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Editorial

Dear Colleagues,

Modern neuroses range from the hysteria described by Charcot to the obsessiveness described by Pierre Janet, and thus, in a certain way, from a highly disturbed image of one's self and of others to the symbolic investment of objects with a phobic dimension.

The range of neurotic symptoms is vast, and is made up of a huge variety of particular signs which are often specific to the personal history of the individual.

However, certain traits are dominant or preponderant, as they affect the relationship between self and others, or with the environment. They do not, however, represent stages or degrees of the pathology, but rather they characterize a clinical case or a given form of the illness.

It would not have been possible, in this collection of articles, to envisage an exhaustive discussion of all the various obsessive symptoms, so we chose to provide the most recent information on obsessive-compulsive disorders.

The notion of compulsion implies the inability of the subject to refuse to obey the orders of his or her subconscious mind to carry out a particular gesture or a particular behaviour. Thus, the only way to find relief (albeit transient) from anxiety is to perform an act that has no rational explanation or logic, but that can often be rationalized secondarily.

The repetition of these gestures or behaviors invades the subject's life, often going as far as rituals that are handicapping and often dangerous.

Several explanatory models have been put forward, the best-known being that of Sigmund Freud. Modern psychiatrists (eg, Robert Spitzer) have left aside the idea of neuroses, to classify obsessive symptoms as "problems" belonging at the same time to the behavioral and somatic domains; the relationship between obsessive-compulsive disorders and possible neuroanatomic and neurophysiologic anomalies favors this classification.

In this issue we wished to present the current state of knowledge about the various aspects of the concept—clinical and pathophysiological aspects, neuroimaging, and therapy. To this end we invited a group of brilliant authors to contribute. Our warm thanks go to them, as well as to Dr Marc-Antoine Crocq and Prof Pierre Schulz, who coordinated this issue.

Sincerely yours,

Jean-Paul Macher, MD

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ISSUE COORDINATED BY: *Marc-Antoine Crocq, with Pierre Schulz*

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In this issue...

Obsessions and compulsions have been described since the 19th century by famous psychiatrists like Étienne Esquirol, Richard von Krafft-Ebing, Pierre Janet, and many others. Ruminative thoughts and ritualized behavior are not limited to the patients who satisfy all the diagnostic criteria of typical obsessive-compulsive disorder (OCD), as expounded in *DSM-IV*. Beyond typical OCD, preoccupying thoughts are also common in individuals with anorexia nervosa. Repetitive acts are a hallmark of both Tourette syndrome and trichotillomania. Clinicians treating patients with body dysmorphic disorder or hypochondriasis often end up wondering whether their patients' beliefs follow a delusional or obsessive logic. It is still uncertain whether disorders like pathological gambling should be included in the diagnostic categories of addiction, compulsive behavior, or disorders of impulse control. All of these examples illustrate the complexity of the delineation of the spectrum of OCD, and we are not surprised that the future status of OCD in *DSM-5* is still under debate.

This issue begins with a ***State of the art*** article by Dennis Murphy (NIMH Intramural Research Program, Bethesda, MD, USA) et al (p 131). The authors describe the current conceptualization of obsessive-compulsive spectrum and obsessive-compulsive-related disorders. They point out the heterogeneity of OCD symptoms in individuals. In addition, they consider two potential etiological subgroups: firstly, OCD cases caused by external factors such as streptococcal infections, brain injury, or atypical neuroleptic treatment; and secondly, a group in which OCD is related to chromosomal anomalies or specific genes.

In the ***Translational research*** section, two articles emphasize the contribution of genetics and imaging. Both papers have in common that they shed light on the glutamate hypothesis of OCD. David Pauls (Harvard Medical School, Boston, Massachusetts, USA, p 149) reviews the current state of the research into the genetics of OCD. Although OCD runs in families, the publication of over 80 candidate gene studies has not led to definitive conclusions. Only studies showing association with the glutamate transporter gene *SLC1A1* could be replicated, whereas this was not the case with genes intervening in dopaminergic and serotonergic neurotransmission. Frank MacMaster (Wayne State University, Detroit, Michigan, USA, p 165) analyzes the glutamate hypothesis of pediatric OCD, and he reviews in particular the neuroimaging evidence.

