Perhaps, volumetric abnormalities of the amygdala only become apparent later in development. Alternatively, our methods may not have been sensitive enough to distinguish

subtle abnormalities in this circuitry. It should be noted that it is often difficult to distinguish the amygdala and hippocampus even at the histologic level (132).

Thalamus

Volumetric abnormalities in ventral prefrontal cortex and the striatum in pediatric OCD patients led to our studying the thalamus, the final subcortical input to frontal cortex. Jenike and co-workers (84) reported no significant differences in thalamic volume in adult OCD patients, many of whom had been treated with psychotropic medication and had long-term illness duration. In contrast, Gilbert and coworkers (76) demonstrated significantly increased thalamic volume as measured by volumetric MRI in 21 treatmentnaive, pediatric OCD patients compared to 21 age- and sex-matched healthy controls (Fig. 113.6). As in the corpus callosum and anterior cingulate cortex, volumetric abnormalities in the thalamus were particularly pronounced in younger patients with OCD (Fig. 113.5D). After monodrug therapy with the SSRI, paroxetine, thalamic volumes decreased to levels comparable to those observed in healthy children. Reduction in thalamic volume was positively correlated with reduction in OCD symptom severity with increased pretreatment thalamic volume predicting better response to paroxetine treatment (Fig. 113.7). In contrast, thalamic volume did not decrease after 12 weeks of CBT in 11 treatment-naive pediatric OCD patients who received no adjunctive medication treatment (133). No significant changes were observed in total brain volume, the striatum, or anterior cingulate cortex with either CBT or paroxetine treatment. In view of serotonin's critical role in thalamocortical development and activity (134), thalamic volumetric reductions in pediatric OCD patients may be specific to SSRI treatment as opposed to a generalized treatment response or spontaneous resolution of symptoms.

It should be noted that the techniques utilized in these investigations were unable to discriminate specific subdivisions of the thalamus. Thus, we were unable to localize changes to specific thalamic target fields. The dorsomedial



FIGURE 113.5. A: Corpus callosum area (A) in pediatric (left [•, normal controls; , --, OCD patients.]) and adult patients with obsessive-compulsive disorder (right). Reprinted from Rosenberg DR, Keshavan MS, Dick EL, et al. Corpus callosal morphology in treatment naive pediatric obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 1997;21: 1269–1283. Breiter HC. Retrocallosal white matter abnormalities in patients with obsessive-compulsive disorder. Arch Gen Psychiatry 1994;51:663–664. **B:** Anterior cingulate volume in pediatric (left $[\circ, \dots, controls (r = .45, p = .055); \bullet, \dots, OCD patients (r = -.12, p = .62)])$ and adult patients with obsessive-compulsive disorder (right). Reprinted from Rosenberg DR, Keshavan MS. Toward a neurodevelopmental model of obsessive-compulsive disorder. Biol Psychiatry 1998; 43:623-640. Szeszko PR, Robinson D, Alvir JM et al. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. Arch Gen Psychiatry 1999;56:913–919. C. Response suppression failures as a function of age for nondepressed, psychotropic medication-naive pediatric patients with OCD and normal controls performing the antisaccadic task. Note the marked inverse correlation between age and total number of response suppression errors in patients with OCD and a trend for such an effect in controls. (•, --, normal controls $[r = -.44, p = .07; \Box, -$ OCD patients [r = -.54, p = .02]). Reprinted from Rosenberg DR, Averbach DH, O'Hearn KM, et al. Oculomotor response inhibition abnormalities in pediatric obsessive-compulsive disorder. Arch Gen Psychiatry 1997;54:831–838. (Figure continues.)



FIGURE 113.5. Continued. **D**: Thalamic volume in pediatric (*left* [•, ——, healthy control (r = .012, p = .959); •, ……, pediatric OCD (r = .425, p = .055)]) and adult patients with obsessive-compulsive disorder (*right*). Adapted from Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric obsessive-compulsive disorder patients taking paroxetine. Arch Gen Psychiatry 2000;57(5):449–456. Jenike MA, Breiter HC, Baer L, et al. Cerebral structural abnormalities in obsessive-compulsive disorder. A quantitative morphometric magnetic resonance imaging study. Arch Gen Psychiatry 1996;53:625–632.

nucleus of the thalamus has been most implicated in the pathogenesis of OCD (15,31). Morphometric analysis of regional subdivisions of the thalamus is currently an active area of investigation in our laboratory.

