Genetic and Imaging Strategies in Obsessive–Compulsive Disorder: Potential Implications for Treatment Development

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In recent years, advances in brain research have resulted in a striking strategic shift in studies designed to develop new, effective treatments for neuropsychiatric disorders. This involves a multidisciplinary approach with recursive interactions among respective disciplines with the ultimate goal of contributing to treatment development. In this review we focus on treatment implications of brain imaging and molecular and pharmacogenetic studies in obsessive–compulsive disorder. Translational components of this research are addressed, including the potential for integrating advances in brain imaging and molecular and pharmacogenetic assessments as they may potentially relate to neurodiagnostic assessment and treatment development. Studies of putative susceptibility alleles in obsessive–compulsive disorder involving the serotonergic, glutamatergic, and dopaminergic systems may provide a focus for these divergent approaches. Taken together, neuroimaging and genetic methods may ultimately lead to a mechanistic understanding of the pathogenesis and maintenance of neuropsychiatric disorders such as obsessive–compulsive disorder that may, in turn, result in the development of new neurodiagnostic and treatment approaches. Biol Psychiatry 2000;48:1210–1222 © 2000 Society of Biological Psychiatry

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Introduction

Understanding of the neurobiological and genetic underpinnings of major neuropsychiatric disorders has lagged behind the establishment of diagnostic criteria and treatment development for these conditions. Hyman (2000) argues persuasively that during the next decade psychiatry must adopt a multidisciplinary approach and integrate advances in neuroscience and genetics “to ask meaningful questions about the relationship among mind, brain, and behavior, and to finally overcome the pervasive Cartesianism that continues to incubate stigma and ignorance about mental illness.” Brain imaging techniques in conjunction with advances in genetics can contribute a great deal to the outstanding questions in neuropsychiatry relevant to enhanced diagnostic rigor and treatment development.

Here we 1) review neurodiagnostic and treatment implications of recent brain imaging and molecular and pharmacogenetic studies relevant to pediatric obsessive–compulsive disorder (OCD) and 2) focus on the translational components of this research—specifically, the potential for integrating advances in brain imaging and molecular and pharmacogenetics as they may relate to enhanced neurodiagnostic assessment and treatment development. Although OCD is used as a model for interfacing brain imaging and genetic techniques, application to other neuropsychiatric disorders is clearly indicated.

Pediatric OCD is a severe, chronically disabling illness characterized by intrusive and distressing ritualistic thoughts and behaviors over which patients often have little if any control. Its lifetime prevalence is 2–3% (Flament et al 1988) and at least 80% of all cases of OCD have their initial onset in childhood and adolescence (Pauls et al 1995). Despite the advent of the selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT), as many as one third of OCD patients do not respond at all to currently available treatment and many “responders” are only partial responders with continued functional impairment (Grados et al 1999). This underscores how critical it is to develop new and more effective treatment approaches for this condition. As described below, taken together, neuroimaging and genetic methods may be especially useful in ultimately developing new biological treatments for neuropsychiatric disorders such as OCD.
Brain Imaging

Brain imaging techniques in conjunction with advances in developmental neurobiology, neuropsychopharmacology, and genetics can contribute a great deal to the outstanding questions regarding childhood-onset neuropsychiatric disorders such as OCD relevant to enhanced diagnostic rigor and treatment development. Neuroimaging techniques permit correlations between brain anatomy, chemistry, and function with baseline and outcome clinical assessment (e.g., Children’s Yale–Brown Obsessive–Compulsive Scale score, SSRI or CBT treatment) (Nemeroff et al 1999). As described below, neuroimaging studies have rather consistently implicated dysfunction within ventral prefrontal cortical (VPFC)–striatal–thalamic neural circuits in OCD (Saxena et al 1998).

