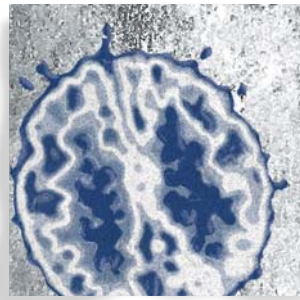# Translational research

Symptom dimensions and subtypes of obsessive-compulsive disorder: a developmental perspective

James F. Leckman, MD; Michael H. Bloch, MD; Robert A. King, MD

Obsessive-compulsive disorder (OCD) is a chronic and potentially disabling condition affecting from 1% to 3% of the general adult population.[1,2] Similar rates have also been reported for children and adolescents.[3-5] Frequently, patients with OCD describe the sudden intrusion into consciousness of unwanted thoughts or unpleasant images. These obsessions are often accompanied by a profound sense of dread and the urge to complete specific compulsions. Compulsions are repetitive acts, typically performed a certain number of times or according to certain private rules, that the individual is driven to complete, even though these acts are perceived as excessive.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision (DSM-IV-TR)*[6] and other standard diagnostic classifications, such as the *International Classification of Diseases, Tenth Edition (ICD-10)*,[7] categorize OCD as a unitary nosological entity. While this parsimony has a certain formal appeal, it is misleading. The symptoms used to define OCD are heterogeneous and include various intrusive thoughts and preoccupations, rituals, and compulsions. Two individuals with OCD may have totally different and nonoverlapping symptom patterns.

From as far back as the earliest descriptions of OCD, investigators have attempted to dissect the phenotype into homogeneous subtypes. For example, Falret[8] made the distinction between "*folie du doute*" (madness of doubt) and "*délire du toucher*" (delirium of touch) in 1869. Most commonly, investigators have distinguished "washers" from "checkers."[9-12] With a few notable excep-

In the absence of definitive etiological markers for obsessive-compulsive disorder (OCD), obsessive-compulsive (OC) symptom dimensions may offer a fruitful point of orientation. These dimensions can be understood as defining potentially overlapping clinical features that may be continuous with "normal" worries first evident in childhood. Although the understanding of the dimensional structure of OC symptoms is still imperfect, a recent large-scale meta-analysis has confirmed the presence of at least four separable symptom dimensions in children, as well as adults, with OCD. A dimensional approach does not exclude other methods to parse OCD. Thus far, a pediatric age of onset, the presence of other family members with OCD, and the individual's "tic-related" status appear to be potentially useful categorical distinctions. Although the OC symptom dimensions appear to be valid for all ages, it is unlikely that the underlying genetic vulnerability factors and neurobiological substrates for each of these symptom dimensions are the same across the course of development.

Author affiliations: The Child Study Center and the Departments of Psychiatry, Psychology and Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA

Address for correspondence: James Leckman, Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT 06520-7900, USA (e-mail: james.leckman@yale.edu)

Translational research

tions, these attempts had limited success in relating the identified subtypes to biological markers, genetic factors, or treatment response, in part because pure subtypes of patients are rare, and the recruitment of sufficient sample sizes of each subtype is difficult and impractical.

The following review considers an alternative approach to obsessive-compulsive (OC) symptoms.[13,14] It begins with an examination of the potential value of a dimensional approach and then considers various potential subtypes of OCD, particularly among early-onset cases.

Obsessive-compulsive symptom dimensions

The first study to factor-analyze the Yale-Brown Obsessive-Compulsive Scale-Symptom Checklist (Y-BOCS-SC)[15] was that of Baer.[16] He factor-analyzed the 13 major categories of the Y-BOCS-SC in a sample of 107 patients and identified three factors, accounting for 48% of the variance; these were named "symmetry/hoarding," "contamination/cleaning," and "pure obsessions." Following Baer's seminal work, Leckman and colleagues[17] evaluated the same 13 a priori categories used to group types of obsessions and compulsions in the Y-BOCS-SC in two large groups of OCD patients totaling over 300 cases.[18,19] In an effort to identify valid "traits," they included any OCD symptoms that patients "ever" experienced over the course of their lifetimes, as opposed to limiting these analyses to current symptoms. Remarkably, both data sets yielded nearly identical results. Four factors were identified that in total accounted for >60% of the variance in each data set.[17] Subsequently, Summerfeldt and colleagues[20] evaluated existing models of OCD symptom structure in 203 individuals. Using confirmatory factor analyses, they deter-

mined that there was an "adequate fit" solely for a four-factor model. A recent meta-analysis examined the data from 21 studies involving 5124 participants and confirmed the validity of the same four factors.[21] Studies were examined if they involved subjects with OCD and included an exploratory factor analysis of the 13 Y-BOCS-SC categories and the items therein.[14] Stratified meta-analysis was conducted to determine the factor structure of OCD in studies involving children and adults separately. The four factors generated were: (Factor I) Forbidden thoughts—aggression, sexual, religious, and somatic obsessions and checking compulsions; (Factor II) Symmetry—symmetry obsessions and repeating, ordering, and counting compulsions; (Factor III) Cleaning—cleaning and contamination; and (Factor IV) Hoarding—hoarding obsessions and compulsions. Factor analysis of studies including adults yielded an identical factor structure compared with the overall meta-analysis. The only differences between the factor structures involving adults and children were: (i) checking compulsions loaded highest on the Forbidden thoughts factor in adults and with the Symmetry factor in children; and (ii) somatic obsessions loaded highest on the Forbidden thoughts factor in adults and with the Cleaning factor in children. The shifting of checking symptoms from one factor to another is likely attributable to the inherent ambiguity of checking symptoms in the Y-BOCS-SC. This ambiguity in the checking category of the Y-BOCS-SC has been addressed in the newly developed dimensional OCD scales such as the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS), which associates specific checking and avoidance OC symptoms with each OC symptom dimension/ factor.[22]

Although the understanding of the dimensional structure of OC symptoms is still imperfect, this quantitative approach to phenotypic traits has the potential to advance our understanding of OCD, and may aid in the identification of more robust endophenotypes. As reviewed below, preliminary data suggest that these dimensional phenotypes may be useful in our efforts to understand the natural history, genetics, neurobiology, treatment response, and outcomes of OCD.[13,14]

A developmental perspective

Typically, developing children engage in a significant amount of ritualistic, repetitive, and compulsive-like activity. This phenomenon reaches a peak at about 24

months of age.[23] Remarkably, the content of these behaviors closely resembles the OC symptom dimensions.[24] For example, parents reported that their children arranged objects or performed certain behaviors until they seemed "just right" on average, beginning at 22 to 25 months of age (Factor II). Similarly, behaviors resembling those associated with the contamination/washing dimension were identified with such checklist items as, "Seemed very concerned with dirt or cleanliness," were found to have a mean age of onset from 22 to 24 months of age (Factor III). Finally, parents reported that their children on average began to "collect or store objects" (resembling the hoarding dimension) from 25 to 27 months of age (Factor IV). Although direct evidence linking the emergence of these behaviors to the later development of OCD is lacking, investigators have found that aspects of these ritualistic and compulsive-like behaviors are correlated with children's fears and phobias.[24-26] Further exploration of the factors that underlie the emergence and resolution of these behaviors in typically developing children may provide valuable insights into neurobiological substrates of OCD, as well as setting the stage for understanding subclinical forms of OCD.