In summary, although not entirely consistent, structural neuroimaging studies implicate abnormalities in corticostriato-thalamo-cortical circuits. The neural network dysplasia of reduced striatal volumes and increased ventral prefrontal and thalamic volumes in treatment-naive pediatric OCD patients is especially intriguing. Rosenberg and Keshavan (88) have hypothesized that a dysplasia in postnatal synaptic pruning may be involved resulting in excess pruning in the striatum and reduced or delayed pruning in ventral prefrontal cortex and the thalamus in pediatric OCD,



34 Thalamus Volume (cc) 30 CY-BOCS Score 26 9 22 8 18 14 6 8 10 12 2 4 Baseline Weeks Mean mg/day paroxetine 10.00 19.00 26.00 35.00 45.00 50.00 Thalamic Volume Obsessive-Compulsive Scale Score Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

FIGURE 113.6. Thalamic volume by diagnostic and treatment condition. Groups not sharing the same letter are significantly different at P < .05. Adapted from Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric obsessive compulsive disorder patients taking paroxetine. Arch Gen Psychiatry 2000;57(5):449–456.

FIGURE 113.7. Decrease in thalamic volume associated with reduction in Obsessive-Compulsive Score of the Children's Yale-Brown Obsessive-Compulsive Scales. Reprinted from Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric obsessive-compulsive disorder patients taking paroxetine. *Arch Gen Psychiatry* 2000;57(5):449–456.

which may be owing to abnormalities in glutamatergic-serotonin neurotransmission. Although morphometric brain imaging studies are instructive, functional neuroimaging studies that actively drive the system and can measure brain chemistry and receptor function may be more sensitive in their ability to detect more subtle and localized abnormalities in brain circuitry (79).

FUNCTIONAL NEUROIMAGING STUDIES OF OCD

Functional Neurocircuitry of OCD

Although structural neuroimaging studies measure the brain in the resting or neutral state, functional neuroimaging procedures including PET, SPECT, and fMRI allow for localized measurement of dynamic rather than static brain function by measurement of regional cerebral blood flow, glucose metabolism, and brain activation (135). To date, most studies have assessed function over a period of seconds to minutes during single session studies so that the temporal dimension has been relatively unexplored. Recent advances are beginning to permit "real-time" analysis of brain function in response to differential stimulation and diagnostic and treatment conditions. This allows for a connectionist approach to brain circuitry and not simply monitoring whether a certain region of interest activates but when and for how long. Such an approach is especially promising for repeated longitudinal assessment of OCD patients before, during, and after treatment intervention.

PET and fMRI studies suggest excess activity in the caudate nucleus, orbitofrontal cortex, thalamus, and amygdala in OCD (38,42,66,136–141). Symptom provocation of OCD symptoms using individually tailored noxious stimuli in adult OCD patients results in an increase in regional cerebral blood flow and activation in these regions (42,140, 141) (Fig. 113.8). It is not entirely clear, however, whether increased activity in these circuits is specific to OCD or



FIGURE 113.8. Results for one normal subject (left) and one patient with obsessive-compulsive disorder (right) (normal subject 2 and patient 9 [trial B]), juxtaposed for comparison. The gradient echo functional data are shown as a – log (p) map (Kolmogorov-Smirnov statistic) in color, superimposed over a T₂-weighted high-resolution instascan image in gray tone, for anatomic reference. Twelve contiguous slices are shown for each subject. The threshold for the control subject is at a lower level to emphasize the absence of activation, while the patient's threshold is at a more stringent level ($P < 10_{-7}$, approximating Bonferroni-corrected P < .01). A, eye movement; B, middle frontal cortex; C, inferior frontal cortex; D, cingulate cortex. Reprinted from Breiter HC, Rauch SL, Kwong KK, et al. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch Gen Psychiatry 1996;53:595–606. See color version of figure.



