Obsessive-compulsive disorder and its related disorders: a reappraisal of obsessive-compulsive spectrum concepts

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Obsessive-compulsive disorder (OCD) is a clinical syndrome whose hallmarks are excessive, anxiety-evoking thoughts and compulsive behaviors that are generally recognized as unreasonable, but which cause significant distress and impairment. When these are the exclusive symptoms, they constitute uncomplicated OCD. OCD may also occur in the context of other neuropsychiatric disorders, most commonly other anxiety and mood disorders. The question remains as to whether these combinations of disorders should be regarded as independent, co-occurring disorders or as different manifestations of an incompletely understood constellation of OCD spectrum disorders with a common etiology. Additional considerations are given here to two potential etiology-based subgroups: (i) an environmentally based group in which OCD occurs following apparent causal events such as streptococcal infections, brain injury, or atypical neuroleptic treatment; and (ii) a genomically based group in which OCD is related to chromosomal anomalies or specific genes. Considering the status of current research, the concept of OCD and OCD-related spectrum conditions seems fluid in 2010, and in need of ongoing reappraisal.

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Obsessive-compulsive disorder (OCD) occurs worldwide, with common features across diverse ethnic groups and cultures. It affects approximately 2% of the population and is associated with substantial social, personal, and work impairment.[1,2] In fact, the World Health Organization identified OCD among the top 20 causes of years of life lived with disability for 15- to 44-year-olds.[3] Although generally longitudinally stable, OCD is known for its substantial heterogeneity, as symptom presentations and comorbidity patterns can vary markedly in different individuals. Moreover, a number of other psychiatric and neurologic disorders have similar phenomenological features, can be comorbid with OCD, or are sometimes even conceptualized as uncommon presentations of OCD. These include the obsessive preoccupations and repetitive behaviors found in body dysmorphic disorder, hypochondriasis, Tourette syndrome, Parkinson's disease, catatonia, autism, and in some individuals with eating disorders (eg, anorexia nervosa).[4-10] These heterogeneous facets of the disorder have led to a search for OCD subtypes that might be associated with different etiologies or treatment responses.

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Selected abbreviations and acronyms

ADHD	*attention deficit-hyperactivity disorder*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
OCD	*obsessive-compulsive disorder*
OCRD	*obsessive-compulsive-related disorder*
OCSD	*obsessive-compulsive spectrum disorder*
PANDAS	*pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections*
PTSD	*post-traumatic stress disorder*

Ruminative, obsessional, preoccupying mental agonies coupled with perseverative, ritualized compulsion-resembling behaviors have been depicted in biblical documents as well as Greek and Shakespearian tragedies. In modern nosology, a number of different approaches have been suggested to characterize this syndrome, yet the question of how best to categorize OCD subgroups remains under debate in 2010.

Currently, the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR)* of the American Psychiatric Association, classifies OCD as an anxiety disorder. There have, however, been questions raised about this categorization on the basis of some phenomenological differences between OCD and the other anxiety disorders. As such, suggestions have been made that, in the forthcoming 2012 *DSM-5*, OCD should be removed from its position as one of the six anxiety disorders—a reformulation still under debate. One solution under discussion is that OCD should constitute an independent entity in *DSM-5* (ie, remain outside of any larger grouping), congruent with its designation as such in the current international diagnostic manual, *ICD-10 (International Statistical Classification of Diseases and Related Health Problems*).[11-14] An alternative suggestion would group OCD and related disorders into a new Obsessive-Compulsive Spectrum Disorders (OCSD) category. The concept of an OCSD classification was first postulated over a decade ago.[15,16] Later, the original OCSD concept was extended with the proposal that OCD and other compulsive disorders may lie along a larger continuum of corelated compulsive-impulsive disorders.[15] Disorders hypothesized at the impulsive end of this spectrum continuum include pathologic gambling, nonparaphilic compulsive sexual activity, and others.[17,18] A general feature of these proposed impulsive disorders is that, although they have some repetitive elements, they are generally egosyntonic (in contrast to the egodystonic nature of OCD), often with minimal anxiety and behaviors that are not resisted, and that are usually associated with pleasure (not with relief as in OCD). However, the concept of a compulsive-impulsive continuum has not been widely subscribed to in either a recent survey of OCD experts or in recent reviews.[19,20] Some of the original proponents of the OCSD groupings and others in the field have softened the stipulations that implied common underlying etiological components of the OCSD, to a more general notion of "obsessive-compulsive-related disorders" (OCRD).[12] This debate continues to wax and wane as additional investigations evaluate the underpinnings of a putative OCD spectrum.[21,22] This review focuses on newer contributions to the OCD spectrum concept and efforts to subtype OCD. It does not reiterate already well-evaluated aspects of OCD spectrum concepts recently published in expert reviews (eg, refs 12,23-27). Rather, it discusses new data primarily from recent epidemiologic and clinical research, as well as new quantitative psychological, physiological, and genetic studies with the aim of reappraising and developing additional elements related to the OCSDs and OCRDs. Particular points of emphasis are questions regarding (i) what OCD phenotypes might be of value in present and future genetic studies; and (ii) other types of etiological contributions to OCRDs, with, of course, the ultimate aim of better treatments for OCRDs that might be based on more than our current descriptive nosologies. Our immediate hope in this review is to spur additional thoughts as the field moves towards clarifying how OCD-related disorders might arise and manifest at the phenomenological and mechanistic levels.

What is OCD?

DSM-IV/DSM-IV-TR characterizes OCD by the symptoms outlined in *Table I*. It is listed within the Anxiety Disorder section. The text highlights that if an individual attempts to resist or delay a compulsion, they can experience marked increases in anxiety and distress that are relieved by the rituals.

OCD symptom heterogeneity in individuals

While the core components of OCD (anxiety-evoking obsessions and repetitive compulsions) are recognizable as the cardinal features of OCD, the specific content of

these symptoms varies widely. Thus, there is clear evidence that within OCD, there is symptom heterogeneity. For example, *Figure 1* depicts the results of a cluster analysis of OCD symptoms based on two separate symptom checklists for OCD (Yale-Brown Obsessive Compulsive Scale Symptom Checklist (YBOCS) and the Thoughts and Behavior Inventory (TBI) accomplished initially using item clusters and subsequently using individual items from these scales, with essentially identical results.[29,30] Notable is that there are distinguishable groupings of symptoms, falling into four major groupings (yellow components) and that both obsessions and compulsions of similar types group together. This clustering is in direct contrast to the current *DSM-IV* notation of obsessions "and/or" compulsions. There also exists an inseparable overlapping of symptom groupings (blue components), such that despite separable conceptual entities, there is an overall merging of these groupings on a more hierarchical level.