Pediatric onset OCD

A dimensional approach does not exclude other methods to parse OCD. Thus far, a pediatric age of onset, the presence of other family members with OCD, and the individual's "tic-related" status appear to be potentially useful categorical distinctions *(Figure 1)*.[27] Epidemiological studies indicate that OCD affecting children and adolescents is a highly prevalent condition, with 2% to 4% of children being affected.[3-5]

Some of the strongest evidence for early-onset being a distinctive subtype of OCD comes from family-genetic studies that have consistently shown that the familial aggregation in OCD is largely concentrated among families with early-onset OCD probands.[19,28,29] For example, in the Nestadt et al[29] study, the age at onset of OC symptoms in the 80 case probands ranged from 5 to 41 years. The median age at onset of symptoms was approximately 11 years; more than 75% of the probands had onset by age 14 years, and 90% by age 17 years. They then dichotomized their OCD cases into early-onset (5 to 17 years) and late-onset (18 to 41 years) groups. The prevalence of OCD in the relatives of probands with early- vs late-onset was 13.8% vs 0% (*P*=.006). The Pauls et al[19]

study also documented the fact that there was a clear increase in the rate of subclinical OCD as well as OCD in the first-degree relatives of the early-onset probands. Family-genetic studies also provide the most compelling evidence that pediatric-onset OCD is etiologically heterogeneous. Specifically, there appears to be: a tic-related subtype; a familial, non-tic-related subtype; as well as a class of sporadic cases where no family history is evident *(Figure 1)*.

Tic-related OCD

The tic-related subtype may account for as many as 10% to 40% of the pediatric-onset OCD cases.[19,30-33] Even in family genetics studies where probands with Tourette syndrome (TS) were actively excluded, at least 10% of the early-onset OC cases were tic-related.[29,30] Consequently, we define "tic-related OCD" as being a condition in which tics are observed either in the proband or in one or more first-degree family members. Early-onset cases with a personal history of tics typically show a male predominance, and prominent OC symptoms in the Symmetry, Forbidden thoughts, and Hoarding dimensions, but fewer OC symptoms in the Cleaning dimension.[16-18] They are also much more likely to report the presence of sensory phenomena.[18,34,35] Another marker of the distinctive nature of early-onset OCD is a differing pattern of psychiatric comorbidity. Children
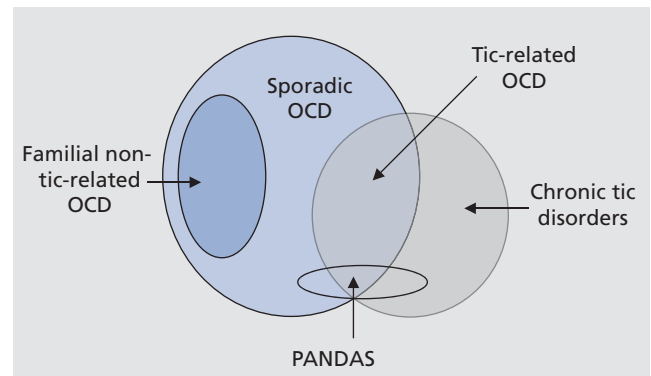
Figure 1. Venn diagram of obsessive-compulsive subtypes. In addition to adult-onset obsessive-compulsive disorder (OCD), there appear to be several subtypes of early-onset OCD. These include cases with a personal or family history of Tourette syndrome or a chronic tic disorder, as well as individuals without tics but with a strong family history of OCD. Other cases are sporadic, and some cases may reflect a postinfectious autoimmune disorder (pediatric autoimmune disorders associated with streptcoccal infections, PANDAS).

with tic-related OCD typically have higher rates of disruptive behavior disorders (attention deficit-hyperactivity disorder [ADHD] and oppositional defiant disorder), and trichotillomania, as well as other specific and pervasive developmental disorders.[36-39]

Thus far, with the possible exception of *Slit and Trk-like 1 (SLITRK1)*, no specific genes have been associated with tic-related OCD.[40] Neuroimaging studies have suggested that caudate volumes in childhood are predictive of future OCD severity in early adulthood as well as future tic severity.[41]

Although pediatric-onset OCD tends to respond well to behavioral interventions, particularly when combined with selective serotonin reuptake inhibitors (SSRIs),[27,42] it appears that the presence of tics reduces the beneficial effects of SSRI treatment but not cognitive-behavioral therapy (CBT) in children and adults.[43-45] In addition, individuals with tic-related OCD respond better to neuroleptic augmentation than do OCD patients without a personal history of a tic disorder.[46] The course and outcome of tic-related OCD may also be distinctive; characterized by an early peak in OC symptom severity at 12.5 years and followed by an increased likelihood of remission.[27,47]

Familial, non-tic-related early-onset OCD

This OCD subtype has been less fully characterized. First-degree family members are known to be at high risk for developing OCD and subclinical OCD, with approximately 25% being affected.[19] Many of these children are likely to be afflicted with obsessional concerns about the safety of close family members as well as contamination and compulsive washing. Higher than expected rates of anxiety and affective disorders are seen in early-onset cases and their first-degree family members. Generalized anxiety disorder (GAD), panic disorder, agoraphobia, separation anxiety disorder (SAD) and recurrent major depression are frequently encountered, especially if a first-degree relative was diagnosed with OCD.[48,49] It also appears that some portion of these early-onset cases will remit before adulthood.[50-53]

A number of small neuroimaging studies have been conducted in pediatric-onset OCD.[54] To a large extent, their findings are consistent with the prevailing frontal-striatal-thalamo-cortical model of the neural substrates of OCD. These studies have also provided evidence to support the role of glutamate in the pathology of OCD. As noted above, these individuals are more likely than the tic-related cases to respond to SSRI treatment.[27,42] They may also benefit from the use of glutamate modulating agents.[55]

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

It has been hypothesized that some susceptible individuals develop OC symptoms and tics as a result of post-infectious autoimmune processes. Infections with group A β-hemolytic streptococci (GABHS) have been hypothesized to be responsible. Swedo and colleagues have proposed that this subgroup, identified by the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), follows a unique "sawtooth" waxing and waning clinical course that is closely temporally linked to GABHS infections.[56] These sudden fluctuations complicate clinical management as well as the interpretation of efficacy and effectiveness of treatment studies.

The strongest evidence that GABHS may be involved in the onset of Tourette syndrome (TS) and OCD comes from a recent report by Mell et al.[57] This is a case-control study of 144 children 4 to 13 years old who received their first diagnosis of OCD, TS, or tic disorder between January 1992 and December 1999. Cases were matched to controls by birth date, sex, primary physician, and propensity to seek health care. Patients with OCD, TS, or tic disorder were more likely than controls to have had streptococcal infection in the 3 months before onset date. The risk was higher among children with multiple streptococcal infections within 12 months. Indeed, having multiple infections with group A β-hemolytic streptococcus within a 12-month period was associated with an increased risk of TS with an odds ratio of 13.6 (95% confidence interval 1.93-51.0). In addition to OCD, TS, and tic disorders, a specific link between ADHD and GABHS has been hypothesized,[58,59] and there is at least one case report and one epidemiological study where a link between GABHS and major depressive disorder (MDD) was also suggested.[58,60]

Brain imaging studies of PANDAS cases have consistently implicated the basal ganglia. Specific findings include the transient enlargement of the striatum and the basal ganglia as a whole.[59,61,62]

Although it has been postulated that GABHS infection must be the initial autoimmune response-inciting event but that subsequent symptom exacerbations can be trig-

gered by other infectious agents,[63] a number of other precipitants have been identified, including the common cold and *Mycoplasma pneumoniae* infections.[64-66] Future prospective longitudinal studies are needed to confirm these findings and to clarify whether there is a common underlying immunological response that triggers symptom worsening.