Treatment studies using biological markers may potentially lead to a mechanistic understanding of the pathogenesis and maintenance of the illness, which may in turn result in the development of new diagnostic and treatment approaches. This is especially critical because OCD is a heterogeneous condition. The identification of particular abnormalities of brain anatomy, chemistry, and function might, for example, represent different etiologic or genetic forms of illness that may respond preferentially to different treatment interventions. Brody et al (1998) have identified distinct patterns of regional brain glucose metabolism in adult OCD patients that predict differential treatment response to SSRIs versus CBT. Neuroimaging studies might identify specific neurobiological subtypes of OCD and help delineate the developmental neurobiological underpinnings of specific phenotypes of illness (Rauch 2000). This is likely to be important in view of the heterogeneity of the illness. Using brain imaging techniques that facilitate the noninvasive, longitudinal, and in vivo assessment of brain anatomy, chemistry, and function provides the advantages of minimizing potentially confounding factors of longer term illness duration and treatment interventions and allows for a developmental framework for conceptualizing specific neuropsychiatric disorders such as OCD.

Identification of Neuroanatomic Structures Involved in Pediatric OCD

Striatal Anatomy in Pediatric OCD

Neurobiological abnormalities in the striatum have been hypothesized to be the primary locus of pathology in OCD (Rauch et al 1998). Increased OCD behaviors are present in patients with basal ganglia disorders (for a review, see Fitzgerald et al 1999). Functional neuroimaging studies in adult OCD patients have demonstrated increased metabolic activity and brain activation in the caudate nucleus correlated with severity of illness and response to treatment (Baxter et al 1992).

Structural neuroimaging studies in adult OCD patients, however, have demonstrated conflicting findings. Using computed tomography (CT), Insel et al (1983) found no difference between adult OCD patients and control subjects in ventricular brain ratios (VBRs). Of the six magnetic resonance imaging (MRI) studies in adult OCD patients, two demonstrated abnormal caudate volumes (Robinson et al 1995; Scarone et al 1992), whereas four found no significant differences between OCD patients and control subjects (Aylward et al 1991, 1996; Bartha et al 1998; Kellner et al 1991). Such discrepancies may be related to different neuroimaging methodologies used in different studies, the heterogeneity of OCD, and potentially confounding factors such as comorbidity, illness duration, and most patients receiving psychotropic medication.

Interestingly, all published structural neuroimaging studies in pediatric OCD patients have detected abnormalities. Behar et al (1984) reported increased VBRs in adolescent OCD patients relative to control subjects. Although increased VBRs could be consistent with decreased striatal volume, the authors did not report striatal measurements. Luxenberg et al (1988) used quantitative CT to demonstrate reduced caudate volumes in late adolescent and young adult male OCD patients. These reductions were most prominent in the youngest male subjects in the sample. Rosenberg et al (1997c) identified reduced striatal volumes associated with OCD symptom severity but not illness duration in 19 treatment-naive OCD patients, 7–17 years, versus 19 case-matched healthy comparison subjects (Figure 1). No abnormalities were observed in case–control pairs in total brain volume.

Figure 1. Striatal volume by group. OCD, obsessive–compulsive disorder.
Prefrontal Cortical Anatomy in Pediatric OCD

Disturbances in VPFC–striatal interactions are believed to be involved in causing OCD (for a review, see Fitzgerald et al 1999). Damage to VPFC circuits results in impairment in the ability to inhibit context-inappropriate emotional responses, leading to inappropriate behaviors (Stuss and Benson, 1983), whereas psychosurgical lesions of VPFC regions such as the anterior cingulate cortex can decrease OCD symptom severity in treatment-refractory patients (Chiocca and Martuza 1990). Eslinger and Damasio (1985) have reported that VPFC lesions cause disruption in “analysis and integration.” This results in impairment of the normal inhibitory control of VPFC circuits with consequent interruption of ongoing purposive behaviors in OCD patients (Flor-Henry et al 1979; Malloy 1987). The ventral prefrontal cortex is often referred to as the paralimbic cortex (Mesulam 1986) and through its connections with limbic regions in the cingulum and temporal lobes plays a critical role in integrating cognitive, motivational, and emotional mechanisms.