Obsessions are:
Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
Thoughts, impulses or images that are not simply excessive worries about real-life problems
The effort by the affected person to ignore and suppress such thoughts, impulses or images, or to neutralize them with some other thought or action
Recognition by the affected person that the obsessional thoughts, impulses or images are a product of his or her own mind rather than imposed from without.
Compulsions are:
Repetitive activities (eg, handwashing, ordering, checking) or mental acts (eg, playing, counting, repeating words silently) that the person feels driven to perform in response to an obsession or according to rigid rules that must be applied rigidly
Behavior or mental acts aimed at preventing or reducing distress or preventing some dreaded event or situation but either clearly excessive or not connecting in a realistic way with what they are designed to neutralize or prevent
Recognition, by the affected person (unless he or she is a child), at some point during the course of the disorder, that the obsessions or compulsions are excessive or unreasonable
Obsessions or compulsion that cause marked distress, are time-consuming (take more than 1 h/day), or interfere substantially with the person's normal routine, occupational or academic functioning, or usual social activities or relationships
Content of the obsessions and compulsions not restricted to any other Axis I disorder, such as an obsession with food in the context of an eating disorder, that is present
Disturbance not due to the direct physiological effect of a substance or a general medical condition

Table I. Criteria for obsessive-compulsive disorders in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.*
Adapted from ref 28: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994. Copyright © American Psychiatric Association 1994

Many other studies over the last decade have attempted to reduce the variability of OC symptom groupings in different populations of OCD patients through factor, cluster, or latent variable analyses of OCD symptom inventories. The majority of such studies have found support for between three to five symptom dimensions,[19] with the most commonly identified solution including four factors: (i) contamination obsessions and cleaning compulsions; (ii) aggressive, sexual, religious, and somatic obsessions with checking-related compulsions; (iii) obsessions regarding symmetry, exactness, and the need for things to be "just right" paired with compulsions relating to ordering, arranging, and counting, and (iv) hoarding obsessions and compulsions. With regard to these four symptom dimensions, it should be noted that current debate exists as to whether hoarding should be considered along with the other core OCD symptoms, or whether it exists as an independent syndrome often comorbid with OCD.[31-33] We will revisit this issue in a subsequent section of this review. An additional concern that has been raised is that in studies of pediatric OCD, changes in the most prominent symptom patterns have been found over time.[34] In contrast, studies of adult OCD populations revealed stability of the most prominent symptom patterns.[35,36] This suggests that perhaps more primary symptom dimensions affecting an individual solidify as an individual matures into adulthood. Family studies, including a sib-pair study, indicate that there is statistically significant within-family preferential sharing of symptom types; however, such correlations are relatively modest.[37]

Given this literature, there does not seem to be an adequate basis for establishing distinct within-OCD subtypes based on OC symptoms that, however, might be useful for distinguishing individuals with OCD for general treatment-directed investigations. There is one important exception with regard to the hoarding subgroup, which has shown several specific genetic-based and brain imag-

ing-based differences from general OCD groups (eg, refs 38-40). Furthermore, given preliminary research that an individual's dominant symptom dimension may in fact be associated with differential treatment response and functional correlates,[41,42] future research into hypothesized multidimensional models is warranted.

It is also worth mentioning that a different, two-dimensional model of OCD phenomenology has been suggested since Janet's 1904 reports on 300 patients[43]; he highlighted the "anakastic" feature of altered risk assessment (related to the later concepts of harm avoidance or neuroticism) as well as the sense of "indecision" and "incompleteness." Someone suffering from incompleteness was "Continually tormented by an inner sense of imperfection, connected with the perception that actions or intentions have been incompletely achieved." [43] This phenomenon has relatively recently been "rediscovered" and seen some empirical study, especially in its narrower sense of the "not just right"[44,45] experience frequently seen in OCD.[46] Although research tools to characterize patients in this respect remain in development, some promising work has been reported.[47,48] Incompleteness symptoms may have more affinity for tic-related phenomena than those strictly encompassed by anxiety-related mechanisms,[49] while Janet's "forced agitations" were also described by him as mental manias.[45]

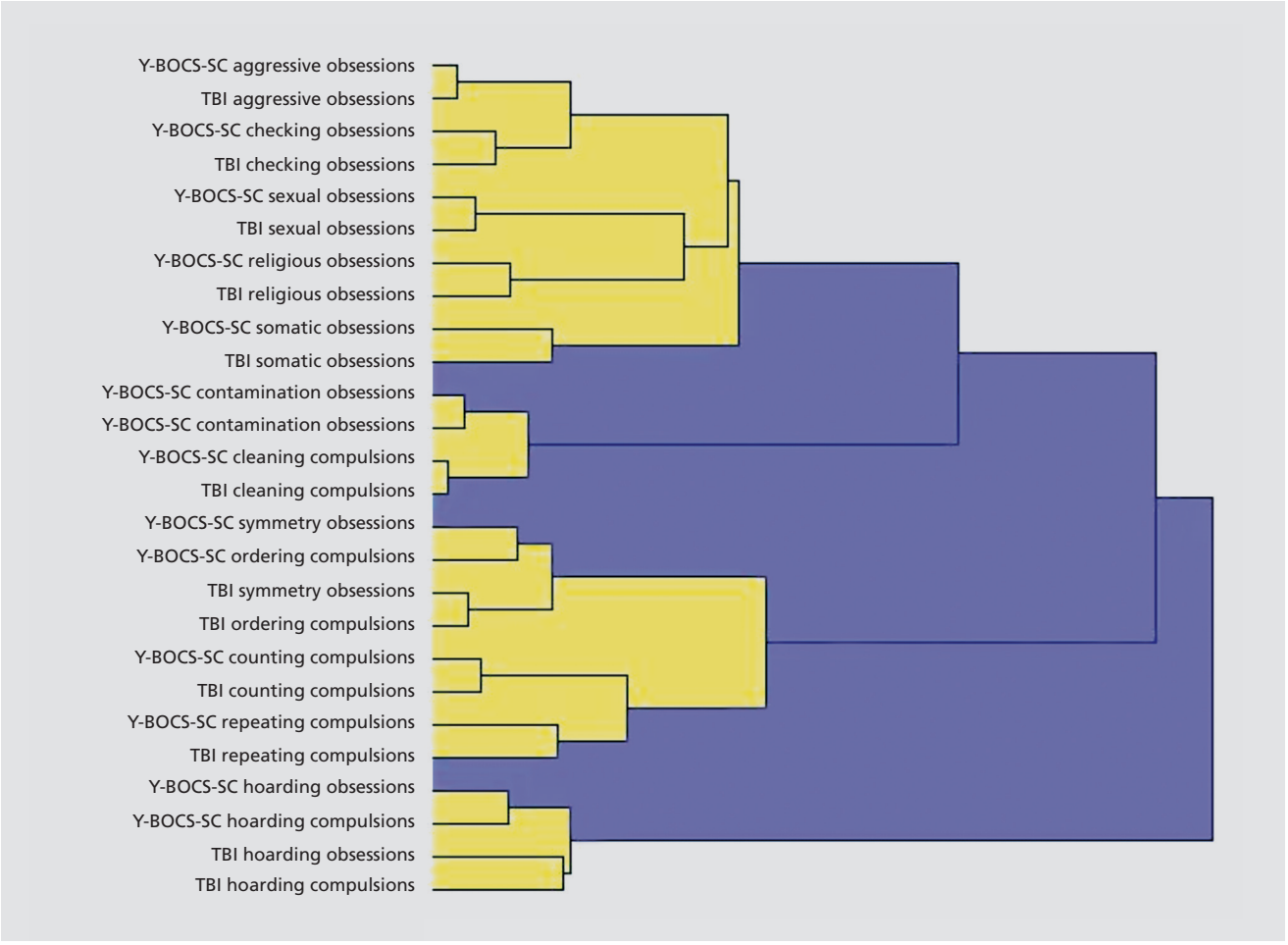

Figure 1. Dendrogram depicting a cluster analysis of OCD symptoms found in 321 OCD probands.
Adapted from ref 29: Hasler G, LaSalle-Ricci VH, Ronquillo JG, et al. Obsessive-compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. *Psychiatry Res*. 2005;135:121-132. Copyright © Elsevier/North Holland Biomedical Press 2005, and ref 30: Schooler C, Revell AJ, Timpano KR, Wheaton M, Murphy DL. Predicting genetic loading from symptom patterns in obsessive- compulsive disorder: a latent variable analysis. *Depress Anxiety*. 2008;25:680-688. Copyright © Wiley-Liss 2008