In clinical longitudinal studies the results have been mixed. One study, which followed unselected OCD and TS cases longitudinally for 1 year, indicated no more than a chance association between newly acquired GABHS infections and tic symptom exacerbations.[67] Similarly, a case-control study found little evidence of increased tic or OC symptoms in the aftermath of well-documented (and treated) GABHS infections, casting some doubt on the hypothesis.[68] Kurlan et al also recently reported equivocal findings from a 2-year prospective longitudinal study. [69] Of note however, this study did report a significantly higher rate of GABHS infections in the PANDAS cases.

Finally, a report based on a more complete data set from the earlier study by Luo et al[67] has recently been published that describes a study in which consecutive monthly ratings of OC, tic, and depressive symptom severity were obtained for 45 cases and 41 matched healthy control subjects over a 2-year period.[70] Cases and controls were prospectively monitored for the onset of new GABHS infections and the level of psychosocial stress. Structural equation modeling for unbalanced repeated measures was used to assess the temporal sequence of newly recognized GABHS infections and psychosocial stress with the severity of tic, OC, and depressive symptoms. Using this state-of-the-art modeling technique for longitudinal data, stringently defined new GABHS infections were predictive of future tic and OC symptom severity, but did not predict future depressive symptom severity. Inclusion of newly recognized GABHS infections in the model enhanced the power of psychosocial stress in predicting future tic severity.

Promising areas of research with the potential to advance the field

Refinement of available instruments and advancing the therapeutics of pediatric OCD

Additional work is needed to examine the factor structure of the next generation rating instrument—the Dimensional Yale-Brown Obsessive-Compulsive Scales

(DY-BOCS).[22] An item level factor analysis of the DY-BOCS is now under way involving >1000 individuals with OCD from Brazil, Spain, the USA, the UK, and Japan. These results will be of interest in resolving how best to understand the somatic symptoms, superstitions, and miscellaneous OC symptoms, as well as other dysfunctional repetitive behaviors including tics, trichotillomania, skin picking, body dysmorphic disorder, and eating disorders. Instruments like the DY-BOCS also have the potential to advance therapeutics by focusing the clinician's attention on specific symptom dimensions. In many respects, CBT for OCD is based on a dimensional perspective.[71] The efficacy of CBT for OCD has been demonstrated in numerous controlled and meta-analytic studies. However, a significant number of patients still remain unimproved, or simply refuse or drop out from this treatment. As reviewed elsewhere, adult patients with hoarding symptoms have been described as having poor compliance with and response to CBT. [13,14] For example, using a dimensional approach, Mataix-Cols and colleagues[72] examined 153 OCD outpatients who participated in a randomized controlled trial of CBT. Results showed that high scorers on the hoarding dimension were more likely to drop out prematurely from the trial and also tended to improve less than nonhoarding OCD patients. In addition, high scorers on the sexual/religious dimension responded less well to CBT. In a meta-analysis, patients with primary obsessive thoughts without rituals tended to improve less with CBT than those who had overt motor rituals.[73] In a study by Alonso and colleagues,[74] the presence of sexual and/or religious obsessions predicted poorer long-term outcome, but, because most patients received both SSRIs and CBT, it was not clear from this study whether these symptoms predicted poorer outcome with SSRIs, CBT, or both. Similar studies need to be undertaken in pediatric populations.

In adult studies, controlled trials with SSRIs have demonstrated a selective efficacy in OCD. However, up to 40% to 60% of patients do not have a satisfactory outcome.[75,76] Nonresponse to treatment in OCD is associated with serious social disability. These differences in treatment outcome emphasize the heterogeneity of OCD and the need for identifying predictors of treatment response. While definitive studies have not been undertaken, recent studies have suggested that a symptom-based dimensional approach may prove to be valuable for identifying significant predictors of treatment outcome. For example, at least five studies have shown that patients

with high scores on the hoarding dimension respond more poorly to SSRIs.[13,14] In another study, high scores on the sexual/religious obsessions factor identified by Matrix-Cols and colleagues were associated with poorer long-term outcome with SSRIs and behavior therapy in 66 adult outpatients who were followed up for 1 to 5 years.[77] Two other groups have recently reported that the presence of sexual obsessions was a predictor of nonresponse to SSRIs.[74,78] In future studies, if individuals with sexual obsessions and related compulsions are shown to be less likely to respond to SSRIs than individuals with obsessions about harm and related compulsions, this may argue for retaining sexual obsessions and related compulsions as a separate dimension as first proposed by Mataix-Cols et al.[77] Finally, preliminary studies from adult subjects indicate that patients with worries about harm (aggressive obsessions and compulsions) respond better to SSRIs than the remaining OCD patients.[79] Again, these studies need to be extended to adolescents with OCD and care needs to be taken to ensure the safety of these agents in prepubertal children.[80]

The importance of subclinical OCD

Obsessions and compulsions are frequently encountered in children and adults without OCD. The rate in children may be as high as 8%.[81] The rate in adults without a mental disorder may be as high as 13% to 15%, based on recent data.[81] Subclinical OCD can cause significant interference. For individuals with anxiety and mood disorders, the presence of fears of doing harm (Forbidden thoughts) is frequently associated with help-seeking behavior.[81] These obsessional thoughts are distressing and prompt avoidance and many of the compulsive rituals including touching, counting, checking doors and windows, and washing. Based on the recent Fullanna et al[81] data, it is clear that these individuals are at increased risk of developing OCD. Early interventions may be especially beneficial for these high-risk individuals.

Longitudinal studies

Variation between individuals at particular points in time can mask detection of potentially important developmental shifts. Longitudinal studies examining changes in risk exposure, OC symptoms, comorbid disorders, particularly when linked to performance on neuropsychological tests, brain processes, and immunological function.

Looking at these changes over a developmental time frame is likely to be a fruitful approach, particularly when linked with the ability to explore potential genetic determinants.[82] They have already proven their worth in studies of the temporal stability of OC symptom dimensions and psychosocial stress.[70,81,83] It is increasingly clear that obsessions and compulsions are common in the adult population, have their roots in childhood, and are associated with interference, risk for comorbid disorders, and help-seeking.[81] Longitudinal analyses could also have important implications in refining therapeutic decisions. Longitudinal studies of high-risk individuals who do not develop psychopathology may be especially valuable in elucidating protective factors, and serve as the basis for developing novel therapeutics.

Genetic studies

A dimensional approach may be particularly valuable for genetic studies, where it increasingly seems that some vulnerability genes may be shared by more than a single disorder, and that subthreshold cases are likely to be found in family members. An initial confirmation of this approach comes from the recent study by Hasler and colleagues,[84] which collected data from 418 sibling pairs with OCD. Among potentially relevant comorbid conditions for genetic studies, they found that bipolar I/II and major depressive disorder were strongly associated with the Forbidden thoughts factor, whereas ADHD, alcohol dependence, and bulimia were associated with the Symmetry factor.