Using morphometric MRI, Robinson et al (1995) found no significant difference between total prefrontal cortical volume in adult OCD patients and control subjects. However, measurement of localized prefrontal regions including the operculum (Jenike et al 1996) and orbitofrontal cortex (Szeszko et al 1998) has revealed abnormalities in adult OCD patients relative to control subjects that were correlated with severity of illness. More recently, Grachev et al (1998) found no difference between adult female OCD patients and matched control subjects in anterior cingulate, orbitofrontal, or opercular cortical volume. However, when they used a more sophisticated and accurate measurement technique, topographic parcellation (Caviness et al 1996), six frontal parcellation units on the right and four parcellation units on the left were noted to be significantly increased in adult female OCD patients relative to matched female control subjects.

Consistent with Robinson and colleagues’ (1995) finding of no significant difference in total prefrontal cortical volume between adult OCD patients and control subjects, Rosenberg et al (1997c) failed to detect a significant difference in total prefrontal cortical volume between 19 treatment-naive pediatric OCD patients, 7–17 years, and case-matched control subjects. However, their subsequent studies of neurocognitive function (Rosenberg et al 1997a) and regional anatomy and signal intensity of the corpus callosum (MacMaster et al 1999; Rosenberg et al 1997b) pointed to abnormalities in the VPFC and suggested that measurement of total prefrontal cortical volume may have averaged out localized volumetric abnormalities in pediatric OCD patients. In a subsequent investigation, Rosenberg and Keshavan (1998) reported that localized increased anterior cingulate volumes associated with OCD symptom severity but not duration of illness were observed in treatment-naive pediatric OCD patients versus healthy comparison subjects (Figure 2A). The normal age-related increase in anterior cingulate volume in healthy children was absent in OCD patients (Figure 2B). Increased anterior cingulate volumes were inversely correlated with decreased striatal volumes in OCD patients.

Thalamic Anatomy in Pediatric OCD

Findings of increased VPFC volumes and reduced striatal volumes in OCD patients led Gilbert et al (2000) to study the thalamus, which serves as the final subcortical motor and sensory input to the frontal cortex, which stimulates

![Figure 2. Anterior cingulate volume by group (A) and anterior cingulate volume versus age for pediatric obsessive–compulsive disorder (OCD) patients as compared to healthy comparison subjects (B).](image-url)
cortical output when released from the inhibitory tonic influence of the corpus striatum (Baxter et al 1996). Partial thalamotomy can reduce OCD symptoms in treatment-refractory OCD patients with severe manifestations of the illness (Chiocca and Martuza 1990). Functional neuroimaging studies of adult OCD patients have also demonstrated increased metabolic rates and regional cerebral blood flow in the thalamus associated with OCD symptom severity and response to treatment (Baxter 1992).

Although Jenike et al (1996) did not observe thalamic volumetric abnormalities between adult OCD patients and control subjects, many of the patients in this sample were on psychotropic medications. Using volumetric MRI, Gilbert et al (2000) reported increased thalamic volumes in 21 treatment-naive pediatric OCD patients relative to case-matched control subjects (Figure 3A). A differential maturation of thalamic volume was also observed in OCD patients relative to control subjects (Figure 3B). Remarkably, after 12 weeks of monodrug therapy with the SSRI paroxetine and no concomitant behavioral psychotherapy, there was a significant decrease in thalamic volume to levels comparable to and not significantly different from thalamic volumes in healthy children (Figure 4). Decrease in thalamic volume was positively correlated with decrease in OCD symptom severity in pediatric OCD patients (Figure 5A). In contrast, no significant differences were observed in 11 treatment-naive pediatric OCD patients before and after CBT only (Rosenberg et al 2000a). No significant reductions in the VPFC, striatal volumes, or total brain volume were observed before and after paroxetine or CBT. Thus, localized reduction in thalamic volumes in pediatric OCD patients may be specific to treatment with the SSRI paroxetine as opposed to a general treatment effect and/or spontaneous remission.

Taken together, these results suggest that volumetric abnormalities in VPFC–striatal–thalamic circuitry may be associated with the clinical presentation of OCD and represent a central developmental neurobiological deficit in the illness. Abnormalities in thalamic anatomy, particularly in younger children, may be reversible with effective SSRI treatment but not with CBT. In contrast, abnormalities in VPFC and striatal volumes may not be reversible with effective SSRI or CBT treatment.

