Obsessive Compulsive Disorder

Current Understanding and Future Directions

Until about two decades ago, obsessive-compulsive disorder (OCD) was considered an uncommon mental illness for which no effective treatment existed. Since then, there has been significant progress in the understanding and treatment of OCD. Recent developments in the field of neuroimaging, genetics and immunology have resulted in newer insights into this disorder. Learning and cognitive theories have contributed to specific treatment approaches. This book brings together some of the recent developments in the field and offers ideas to future research. The contributors to this book are well-known researchers in the area.

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Obsessive-Compulsive Disorder Current Understanding and Future Directions
Editors: Y C Janardhan Reddy, Shoba Srinath

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The symposium was held to commemorate completion of a decade of specialty OCD CLINIC at NIMHANS, Bangalore.

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Foreword

Obsessive-compulsive disorder (OCD) is a common and disabling mental disorder. It is twice as common as schizophrenia and bipolar disorder. OCD is largely underdiagnosed and inadequately treated. OCD mostly presents for the first time in adolescence and can thus incapacitate a person throughout his/her life. Despite its relatively early age at onset, only a minority of sufferers receive treatment early in the course of illness. OCD also has its relative share of stigma, resulting in long delays in treatment. This is compounded by the fact that most medical professionals are unfamiliar with its clinical characteristics resulting in delay in diagnosis and appropriate treatment.

Considerable progress has occurred in the last two decades in the treatment and understanding of this common psychiatric illness. Serotonin reuptake inhibitors and cognitive behavior therapy, both have improved the outcome of this illness, which was otherwise considered difficult to treat. There is also significant advance in the understanding of the neurobiology of OCD with respect to neural correlates of obsessional behavior, genetics and immunology.

However, despite the advances in understanding the neurobiology and the cognitive factors in the causation of OCD and availability of effective treatments, about 40% to 60% of the patients do not show satisfactory improvement. This shows that there is still much to be understood. This monograph brings together some of the latest developments in the understanding and treatment of OCD. The contributors to this monograph are well known researchers in the field, have put together a summary of the

latest developments in the field, and offer some fresh insights in to the future direction of research in the area.

This monograph is the proceedings of the symposium held in commemoration of completion of a decade of specialty OCD services at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore.

I hope this monograph serves as a useful reference source to all the mental health professionals involved in the care of persons suffering from OCD.

Dr. D. Nagaraja
Director & Vice-chancellor
NIMHANS

Preface

Considerable progress has occurred in the understanding and treatment of obsessive-compulsive disorder (OCD) in the last two decades. Serotonin reuptake inhibitors and cognitive behavior therapy have emerged as the mainstay of treatment in OCD replacing the ineffective and often long-drawn psychoanalytical treatment. There is considerable advancement in understanding the neurobiological basis of the disorder based on neuroimaging and neuropsychological studies. Genetic basis of the disorder is being explored vigorously. Immunological basis of the childhood OCD has received special attention from some researchers. In addition to these major advances in the field, there have been efforts in understanding OCD from the perspective of a spectrum concept. What is more, it is increasingly realized that OCD is perhaps not a unitary disorder. Researchers working with children point to the possibility of a developmental subtype of childhood OCD.

Despite the advances in the understanding and treatment of OCD and its improved prognosis, there are many areas of concern and disagreement among researchers. For example, some researchers try to understand the disorder entirely from a biological perspective and others from a cognitive and learning perspective. We are sure there must be a meeting point for researchers from diverse backgrounds and viewpoints. Of course, diverse viewpoints and disagreements often boost the efforts at better understanding and improve the quality of research. We know that 40 to 60% of the patients still do not show satisfactory response to treatment. All this implies that there is still much to be understood.

Several leading researchers in the area have contributed to this monograph. Their viewpoint and insight in to the nature of the disorder reflects to some extent at least the direction of the research in the area. The topics covered are most contemporary in the field and include diverse but related areas such as phenomenology, course and outcome, neurobiology, genetics, immunology and treatment of resistant OCD. The monograph also covers the role of psychotherapy in the treatment of OCD. There is an effort to understand the uniqueness of the disorder in children.