Twin and family studies suggest that genetic factors play a role in the expression of OCD.[85] Recent advances in molecular genetics have greatly increased the capacity to localize disease genes on the human genome. These methods are now being applied to complex disorders, including OCD. Although earlier studies have indicated that the vertical transmission of OCD in families is consistent with the effects of a single major autosomal gene, it is likely that there are a number of vulnerability genes involved. One of the major difficulties in the application of these approaches is the likely etiologic heterogeneity of OCD and related phenotypes. Heterogeneity reduces the power of gene-localization methods, such as linkage analysis.[86-88] Etiologic heterogeneity may be reflected in phenotypic variability, making it highly desirable to dissect the syndrome, at the level of the phenotype, into valid quantitative heritable components.

van Grootheest et al[89] recently reviewed the twin literature and concluded that in pediatric onset OCD, OC symptoms are heritable, with genetic influences in the range of 45% to 65%. In adult onset, the evidence indicates a somewhat lower estimate, ranging from 27% to 47%. OC symptom dimensions have rarely been evaluated in the context of twin studies, with the one exception being a recent study by van Grootheest et al[90] In this study, data from a population sample of 1383 female twins from the Virginia Twin Registry was examined. OC symptoms were measured by a self-report questionnaire with 20 items from the Padua Inventory. Investigators found that each of the OC symptom dimensions shared variation with a latent common factor. Variation in this common factor was explained by both genes (36%) and environmental factors (64%). In their data only the Contamination dimension appeared to be influenced by specific genes.

Like many other psychiatric disorders, family and affected sibling studies also suggest that genetic factors play a role in the expression of OCD. Alsobrook and colleagues[91] were the first to use OC symptom dimensions in a family-genetic study. They found that the relatives of OCD probands who had high scores on the obsessions/checking and symmetry/ordering factors were at greater risk for OCD than were relatives of probands who had low scores on those factors. The finding that relatives of OCD probands who had high scores on symmetry/ordering were at greater risk for OCD than were relatives of probands who had low scores has been replicated in a second independent family study.[92]

Using data collected by the Tourette Syndrome Association International Consortium for Genetics Affected Sibling Pair Study, Leckman and colleagues[93] selected all available affected TS pairs and their parents for which these OC symptom dimensions (factor scores) could be generated using the four-factor algorithm. Remarkably, 50% of the siblings with TS were found to have comorbid tic-related OCD and >30% of mothers and 10% of fathers also had a diagnosis of OCD. The scores for both Factor I (aggressive, sexual, and religious obsessions and checking compulsions) and Factor II (symmetry and ordering) were significantly correlated in sibling pairs concordant for TS. In addition, the mother-child correlations, but not father-child correlations, were significant for these two factors. Based on the results of the complex segregation analyses, significant evidence for genetic transmission was obtained for all factors.

A recent study of 418 sibling pairs with OCD[94] found robust sibling-sibling intraclass correlations (after controlling for sex, age, and age of onset) for Factor IV (hoarding obsessions and compulsions) and Factor I (aggressive, sexual, and religious obsessions and checking compulsions). A smaller, but still significant, sib-sib intraclass correlation was found for Factor III (contamination/cleaning; *P*=.02) and Factor II (symmetry/ordering/arranging). Limiting the sample to female subjects more than doubled the sib-sib intraclass correlations for Factor II. Another much smaller study of 40 sibling pairs from Brazil found significant, sib-sib intraclass correlations when both siblings were female for Factor IV (hoarding).[94] When both siblings were male, they also reported a significant sib-sib intraclass correlation for Factor III (contamination/washing).

Future efforts to define the genetically determined host factors that may predispose someone to develop PANDAS is also clearly needed. Thus far, the only hint has been that patients with rheumatic fever typically have positive family histories of OCD, and that PANDAS cases have a higher rate of rheumatic fever in their familes.[69,95]

In sum, the use of quantitative traits that are familial may provide a powerful approach for detecting the genetic susceptibility loci that contribute to OCD. Our prediction is that some genes will be specific to certain OC symptom dimensions, while others will be "generalist" genes that influence the expression of OCD and closely related disorders including tic disorders, trichotillomania, body dysmorphic disorder, and various eating disorders. These generalist genes may exist within modules of coexpressed genes that are functionally related. Using this framework, it will be worthwhile to determine whether overlapping transcriptional networks underlie the expression of the OC spectrum of normal phenomena as they are regulated by specific evolutionarily conserved neural networks. Then when these networks become dysregulated, for whatever reason, OCD and related disorders emerge as disorders of mind, brain, and behavior.

Nongenetic risk factors

Despite our enthusiasm for the identification of dimension specific and subtype specific OCD vulnerability genes, it should also be noted that environmental factors doubtless play an important role in the transmission of these traits across generations. Indeed, the bulk of the

evidence concerning familial risk has come from affected sibling-pair studies and genetic family studies. In contrast to twin and adoption studies, the design of these studies simply tests for familial transmission; they do not exclude the likely role of nongenetic familial transmission, in which family members can serve as models for dysfunctional behaviors. More work is needed to identify the environmental factors that foster the onset and course of these symptoms. To date, the strongest evidence points to maternal adverse perinatal events,[96-98] and early psychosocial adversities as being associated with the future development of OCD.[99-103] Psychosocial stress is also a powerful determinant of future OCD severity, which in turn is predictive of the severity of future depressive symptoms.[70,83] Finally, sorting out the complexities of the interface between the central nervous system and the developing innate and adaptive immune systems is another major challenge for the field.[104]

Imaging studies

Functional neuroimaging studies have the potential to provide further validation of a dimensional approach to OCD and its various subtypes. Taken as a whole, these studies strongly link OC symptoms with altered activation of the orbito-frontal cortex, with less consistent involvement of anterior cingulate gyrus, lateral frontal and temporal cortices, caudate nucleus, thalamus, amygdala, and insula.[54,105-117] A growing number of imaging studies are now incorporating ratings of OC symptom dimensions. In the first such study, using positron emission tomography, Rauch et al[108] found that checking symptoms correlated with increased, and symmetry/ordering with reduced, regional cerebral blood flow in the striatum, while washing symptoms correlated with increased regional cerebral blood flow in the bilateral anterior cingulate and left orbitofrontal cortex. Phillips et al,[109] using functional magnetic resonance imagine (fMRI) compared OCD patients with mainly washing (n=7) or checking (n=7) symptoms, while they viewed pictures of either normally disgusting scenes or washer-relevant pictures. When viewing washing-related pictures, only washers demonstrated activations in regions implicated in emotion and disgust perception (ie, visual regions and insular cortex), whereas checkers demonstrated activations in frontostriatal regions and the thalamus. In a similar study, eight OCD patients with predominantly washing symptoms demonstrated greater

activation than controls in the right insula, ventrolateral prefrontal cortex, and parahippocampal gyrus when viewing disgust-inducing pictures.[110] Another study[111] found increased amygdala activation in a group of 11 washers during the presentation of contamination-related pictures. Saxena et al[112] found that 12 patients with predominantly hoarding symptoms showed reduced glucose metabolism in the posterior cingulate gyrus (vs controls) and the dorsal anterior cingulate cortex (vs nonhoarding OCD patients) and that severity of hoarding in the whole patient group (n=45) correlated negatively with metabolism in the latter region.