FIGURE 113.9. Positron emission tomography (PET) statistical parametric map of provoked minus control conditions for pooled data from three anxiety disorders. Horizontal slices from the statistical parametric map, at 16 and 4 mm inferior to the anterior commissure-posterior commissure plane respectively, are oriented according to neuroimaging convention (top, anterior; bottom, posterior; right, left; left, right), and each is displayed in two ways. In the upper panels, Z-score values are illustrated via a Sokoloff color scale. White dashed outlines reflecting the boundaries of brain regions of interest, as defined via a digitized version of the Talairach atlas, are superimposed for anatomic reference; solid lines demarcate the boundaries of the whole brain slice. In the lower panels, contiguous pixels exceeding a Z-score threshold of 3.5 (corresponding to approximately P < .05, corrected for multiple comparisons) are shown in red. The findings are superimposed over a structural (T2-weighted) magnetic resonance image transformed to Talairach space for approximate anatomic reference. The magnetic resonance reference image is from a nominally normal subject, who did not participate in these PET studies. Reprinted from Rauch SL, Savage CR, Alpert NM, et al. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 1997;42(6): 446–452. See color version of figure.

 $Z \approx 3.5$

 $Z \simeq 3.6$

represents a nonspecific finding generalized to all anxiety states (142). For example, increased regional cerebral blood flow in frontal cortex has been found to be associated with anxiety in OCD patients (143,144). In healthy adult volunteers, cholecystokinin induces anxiety with increased regional cerebral blood flow in anterior cingulate and the amygdala, whereas anticipation of an anxiety-provoking stimulus has been associated with increased activation of orbital frontal cortex (145). Therefore, Rauch and associates (146) reviewed pooled data from their PET symptom provocation studies of patients with OCD, simple phobia and posttraumatic stress disorder in an effort to determine which patterns of activation were specific to OCD and which were generalized across different anxiety disorders. They found that activation of paralimbic circuits, including posterior medial orbital frontal cortex, anterior cingulate, and temporal limbic regions were associated with all anxiety conditions and not specific to OCD. In contrast, activation of anterior orbital frontal cortex and the caudate nucleus were specific to OCD, suggesting that these regions may be primary loci of abnormality in the illness (Fig. 113.9).

Functional Neuroimaging Studies in OCD: Implications for Treatment Development

Recent investigation suggests that differential baseline patterns of brain activity in OCD patients may predict differential response to specific treatment interventions (e.g., CBT,



FIGURE 113.10. Positron emission tomography studies demonstrating increased right caudate glucose metabolism in a patient with obsessive-compulsive disorder compared to a healthy volunteer (*top*). Note the significant decrease in right caudate glucose metabolism after pharmacotherapy (*middle*) and cognitive behavioral therapy (*bottom*). Reprinted from Schwartz JM. Brain lock. New York: HarperCollins, 1996. Baxter LR, Schwartz JM, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49:681–689. See color version of figure.

SSRI) (147). For example, PET scans performed before and after 10 weeks of treatment with either CBT or the SSRI, fluoxetine have identified significant and comparable reductions in right caudate glucose metabolism associated with reduction in OCD symptom severity (38,148) (Fig. 113.10). Pathological correlations among orbital frontal cortex, the caudate nucleus and the thalamus were observed in pretreatment OCD patients but not in healthy volunteers. These pathologic correlations were eliminated after effective treatment with either SSRI or CBT. Subsequent



FIGURE 113.11. Mean pretreatment and posttreatment metabolic ratios (\pm SD) in right anterior lateral orbital frontal cortex (ALOFC) and right caudate, normalized to ipsilateral hemisphere (ROI/Hem), in responders versus nonresponders to paroxetine. There was a significant difference in the magnitude of change in right ALOFC/Hem between responders (1.11 \pm .05 pretreatment to 1.02 \pm 0.05 posttreatment) and nonresponders (1.10 \pm .06 pretreatment to 1.07 \pm .08 posttreatment). Mean right Cd/Hem decreased significantly in treatment responders (1.27 \pm .06 to 1.22 \pm .05) but not in nonresponders (1.23 \pm .04 to 1.24 \pm .05). **P* = .04; ***P* = .01). Reprinted from Saxena S, Brody AL, Maidment KM, et al. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 1999;21:683–693.

analysis of this data (38,148) has demonstrated that specific patterns of metabolic activity in left orbital frontal cortex predicted response to CBT and the SSRI, fluoxetine (68). Specifically, decreased left orbital frontal-to-hemisphere metabolic ratios at baseline predicted better response to fluoxetine, whereas increased left orbital frontal-hemisphere metabolic ratios at baseline predicted better response to CBT. Saxena and colleagues (147) has extended this finding in OCD patients treated with paroxetine noting significant decreases in glucose metabolism in right anterior orbital frontal cortex and the right caudate nucleus in treatment responders but not in nonresponders (Fig. 113.11). Decreased metabolic activity in the left and right orbital frontal cortex predicted better response to paroxetine with greater reduction in OCD symptom severity (Fig. 113.12).