Seven papers are devoted to ***Clinical research***. Donald Black et al (Department of Psychiatry, University of Iowa, USA, p 175) review both compulsive buying (CB) and pathological gambling (PG). PG has recently been proposed as a candidate for inclusion in "behavioral addictions" in *DSM-5*. The authors conclude that CB and PG are probably not related to OCD, and that both CB and PG should be conceptualized as impulse-control disorders. The next three papers discuss treatment options for OCD. Michael Kellner (University of Hamburg, Germany, p 187) reviews pharmacological treatment strategies. Although serotonergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are the established pharmacologic first-line treatment, about half of the patients do not respond adequately. In case of treatment resistance, traditional possibilities include augmentation with second-generation antipsychotics or switch to cognitive behavioral therapy. Several glutamergic agents (eg, memantine, riluzole, D-cycloserine) are at various stages of clinical testing. Edna Foa (University of Pennsylvania, Philadelphia, USA, p 199) summarizes the history of psychological interventions in OCD and describes current cognitive behavorial therapy. Traditional psychoanalysis did not lead to efficient treatment, and the first breakthrough came with exposure and ritual or response prevention. Dieter Naber, Steffen Moritz, et al (University of Hamburg, Germany, p 209) have developed a self-help manual entitled "My MetaCognitive Training for OCD" (myMCT) aimed at raising patients' awareness about cognitive biases. This training is particularly useful for patients currently unable to attend conventional therapy or in cases where such a treatment option is not available. The next two articles address disorders that occupy unique positions within the spectrum of OCD. Katharine Phillips et al (Providence, Rhode Island, USA, p 221) provide an overview of research findings on body dysmorphic disorder (BDD, formerly known as "dysmorphophobia"). BDD is at times delusional, and patients' insight varies. BDD might be more prevalent than initially assumed, and underdiagnosed in clinical settings. Jessica Grisham and Melissa Norberg (University of New South Wales, Sydney, Australia, p 233) offer a brilliant description of the evolving controversy regarding the diagnostic status of compulsive hoarding, a syndrome characterized by excessive collecting and saving behavior that results in a cluttered living space. The authors highlight accumulating evidence suggesting that hoarding might be best conceptualized as a separate syndrome. Peter Kaplan (Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, p 241) discusses the link between temporal lobe epilepsy (TLE) and OCD. Controlled studies have noted that TLE patients present with obsessive qualities of washing, symmetry, exactness, and ordering, and with greater preoccupation with certain aspects of religion, compared with controls or patients with idiopathic generalized epilepsy.

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In this issue...

In a ***Brief report***, Peter Brugger (University Hospital Zurich, Switzerland, p 250) and Isabelle Viaud-Delmon (CNRS, Paris, France) discuss the putative continuum between superstitiousness and OCD. Further, they elaborate on the distinction between superstitious behavior from superstitious belief, and they propose that different brain circuits may be responsible for these two forms of superstitiousness.

Finally, a ***Free paper*** by Izzie J. Namer et al (University of Strasbourg, France, p 255) reports on caffeine effects on cerebral perfusion in humans using single photon emission computed tomography. They show that caffeine activates regions involved in the control of vigilance, anxiety, and cardiovascular regulation, but does not affect areas involved in reinforcing and reward.

Marc-Antoine Crocq, MD

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

Dennis L. Murphy, MD; Kiara R. Timpano, PhD; Michael G. Wheaton; Benjamin D. Greenberg; MD, PhD; Euripedes C. Miguel, MD, PhD

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.