Investigators have additionally attempted to subgroup OCD patients using specific phenomenological characteristics, such as overall OCD severity, familiality, gender, age of OCD onset, and comorbidity patterns.[24,26,29,50-53] There is considerable indication that OCD which emerges in childhood is meaningfully different from OCD that occurs later in adulthood, including gender and comorbidity differences (eg, a higher prevalence of tic disorders and Tourette syndrome).[26,54-56] In addition, some have subgrouped OCD on the basis of the patients' insight into the senselessness of their obsessions and compulsions. Some evidence suggests that OCD patients with poorer insight experience more severe symptoms, are less responsive to treatment, and have more family history of the disorder, though this has not always been observed.[57] Interestingly, hoarding symptoms again appear to be distinct from the other OCD symptoms in this regard, in that hoarders typically evidence less insight.[53,58,59]

In one latent class analysis of comorbid psychiatric conditions, two OCD subgroups were identified: a dimensional anxiety plus depression class and a panic plus tic disorder class.[60] Another latent class analysis using a novel latent variable mixture model following a confirmatory factor analysis of 65 OCD-related items in 398 OCD probands found two statistically significant separate OCD subpopulations.[30] One group had a significantly higher proportion of OCD-affected relatives (ie, a familial group) and was associated with an earlier age of OCD onset, more severe OCD symptoms, greater psychiatric comorbidity, and more impairment compared with the second group.[30] However, because of considerable overlap among groups of OCD symptoms/dimensions and subgroup composition as identified by different statistical methods, discrete subgroup membership for any specific OCD proband is not yet available.[30]

OCD and its relationship to the anxiety disorders

At the same time as the field attempts to refine and clarify subtypes within OCD, broader questions about the disorder have also been asked, with some proposing that OCD is miscategorized as an anxiety disorder.[61] Some have suggested that OCD bears more in common with other disorders categorized by repetitive thoughts and behaviors, and should be moved to a new category of disorders including OCSDs and OCRDs. This proposal requires elucidation of what constitutes the core of OCD: anxiety, obsessions, or repetitive behaviors. It is of note that, under the key features of OCD described in *DSM-IV/DSM-IV-TR* anxiety, as a feature is mentioned just once.

Nonetheless, many studies of OCD, and particularly investigations of OCD treatment that used quantitative self- and observer ratings, have documented very high anxiety ratings in individuals with untreated OCD. The levels of these anxiety ratings were as high or even higher than those reported in similar studies of panic disorder, generalized anxiety disorder, social phobia, and specific phobias. Thus, for the present time, OCD's close affinity with other disorders characterized by high anxiety would suggest that it remain under this categorization, unless it becomes recognized as a distinctly separate diagnostic entity in *DSM-5*, as noted above.[14,62,63]

OCD and its relationship to mood disorders

Some proponents of moving OCD from its categorization as an anxiety disorder have suggested that, at its core, OCD is an affective disorder. In fact, depressive features are common in OCD and major depressive disorder is the single most frequently comorbid disorder in OCD probands *(Table II)*. Cumulatively, mood disorders occur in 50% to 90% of OCD probands (not taking into account individuals with overlapping mood diagnoses) *(Table II)*. However, some have found that depressive symptoms most typically emerge following OCD onset, perhaps, it is speculated, as a consequence of long-term anxiety, stresses, and functional impairment associated with OCD symptoms.[64] A special comorbid relationship has been noted between OCD and bipolar I and II disorders,[1,65,66] also raising the question of a cyclothymic form of OCD.[67] As with the affective disorders, modulating factors that seem to affect the expression and some features of OCD include gender and degree of insight into symptoms.[53,67,68]

It is important to note that, although across OCD groups there exist patterns of frequent comorbidity with other anxiety, mood and other disorders, an "uncomplicated" noncomorbid OCD presentation has nonetheless been documented.[69,70] This group, comprising ~10% of OCD probands in several studies, represents a relatively understudied entity,[71,72] despite some indications that "uncomplicated" OCD may be of high value in refining the question of "What is OCD?"

OCD: its relationship to OCD-comorbid disorders as part of a description-based OCD spectrum

The original conceptualization of the OCD spectrum: considerations of symptomatology

Although there are a number of different approaches and considerations with regard to OCD spectrum disorders, we first present one prevalent view that the spectrum consists of disorders with diverse phenomenological features, but which share commonalities that tie them together. *Figure 2* provides a depiction of the original and modified groupings of OCSD and OCRD disorders, including notation of other disorders considered by some as part of a compulsive-impulsive spectrum group of disorders. Some re-evaluations of these relationships have been published recently,[12,19,21,27,61,73-75] and reflect the ongoing debate about genetic and environmentally-shaped, neurodevelopmental elements related to OCD onset that also may impact the future status of OCD in *DSM-5*.