It should be noted, however, that functional imaging data sets have not been entirely consistent in OCD patients studied before and after treatment intervention. Benkelfat and colleagues (149), for example, observed a significant decrease in caudate and anterior orbital frontal glucose metabolism but only the decrease in caudate metabolism was associated with reduction in OCD symptom severity. In contrast, Swedo and co-workers (150) reported no change in caudate metabolic activity after 2 months of clomipramine treatment in OCD patients with childhood onset of



illness. Decreased baseline right orbitofrontal and anterior cingulate metabolic rates, however, did predict better response to clomipramine treatment. Rubin and associates (151) also observed no caudate metabolic changes before and after SSRI treatment but found that decreased metabolism in orbitofrontal cortex before treatment predicted greater reduction in OCD symptom severity.

Strikingly, there have been no published functional neuroimaging studies in children or adolescents with OCD. Techniques such as fMRI may be especially relevant to the study of childhood populations because there are no putative ionizing radiation risks facilitating repeated study for longitudinal follow-up with a neurodevelopmental perspective. This is an active area of investigation in our laboratory where preliminary symptom provocation modeling investigation of adult OCD patients (42,141) has demonstrated increased activation in ventral prefrontal–striatal circuitry (unpublished data). This is especially relevant in view of recent clinical neurodevelopmental models of OCD (88).

Taken together, functional neuroimaging studies are already beginning to integrate and translate advances in neuroscience into treatment development so that specific neural network activations might help predict patients more (or less) likely to respond to a particular treatment (e.g., CBT or SSRI) (147). Recent advances allowing for the noninvasive real-time measurement of brain activity provide an unprecedented window of opportunity for unlocking the mechanisms underlying the pathogenesis of OCD with important implications for treatment development. **FIGURE 113.12.** A: Scatter plot of pretreatment glucose metabolic rate in left orbitofrontal cortex, normalized to ipsilateral hemisphere (left OFC/Hem), and change in Y-BOCS score after paroxetine treatment (Kendall's tau = -.39, P = .01); **B**: Scatter plot of pretreatment glucose metabolic rate in right orbitofrontal cortex, normalized to ipsilateral hemisphere (right OFC/Hem), and change in YBOCS score after paroxetine treatment (Kendall's tau = -.35, P = .02). Reprinted from Saxena S, Brody AL, Maidment KM, et al. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 1999;21:683–693.

NEUROCHEMICAL STUDIES IN OCD

Neuronal Viability

To our knowledge, there have only been four neuroimaging studies directly measuring brain chemistry in OCD. Proton magnetic resonance spectroscopy (1-H MRS), which can measure compounds including the neuronal marker, *N*-ace-tyl-aspartate (NAA) (152), cytosolic choline containing compounds (Cho), glutamatergic compounds including glutamate, glutamine and GABA (Glx), creatine/phosphocreatine (Cr), and myoinositol (mI). Like fMRI, there are no ionizing radiation risks, making it a particularly child-friendly technique facilitating longitudinal monitoring of patients before and after treatment intervention.

Prior investigation in adult OCD patients and those with epilepsy has found that 1-H MRS NAA measurement may be a more sensitive method for identifying neuronal dysfunction than morphometric MRI assessment (79,153). Reduced striatal NAA levels without striatal volumetric differences were observed in OCD patients compared to controls, suggesting that 1-H MRS NAA measurement can detect neuronal loss at a magnitude undetectable by morphometric MRI (79). Ebert and colleagues (154) also reported reduced NAA/Cr levels in the striatum and anterior cingulate cortex but not parietal white matter of adult OCD patients. Volumetric data for the regions of interest were not provided.