Increased anterior cingulate and thalamic volumes in pediatric OCD patients were consistent with prior observations in childhood OCD patients of increased size and myelination of the genu (MacMaster et al 1999; Rosenberg et al 1997b), the region of the corpus callosum connecting the VPFC, and reports of increased metabolic rates in VPFC–striatal–thalamic circuitry in adult OCD patients (Baxter 1992). A growing body of evidence suggests that hyperactivity in the VPFC is directly linked
to structures of the basal ganglia and thalamus in a parallel circuit that mediates the expression and manifestation of OCD symptoms (Rapoport and Wise 1988). Increased volume in the VPFC and thalamus in pediatric OCD patients may, however, represent an epiphenomenon related to increased metabolic activity and cerebral blood flow in these brain regions. Differences in regional brain volumes between pediatric OCD patients and healthy control subjects does not necessarily indicate that these differences are pathogenic. They may, for example, represent attempts to adapt or to compensate for the presence of obsessive thoughts or compulsive behaviors.

Since illness duration and age of onset of clinical OCD were not associated with anterior cingulate, thalamic, or striatal volumes, abnormalities in these regions are not consistent with a degenerative process in OCD but rather suggest that these abnormalities may be early neurobiological markers of the developmental pathogenesis of the illness. Ventral prefrontal cortical and striatal volumetric abnormalities may be biological markers associated with illness presentation, whereas thalamic volumetric abnormalities may be reversible with effective SSRI treatment.

It should be noted that the aforementioned studies involved relatively small sample sizes (21 OCD patients and 21 matched control subjects). Thus, these results must be considered preliminary, given the small sample size, and require replication. Refinements in measurement of regions, including the thalamus, whose reliabilities are difficult to measure are also critical for determining the underlying developmental neurobiology of OCD.

The aforementioned studies were also cross-sectional, so that degenerative processes cannot be excluded. Longitudinal studies in affected OCD patients are currently ongoing in our laboratory and designed to monitor neuroanatomic progression of illness over the course of illness as well as to determine whether neuroanatomic abnormalities persist after treatment discontinuation. Similar studies

Figure 5. (A) Decrease in thalamic volume (green) associated with reduction in Obsessive–Compulsive score of the Children’s Yale–Brown Obsessive–Compulsive Scale (CY-BOCS; red). (B) Left caudate glutamatergic concentrations versus obsessive-compulsive symptom severity as measured by the CY-BOCS versus paroxetine dosage. Green, glutamate/glutamine/γ-aminobutyric acid (Glx); red, CY-BOCS. (C) Schematic diagram showing selected aspects of cortical–striatal–thalamic connections in the neurodevelopment of obsessive–compulsive disorder. Neurotransmitters: Glu, glutamate; DA, dopamine; 5-HT, serotonin. Brain regions: VPFC, ventral prefrontal cortex; AC, anterior cingulate; VS, ventral striatum; Thal, thalamus; TLC, temporal lobe cortex; RN, raphe nucleus; SN, substantia nigra; VT, ventral tegmentum.
are being conducted in offspring and siblings of OCD patients at increased risk for developing the illness.

The abnormalities in the normal developmental maturation of frontal–striatal–thalamic anatomy have been referred to as a “neural network dysplasia of OCD” (Rosenberg and Keshavan 1998). Such abnormalities may reflect disturbances in postnatal pruning, with increased pruning and resultant reduction in neural tissue in the striatum and decreased pruning resulting in increased neural brain elements in the VPFC and thalamus. Pruning of brain elements occurs during normal development (Keshavan et al 1994) but might be exaggerated in the striatum and reduced in the VPFC and thalamus.

The identification of potential critical windows of abnormal maturation of VPFC–striatal–thalamic circuitry in pediatric OCD patients (Gilbert et al 2000; Rosenberg and Keshavan 1998) may, in part, explain why some studies of adult OCD patients have failed to detect comparable abnormalities. This is not meant to imply that OCD patients “grow out of the illness”; in fact, older OCD patients can also be significantly impaired. However, putative windows of aberrant maturation of particular brain regions may ultimately prove helpful in the identification of differential treatment at different stages of development.