Keywords: *obsession; compulsion; anxiety; comorbid disorder; environmental influence; genetics; genomics; Tourette syndrome; compulsive hoarding; depression*

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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

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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-

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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]

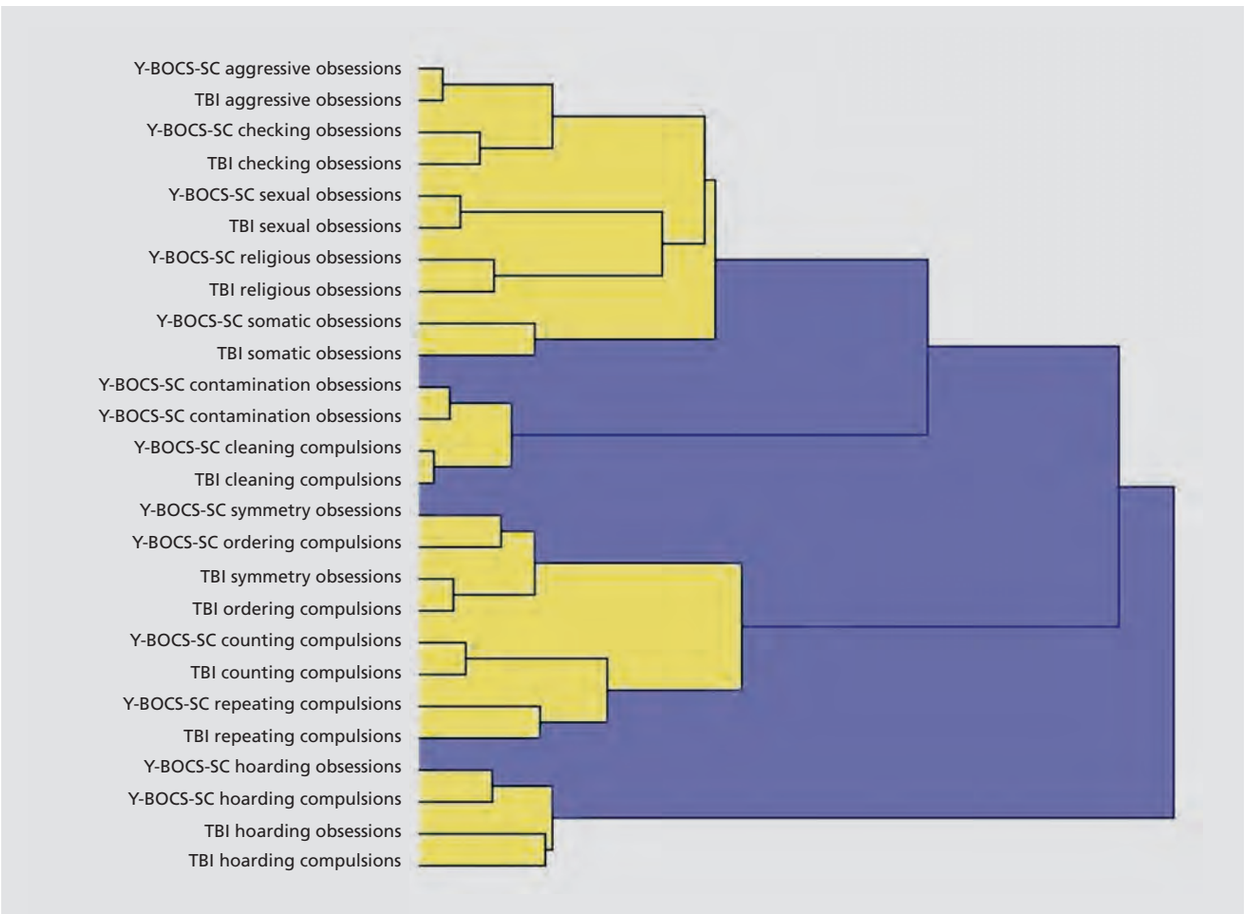

Figure 1. Dendrogram depicting a cluster analysis of OCD symptoms found in 321 OCD probands.
Adapted from ref 29: Hasler G, LaSalle-Ricci VH, Ronquillo JG, et al. Obsessive-compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. *Psychiatry Res*. 2005;135:121-132. 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

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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?"

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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*.