One elegant fMRI study[113] used a symptom provocation paradigm to examine, within the same patients, the neural correlates of washing, checking, and hoarding symptom dimensions of OCD. Each of these dimensions was mediated by distinct but partially overlapping neural systems. While patients and controls activated similar brain regions in response to symptom provocation, patients showed greater activations in the bilateral ventromedial prefrontal regions (washing experiment), putamen/globus pallidus, thalamus, and dorsal cortical areas (checking experiment), left precentral gyrus, and right orbitofrontal cortex (hoarding experiment). These results were further supported by correlation analyses within the patient group, which revealed highly specific positive associations between subjective anxiety, questionnaire scores, and neural response in each experiment. Another recent study[114] demonstrated that eight patients with predominant washing symptoms showed increased neural responses to disgusting (but not fearful) faces, compared with nonwashing OCD patients (n=8) and healthy controls (n=19). Specifically, washers showed greater activation in the left ventrolateral prefrontal cortex (Brodmann area 47) compared with the other two groups. Finally, a study by Rauch and colleagues[115] tested for associations between OCD symptom factors and regional brain activation during an implicit learning task. They found that activation within the right caudate was inversely correlated with the symmetry/arranging (Factor II) and contamination/washing (Factor III) symptom dimensions; left orbitofrontal activation was directly correlated with the sexual/religious/aggressive/counting factor (Factor I) symptom severity.

Many of the most recent imaging studies have not included dimensional measures, or alternatively they have excluded OCD cases with prominent hoarding symptoms as a means of studying a more homogeneous

subgroup of cases.[116,117] The variability in these studies raises the question of whether the inconsistencies in previous imaging studies of OCD could be accounted for by phenotypic variations among their subjects. If these preliminary findings are confirmed, and a consistent pattern of results can be documented by symptom factor, this would suggest that discrete neural systems are activated in association with the evocation of specific OCS. We would predict that if a dimensional approach is useful, then a significant portion of the individual variation seen in these studies may be accounted for by the unique mix of symptom dimensions seen in any given patient. Initial studies generally support this conclusion.

The pursuit of endophenotypes

Neuropsychological testing in adults with OCD has demonstrated deficits in visuospatial skill, inhibitory control reversal learning, and less consistent deficits in cognitive set shifting and executive planning.[118-124] In adults with OCD, the most exciting findings to date are those recently reported by Chamberlain et al.[107] They have reported abnormally reduced activation of several cortical regions, including the lateral orbitofrontal cortex, during reversal learning in OCD patients and their clinically unaffected close relatives, supporting the existence of an underlying previously undiscovered endophenotype. If this truly is a "trait" finding, then it will be critical to determine when these patterns first become evident, and whether or not they are associated with specific OC symptom dimensions or subtypes of disease. Neuropsychological testing data on children with OCD is comparably sparse. On the other hand, measures of intelligence in children with OCD have been fairly well studied. Higher full-scale intelligence in childhood has been associated with the future development of OCD in a population-based sample.[39] This finding was replicated in a longitudinal follow-up study of long-term outcome of children with tic-related OCD, in which a higher childhood IQ was associated with increased severity of OC symptoms in adulthood.[47] Recently, Bloch et al (unpublished data) reported that a greater verbal-performance IQ discrepancy was associated with pediatric onset OCD. This association of verbal-performance IQ discrepancy and OCD was still significant after adjusting for full-scale IQ, age, and gender and excluding OCD subjects with comorbid ADHD or TS. Again, it will be crucial to determine if this is a "trait" marker. If it is, then it will be important to deter-

mine when this neurophysiological profile first becomes evident, and whether or not it is associated with specific OC symptom dimensions or subtypes of disease.

A final promising endophenotype concerns potential deficits in sensorimotor gating and the use of electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings to identify at-risk individuals. As in TS and schizophrenia, some individuals with OCD present with deficits in sensorimotor gating typically defined through a reduction in prepulse inhibition.[125,126] These deficits may help us understand how normally occurring intrusive thoughts (eg, a thought about harm coming to one's own child) come to be regarded as highly meaningful (eg, "This thought means I am a terrible person and a potential danger to my child"); and how once they are established they can create a vicious cycle that to some degree is self rinforcing. We speculate that neurons within the frontal-striatal-thalamo-cortical circuits form behavior-dependent oscillating networks of various sizes and frequencies that bias input selection in favor of these normally occurring thoughts and their negative appraisal, and that at least in some cases this is due to a loss of striatal interneurons.[127-129] Coherent activity within these networks is likely to modulate sensorimotor gating as well as to lead to goal-directed motor actions. When these networks are dysrhythmic, there may be a loss of control of sensory and cognitive inputs and subsequent motor action. The known electrophysiological effects of medications, repetitive transcranial magnetic stimulation, and surgical interventions used to treat OCD are likely to have an ameliorative effect on these aberrant oscillations.[130,131] Similarly, a case can be made that successful behavioral treatments involve the willful training of regions of the prefrontal cortex not to make a motor response to these unwanted cognitive and sensory urges, so that these prefrontal regions can become effective modulators of aberrant thalamocortical rhythms.

Conclusions

In addition to the existence of subtypes of OCD, a strong case can be made to support the use of a dimensional approach to OC symptoms. A dimensional approach, combined with a developmental framework, should permit the integration of new knowledge from a broad range of scientific disciplines from genetics and neurobiology to the development of safe and effective treatments, perhaps ones tailored to specific dimensions. The quantita-

tive nature of these dimensions should also prove to be another important asset, as it will add statistical power and readily allow the inclusion of subthreshold cases across a broad range of studies, including population-based studies.[81]

As we are currently in the midst of revising our diagnostic manuals, it is worth noting that the available data strongly support current dimensional views of psychopathology in general and OCD in particular and have implications for DSM-V. First, the specification of subtypes of OCD as well as the major symptom dimensions of OCD in the DSM-V would better capture the heterogeneity of the disorder and encourage further research in the field.[132] Second, it will be important to specify the presence of subsyndromal OCD, as it is frequently associated with help-seeking behavior and a variety of comorbid conditions.[81] ❏