Fitzgerald and co-workers (155) compared 11 treatmentnaive pediatric OCD patients and 11 age- and sex-casematched healthy comparison subjects and found localized



lateral thalamus (*B*). Individual peaks for choline compounds (Cho), creatine/phosphocreatine (Cr), and *N*-acetylaspartate (NAA) were resolved from the original spectrum, leaving a residual. NAA/ (Cr + Cho) metabolite ratios by group (*bottom*) for left (*A*) and right (*B*) medial thalamus. OCD, obsessive- compulsive disorder. Adapted from Fitzgerald KD, Moore GJ, Paulson LD, et al. Proton spectroscopic imaging of the thalamus in treatment-naive pediatric obsessive-compulsive disorder. *Biol Psychiatry* 2000;47:174–182.

functional neurochemical marker abnormalities in right and left medial but not lateral thalamus. Reduced NAA/Cho + Cr levels associated with OCD symptom severity were observed in OCD patients compared to controls (Fig. 113.13). This is intriguing because the dorsomedial nucleus of the thalamus has been especially implicated in the pathogenesis of OCD (15).

Neuronal dysfunction or loss in specific fronto-striatalthalamic circuits in OCD could be related to excess brain activity measured in this circuitry with functional neuroimaging (154). Moreover, reduced NAA levels in fronto-striatal-thalamic regions may result from increased glutamatergic afferent projections to the thalamus and striatum (79,156). Excess glutamatergic afferent input could be neurotoxic to fronto-striatal neurons and, thereby, result in reduced NAA levels.

Glutamatergic Dysfunction in OCD

Rosenberg and Keshavan (88) hypothesized that anatomic and functional abnormalities in cortico-striatao-thalamocortical networks may result from disruptions in gluta-

matergic modulation of serotonin neurotransmission. The majority of axon terminals in the basal ganglia are glutamatergic afferents (31,157,158), with the caudate nucleus receiving an especially massive glutamatergic innervation from ventral prefrontal cortex (15,159,160). Ablation of frontal cortex results in a dramatic reduction in caudate glutamate concentrations (159,161). Becquet and associates (160) have shown that glutamate exerts a potent inhibitory effect on serotonin release in the caudate nucleus. Conversely, serotonergic neurons can modulate glutamate release (160) with stimulatory 5-HT2a receptors on GABAergic interneurons inhibiting glutamatergic projections from ventral prefrontal cortex to the striatum and thalamus (158). Increased glutamatergic afferent input from ventral prefrontal cortex to the striatum and thalamus, therefore, may be consistent with increased activation in this circuitry as measured by functional neuroimaging (141) and be related to the pathogenesis and maintenance of OCD. Chronic treatment with SSRIs results in a marked increase in 5-HT release in orbital frontal cortex of guinea pigs (162). SSRI treatment may, therefore, stimulate 5-HT2a receptors with consequent alterations in serotonergic release from cell bod-

В



FIGURE 113.14. Illustration of cortico-striato-thalamo-cortico network in obsessive-compulsive disorder. Neurotransmitters: Glu, Glutamate; GABAgamma-aminobutyric acid; DA, dopamine; 5-HT, serotonin. Brain regions: AC, anterior cingulate; RN, raphe nucleus; SN, substantia nigra; Thal, thalamus; TLC, temporal lobe cortex; VPFC, ventral prefrontal cortex; VS, ventral striatum; VT, ventral tegmentum. Adapted from Rosenberg DR, Keshavan MS. Toward a neurodevelopmental model of obsessivecompulsive disorder. *Biol Psychiatry* 1998;43: 623–640.

ies in frontal cortex, which would alter cortico-striato-thalamic glutamate projections (Fig. 113.14).

Rosenberg and co-workers (98) recently reported significantly increased glutamatergic concentrations in the caudate nucleus but not occipital cortex of 11 treatment-naive pediatric OCD patients compared to 11 age- and sex-matched healthy controls (Fig. 113.15). After 12 weeks of monodrug therapy with paroxetine, a significant decrease in caudate but not occipital glutamatergic concentrations was observed (Fig. 113.16). Decrease in caudate glutamatergic concentrations was associated with reduction in OCD symptom severity so that higher pretreatment caudate glutamatergic concentrations predicted better response to paroxetine (Fig. 113.17). An active area of investigation in our laboratory involves comparisons of the impact of CBT, SSRI, and combination therapy on glutamatergic concentrations in the caudate and other brain regions as well as measuring the long-term stability of these changes (e.g., do changes persist after medication is discontinued?).