This monograph is a compilation of the proceedings of the international symposium held at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India on November 10 & 11, 2007. The symposium is being held to commemorate completion of a decade of specialty OCD services at the institute. The specialty OCD clinic was pioneered in 1997 by Dr. Sumant Khanna, a well-known clinician and researcher in the field. Although Dr Khanna's serious interest was in biological psychiatry and psychopharmacology, he is also largely responsible for popularizing the approaches of exposure and response prevention in treating OCD at our centre. He also collaborated with colleagues in child psychiatry to do some early work on the phenomenology of childhood OCD.

The OCD clinic at NIMHANS is very popular and caters to around 120 to 150 new patients per year and follows up close to 1000 patients in a year. Patients are often referred from across the country for management of resistant OCD.

This monograph is special for us for two important reasons. Firstly,

eminent researchers in the field have contributed to this monograph which enhances the authenticity of the issues discussed. Second, this monograph is symbolic of our obsession to provide specialized services to the sufferers of OCD and boost the research in the area. We hope the monograph serves as a useful reference to clinicians and researchers in the area.

Y C Janardhan Reddy
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Contents

Chapter 1

The Obsessive-Compulsive Spectrum of Disorders: Towards DSM-V and ICD-11

Dan J. Stein

There has been a good deal of interest in recent years in the concept of an obsessive-compulsive spectrum of disorders. Advances in the neurochemistry and neuroanatomy of Obsessive-Compulsive Disorder (OCD) have led to the question of whether disorders characterized by similar phenomenology and psychobiology are best conceptualized as OCD-related. This question is not merely a conceptual one; insofar as an OC spectrum construct would encourage more appropriate diagnosis and treatment of these putative OCD-related disorders, it would have important practical and clinical implications.

Much of the work on this debate has focused on data that emerges from family investigations, brain imaging research, and molecular genetic studies. In this paper, a conceptual approach is adopted, beginning with the question of what is a spectrum of disorders. A number of solutions are put forward, and then used to address some of the relevant psychobiological data.

From OCD to OCD Spectrum

At the start of the twentieth century, there were those who held that OCD was a rare disorder, caused by psychological conflicts, and poorly responsive to treatment. This century witnessed important advances in psychiatric

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diagnosis and epidemiology, in neuroimaging and molecular neuroscience, and in psychopharmacology and psychotherapy. By the end of the century, there was good evidence to suggest that OCD was a not uncommon disorder, that it was mediated by particular psychobiological mechanisms, and that it responded to both specific pharmacotherapies and psychotherapies (1).

Advances in OCD raised the question of whether conditions with similar phenomenology and psychobiology, would respond to pharmacotherapies and psychotherapies effective for OCD. Early work demonstrated that OCD responded more robustly to the serotonin reuptake inhibitor clomipramine than to the noradrenaline reuptake inhibitor desipramine. A range of investigators began to explore whether clomipramine was also more effective than desipramine in disorders such as body dysmorphic disorder, trichotillomania, as well as in various body-focused repetitive conditions and symptoms (2).

A narrow approach to defining the OCD spectrum has focused on disorders where there is significant psychobiological overlap with OCD. An early psychodynamic view was that OCD and related disorders were accounted for by similar defense mechanisms. More recent work has emphasized neurobiological overlap. Tourette's disorder is perhaps the OCD spectrum par excellence in this work, for it has a particularly close familial relationship with OCD (3). Moreover, within a particular family, irrespective of whether patients suffer from OCD or tics, they may have similar underlying abnormalities in brain imaging (4) suggesting a common endophenotype.