REFERENCES

1. Karno M, Golding J, Sorenson S, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45:1094-1099.
2. Weissman M, Bland R, Canino G, et al. The cross national epidemiology of obsessive compulsive disorder. *Am J Psychiatry*. 1994;55(suppl):5-10.
3. Flament M, Whitaker A, Rapoport J, et al. Obsessive compulsive disorder in adolescence: an epidemiological study. *J Am Acad Child Adolesc Psychiatry*. 1988;27:764-771.
4. Valleni-Basile L, Garrison C, Jackson K, et al. Frequency of obsessive-compulsive disorder in a community sample of young adolescents. *J Am Acad Child Adolesc Psychiatry*. 1994;33:782-791.
5. Douglass HM, Moffitt TE, Dar R, McGee R, Silva P. Obsessive-compulsive disorder in a birth cohort of 18-year-olds: prevalence and predictors. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1424-1431.
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
7. World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organization; 1992.
8. Hantouche EG, Lancrenon S. Modern typology of symptoms and obsessive-compulsive syndromes: results of a large French study of 615 patients [French]. *Encephale*. 1996;22:9-21.
9. Rachman SJ, Hodgson RJ. *Obsessions and Compulsions*. Englewood Cliffs, NJ: Prentice-Hall; 1980.
10. Khanna S, Mukherjee D. Checkers and washers: valid subtypes of obsessive compulsive disorder. *Psychopathology*. 1992;25:283-288.
11. Horesh N, Dolberg OT, Kirschenbaum-Aviner N, Kotler M. Personality differences between obsessive-compulsive disorder subtypes: washers versus checkers. *Psychiatry Res*. 1997;71:197-200.
12. Matsunaga H, Kiriike N, Matsui T, et al. A comparative study of clinical features between pure checkers and pure washers categorized using a lifetime symptom rating method. *Psychiatry Res*. 2001;105:221-229.
13. Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry*. 2005;162:228-238.
14. Leckman JF, Rauch SL, Mataix-Cols D. Symptom dimensions in obsessive-compulsive disorder: implications for the DSM-V. *CNS Spectr*. 2007;12:376-387.
15. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
16. Baer L. Factor analysis of symptom subtypes of obsessive-compulsive disorder and their relation to personality and tic disorders. *J Clin Psychiatry*. 1994;55(suppl):18-23.
17. Leckman JF, Grice DE, Boardman J, et al. Symptoms of obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:911-917.
18. Leckman JF, Walker W K, Goodman WK, Pauls DL, Cohen DJ. "Just right" perceptions associated with compulsive behaviors in Tourette's syndrome. *Am J Psychiatry*. 1994;151:675-680.
19. Pauls DL, Alsobrook J, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive compulsive disorder. *Am J Psychiatry*. 1995;152:76-84.
20. Summerfeldt LJ, Richter MA, Antony MM, Swinson RP. Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analytic study. *Behav Res Ther*. 1999;37:297-311.
21. Bloch MH, Landeros-Weisenberger A, Rosario-Campos MC, Pittenger C, Leckman JF. Systematic review of the factor structure of obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165:1229-1233.
22. Rosario-Campos MC, Miguel EC, Quatrano S, et al. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. *Mol Psychiatry*. 2006;11:495-504.
23. Gesell A, Ilg F. *Infant and Child in the Culture of Today. The Guidance of Development in Home and Nursery School*. New York, NY: Harper & Brothers Publishers; 1943.
24. Evans DW, Leckman JF, Carter A, Reznick JS, Henshaw D, Pauls DL. Ritual, habit, and perfectionism: the prevalence and development of compulsive like behavior in normal young children. *Child Dev*. 1997;68:58-68.
25. Zohar AH, Felz L. Ritualistic behavior in young children. *J Abnorm Child Psychol*. 2001;29:121-128.
26. Evans DW, Gray FL, Leckman JF. The rituals, fears and phobias of young children: insights from development, psychopathology and neurobiology. *Child Psychiatry Hum Dev*. 1999;29:261-276.
27. Geller DA. Obsessive-compulsive and spectrum disorders in children and adolescents. *Psychiatr Clin North Am*. 2006;29:353-370.
28. Leonard HL, Lenane MC, Swedo SE, Rettew DC, Gershon ES, Rapoport JL. Tics and Tourette's disorder: A 2- to 7-year follow-up of 54 obsessive-compulsive children. *Am J Psychiatry*. 1992;149:1244-1251.
29. Nestadt G, Samuels J, Riddle M, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:358-363.
30. Grados MA, Riddle MA, Samuels JF, et al. The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biol Psychiatry*. 2001;50:559-565.
31. Chabane N, Delorme R, Millet B, Mouren MC, Leboyer M, Pauls D. Early-onset obsessive-compulsive disorder: a subgroup with a specific clinical and familial pattern? *J Child Psychol Psychiatry*. 2005;46:881-887.
32. do Rosario-Campos MC, Leckman JF, Curi M, et al. A family study of early-onset obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2005;136B:92-97.
33. Leckman JF, Grice DE, Barr LC, et al. Tic-related vs. non-tic-related obsessive compulsive disorder. *Anxiety*. 1994;1:208-215.
34. Miguel EC, do Rosário-Campos MC, Prado HS, et al. Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. *J Clin Psychiatry*. 2000;61:150-156.
35. Prado HS, Rosário MC, Lee J, Hounie AG, Shavitt RG, Miguel EC. Sensory phenomena in obsessive-compulsive disorder and tic disorders: a review of the literature. *CNS Spectr*. 2008;13:425-432.
36. Khalifa N, von Knorring A-L. Prevalence of the tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol*. 2003;45:315-319.
37. Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34:19-27.

Dimensiones sintomáticas y subtipos del trastorno obsesivo-compulsivo: una perspectiva del desarrollo

Debido a la ausencia de marcadores etiológicos específicos para el trastorno obsesivo-compulsivo (TOC), las dimensiones de síntomas obsesivo-compulsivos (OC) pueden ofrecer una orientación útil. Estas dimensiones pueden ser entendidas como una definición virtual de características clínicas que se sobreponen y que pueden constituir un continuo con las preocupaciones "normales" que se manifiestan tempranamente en la niñez. Aunque la comprensión de la estructura dimensional de los síntomas OC aun es imperfecta, un reciente meta-análisis de gran escala ha confirmado la presencia de a lo menos cuatro dimensiones de síntomas identificables tanto en niños como en adultos con TOC. Una aproximación dimensional no excluye otros métodos para analizar el TOC. Hasta ahora, las diferencias categóricas que parecerían ser potencialmente útiles son: el inicio del cuadro en edad pediátrica, la presencia de otros miembros de la familia con TOC y los "tics relacionados" que tenga el sujeto. Aunque las dimensiones de síntomas OC parecen ser válidas para todas las edades, es improbable que los factores de vulnerabilidad genética y los sustratos neurobiológicos subyacentes a cada una de estas dimensiones de síntomas sean los mismos a través del curso del desarrollo.

Sous-types et importance des symptômes des troubles obsessionnels compulsifs : perspective de développement

En l'absence de marqueurs étiologiques explicites pour les troubles obsessionnels compulsifs (TOC), les dimensions symptomatiques peuvent offrir une voie d'orientation fructueuse. Ces dimensions peuvent s'expliquer en définissant des tableaux cliniques potentiellement chevauchants, en continuité avec les inquiétudes « normales » se manifestant d'abord dans l'enfance. Bien que la compréhension de la structure dimensionnelle des symptômes OC soit encore imparfaite, une métaanalyse récente à grande échelle a confirmé la présence d'au moins quatre dimensions distinctes chez l'enfant, comme chez les adultes ayant des TOC. Cette approche dimensionnelle n'exclut pas d'autres méthodes pour analyser les TOC. Jusqu'ici, un âge de début durant l'enfance, la présence de TOC chez d'autres membres de la famille et la présence de tics ou apparentés semblent être utiles pour distinguer les catégories. Les dimensions symptomatologiques du TOC semblent être adaptées pour tous les âges, mais il est improbable que pour chacune de ces dimensions les substrats neurobiologiques et les facteurs de vulnérabilité génétiques sous-jacents soient les mêmes au cours du développement.