**Brain Chemistry in Pediatric OCD**

Rosenberg and Keshavan (1998) hypothesized that the frontal–striatal–thalamic abnormalities observed in pediatric OCD patients might involve neuronal dysfunction and abnormalities in glutamatergic tone impacting on serotonin circuits. Proton magnetic resonance spectroscopy (1H MRS) permits the direct, in vivo, and noninvasive measurement of N-acetyl-aspartate (NAA), a reliable marker of neuronal viability (Birken and Oldendorf 1989), and glutamatergic compounds (glutamate/glutamine/γ-aminobutyric acid).

**Neuronal Dysfunction in OCD**

It has been hypothesized that the clinical symptomatology of OCD reflects impaired gating of sensorimotor information in VPFC–striatal–thalamic circuitry that results in the circuit’s firing continuously (Ebert et al 1997). The neuronal marker NAA, measured by 1H MRS, is localized primarily within neurons in the brain (Urenjak et al 1992). Decreased NAA levels are observed in diseases involving neuronal loss such as Alzheimer’s disease (MacKay et al 1996). Recent investigation suggests that reductions in NAA levels may represent an early marker of neuronal loss, dysfunction, or damage before such changes are detectable by structural MRI (Bartha et al 1998). Therefore, NAA serves as a marker of both neuronal number and neuronal function/dysfunction (Tsai and Coyle 1995).

Proton magnetic resonance spectroscopy studies have found decreased NAA levels in brain regions implicated in the pathophysiology of OCD, including the striatum (Bartha et al 1998; Ebert et al 1997) and VPFC (Ebert et al 1997) but not parietal cortex (Ebert et al 1997), a region not believed to be involved in the formation of OCD symptoms. Recently, Fitzgerald et al (2000) identified localized functional neurochemical marker abnormalities in the medial thalamus associated with OCD symptom severity but not illness duration. No abnormalities were observed in the lateral thalamus (Figure 6). This is an especially exciting finding, as the dorsomedial nucleus of the thalamus has been implicated in the pathophysiology of OCD (Modell et al 1989). It is important to point out that measurement of chemical spectra in the more medially placed thalamic voxels may be confounded by possible cerebrospinal fluid contamination. White matter contamination of more laterally placed thalamic voxels is also possible. It should be noted that controlling for thalamic volume confirmed significant differences between OCD patients and control subjects.

The previously reported pathologic correlations observed between VPFC–striatal–thalamic metabolic activity in OCD patients (Baxter 1992) may be especially relevant in view of NAA abnormalities in OCD patients in these regions. Specifically, NAA abnormalities in VPFC–striatal–thalamic circuitry might result from persistent increased metabolic activity in these circuits. Glutamatergic neurons project from the VPFC to the striatum and thalamus (Becquet et al 1990; Salt and Eaton 1996). Increased cortical–striatal–thalamic glutamate projections could lead to neurotoxicity and neuronal dysfunction.

**Glutamate in Pediatric OCD**

Rosenberg and Keshavan (1998) hypothesized that abnormalities in glutamate–serotonin interactions might underlie OCD. This hypothesis was based on a variety of reports in the literature that are only briefly reviewed here. The caudate nucleus, a region hypothesized to be the principal locus of abnormality in OCD (Rauch et al 1998), receives a particularly dense glutamate innervation from the frontal cortex (Becquet et al 1990) so that ablating frontal cortex results in a profound decrease in caudate glutamate concentrations (Calabresi et al 1996; Kim et al 1977). Neurobiological studies have also consistently demonstrated a potent presynaptic inhibition of serotonin release by corticostriatal glutamate in the caudate nucleus (Becquet et al 1990; Reisine et al 1982), whereas serotonergic neurons have also been shown to have a potent impact on glutamate neurotransmission (Edwards et al 1996).
Using a short echo single-voxel $^1$H MRS approach, Rosenberg et al (2000b) observed significantly greater caudate glutamatergic concentrations in 11 pediatric OCD patients versus 11 case-matched healthy comparison subjects, with no case-control differences noted in occipital gray matter. Caudate glutamatergic concentrations decreased significantly after 12 weeks of paroxetine mono-drug therapy to levels comparable to those observed in control subjects (Figure 7). Reduction in caudate glutamatergic concentrations was positively correlated with reduction in OCD symptom severity (Figure 5B). Increased pretreatment caudate glutamatergic concentrations in OCD patients predicted enhanced response to paroxetine intervention. Ongoing studies in our laboratory are focused on examining glutamatergic concentrations in the VPFC and thalamus.