A broader approach to defining the OCD spectrum has included a much

larger number of disorders, ranging for example from those that are more compulsive (like OCD) to those that are more impulsive (5). In such a view, compulsive and impulsive traits can be seen in disorders that fall into a range of categories in standard classification symptoms. Examples of this would include disorders ordinarily diagnosed in childhood (such as Tourette's), in somatoform disorders (such as body dysmorphic disorder and hypochondriasis), in impulse control disorders (such as kleptomania, pathological gambling, and trichotillomania), and in eating disorders (such as anorexia and bulimia).

What is a Spectrum of Psychiatric Disorders?

It is useful to distinguish between two long-standing approaches to psychiatric classification (6, 7). A classical approach has emphasized the idea that psychiatric disorders are natural kinds, which can be defined in terms of their necessary and sufficient criteria. Just as a square can be defined as a figure with four equal sides at right angles, so a psychiatric disorder can be defined in terms of particular operational criteria. This approach has a venerable history; it draws on a long line of philosophical thinking about science, about language, and about medicine, and has had an important influence on contemporary psychiatric nosology.

A critical approach, on the other hand, has emphasized the idea that psychiatric disorders are socially constructed categories. Just as what is considered a weed reflects human practices that vary from time to time and place to place, so what counts as a psychiatric disorder says more about those who construct nosologies than about reality per se. This approach too has a long history; there are many who have argued that classical concepts of

science, language and medicine do not stand up to careful scrutiny, and this kind of thinking has had an important influence on contemporary critiques of psychiatric nosology.

From a classical perspective, two disorders fall on a spectrum if their necessary and sufficient criteria are closely related. Orange and red fall on a spectrum of light, precisely because they can be defined in terms of wavelengths of light which are very similar. From a critical perspective, the idea of putting two disorders on a spectrum mostly reflects sociopolitical machinations. If obsessive-compulsive disorder is taken out of the anxiety disorders, this may for example reflect that new drugs are available for OCD, and that the medical-industrial complex has chose to extend its power, by creating knowledge of and marketing for, the so-called OCD spectrum disorders.

It may be possible to construct an integrative approach to classification which is based on cognitive-affective science, and which goes beyond the classical and critical perspectives. The particular way in which our brain-minds are built means that there are a series of universal basic-level constructs that humans are familiar with. Pain, for example, is an experience that has existed across history and geography. However, our brain-minds are situated in a complex natural and social world, and so employ a range of more complex categories often based on metaphoric extension. Thus, many cultures might talk of the pain of losing a friend. Human categories have more central categories (eg. physical pain is a central example of pain, a robin is a typical bird) and more peripheral ones (eg., the loss of a friend is an atypical kind of pain, an ostrich is an atypical bird).

There is a broad range of scientific data in this area. Cognitive psychology has a rich empirical literature on prototypic categories (such as birds) (8). Artificial intelligence has built parallel distributed networks which model the graded nature of many categories (9). Linguistics has shown that many of our abstract concepts are structured using extensions of basic-level sensorimotor experience (10). Neuroscientists and anthropologists have explored categories such as color categories, and shown how these reflect both basic-level experience (eg. primary colors), but are extended differently in different languages (11). Developmental psychologists have shown how basic-level categories develop over time to cover more abstract phenomena (12).

Similarly, disorder is a prototypic but structured category. We cannot define disorder in an essentialist way, as our concepts of disorder emerge within our social practices (eg. in determining whether someone is distressed and impaired). At the same time, our categories of disorders are not simply wholly arbitrary or relativistic, they reflect particular extensions of basic-level experience, which can be more or less reasonable. Metaphors of disorder include those which structure disorder in terms of a pathway (eg. as suffering an impediment or a breakdown), a possession (eg. having attracted a contamination or an attack), or as an imbalance.

Thus, meningitis with decreased consciousness is a typical neuropsychiatric disorder; it can be structured using the metaphor of having a contamination, for which the patient has no responsibility, and deserves treatment. Substance abuse is a more atypical disorder, where we may reasonably use the idea of change brought by an external agent to argue that it is similarly structured to an infection, but where there may also be an acknowledgment of the agent's

responsibility for having developed the disorder, and where both treatment and increased responsibility for that treatment are required.