Findings of increased caudate glutamatergic concentrations that decreased after paroxetine treatment are consistent with functional neuroimaging studies that have reported increased metabolic rates, regional cerebral blood flow, and brain activation that decreased after SSRI treatment (38,147). Glutamatergic afferent terminals influence brain glucose metabolism so that regional brain glucose metabolism parallels glutamatergic activity (163). Serotonin agonists have also been shown to reduce glucose metabolism (164). Taken together, these data suggest a reversible glutamatergically mediated dysfunction in cortico-striato-thalamo-cortico circuitry.

Serotonergic Role in OCD

Perhaps the most compelling evidence for a serotonergic role in OCD comes from investigation that has consistently found serotonin reuptake inhibitors to be effective in reducing OCD symptoms, whereas medications affecting norepinephrine and dopamine appear to be less effective (165). Indirect support for the serotonin hypothesis of OCD comes from a plethora of platelet, cerebrospinal fluid (CSF), and pharmacologic challenge studies suggesting a serotonergic role in OCD. Platelet 3-H imipramine binding sites are considered to be putative markers of 5-HT function and are quite similar to those on presynaptic 5-HT neurons (166). Although a number of studies have reported decreased 5-HTPR in platelets of medication-free OCD patients (166–170), there are contradictory reports (171–174).

Studies of the serotonin metabolite, 5-hydroxy-indole acetic acid (5HIAA) have also found increased 5HIAA levels in OCD patients compared to controls (172,175), although contradictory reports exist (176). Swedo and colleagues (177) reported that higher pretreatment CSF 5HIAA levels were correlated with increased OCD symptom severity and predicted better response to clomipramine. In contrast, Asberg and co-workers (178) noted that OCD symptom severity was associated with lower pretreatment CSF 5HIAA levels, although higher pretreatment 5HIAA levels did predict better response to clomipramine. Blood and CSF serotonin measures can be influenced by a person's height, diet, season of the year, activity level, and menses (179), thereby limiting the reliability of these markers as indices of brain serotonin function.



compulsive disorder (*right*). MI, myo-inositol; Cho, choline compounds; Cr, creatine/phosphocreatine; Glx, glutamate/glutamate/GABA; NA, N-acetylasparate. Adapted from Rosenberg DR, Mac-Millan SN, Moore GJ. Brain anatomy and chemistry may predict treatment response in pediatric obsessive-compulsive disorder. Int J Neuropsychopharmacol 2001;4:179–190.

5-HT receptor subtypes are localized to different areas of the brain (180). In order to better elucidate regional abnormalities of serotonin function that might contribute to OCD, Hollander and co-workers (181) combined pharmacologic challenge with functional neuroimaging. They used SPECT to measure the impact of the mixed 5-HT agonist-antagonist, meta-chlorophenylpiperazine (mCPP) in seven OCD patients. mCPP is a metabolite of trazodone, which acts most strongly at the postsynaptic 5-HT-2C receptor. Its administration results in exacerbation of OCD symptoms (181–188), although contradictory findings have been reported (189,190). Hollander and associates (181) noted a significant global increase in cortical blood flow in OCD patients that was associated with mCPP symptom exacerbation. Ho Pian and co-workers (190), also using SPECT, were unable to confirm this finding and, instead, reported decreased blood flow in the frontal cortex, striatum, thalamus, and cerebellum as well as global decreased blood flow in seven OCD patients with no mCPP response. The advent of more specific probes of serotonin synthesis and receptor function may help clarify putative serotonin dysregulation in OCD.

Recent PET investigation using the probe, α -C-11methyl-L-tryptophan (AMT), an analogue of tryptophan may be especially instructive. Tryptophan is the amino acid precursor to serotonin so that AMT is converted to α -C-11-methyl serotonin. A-C-11-methylserotonin is a 5-HT variant that is not degraded by monoamine oxidase; therefore, AMT-derived serotonin is effectively "kept" in serotonin neurons making it measurable by PET (191). In healthy volunteers, Chugani and associates (191) used AMT PET studies and found high regional AMT uptake in frontal cortex, the striatum, thalamus, and temporal lobe, regions that receive dense serotonergic projections from the raphe nuclei in the midbrain. More recently, Chugani and colleagues (192) reported reduced AMT uptake, suggestive of decreased serotonin synthesis in the frontal cortex and thalamus in autistic boys 4 to 11 years old. The repetitive, ritualistic thoughts and behaviors of autism can be similar to those in OCD. SSRIs sometimes can be beneficial in treating compulsive behaviors observed in autistic patients such as head banging and other rituals (193).