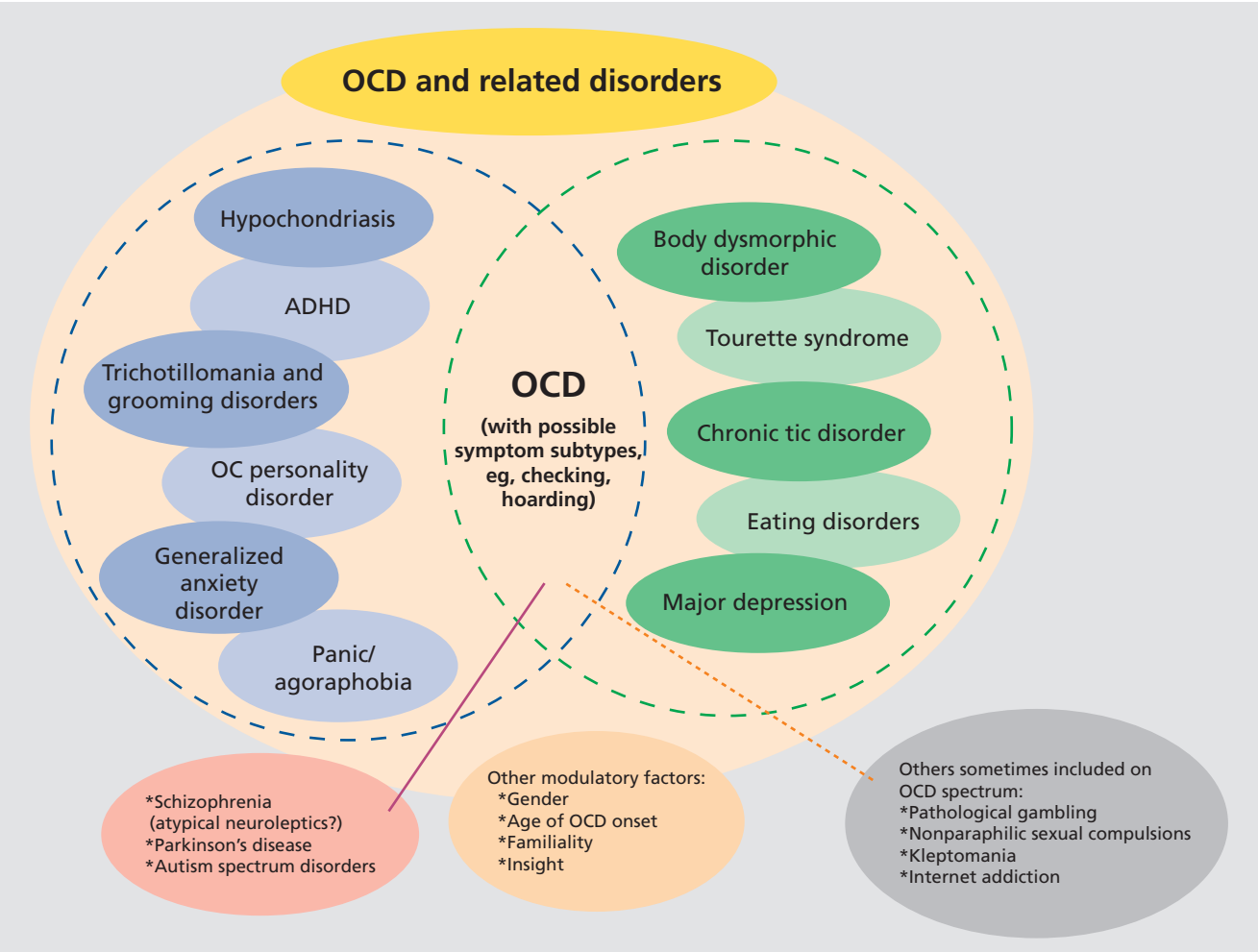

Figure 2. OCD and disorders comorbid with OCD.
Adapted from ref 12: Hollander E, Kim S, Braun A, Simeon D, Zohar J. Cross-cutting issues and future directions for the OCD spectrum. *Psychiatry Res*. 2009;170:3-6. Copyright © Elsevier/North-Holland Biomedical Press 2009, ref 19: Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry*. 2005;162:228-238. Copyright © American Psychiatric Association 2005, and ref 76: Murphy DL, Timpano KR, Wendland JR. Genetic contributions to obsessive-compulsive disorder (OCD) and OCD-related disorders. In: Nurnberger J, Berrettini W, eds. *Principles of Psychiatric Genetics*. Cambridge, UK: Cambridge University Press; 2010. Copyright © Cambridge University Press, 2010

Table II indicates the frequency of comorbid disorders found in adult probands with OCD compared with the incidence of these disorders in the general US population. As is evident, two- to sixfold higher prevalence rates of most psychiatric disorders are found in individuals with OCD. Most striking are the high frequencies of all anxiety disorders taken together, and likewise, all affective disorders. Also of interest are the lack of differences in alcohol-related and substance abuse disorders between those with OCD and the general US population. Specific symptomatologic features that potentially may be useful for grouping OCD into more homogeneous and familial phenotypes for etiologic investigations include those of comorbid tic, affective, anxiety and the other disorders listed, as well as obsessive-compulsive personality disorder.

An example of one OCD-comorbid disorder (not listed in *Table II* but recently identified as a potential OCRD disorder) is attention-deficit hyperactivity disorder (ADHD).[80,81] While some of the original OCD comorbid spectrum disorders remain in this grouping simply on the basis of consistent co-occurrence with OCD in descriptive samplings or overlapping features, others such as ADHD have been validated via segregation analysis. In evaluations of the OCD-ADHD relationship, relatives of probands with both disorders have been found to have a significantly higher frequency of OCD plus ADHD compared with the relatives of probands with ADHD only.[80,81]

Apparent environmental etiology-based OCD-related disorders

Three examples of full-blown OCD occurring apparently acutely de novo following putative causal events include: (i) OCD related to an infection such as that associated with streptococcal infections (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections [PANDAS] syndrome); (ii) trauma-related OCD following acute brain injuries; and (iii) OCD occurrence during treatment of schizophrenia with atypical neuroleptic agents. These would seem to constitute an etiologically-based OCD subtype, since most cases of primary, idiopathic OCD have an insidious onset with a gradual development of symptoms and impairment over a longer timeline of months or years.

Population	OCD (N = 334)[71]	OCD (N = 206)[60]	OCD (N = 80)[77]	OCD (N = 630)[79]	OCD (N = 418)[37]	OCD (N = 2073)[72]	General US Population (N = 8098)[78]
Major Depressive Disorder	66	38	54	70	67	41	17.1
Dysthymia	24	---	8	11	14	13	6.4
Social Phobia	23	---	36	37	43	44	13.3
Panic Disorder	23	19	21	6	21	20	3.5
Alcohol Abuse/Dependence	23	---	15	8	16	39	23.5
Generalized Anxiety Disorder	18	43	13	35	46	8	5.1
Agoraphobia	18	---	17	6	16	8	5.3
Substance Abuse/Dependence	14	---	8	2	9	22	11.9
Specific Phobia	12	---	31	---	39	43	11.3
Trichotillomania	10	---	---	36	9	---	---
Bulimia Nervosa	10	---	---	3	5	---	---
Anorexia Nervosa	9	---	---	3	6	---	---
Post Traumatic Stress Disorder	8	---	---	16	10	19	---
Bipolar I/II Disorders	13	7	1	10	7	23	1.6
Body Dysmorphic Disorder	6	---	---	12	12	---	---
Tourette's Disorder	4	---	---	7	---	---	---
Autism Spectrum Disorders	3	---	---	---	---	---	---
Binge-Eating Disorder	1	---	---	---	1	---	---
No Comorbid Disorder	8	---	---	---	---	10	52.0

Table II. Disorders occurring together with OCD in five clinical investigations[57,60,71,77,79] and one epidemiologic[72] investigation of adult OCD (modified from refs 60,71,77 compared with the incidence of these disorders in the general US population[78]). (Percent of total N of individuals with OCD or in the general population).