How does this approach conceptualize a spectrum of disorders? A first point would be that on a spectrum of psychiatric disorders, there are unlikely to be evenly spaced naturally cleaved division points (as there are on the light spectrum). Instead, some conditions are likely to be more central to the category, and others more peripheral or atypical. A second point would be that there is no single validator for configuring a nosology. Rather, any nosology reflects a broad range of considerations; these include both a number of different validators (each of which, if highlighted alone, might result in a somewhat different classification), as well considerations about clinical utility. In thinking about the OCD spectrum disorders, various aspects of clinical utility, can be considered this is discussed in detail in the next section.

Validation and Utility of the OCD Spectrum

A key validator of the OCD spectrum concept was mentioned earlier; the finding that a number of different disorders characterized by unwanted repetitive behavior responded more robustly to clomipramine than to desipramine. This finding perhaps fell on particularly receptive soil because it has immediate clinical utility. A range of disorders, which had previously been neglected, could now be effectively treated. Swedo and colleagues' work on clomipramine and desipramine in trichotillomania (13), for example, gave significant impetus to the birth of a whole range of studies on this disorder, many of them framed within the paradigm of exploring the obsessive-compulsive spectrum of disorders.

Nevertheless, it is notable that OCD and trichotillomania have many phenomenological and psychobiological differences. In direct contrast, although there is growing evidence that OCD and Tourette's involve a similar underlying endophenotype, perhaps a genetically mediated vulnerability to developing striatal dysfunction, these disorders are treated with different pharmacotherapies (serotonergic versus dopaminergic drugs) and psychotherapies (exposure vs. habit reversal therapies). Still there may be clinical utility in classifying OCD and TS together, for example, in encouraging assessment of tics in OCD, and OCD in TS.

The OCD spectrum concept has largely emerged from a biological psychiatry literature. The majority of this writing ignores the question of whether the functional analysis, in cognitive-behavioral terms, of symptoms in putative OCD spectrum disorders is similar or not. Certainly, a neuropsychiatric perspective on OCD has been valuable in encouraging exploration of underlying neurocircuitry and neurochemistry, as well as investigations of medications that act on these neurobiological mechanisms. At the same time, it is important not to neglect the possibility that higher level explanations may be crucial validators of the OCD spectrum concept, and that building such constructs into a classification system may have important clinical utility. Indeed, in deciding on what falls on the OCD spectrum, and how it should be configured, a whole range of sometimes conflicting findings must be weighed.

Cutting Edge of the OCD Spectrum

Given such considerations, in the near future it is not unlikely that OCD will remain conceptualized as an anxiety disorder. The complexity of nosological

decision-making should not, however, be equated with a sense of pessimism about future possibilities. Advances in our understanding of obsessive-compulsive disorder have certainly reinforced the possibility of a more conceptually rigorous and clinically useful classification system than that which existed in DSM-II and DSM-III. It can be speculated that advances in the cognitive-affective neuroscience of key cognitive-affective processes relevant to OCD, will ultimately lead to a better understanding of, and treatment approach to, both this disorder and putative OCD spectrum disorders.

One interesting possibility is concepts of OCD and spectrum disorders will emphasize reward processing more. Animal models and functional imaging have allowed the neurocircuitry of reward processing to be delineated, and show that the ventral striatum plays a key role (14). These methodologies have also provided data about the particular neurotransmitters involved in mediating the processing of rewards, dopamine plays a particularly important role (15). Such basic work has proved particularly relevant to understanding drug addiction; patients with substance use show abnormalities in the neurobiology of reward processing, and may respond to treatments acting on these pathways (16, 17).