Increased caudate glutamatergic concentrations in untreated OCD patients that decreased after paroxetine treatment are also consistent with functional imaging studies of the caudate nucleus in adults that have found increased metabolism, brain activation, and regional cerebral blood flow, which may decrease after effective SSRI treatment (Baxter et al 1992). Glutamatergic activity has been reported to parallel glucose metabolism in the brain (Sibson et al 1997). The VPFC sends glutamatergic projections to the striatum and thalamus (Becquet et al 1990; Calabresi et al 1996; Salt and Eaton 1996). Sustained SSRI administration also stimulates serotonin release by desensitizing terminal serotonin autoreceptors in the VPFC (El Mansari et al 1995) and could lead to altered serotonergic transmission in the cell bodies of the VPFC, which could influence frontal–striatal–thalamic glutamatergic concentrations.

![Figure 6](image_url)

**Figure 6.** (Top) Sample spectra for voxels placed in the left medial thalamus (A) and left lateral thalamus (B). Individual peaks for choline compounds (Cho), creatine/phosphocreatine (Cr), and N-acetyl-aspartate (NAA) were resolved from the original spectrum (at the top of each box) leaving a residual. (Bottom) Left and right medial thalamus NAA/(Cho + Cr) metabolite ratios by group in pediatric obsessive–compulsive disorder (OCD) patients relative to healthy comparison subjects.
tergic compound projection with changes in VPFC–striatal–thalamic glutamate concentrations (Rosenberg et al 2000b).

In summary, this integrated series of brain imaging studies in pediatric OCD patients suggests a reversible glutamatergically mediated thalamocortical–striatal dysfunction in OCD that may serve as a pathophysiologic and treatment response marker in pediatric OCD (Figure 5C). Critical neurodevelopmental changes in VPFC–striatal–thalamic circuitry may be associated with the initial presentation of OCD. Treatment studies using biological outcome markers may lead to a mechanistic understanding of the illness that may result in the development of new neurodiagnostic and treatment approaches. Neuroimaging studies performed in conjunction with pharmacogenetic and molecular genetic studies (described below) may represent a unique and unprecedented opportunity for guiding a mechanistic understanding of neuropsychiatric disorders such as OCD and translating these advances into treatment development.

**Potential Relevance of Molecular Genetic and Pharmacogenetic Studies**

The potential contributions of molecular genetic and pharmacogenetic strategies to neuroimaging studies and treatment development in psychiatry have begun to receive some discussion (Weinberger 2000; Weinshilboum 2000). It has been suggested that various neuroimaging techniques may be used to understand the biological expression of susceptibility genes for mental illness and to identify genetically determined responses to specific drugs. However, the recurrent difficulties in replicating findings of susceptibility loci for common psychiatric disorders preclude combining neuroimaging with most putative genetic markers in the near future. Instead, progress may be made by combining those strategies to investigate less common neuropsychiatric disorders—such as fragile X syndrome, Rett’s disorder, Prader–Willi syndrome, and velocardiofacial syndrome—or to quantify the brain expression of genes with acknowledged behavioral effects (Lachman et al 1996; Lesch and Mössner 1998).

It is expected that pharmacologic imaging will draw upon the discipline of pharmacogenetics—the study of the role of inheritance in individual variations in drug response. Pharmacogenomics is an overlapping field of research using genetic information in drug design and therapeutics that is likely to eventually intersect with neuroimaging studies of psychiatric disorders (Anderson and Cook 2000). As suggested by the preceding review of the neurobiology of OCD, studies of putative susceptibility loci in OCD involving the serotonergic, glutaminergic,
and dopaminergic systems may provide a focus for otherwise divergent genetic, neurobiological, and pharmacologic approaches to this complex brain disorder. The integration of genetic strategies into neuroimaging studies of early-onset OCD eventually may be rewarding because that form of the disorder appears to be highly familial (Hanna 2000; Nestadt et al 2000; Pauls et al 1995).