OCD and infections: the example of PANDAS syndrome

A potential environmental contributor to the development of OCD, particularly in childhood, is a suspected relationship between group A streptococcal infections and onset of OCD and/or tics/Tourette syndrome, akin to the development of Sydenham's chorea reported previously following streptococcal infection.[82-84] In fact, an increased prevalence of obsessive-compulsive symptoms[85-87] and OCD[88] has also been noted in patients with rheumatic fever (RF) with or without Sydenham's chorea. Initially, these findings were reported in children during an active phase of rheumatic fever.[88] Subsequent studies revealed the presence of OCSDs in adults with a previous history of rheumatic fever (not active), suggesting that the streptococcal infection may trigger OCD, which may persist throughout life regardless of the activity of the rheumatic fever.[85,86] Recent family studies have reported that OCSDs and OCRDs (such as tic disorders, body dysmorphic disorder, trichotillomania, grooming behaviors, and others) aggregate more frequently in first-degree relatives of rheumatic fever probands when compared with controls.[89,90] Moreover, two polymorphisms of the promoter region of the tumor necrosis factor-alpha (TNF-α) gene have been associated with both OCD and rheumatic fever, which is an interesting finding since the TNF-α gene is a proinflammatory cytokine involved in rheumatic fever and several other autoimmune diseases,[91,92] suggesting that both obsessive-compulsive related disorders and rheumatic fever share a common genetic vulnerability.

Thus, PANDAS OCD could be a mild expression of rheumatic fever whose incidence is higher in developing countries, while the full development of rheumatic fever-related disorders may be attenuated by the appropriated antibiotic prophylaxis in developed countries. Consistent with this hypothesis, there was a higher family history of rheumatic fever in PANDAS OCD patients. Thus, abnormal immune response to this streptococcal infection, with abnormal antibody production leading to basal ganglia damage has been focused upon as a likely mechanism for both rheumatic fever and PANDAS OCD.[52,93,94] This proposed mechanism is supported by behavioral changes and brain lesion development in mice following immunization with streptococcal antigens,[95] with resemblances to similar studies investigating immune mechanisms in Sydenham's chorea.[83]

Abnormal brain autoantibody production may itself be mediated by specific genetic factors, posing a possible gene X environment (G x E) pathogenesis for a PANDAS subgroup. However, a puzzling anomaly potentially reflecting a different possible G x E interaction, or even a confound to the importance of streptococcal infections and autoantibodies in OCD, is that OCD patients with suspected PANDAS had an equal number of OCD-affected relatives as the non-PANDAS comparison OCD population.[96] Some recent reviews have concluded that the relationship between strep infections and OCD may be indirect and complex and thus "elusive," [97-99] although other controlled studies continue to support an association.[100]

Besides streptococcal infections and PANDAS, there are interesting examples of other apparent infection-related OCD development. Both bacterial and viral infections have been noted to be associated with acute OCD onset, including *Mycoplasma pneumoniae*, varicella, toxoplasmosis, Borna disease virus, Behcet's syndrome, and encephalitis, with some infections accompanied by striatal and other brain region lesions.[101-106] In some cases, marked OCD symptoms subsided with antibiotic treatment.

Onset of OCD and/or hoarding after acute traumatic brain injury and in association with other types of neuropathology

A number of reports have described new onset of OCD in previously healthy individuals who suffered documented brain injury, usually after accidents (reviews: refs 45,107-109). Besides OCD, other psychiatric disorders that follow brain injuries have been documented in epidemiologic studies.[110] In one of these, which retrospectively evaluated 5034 individuals among whom 361 (8.5% weighted average) reported a history of brain trauma with loss of consciousness or confusion, lifetime prevalence was significantly increased (P<0.03–0.0001) for many disorders, including OCD, compared with those without head injuries. An odds ratio of 2.1 was reported for OCD, representing a greater than twofold increase of the occurrence of OCD compared with controls without head injuries, after corrections for age, gender, marital status and socioeconomic status.[110] Of note, although similar odds ratios have been found for major depression and panic disorder, rates of schizophrenia or bipolar disorder were not increased in this sample of individuals with brain trauma.[110]

Some case report series noted acute onset of OCD within a day to a few months following traumatic brain injury.[107,111,112] One of three studies documented a typical array of OCD symptoms using YBOCS ratings; a subgroup of patients had the generally unusual symptom of "obsessional slowness." [107] Compared with matched controls, the patients with post-brain injury OCD symptoms had poorer performance on an array of cognitive measures, including executive functions. Also, the patients with the most severe traumatic brain injury had more frequent abnormal magnetic resonance imaging (MRI) exams involving the frontotemporal cortex and the caudate nucleus.[107] Some of these reports specifically emphasized the lack of prior personal or familial OCD symptoms or diagnoses.

Smaller survey studies of post-brain injury patients with Ns of 100 or less and using various types of diagnostic evaluations, some quite brief, have infrequently noted cases of OCD, although OCD symptoms have been reported as present in other types of brain disorders, including surgery for seizure disorders and carbon dioxide poisoning, as well as brain tumors and stroke lesions affecting portions of the cortico-striato-pallido-thalamic circuits.[109,113] OCD and OC symptoms have also been associated with other neurological disorders and neuropathology found in Parkinson's disease, postencephalopathic disorders, and other brain disorders.[114,115]

Influenced in part by the literature that focal injury to the basal ganglia was associated with OCD emergence, we recently observed an MRI abnormality suggesting elevated iron deposition in the globus pallidus in OCD patients whose symptom onset was from around adolescence to early adulthood.[116] This initial result adds to the literature suggesting that age of onset is likely to be an important consideration in attempts to separate OCD into etiologically meaningful subgroups. Age of onset may also be an important variable in regard to the repetitive-compulsive OC traits and OCD itself which are well documented in conjunction with autism spectrum disorders, including Asperger's syndrome.[117,118]

Apparent acute new onset of OCD in patients with schizophrenia during treatment with atypical antipsychotic medications

One recently-recognized OCD-related disorder is atypical neuroleptic-related OCD, as reported in schizophrenic patients successfully treated with clozapine, ritanserin, and other newer neuroleptic agents.[119-122] Some have suggested that this syndrome represents OCD-like symptoms induced by the atypical neuroleptics—ie, a drug side effect. Others subscribe to the hypothesis that suppression of overt and more dominant psychotic symptoms by clozapine and other atypical neuroleptics unveils coexisting OCD, permitting diagnosis. The latter would be in accord with some suggestions from earlier studies that reported as many as 5% to 20%, or more of individuals with schizophrenia have comorbid OCD.[123-125] It seems more studies are required to evaluate these two somewhat opposing views of this syndrome.

Of note, other detrimental, traumatic life events of a psychological or social nature have been associated with OCD with different possible implications. For instance, one study compared patients with OCD plus post-traumatic stress disorder (PTSD) who developed OCD after clinically significant trauma (designated "post-traumatic OCD") to general OCD patients in terms of sociodemographic and clinical features. Compared with general OCD patients, "Post-traumatic OCD" presented several phenotypic differences such as: later age at onset of obsessions; increased rates of some obsessive-compulsive dimensions (such as aggressive and symmetry features); increased rates of mood, anxiety, impulse-control and tic disorders; greater "suicidality and severity of depressive and anxiety symptoms; and a more frequent family history of PTSD, major depressive disorder and generalized anxiety disorder." [79,126] One study of a treatment-resistant OCD subgroup found that all subjects who met formal criteria for OCD and comorbid PTSD had PTSD onset that preceded OCD onset.[127]

What is there to make of this diversity of antecedent events suggested to trigger typical OCD? One concept, elaborated below, is that severe acute or more chronic stresses that impact executive (or "ego") functions may elicit a kind of regression to or activation of less goal-oriented but more simplified, ritual-based action patterns that may act to prevent further disorganization of the self.[128,129] In this view, OCD "strategies" and symptoms may provide a common pattern of behaviors that are of advantage in the short term, but which may become deleterious if sustained beyond the time of stress.