One way of conceptualizing OCD is in terms of the absence of a feeling of goal completion after an action is performed; people continue with their compulsions repetitively until there is finally the sense that things are now just right. Furthermore, at the level of neurocircuitry, structural and functional imaging studies of OCD demonstrate that the ventral striatum plays an important role in mediating obsessive-compulsive symptoms (18) perhaps

disruption of this neurocircuitry underpins the failure of the signal that denotes goal completion. Finally, at a neurotransmitter level, dopamine is released in the ventral striatum under conditions of maximal uncertainty about subsequent reward, and also appears to plays a key role in mediating the symptoms of OCD (15), perhaps underpinning the sense of uncertainty about goal completion in OCD.

Reward processes are disrupted in a range of disorders, including mood disorders (19). A number of conditions involve repetitive goal-seeking behaviors; pathological gambling(PG) and hypersexual disorder, for example, may be characterized by disturbances in the processing of rewards (20, 21). Finally, Tourette's disorder, and stereotypic disorders such as trichotillomania, have also been described in terms of reward-deficiency by some authors (22). It turns out that in OCD patients, one cluster of putative comorbid OCD disorders comprises PG, hypersexual disorder, Tourette's, and trichotillomania (23), again raising the question of whether these diverse disorders share some underlying psychobiological features.

Of course, these various disorders, even if sometimes called 'compulsive', differ from OCD in key phenomenological and functional ways. PG, hypersexual disorder, and trichotillomania may involve a sense of pleasure at the time of the behavior, depression involves an inability to feel pleasure, whereas OCD is typically characterized by anxiety-inducing obsessions and anxiety-relieving compulsions. Perhaps different kinds of disturbances in reward processing result in a spectrum of diverse reward-related disorders. In terms of their underlying neurocircuitry, OCD is characterized by increased cortico-striatal activity, whereas PG, substance use disorders, and depression

tend to be associated with reduced orbitofrontal activity (17, 18). On the other hand, substance use disorders and OCD may both be characterized by low striatal D2 receptor availability (24, 17), and by glutamate dysfunction (25).

Conclusions

OCD is currently conceptualized as an anxiety disorder. Findings that various disorders have similar phenomenology and psychobiology, and sometimes respond to similar treatments, raise the question of whether to create a new category of OCD spectrum disorders in DSM-V and ICD-11. Many complexities remain in considering whether to configure such a new category, and if so then how best to do it. The analysis provides here on the nature of our constructs of disorder and of spectrums helps explain the nature of the many considerations that come into play. In the interim, the construct of an OCD spectrum has significant heuristic appeal, insofar as it encourages clinicians to screen for a range of neglected disorders, and to consider the use of potentially effective treatments that are also often ignored (2).

There is a good deal of evidence that OCD is characterized by disruptions in striatally and serotonergically mediated control processes (1). Such a view can potentially integrate a range of findings about compulsive and impulsive phenomena in OCD and related disorders, as well as about their underlying neurobiology. Thus, OCD is characterized by sudden intrusive symptoms, by inappropriate behavioral sequences, and by evidence of behavioral and cognitive disinhibition on neuropsychological testing (26), and perhaps increased frontal compensatory activity. In OCD, one cluster of comorbid OC spectrum disorders comprises intermittent explosive disorder,

kleptomania, eating disorders, and stereotypic self-injurious behaviors (23). In this view, compulsivity and impulsivity are not diametrically opposed, but rather may lie on orthogonal planes.

Future work on cognitive-affective processes relevant to OCD may ultimately result in a reconfiguration of the way in which we currently view the OCD spectrum of disorders. There is currently a good deal of excitement about advances in understanding reward processes, and the possibility that these may ultimately lead to a better way of conceptualizing and treatment these conditions. However, much additional work is needed in this area. Furthermore, it is quite possible that progress in other areas for example, understanding the psychobiology of disgust (27), may ultimately prove more important in addressing the question of whether the concept of OCD spectrum disorders is a valid one, and whether it has clinical utility in practice.

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Chapter 2

Is Obsessive-Compulsive Disorder a Unitary Disorder?