Studies have suggested that a functional polymorphism in the promoter region of the serotonin transporter (SLC6A4) is associated with anxiety-related traits. The initial study found that subjects with one or two copies of the short variant had higher neuroticism scores than did individuals homozygous for the long variant (Lesch et al 1996). In a subsequent study, linkage but not association was found between the polymorphism and anxiety-related traits, suggesting that the earlier finding may be related to another allele in the gene (Mazzanti et al 1998). Indeed, recent studies of the promoter region in the serotonin transporter gene revealed an internal fragment not reported in previous publications (Flattem and Blakely 2000; Mortensen et al 1999). This novel fragment contains consensus sequences for several transcription factors that require further study. The feasibility of examining the relationship between serotonin transporter genotype and in vivo protein expression has been demonstrated in a recent study of alcohol neurotoxicity (Heinz et al 2000).

As suggested by the studies of a possible relationship between the serotonin transporter gene and anxiety-related traits, the serotonin transporter is a plausible candidate gene for OCD and other psychiatric disorders responsive to potent serotonin reuptake inhibitors (SRIs). A study using the transmission disequilibrium test (TDT) provided preliminary evidence for association and linkage disequilibrium between the long allele in the serotonin transporter promoter region and OCD (McDougle et al 1998). There was also a trend for the long allele to be preferentially transmitted in the OCD patients who failed to respond to SRIs. However, case–control studies of the promoter polymorphism in OCD have yielded inconsistent results (Bengel et al 1999; Billett et al 1997). The larger of the two case–control studies found that patients with OCD were more likely to carry two copies of the long allele than matched control subjects (Bengel et al 1999). If the relationship between OCD and the serotonin transporter promoter polymorphism receives further confirmation with family-based association tests, it may be revealing to investigate the relationship between the polymorphism and brain expression of the gene in patients with OCD.

Two studies of depressed inpatients demonstrated that subjects with one or two copies of the long variant in the serotonin transporter promoter region had a better treatment response to fluvoxamine (Smeraldi et al 1998) and paroxetine (Zanardi et al 2000). This is in contrast to the trend noted in the TDT study of the promoter polymorphism in OCD (McDougle et al 1998). In another study of inpatients with bipolar depression, subjects homozygous for the long allele had a greater improvement in mood after total sleep deprivation (Benedetti et al 1999). It was suggested that having two copies of the long allele may allow more pronounced changes in serotonergic functioning that are necessary for the antidepressant response to total sleep deprivation (Benedetti et al 1999; Hanna et al 1998). Further studies of the serotonin transporter promoter polymorphism may provide a better understanding of the wide variation in treatment response in OCD. The polymorphism may be particularly useful in predicting treatment response in the substantial number of OCD patients with comorbid depressive disorders (Hanna 1995; Welner et al 1976).

A preliminary genome scan of early-onset OCD with 65 individuals from seven families found maximum nonparametric LOD* scores above 1.5 on chromosomes 2, 9, and 17 (Hanna et al 1999). Although none of the results reached the level of statistical significance required for genetic linkage, the nonparametric LOD* score analyses suggested that three chromosomal regions may harbor susceptibility loci for early-onset OCD. The 2q region contains the serotonin 2B receptor gene (HTR2B; Le Coniat et al 1996). Activation of the 5-HT2B receptor in the rat causes anxiolysis and reduced grooming (Duxon et al 1997; Kennett et al 1997). No functional mutation was found, however, in the sequenced regions of the HTR2B in the probands from the families in the genome scan (Kim et al 2000).

9p monosomy has been previously associated with Tourette’s syndrome and OCD (Taylor et al 1991). The 9p region contains a neuronal glutamate transporter gene (SLC1A1; Smith et al 1993), which is provocative given the neuroimaging data previously described on the possible role of glutamate in the pathogenesis of OCD. Again, no evidence was found for a functional mutation in the gene (Veenstra-VanderWeele et al, in press). Further linkage analyses with a larger number of families are warranted because other genes in the region may be considered positional candidates. Genome scans have the potential of identifying chromosomal regions likely to contain susceptibility genes for OCD without having a priori hypotheses about the pathogenesis of the disorder (Burmeister 1999). Given the previous problems with mapping genes for psychiatric and other common disorders, however, it may be possible to obtain consistent linkage findings with early-onset OCD only if it represents a more homogeneous form of the disorder (Hanna 2000; Nestadt et al 2000).