Putative chromosomal or gene-based, genomic OCD-related disorders

At present, studies of possible genetic contributions to OCD and OCSD remain quite limited. Apart from

investigations of specific candidate genes and gene-related syndromes, as noted below, the greatest effort in the last decade has been directed towards genome-wide linkage and, more recently, genome-wide association studies that are primarily based upon groups of individuals with *DSM-IV*-diagnosed OCD without concern for OCD-related subgroups. As reviewed previously and in this same issue, there have been several recent evaluations of genetic contributions to OCD.[130-133] In addition, specific investigations of some candidate genes have been subject to meta-analysis with positive results, eg, the *SLC6A4* (serotonin transporter gene) polymorphisms,[134] plus positive results from investigations of rare variants in *SLC6A4* (review in ref 135).

However, in large part these reviews and evaluations of specific genes have not gone beyond generic OCD to address possible associations with OCD spectrum disorders. One notable exception deserves comment. Among five positive studies of variants in *SLC1A1* (the neuronal glutamate transporter gene), one study reported separable results for different single-nucleotide polymorphisms associated with overall OCD from associations of a novel 5'-prime region variant (that was not found in the overall OCD sample) with hoarding compulsions.[39] This is reminiscent of the report of different patterns of associations with hoarding compulsions compared to associations with overall OCD or with Tourette syndrome for chromosomal regions in genome linkage studies.[38,136] In one of these studies, those with OCD plus hoarding exhibited a novel peak on chromosome 14; likewise, in a subgroup of individuals with OCD but from which the individuals with hoarding had been deleted, the peak on chromosome 3q became more distinct.[38,137]

In keeping with these results, prior studies from different vantage points have suggested that individuals with OCD and hoarding might differ from others with OCD without hoarding, and that hoarding itself might represent a separate syndrome within the OCRDs.[31,32] Providing further support for this notion, brain imaging results have indicated that individuals with OCD have distinctly different patterns of cerebral glucose utilization from nonhoarding OCD patients.[40] Additionally, hoarding is more frequent in the first-degree relatives of hoarding probands, and hoarding is associated with other biological and gender differences.[31,33,37,68,71,138-141]

Thus, with only a few interesting exceptions, the chromosomal regions discovered in the genome-wide linkage studies of OCD as possibly harboring OCD-related genes are relevant only to OCD in general, without much attention to OCD diversity and heterogeneity, or with regard to other OCSDs. The same is true for those studies focusing on a single candidate gene. One other exception of possible future interest in regard to likely gene-related subgroupings is age of OCD onset.[137]

Common gene variants plus rare gene and genetic syndromes associated with OCD and OCD/Tourette syndrome subgroups and/or OCD-related disorders

Uncommon chromosomal anomalies and both rare and common gene variants have come under increasing scrutiny in OCD and OCD-related or OCD-comorbid disorders. Several uncommon chromosomal region abnormalities that are associated with multiple phenotypes have been found to include individuals with OCD. Thus, OCD diagnoses have been made in individuals with the 22q11 microdeletion syndrome (also known as velocardiofacial syndrome).[142-145] In one comprehensive study that used the YBOCS scale together with psychiatric interviews in evaluating a VCSF clinic sample, 33% received an OCD diagnosis.[142]

OCD has also been diagnosed in some individuals with the myoclonus dystonic syndrome related to chromosome 7q.[146-149] In one study of three extended myoclonus dystonic syndrome families, OCD meeting direct interview-based *DSM-IV* criteria was present in 25% (4/16) of symptomatic myoclonus dystonia syndrome carriers with the 7q21 haplotype, but in only 9% (1/11) of nonsymptomatic carriers and 0% (0/28) of the nonhaploytpe carriers.[146] This is of special interest because its 7q21-q31 locus is near the chromosomal anomalies described in other individuals with OCD or Tourette syndrome but without the myoclonus dystonic syndrome who have anomalies in chromosome regions 7q31 and 7q35-36.[150-152] Additionally, a family-based association study using markers in the 7q31 region demonstrated biased transmission of these marker alleles in individuals with comorbid Tourette syndrome, OCD, and ADHD.[153]

For the 22q11 and 7q variants, insufficient data exist for OCD, OCD spectrum disorders like other dystonias,[154-157] and possibly related disorders like autism spectrum disorder to draw firm conclusions as to how these different disorders might be related. However, these findings from uncommon chromosomal regions and rare genes suggest distinct and different etiologies for an OCD phenotype that may represent a type of OCD spectrum disorder, ie, a genomic group of OCSDs. For example, as noted above,

one common candidate gene, *SLC1A1*, manifested a variant associated with complex hoarding, while different variants were strongly associated with OCD in general.[135]

Discussion: what might be common elements that could contribute to OCD spectrum disorders?

The relationships among OCD comorbid disorders and additional OCD spectrum disorders: old and new postulated groupings

From an overview perspective, OCD remains as a distinct clinical entity, with classic symptoms and behaviors involving obsessions and compulsions plus high anxiety and, over the lifetime, the occurrence of mood and other anxiety disorders. OCD differs from the other anxiety disorders by its earlier age of onset, more complex comorbidity, and severity of obsessional thoughts and compulsive behaviors. OCD as defined in *DSM-IV/IV-TR* also occurs concomitantly with other DSM-defined disorders ranging from body dysmorphic disorder, Tourette syndrome, eating disorders, and autism spectrum disorders,[118] as well as