David Mataix-Cols and James F. Leckman

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (1) and other standard diagnostic classifications such as ICD-10 (2), regard ObsessiveCompulsive Disorder (OCD) as a unitary nosological entity. While this parsimony has a certain formal appeal, it is misleading. The symptoms used to define OCD are remarkably heterogeneous and 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 and mutually exclusive subtypes (Table1). For example, Falret made the distinction between *Folie du doute* (madness of doubt) and *Délire du toucher* (delusion of touch) in 1866. (4) With a few notable exceptions, such as the tic-related and early onset subtypes, these attempts had limited success in relating the identified subtypes to biological markers, genetic factors or treatment response. This was in part because pure subtypes of patients are rare, and the recruitment of sufficient sample sizes of each subtype is difficult and highly impractical (16-18).

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Table 1. Some attempts to classify obsessive-compulsive disorder patients into homogeneous, mutually exclusive subtypes.
Adapted from Mataix-Cols et al (17)

Obsessive-Compulsive Disorder Subtype	References
Folie du doute vs. *Délire du toucher*	3
Obsessions vs. compulsions	4
Primary obsessional slowness	5
Washers vs. checkers	6-9
Impulsive vs. non-impulsive	10
Early vs. late onset	11
Abnormal risk, pathologic doubt, incompleteness	12
Tic-like vs. no-tic-like	13
Primary vs. developmental	14
Autogenous vs. reactive obsessions	15

The following review considers an alternative dimensional approach to obsessivecompulsive (OC) symptoms that aims to identify valid quantitative dimensions for use in genetic, neurobiological, cognitive-behavioral and treatment outcome studies. The review then proceeds to examine the potential value of a dimensional approach from a developmental perspective. Finally, the results of a recent survey among international OCD experts and implications for the fifth edition of the DSM will be discussed.

Factor and Cluster Analytical Studies of OC Symptom Dimensions

Similar to phobias (19), there are a finite number of themes patients obsess

about and a corresponding limited range of ritualistic behaviors. From an evolutionary point of view, this suggests that obsessivecompulsive behaviors may have evolved to protect against particular kinds of threat (see discussion below). An increasing number of factor and cluster analytical studies of OCD symptoms support this idea. Mataix-Cols et al (16) recently summarized this literature and found strong evidence for at least four symptom dimensions, namely contamination/cleaning, hoarding, symmetry/order and obsessions/checking (Figure 1). Since publication of that review, at least eight large studies have been published replicating and further supporting this factor structure in adults with OCD (20-27). There is some controversy regarding whether or not that same dimensional structure is present in children and adolescents. Currently, three out of the four studies conducted in pediatric samples found evidence of a symptom structure largely congruent with that found in adults (28-31). The consistency in this literature is remarkable despite the use of different instruments (Yale Brown ObsessiveCompulsive Scale Symptom Checklist (YBOCS-SC) versus ObsessiveCompulsive Inventory) and methods (current versus lifetime symptoms, dichotomous versus ordinal versus interval scoring, a priori categories versus item-level analysis, exploratory versus confirmatory factor analysis, factor versus cluster analysis). In a recent study, Hasler et al (20) demonstrated that the use of factor and cluster analysis in the same sample of patients yielded identical results. An important limitation, however, is that most studies employed the YBOCS-SC which was not designed to be used as a quantitative rating scale. Some of the symptom dimensions have been consistently replicated across studies (e.g. contamination/washing, symmetry/ordering, hoarding) but the aggressive/checking and sexual/religious dimensions need further study, as it is unclear whether they form a unique factor or can be broken down into

multiple separate dimensions. Similarly, it is unclear how to regard somatic obsessions, since they appeared on different dimensions in different studies. Thus, although this factor structure is still provisional and limited by the available instruments of measure, researchers have begun to examine the biological, behavioral and cognitive correlates of each of these symptom dimensions and, more importantly, to develop specific treatments for each particular problem.