38. Stewart SE, Jenike MA, Keuthen NJ. Severe obsessive-compulsive disorder with and without comorbid hair pulling: comparisons and clinical implications. *J Clin Psychiatry*. 2005;66:864-869.
39. Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. *J Am Acad Child Adolesc Psychiatry*. 2001;40:685-695.
40. Abelson JF, Kwan KY, O'Roak BJ, et el. Mutations in SLITRK1 are associated with Tourette syndrome. *Science*. 2005;310:317-320.
41. Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology*. 2005;65:1253-1258.
42. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292:1969-1976.
43. McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR, Price LH. The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. *J Clin Psychopharmacol*. 1993;13:354-358.
44. March JS, Franklin ME, Leonard H, et al. Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 2007;61:344-347.

45. Storch EA, Merlo LJ, Larson MJ, et al. Impact of comorbidity on cognitive-behavioral therapy response in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2008;47:583-592.
46. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11:622-632.
47. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med*. 2006;160:65-69.
48. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. *Psychol Med*. 2001;31:481-487.
49. Carter AS, Pollock RA, Suvak MK, Pauls DL. Anxiety and major depression comorbidity in a family study of obsessive-compulsive disorder. *Depress Anxiety*. 2004;20:165-174.
50. Leonard HL, Swedo SE, Lenane MC, et al. A 2- to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. *Arch Gen Psychiatry*. 1993;50:429-439.
51. Geller DA, Biederman J, Faraone S, et al. Developmental aspects of obsessive compulsive disorder: findings in children, adolescents, and adults. *J Nerv Ment Dis*. 2001;189:471-477.

52. Reddy YC, Srinath S, Prakash HM, et al. A follow-up study of juvenile obsessive-compulsive disorder from India. *Acta Psychiatr Scand*. 2003;107:457-464.

53. Stewart SE, Geller DA, Jenike M, et al. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. *Acta Psychiatr Scand*. 2004;110:4-13.

54. MacMaster FP, O'Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2008;44:1262-1272.

55. Pittenger C, Kelmendi B, Wasylink S, Bloch MH, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a series of 13 cases, with long-term follow-up. *J Clin Psychopharmacol*. 2008;28:363-367.

56. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155:264-271.

57. Mell LK, Davis RL, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. *Pediatrics*. 2005;116:56-60.

58. Leslie Dl, Kozma L, Martin A, et al. Neuropsychiatric disorders associated with streptococcal infection: a case-control study among privately insured children. *J Am Acad Child Adolesc Psychiatry*. 2009. In press.

59. Peterson BS, Leckman JF, Tucker D, et al. Preliminary findings of anti-streptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch Gen Psychiatry*. 2000;57:364-372.

60. Fernández-Rivas A, Terreros MT, Ibarmia J, Lantarón G, González-Torres MA. Recurrent depression: infectious-autoimmune etiology? *J Am Acad Child Adolesc Psychiatry*. 2000;39:810-812.

61. Tucker DM, Leckman JF, Scahill L, et al. A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1684-1691.

62. Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry*. 2000;157:281-283.

63. Hoekstra PJ, Manson WL, Steenhuis M-P, Kallenberg CG, Minderaa RB. Association of common cold with exacerbations in pediatric but not adult patients with tic disorder: a prospective longitudinal study. *J Child Adolesc Psychopharm*. 2005;15:285-292.

64. Müller N, Riedel M, Blendinger C, Oberle K, Jacobs E, Abele-Horn M. Mycoplasma pneumoniae infection and Tourette's syndrome. *Psychiatry Res.* 2004;129:119-125.

65. Termine C, Uggetti C, Veggiotti P, et al. Long-term follow-up of an adolescent who had bilateral striatal necrosis secondary to Mycoplasma pneumoniae infection. *Brain Dev*. 2005;27:62-65.

66. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G. Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. *J Child Neurol*. 2008; 23:338-340.

67. Luo F, Leckman JF, Katsovich L et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. *Pediatrics*. 2004;113:e578-e585.

68. Perrin EM, Murphy ML, Casey JR, et al. Does group A ß-hemolytic streptococcal infection increase risk for behavioral and neuropsychiatric symptoms in children? *Arch Pediatr Adolesc Med*. 2004;158:848-856.

69. Kurlan R, Johnson D, Kaplan EL; and the Tourette Syndrome Study Group. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. *Pediatrics*. 2008;121:1188-1197.

70. Lin H, Williams KA, Katsovich L, et al. Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. In press.

71. McKay D, Abramowitz JS, Calamari JE, et al. A critical evaluation of obsessive-compulsive disorder subtypes: symptoms versus mechanisms. *Clin Psychol Rev*. 2004;24:283-313.

72. Mataix-Cols D, Marks IM, Gresit JH, Kobak KA, Bear L. Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behavior therapy: results from a controlled trial. *Psychother Psychosom*. 2002;71:255-262.

73. Foa EB, Goldstein A. Continuous exposure and complete response prevention in the treatment of obsessive-compulsive neurosis. *Behav Ther*. 1978;9:821829.

74. Alonso MP, Menchon JM, Pifarre J, et al. Long-term follow-up and predictors of clinical outcome in obsessive-compulsive patients treated with serotonin reuptake inhibitors and behavioral therapy. *J Clin Psychiatry*. 2001;62:535-540.

75. Hollander E, Bienstock CA, Koran LM, et al. Refractory obsessive-compulsive disorder: state-of-the-art treatment. *J Clin Psychiatry*. 2002;63:20-29.

76. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11:622-632.

77. Matrix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 1999;156;1409-1416.

78. Ferrao YA, Shavitt RG, Bedin NR, et al. Clinical features associated to treatment response in obsessive-compulsive disorder. *J Affect Disord*. 2006;94:199-209.

79. Landeros-Weisenberger A, Bloch MH, Kelmendi B, Wegner R, Leckman JF, Coric V. Dimensional predictors of response to SRI pharmacotherapy in obsessive-compulsive disorder. *Neuropsychopharmacology*. 2006;31:S94-S94.

80. Leckman JF, King RA. A developmental perspective on the controversy surrounding the use of SSRIs to treat pediatric depression. *Am J Psychiatry*. 2007;164:1304-1306.

81. Fullana MA, Mataix-Cols D, Caspi A, Harrington H, Grisham JR, Moffitt TE, Poulton R. Obsessions and compulsions in the community: prevalence, interference, help-seeking, developmental stability and co-occurring psychiatric conditions. *Am J Psychiatry*. 2009. In press.

82. National Advisory Mental Health Council, Workgroup on Neurodevelopment. *Transformative Neurodevelopmental Research in Mental Ilness*. 2008.

83. Lin H, Katsovich L, Ghebremichael M, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *J Child Psychol Psychiatry*. 2007;48:157-166.

84. Hasler G, Pinto A, Greenberg BD, et al. Familiarity of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD Collaborative Genetics Study. *Biol Psychiatry*. 2007;61:617-625.

85. Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genet C Semin Med Genet*. 2008;148:133-139.

86. Alcais A, Abel L. Maximum-Likelihood-Binomial method for genetic model-free linkage analysis of quantitative traits in sibships. *Genet Epidemiol*. 1999;17:102-117.