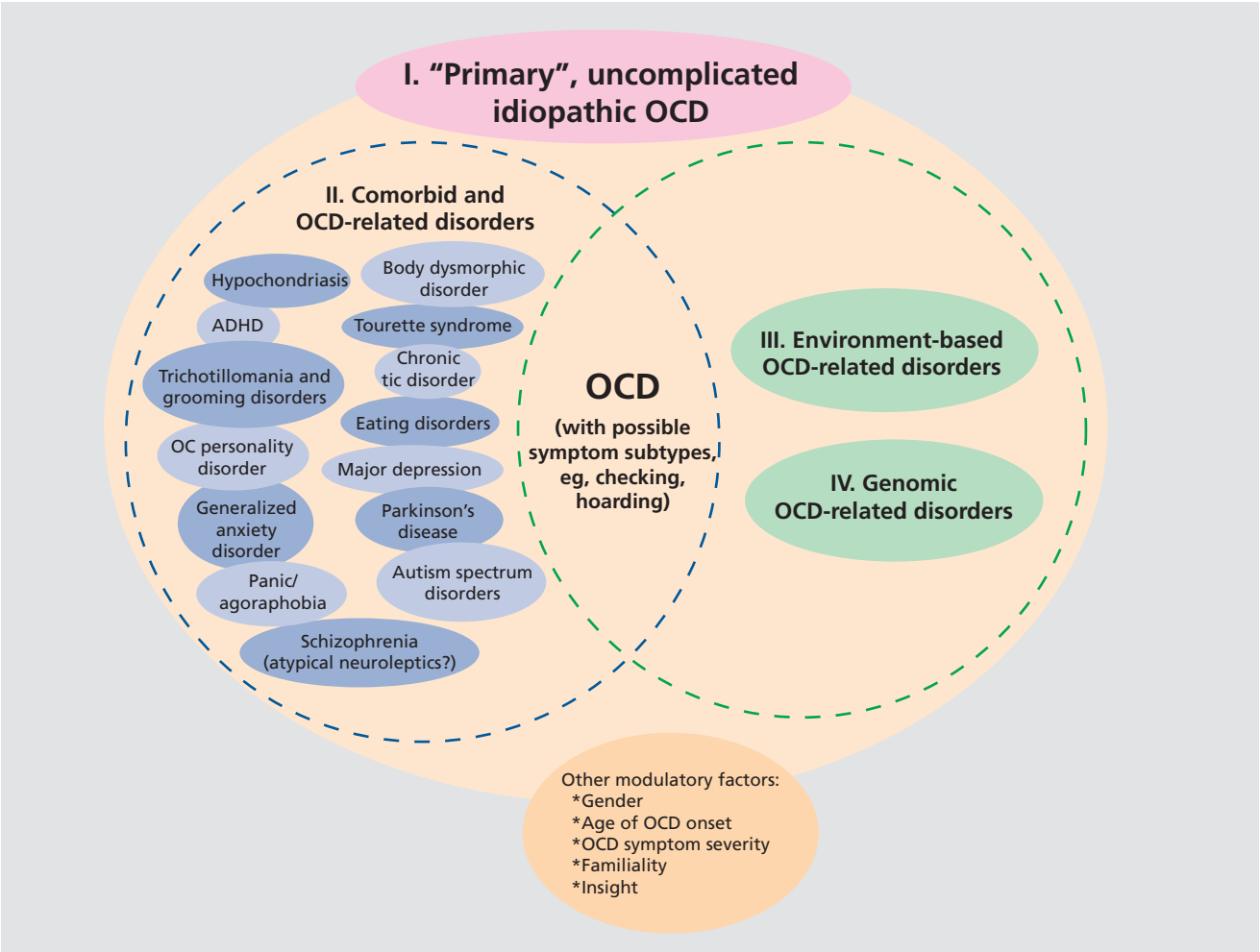

Figure 3. OCD and related disorders: update 2010.
Adapted from ref 12: Hollander E, Kim S, Braun A, Simeon D, Zohar J. Cross-cutting issues and future directions for the OCD spectrum. *Psychiatry Res*. 2009;170:3-6. Copyright © Elsevier/North-Holland Biomedical Press 2009, ref 19: Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry*. 2005;162:228-238. Copyright © American Psychiatric Association 2005, and ref 76: Murphy DL, Timpano KR, Wendland JR. Genetic contributions to obsessive-compulsive disorder (OCD) and OCD-related disorders. In: Nurnberger J, Berrettini W, eds. *Principles of Psychiatric Genetics*. Cambridge, UK: Cambridge University Press; 2010. Copyright © Cambridge University Press, 2010

multiple other disorders. Individuals with these other primary disorders may have separately defined OCD meeting full criteria. There seem to be two views about this overlap: (i) All of these disorders together constitute an OCD spectrum group, with implications that they are all manifestations of a single OC-based entity; or (ii) each may be an independent coexisting disorder. For some individual patients, it may be that a mixture of both may be operative for different components of these disorders. Thus, the relationship among OCD-related disorders remains uncertain.

We have noted that a number of other disorders have sometimes been named in an extended list of OCD spectrum disorders *(Figure 2)* such as the impulsive disorders; however we will not discuss them further, as their association to OCD is tenuous and not acknowledged by most experienced clinicians and researchers or recent reviews.[19] On the other hand, we have explicitly added two additional groupings of OCD-related disorders that are not based on descriptive nosology, but rather on etiologic considerations *(Figure 3)*. One of these links acute OCD onset to environmental events such as the consequences of infection, traumatic brain injury, and other neurological disease insults. The other newly suggested OCD spectrum encompasses etiologies related to specific gene or narrow chromosome region-related syndromes—a fourth genomic OCD-related group. Some of this latter group also overlaps with disorders such as Tourette syndrome, with its common tripartite combination of tic disorders, OCD, and ADHD. It is of interest that some considerations for *DSM-5* and future *DSMs* are beginning to show additional elements beyond clinical symptoms as bases for designation of an entity. These include biological, psychophysiological, and brain imaging data as well as potential etiological factors including genetic elements and brain neurocircuitry contributions.[6,12,14,19,22,25-26]

Evaluations of treatment responses and familiality of treatment responses as possible bases for OCD-related subgroups

Like OCD, many of the OCD-related spectrum disorders respond to serotonin reuptake inhibitors (SRIs), which some have used as evidence for an association between these conditions. However, given that individuals with these disorders often suffer from comorbid disorders that also respond to SRIs (eg, major depressive disorder and other anxiety disorders), as well as the fact that many other neuropsychiatric and medical disorders with no postulated relationship to OCD also respond to SRI treatment, this treatment responsivity seems patently a weak hypothesis. On the other hand, it is notable that many anxiety disorders, but not OCD, benefit from monotherapy with other types of anxiolytic agents such as benzodiazepines.

Psychological treatments with specificity for OCD provide a more discriminating test for grouping disorders together based on treatment response. Exposure and Ritual Prevention (ERP) is one treatment of choice for OCD, and several studies have demonstrated that body dysmorphic disorder and hypochondriasis also respond to psychological treatments incorporating elements of ERP. Worthy of additional study would be comparative examination of whether nonresponse to other antidepressants compared with anxiolytics such as benzodiazepines might characterize subgroups of these other OCD-related disorders. Data from such approaches are sparse, with very few head-to-head studies like those done in OCD of SRIs versus norepinephrine transporter inhibitors such as desipramine or drugs affecting other neurotransmitter systems that have been reported (eg, ref 158).

Likewise, while there is evidence for some features of OCD to exhibit family-based relationships in treatment responses, as recently reviewed,[26] similar data are very meager for OCD-related disorders other than major depression. Thus, these notions have not yet been adequately explored across more than a handful of disorders related to OCD to provide an adequate treatment-based subcategorization of these disorders or to provide a common understanding of them.