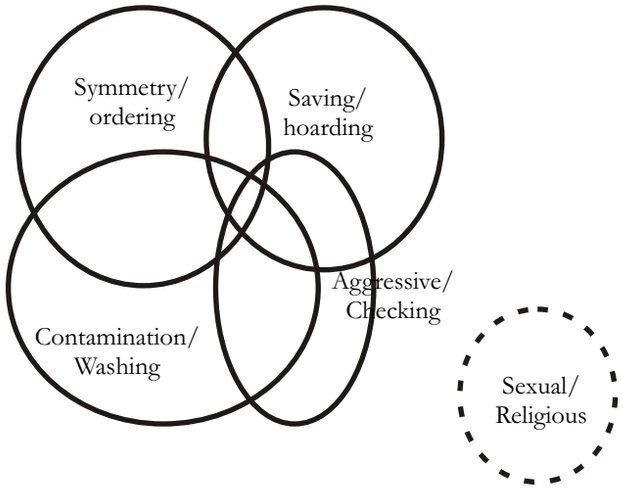

Figure 1. Schematic representation of the major symptom dimensions of OCD. Most studies consistently identified four symptom dimensions (continuous lines), while some others identified a fifth dimension consisting of sexual and religious obsessions (dashed line) but more research is needed to determine its validity. Note the overlap between these dimensions as mono-symptomatic patients are very rare.
Adapted from Mataix-Cols (17)

Temporal Stability of OCD Symptom Dimensions

Preliminary data support the temporal stability of the OC symptom

dimensions, at least in adult patients. Over a period of two to seven years, Rettew et al (32) assessed the longitudinal course of OC symptoms in 76 children and adolescents with OCD using the categories of the Y-BOCS-SC. They found that none of the patients maintained the same constellation of symptoms from baseline to follow-up. Nevertheless, these authors acknowledged that these changes could have occurred within, rather than, between symptom dimensions. This hypothesis was however not tested.

Two other studies, with large samples, have found that adult patients maintain their symptoms across time intervals as long as six years and the most robust predictor of having a particular symptom was having exhibited the particular symptom previously (33, 34). For symptoms that changed across time, changes typically occurred within, rather than between, previously identified symptom dimensions. This suggests that the symptoms of adult OCD patients are more stable than it is often assumed. A small study on children and adolescents also suggests that OCD symptom dimensions may be temporally stable in pediatric patients although this will require replication in larger samples (29). Finally, a recent two-year prospective study has found that the content of OC symptoms is also temporally stable in nonclinical samples (35). Longer longitudinal studies following patients from childhood to adulthood are needed to gain a more complete understanding of the natural history of OC symptoms.

The Relationship between OCD Symptom Dimensions and Comorbidity

Baer (36) reported that patients with high scores on his symmetry/hoarding factor were more likely to have a comorbid diagnosis of chronic tics and OC personality disorder (OCPD). Similarly, Leckman et al (37) found that patients

with high scores on the obsessions/checking and symmetry/ordering factors were more likely to present with tics. Mataix-Cols et al (38) found that male but not female OCD patients with chronic tics scored higher than patients without tics on the symmetry/ordering dimension. More recently, Hasler et al (20) found that the obsessions/checking dimension was broadly associated with comorbid anxiety disorders and depression, while the symmetry/ordering dimension was associated with bipolar disorders and panic disorder/agoraphobia. In the initial characterization of the DY-BOCS scale, depression and anxiety symptoms were also found to correlate with the severity of the aggressive obsessions and related compulsions (39).

There also appears to be a clear overlap with eating disorders. For example, Halmi et al (40) reported that approximately 70% of patients with anorexia nervosa (AN) had lifetime OC symptoms, especially symmetry and somatic obsessions and ordering and hoarding compulsions. And in another recent study, Halmi et al (41) emphasized the importance of 'perfectionism' as well as OCD and OCPD. In contrast, Hasler et al (20) reported an association between eating disorders and the contamination/cleaning dimension.