Genetic studies of the dopaminergic system may also be
useful in understanding some aspects of the comorbidity or neurobiological heterogeneity of OCD. The distinction between tic-related and non–tic-related OCD has received support from phenomenological (Leckman et al 1995), natural history (Leonard et al 1992), neuroendocrine (Hanna et al 1991), pharmacologic (McDougle et al 1994), and family studies of OCD (Pauls et al 1995). A case–control study of the dopamine D4 receptor gene in OCD patients found a higher rate of a seven-repeat allele in those patients with comorbid tics (Cruz et al 1997). Similarly, in a family-based association study of Tourette’s syndrome using the TDT, the seven-repeat allele of the D4 receptor gene was preferentially transmitted (Grice et al 1996). Another case–control study found significant differences between OCD patients and matched control subjects in allele frequencies of a 48–base pair repeat in the D4 receptor gene (Billet et al 1998). Replication with family-based association studies is required before any conclusions can be entertained about the role of the dopamine D4 receptor gene in OCD. If an association is confirmed, genotypic information about the D4 receptor may be productively integrated into neuroimaging or treatment studies of OCD.

Case–control and family-based association studies have implicated the genes for two enzymes involved in monoamine metabolism, monoamine oxidase A (MAOA) and catechol O-methyltransferase (COMT), in the susceptibility to OCD (Karayiorgou et al 1997, 1999). However, no linkage was found for a functional polymorphism in the COMT gene to Tourette’s syndrome and OCD (Barr et al 1999). As with the dopamine D4 receptor gene, further studies of the MAOA and COMT genes are needed to determine whether either gene is possibly associated with OCD or with another disorder that frequently coexists with OCD.

The genetic contribution to OCD is almost certainly complex, so current linkage and association techniques may be inadequate for mapping most of the important susceptibility loci for the disorder (Burmeister 1999; Hanna 2000). Gene chips and expression array technology hold promise for dealing with the genetic complexity of OCD and other common psychiatric disorders (Watson and Akil 1999). Assuming some progress in this area, each susceptibility gene may provide an option for treatment development. Advances in combinatorial chemistry and structure-based drug design have substantially increased the capacity to develop new drugs once targets are identified. Since the susceptibility genes for OCD may have to occur in a particular combination for symptoms to arise, it is possible that a drug targeting one of the susceptibility genes may be sufficient to treat the disorder (Anderson and Cook 2000).

Conclusions

Rauch (2000) suggested that brain imaging profiles may provide biological phenotypes (“endophenotypes”) for genetic studies of OCD that are more etiologically homogeneous than current clinical phenotypes and that the imaging profiles may be analyzed as either categoric or quantitative traits. Brain imaging profiles may be useful in clarifying the genetic heterogeneity of OCD or, more simply, in delineating biological differences between familial and sporadic OCD. Yet it remains uncertain whether an advance in either neuroimaging or genetic studies of OCD will necessarily lead to an advance in the other area.

Studies of common childhood neuropsychiatric disorders have rarely integrated genetic and neuroimaging strategies. A notable exception is the study by Castellanos and colleagues (1998) of attention-deficit/hyperactivity disorder. The cost of coupling a genome scan with neuroimaging is potentially prohibitive. However, if one or more candidate genes such as those described above are consistently associated with OCD, it may be become feasible to integrate genetic information into neuroimaging studies.

Neuroimaging studies may have their greatest value in psychiatry when they can be used to detail the brain expression of susceptibility genes for a complex neuropsychiatric disorder such as OCD and to monitor the effects of biological and psychosocial treatments (Weinberger 2000). Once susceptibility genes for OCD are identified, it should be possible to use pharmacogenomic techniques to develop more rational drugs for the disorder and to use neuroimaging techniques to further refine the effects of those treatments. Furthermore, expression array technology and pharmacologic imaging may have the potential to identify genetically determined responses to specific drugs.

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