Additional approaches to understanding OCSDs and OCRDs: brain imaging studies, putative endophenotypes (including neuropsychological and neurophysiologic measures) and hints from animal models

Brain imaging investigations of OCD patients have only relatively recently been expanded to include some subgroups such as body dysmorphic disorder and compulsive hoarding. Specific investigations have included positron emission tomography (PET) studies of glucose utilization and MRI-based volumetric studies of components of the cortico-striato-pallido-thalamic circuits

most implicated in OCD. Another approach has been PET studies using specific ligands and magnetic resonance spectroscopy-based studies of specific brain chemicals to evaluate receptor and transporter elements of neurotransmitter signaling pathways.[159,160]

Most studies thus far have endeavored to compare OCD patients with controls, or occasionally other neuropsychiatric patient groups, or pre- and post-treatment comparisons. There has been a decided lack of investigations considering the OCD-related disorders. Expense, difficulty, and time limit the numbers of individuals that can be studied, and thus there are only a very few studies of OCD subgroups, such as one comparing OCD patients with and without hoarding[40] and studies comparing the symptom dimensions of OCD.[161] A similar situation exists for psychological and physiological measures or endophenotypes and for animal models, all of which are at the stage of mostly searching for relevant measures for OCD phenotypes.[162-164]

One rodent model, which documented changes in microneuroanatomical structures in pathways that were associated with shifts from normal goal-directed behaviors to more limited, habit-based "compulsive" behaviors following multiple types of chronic stressors would seem of relevance to environmental trauma and stress as discussed above regarding the genesis of an environmental OCD spectrum.[128] Conceptually, combinations of stresses (from the environment such as psychological traumatic events and from disease-based etiologies such as neurologic disorders or comorbid anxiety, mood, or other neuropsychiatric disorders), plus genetic vulnerabilities might be envisaged as combining to lead towards temporarily adaptive OCD-related thoughts and behaviors that limit further nonadaptive disorganization. Their continuation, however, past the times of most marked stress, may become nonadaptive— a sustained reduction in abilities to act towards more adaptive, social, and occupational goal-directed functions. Prior clinical data and theoretical formulations have led to some similar suggestions resembling this interpretation and application to OCD of this experimental animal model.[128]

Conclusions

Thus, we are left with a multifaceted array of obsessive-compulsive features that cut across traditional *(DSM-IV/TR)* as well as draft plans for the *DSM-5*. Before elaborating what comprises OCSD and OCRD, it seems important to consider "uncomplicated," OCD, as such individuals may be important to study for many purposes and comparisons.[69,70] For example, if our current nosologic distinctions retain some validity, detailed knowledge of uncomplicated OCD may help to clarify which genes are more directly OCD-related when coexisting mood, anxiety, and other groupings of comorbid disorders and their underlying genes are also present. However, even uncomplicated OCD demonstrates symptom heterogeneity, leading to continuing efforts such as using latent class modeling to go beyond factor and cluster analyses in order to parse the condition into more valid groups. Considering underlying features, stressors and the other environmental contribution to symptoms may be additional factors to consider in these investigations.

In view of the present diagnostic scheme, there is some consensus that entities such as body dysmorphic disorder, hypochondriasis, and obsessive-compulsive personality disorder share the highest apparent phenotypic overlap with OCD. At the same time, the most commonly occurring disorders comorbid with an OCD diagnosis are anxiety and mood disorders, especially major depressive disorder and dysthymia, and even bipolar disorder.[165] Another interesting connection with additional disorders arises from segregation, and other analyses that have shown that ADHD and bipolar disorder occur in OCD and the families of OCD probands as frequently as these disorders occur in family studies of each of the primary disorders, ADHD, and bipolar disorder.[71,80,81] Thus it is apparent that OCD does co-occur with a wide variety of disorders, and certainly some share enough in common to be considered OCD-related.

The search for OCD subtypes and spectrum conditions over the past 15 years has sought to clarify the constellation of features associated with OCD, but has proved to be a monumental task, sometimes beset by false paths and perhaps spurious associations such as the suggestion of an impulsive-compulsive continuum and a range of problems only very distantly resembling OCD (eg, *Figure 2*, lower right). Recently, however, efforts have been made to emphasize shared underlying mechanisms and etiologies. For example we have reviewed two examples of etiologically based OCD presentations that could comprise new OCD-related disorder groupings. Another avenue of approach is the weaving together of model approaches from experimental (eg, brain imaging) and genetic models, combined with more detailed empirical studies of the

phenotypical heterogeneity of individuals with OCD and similar disorders.[129,164,166,167] With recent advances from ongoing clinical investigations and other research, the state of OCD and OCD-related spectrum disorders is evolving rapidly, with many interesting new developments, as elaborated in a surge of recent publications. It is to be hoped that, together, this work will result in an etiologically based diagnostic scheme that in turn will help advance diagnosis and treatment of these disabling illnesses. ❑

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El trastorno obsesivo-compulsivo y sus trastornos relacionados: una reevaluación de los conceptos del espectro obsesivo-compulsivo

El trastorno obsesivo-compulsivo (TOC) es un síndrome clínico cuyo sello distintivo son los pensamientos desmedidos que provocan ansiedad y conductas compulsivas, los cuales habitualmente no son reconocidos como razonables, pero que causan un distrés y un deterioro significativos. Cuando éstos son los síntomas exclusivos, constituyen un TOC no complicado. El TOC también puede presentarse en el contexto de otras patologías neuropsiquiátricas, principalmente en otros trastornos ansiosos y del ánimo. La pregunta que persiste es si acaso estas combinaciones de trastornos deben considerarse como cuadros independientes, trastornos que co-ocurren o como manifestaciones diferentes de una constelación parcialmente comprendida de los trastornos del espectro del TOC con una etiología común. También se entregan consideraciones adicionales para dos subgrupos según sus potenciales bases etiológicas: 1) un grupo de base ambiental en el cual el TOC ocurre a continuación de acontecimientos aparentemente causales como las infecciones por estreptococo, el daño cerebral o el tratamiento con neurolépticos atípicos y 2) un grupo de base genómica en que el TOC se relaciona con anomalías cromosómicas o de genes específicos. Considerando el estado actual de la investigación, parece fácil de manejar el concepto de TOC y de las condiciones del espectro relacionado con el TOC en 2010, pero requiere de una reevaluación permanente.

Trouble obsessionnel-compulsif et troubles associés : réévaluation du concept de spectre obsessionnel-compulsif

Le trouble obsessionnel-compulsif (TOC) est un syndrome clinique caractérisé par des comportements compulsifs et des pensées excessives à type d'anxiété, généralement reconnus comme déraisonnables, causant une souffrance et un handicap significatifs. Quand ces symptômes sont les seuls, on parle de TOC non compliqué. Mais le TOC peut également survenir dans le contexte d'autres troubles neuropsychiatriques, plus couramment dans le cadre d'autres troubles anxieux ou de troubles de l'humeur. Il reste à savoir si ces troubles doivent être considérés comme indépendants, simultanés ou comme des manifestations différentes d'une constellation incomplètement comprise de troubles du spectre du TOC avec une étiologie commune. Cet article propose des réflexions supplémentaires sur deux sous-groupes éventuels d'origine étiologique : 1) un groupe d'origine environnementale dans lequel le TOC survient après des événements apparemment causaux comme une infection streptococcique, une lésion cérébrale ou un traitement neuroleptique atypique ; et 2) un groupe d'origine génomique dans lequel le TOC est lié à des anomalies chromosomiques ou à des gènes spécifiques. Au stade actuel de la recherche, le concept de TOC et de trouble du spectre obsessionnel compulsif semble flou en 2010 et nécessite une réévaluation.

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