Mataix-Cols et al (42) examined the presence of all DSM-III-R Axis II diagnoses and their relation to OC symptom dimensions in a sample of 75 OCD patients. They found that hoarding symptoms were strongly related to the presence and number of all personality disorders, especially from the anxious-fearful cluster. Similarly, Frost et al (43) found that hoarding was associated with higher levels of comorbidity (i.e. anxiety, depression, personality disorders), as well as work and social disability, compared to nonhoarding OCD and other anxiety disorders. In another study (44), the

presence of hoarding was associated with increased prevalence of comorbid social phobia, personality disorders and pathological grooming conditions (skin picking, nail biting, and trichotillomania).

Taken together, these preliminary studies suggest that the presence of certain symptom dimensions may be associated with specific patterns of comorbidity. If confirmed in larger patient samples, these findings will have management implications as different treatment approaches may be indicated in each case.

Initial Validation from Family Genetic Studies

Family and twin studies suggest that genetic factors play a role in the expression of OCD. 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 (45, 46), it is virtually certain 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 (47-49). Etiologic heterogeneity may be reflected in phenotypic variability, thus it would be highly desirable to dissect the syndrome, at the level of the phenotype, into valid quantitative heritable components.

Alsobrook et al (50) were the first to use OC symptom dimensions in a

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. These findings have been recently replicated in a second independent family study (51).

The data used in genetics affected sibling pair study done by Leckman et al (52) was collected by the Tourette Syndrome Association International Consortium. Leckman et al (52) selected all available affected Tourette Syndrome (TS) pairs and their parents for which these OC symptom dimensions (factor scores) could be generated using the four factor algorithm first presented by Leckman et al (37). Over 50% of the siblings with TS were found to have comorbid OCD and more than 30% of mothers and 10% of fathers also had a diagnosis of OCD. The scores for both Factor I (obsessions/checking) and Factor II (symmetry/ordering) were significantly correlated in sibling pairs concordant for TS. In addition, the mother-child correlations (but not father-child correlations) were also 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 genome scan of the hoarding dimension was completed using the same TSAICG data set (53). The analyses were conducted for hoarding as both a dichotomous trait and a quantitative trait. Not all sib pairs in the sample were concordant for hoarding. Standard linkage analyses were performed using Genehunter and Haseman-Elston methods. Significant allele sharing was observed for both the dichotomous and the quantitative hoarding phenotypes for markers at 4q34, 5q35.2 and 17q25. The 4q site is in proximity to D4S1625, which was identified by the TSAICG as a region, linked to the TS phenotype. A

recursive-partitioning analytic technique also examined multiple markers simultaneously. Results suggest joint effects of specific loci on 5q and 4q. Another large linkage study in 219 families with multiple affected individuals found an association between the hoarding phenotype and a region in chromosome 14 (54). The inconsistencies between the Zhang et al (53) and Samuels et al (54) studies are most certainly due to marked differences in the family selection criteria (in the former study all probands had TS, whereas the latter excluded probands with TS). It is important to note that both studies were probably underpowered to find genes that are likely to have a small effect.

A recent study involving 418 sibling pairs with OCD (55) found that after controlling for sex, age and age of onset, robust sib-sib intraclass correlations were found for Factor IV (hoarding; $p = .001$) and Factor I (obsessions/checking; $p = .002$). Smaller, but still significant, sib-sib intraclass correlations were found for Factor III (contamination/cleaning; $p = .02$) and Factor II (symmetry/ordering; $p = .04$). Limiting the sample to female subjects more than doubled the sib-sib intraclass correlations for Factor II ($p = .003$).

Two studies (21, 56) have genotyped OCD patients for the functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) and both found that the frequencies of the S allele and the SS genotype were associated with the symmetry/order dimension. This is promising given that 5-HTTLPR remains a major candidate gene for OCD (57). This observation may also be consistent with the findings of Sutcliffe et al (58) who reported that within a large group of individuals with autism with rigid compulsive behaviors including ordering, symmetry and arranging - were more likely to have coding substitutions at highly conserved positions