Pilot AMT PET studies in our laboratory have compared AMT uptake in pediatric OCD patients, 8 to 17 years old



FIGURE 113.16. Magnetic resonance studies on a 9-year-old boy with obsessive-compulsive disorder. **A:** ¹H MR spectra were obtained from a 0.7-cc volume of interest centered in the left caudate as shown by the box on the T₁-weighted MR image. **B:** Spectrum obtained at baseline in the treatment-naive state. **C:** Spectrum obtained after a 12-week trial of the selective serotonin reuptake inhibitor, paroxetine. Cho, choline compounds; Cr, creatine/phosphocreatine; GIx, glutamate/glutamine; mI, myoinositol; MR, magnetic resonance; NA, *N*-acetylaspartate. Reprinted from Moore GJ, MacMaster FP, Stewart C, et al. Case study: caudate glutamatergic changes with paroxetine therapy for pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 1998;37(6):663–667.



FIGURE 113.17. Decrease in left caudate glutamatergic concentrations associated with reduction in obsessive-compulsive score of the Children's Yale-Brown Obsessive-Compulsive Scales (CY-BOCS) (CY-BOCS, ——; Glx [glutamate/glutamine/GABA], ………). Reprinted from Rosenberg DR, Hanna GL. Review of genetic and imaging strategies in obsessive-compulsive disorder. Potential implications for treatment development. *Biol Psychiatry* 2000;48:1210–1222.

as compared to their unaffected siblings (194). Decreased uptake of AMT in the caudate nucleus and a trend for decreased uptake of AMT in anterior cingulate cortex was observed in the OCD patients. Because of the putative radiation risks associated with PET, we are not able to study healthy children as a comparison group. The radiation risks also make repeated studies in the same subjects less viable. Recent study has also suggested that the AMT tracer may be more reflective of free tryptophan than of serotonin synthesis (195). This is currently an active area of investigation in our center.

Other ligands such as 18F-altanserin, a 5-HT2a postsynaptic receptor antagonist may be relevant to the study of OCD. Goldman and associates (196) reported consistent 5-HT2a associations in two independent populations in two countries, implicating 5-HT2a in anorexia nervosa and OCD. Kaye and co-workers (197) have studied anorexic and bulimic women after long-term recovery with regular menstrual cycles and normalized eating and weight and found significantly reduced 18F altanserin binding in bilateral orbital frontal regions but not in other brain regions as compared to healthy female controls. The authors hypothesized that increased extracellular 5-HT could compete with 18F altanserin binding at 5-HT2a receptors and, thereby down-regulate 5-HT2a postsynaptic receptors. Anorexia nervosa and bulimia share certain characteristics with OCD and both conditions can also benefit from SSRI treatment (198). This ligand as well as others being developed and in the pipeline may ultimately clarify more precisely the role of serotonin in OCD.

CONCLUSION

Advances in brain imaging and neuroscience are making the brain mechanisms involved in the pathogenesis and maintenance of OCD accessible as never before. Indeed, the time is now ripe to use brain imaging to exploit advances across several disciplines. For example, sophisticated brain imaging studies may facilitate more informed genetic studies and vice versa. Rauch (67) has argued persuasively that brain-imaging studies may help delineate specific endophenotypes for genetic studies in OCD. Such an approach might help discriminate between familial and sporadic OCD, thereby clarifying some of the genetic heterogeneity of OCD (11). To our knowledge, no prior study has employed both genetic and neuroimaging approaches in the same population, although there is precedent for such an approach in the study of ADHD (199). Obviously, costs of such an endeavor prohibit routine use of both techniques. It will be critical to delineate areas of maximum utility where these techniques are likely to provide the best yield and, therefore be most cost effective (67). For example, identified candidate serotonin or glutamatergic genes might be integrated into specific neuroimaging paradigms (11). Neuroimaging studies may also help clarify the role of established susceptibility genes as well as facilitating an enhanced understanding of the developmental neurobiologic underpinnings of OCD. Combination of these approaches may be especially effective in the identification of meaningful surrogate neurobiologic markers predictive of treatment response (or lack thereof). Ample evidence exists across various medical disciplines that increased understanding of the biologic mechanisms underlying an illness inevitably translates into critical advances in diagnosis and treatment (200).

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