87. Gu C, Province M, Todorov A, Rao DC. Meta-analysis methodology for combining non-parametric sibpair linkage results: genetic homogeneity and identical markers. *Genet Epidemiol*. 1998;15:609-626.

88. Zhang H, Risch N. Mapping quantitative-trait loci in humans by use of extreme concordant sib pairs: selected sampling by parental phenotypes. *Am J Hum Genet*. 1996;59:951-957.

89. van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive-compulsive disorder: A review. *Twin Res Hum Genet*. 2005;8:450-458.

90. van Grootheest DS, Boomsma DI, Hettema JM, Kendler KS. Heritability of obsessive-compulsive symptom dimensions. *Am J Med Genet B Neuropsychiatr Genet*. 2008;47B:473-478.

91. Alsobrook II JP, Leckman JF, Goodman WK, Rasmussen SA, Pauls DL. Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. *Am J Med Genet*. 1999;88:669-675.

92. Hanna GL, Fischer DJ, Chadha KR, Himle JA, Van Etten M. Familial and sporadic subtypes of early-onset obsessive-compulsive disorder. *Biol Psychiatry*. 2005;57:895-900.

93. Leckman JF, Pauls DL, Zhang H, et al. Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2003;116:60-68.

94. Chacon P, Rosario-Campos MC, Pauls DL, et al. Obsessive-compulsive symptoms in sibling pairs concordant for obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B:551-555.

95. Hounie AG, Pauls DL, Do Rosario-Campos MC, et al. Obsessive-compulsive spectrum disorders and rheumatic fever: a family study. *Biol Psychiatry*. 2007;61:266-272.

96. Santangelo SL, Pauls DL, Goldstein JM, Faraone SV, Tsuang MT, Leckman JF. Tourette's syndrome: what are the influences of gender and comorbid obsessive-compulsive disorder? *J Am Acad Child Adolesc Psychiatry*. 1994;33:795-804.

97. Vasconcelos MS, Sampaio AS, Hounie AG, et al. Prenatal, perinatal, and postnatal risk factors in obsessive-compulsive disorder. *Biol Psychiatry*. 2007;61:301-307.

98. Geller DA, Wieland N, Carey K, et al. Perinatal factors affecting expression of obsessive compulsive disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 2008;18:373-379.

99. Hollingsworth CE, Tanguay PE, Grossman L, Pabst P. Long-term outcome of obsessive-compulsive disorder in childhood. *J Am Acad Child Psychiatry*. 1980;19:134-144.

100. Khanna S, Rajendra P, Channabasavanna S. Life events and onset of obsessive compulsive disorder. *Int J Soc Psychiatry*. 1980;113:823-832.

101. McKeon J, Roa B, Mann A. Life events and personality traits in obsessive compulsive neurosis. *Br J Psychiatry*. 1984;144:185-189.

102. Toro J, Cervera M, Osejo E, Salamero M. Obsessive compulsive disorder in childhood and adolescence: a clinical study. *J Child Psychol Psychiatry*. 1992;33:1025-1037.

103. Lensi P, Cassano G, Correddu S, Ravagli J, Kunovac J, Akiskal H. Obsessive compulsive disorder: familial development history symptomatology, comorbidity and course with special reference to gender related differences. *Br J Psychiatry*. 1996;169:101-107.

104. Kirvan CA, Swedo SE, Kurahara D, Cunningham MW. Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. *Autoimmunity*. 2006;39:21-29.

105. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;23:563-586.

106. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. 2008;32:525-549.

107. Chamberlain SR, Menzies L, Hampshire A, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008;321:421-422.

108. Rauch SL, Dougherty DD, Shin LM, et al. Neural correlates of factor-analyzed OCD symptom dimension: a PET study. *CNS Spectr*. 1998;3:37-43.

109. Phillips ML, Marks IM, Senior C, et al. A differential neural response in obsessive-compulsive patients with washing compared with checking symptoms to disgust. *Psychol Med*. 2000;30:1037-1050.

110. Shapira NA, Liu Y, He AG, et al. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. *Biol Psychiatry*. 2003;54:751-756.

111. Van den Heuvel OA, Veltman DJ, Groenewegen HJ, et al. Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. *Psychiatry Res*. 2004;132:225-237.

112. Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. *Am J Psychiatry*. 2004;161:1038-1048.

113. Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2004;61:564-576.

114. Lawrence NS, An SK, Mataix-Cols D, Ruths F, Speckens A, Phillips ML. Neural responses to facial expressions of disgust but not fear are modulated by washing symptoms in OCD. *Biol Psychiatry*. 2007;61:1072-1080.

115. Rauch SL, Wedig MM, Wright CI, et al. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry*. 2007;61:330-336.

116. Menzies L, Williams G, Chamberlain SR, et al. White matter abnormalities in patients with obsessive-compulsive disorder and their first-degree relatives. *Am J Psychiatry*. 2008;165:1308-1315.

117. Szeszko PR, Christian C, Macmaster F, et al. Gray matter structural alterations in psychotropic drug-naive pediatric obsessive-compulsive disorder: an optimized voxel-based morphometry study. *Am J Psychiatry*. 2008;165:1299-1307.

118. Tallis F. The neuropsychology of obsessive-compulsive disorder: a review and consideration of clinical implications. *Br J Clin Psychol*. 1997;36(Pt 1):3-20.

119. Savage CR, Baer L, Keuthen NJ, Brown HD, Rauch SL, Jenike MA. Organizational strategies mediate nonverbal memory impairment in obsessive-compulsive disorder. *Biol Psychiatry*. 1999;45:905-916.

120. Savage CR, Deckersbach T, Wilhelm S, et al. Strategic processing and episodic memory impairment in obsessive compulsive disorder. *Neuropsychology*. 2000;14:141-151.

121. Savage CR. Neuropsychology of OCD: research findings and treatment implications. In: Jenike MA, Baer L, Minichello WE, eds. *Obsessive-Compulsive Disorders: Practical Management*. St. Louis, MO: Mosby; 1998;254-275.

122. Chamberlain SR, Fineberg NA, Menzies LA, et al. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2007;164:335-338.

123. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. 2008;32:525-549.

124. Chamberlain SR, Menzies L, Hampshire A, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008;321:421-422.

125. Rossi S, Bartalini S, Ulivelli M, et al. Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. *Biol Psychiatry*. 2005;57:16-20.

126. Hashimoto T, Shimizu E, Koike K, et al. Deficits in auditory P50 inhibition in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:288-296.

127. Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A*. 1999;96:15222-15227.

128. Leckman JF, Vaccarino FM, Kalanithi PS, Rothenberger A. Tourette syndrome: a relentless drumbeat--driven by misguided brain oscillations. *J Child Psychol Psychiatry*. 2006;47:537-550.

129. Kalanithi PS, Zheng W, Kataoka Y, et al. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. *Proc Natl Acad Sci U S A*. 2005;102:13307-13312.

130. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). *Int J Neuropsychopharmacol*. 2006;9:95-100.

131. Greenberg BD, Gabriels LA, Malone DA Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry*. In press.

132. Mataix-Cols D, Pertusa A, Leckman JF. Issues for DSM-V: How should obsessive-compulsive disorder be classified? *Am J Psychiatry*. 2007;164:1313-1314.