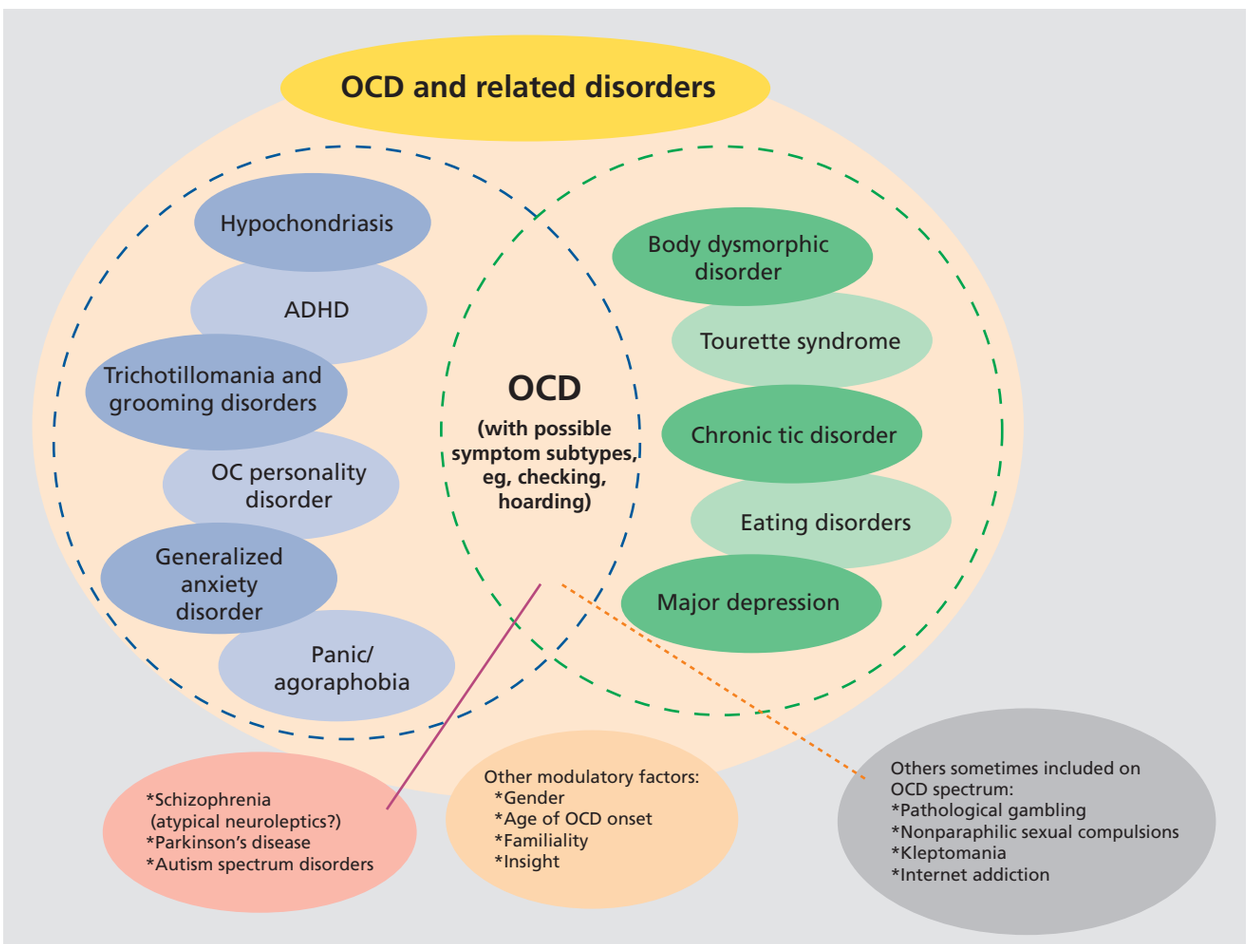

Figure 2. OCD and disorders comorbid with OCD.

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

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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).

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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]

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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-pallidothalamic 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

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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,

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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

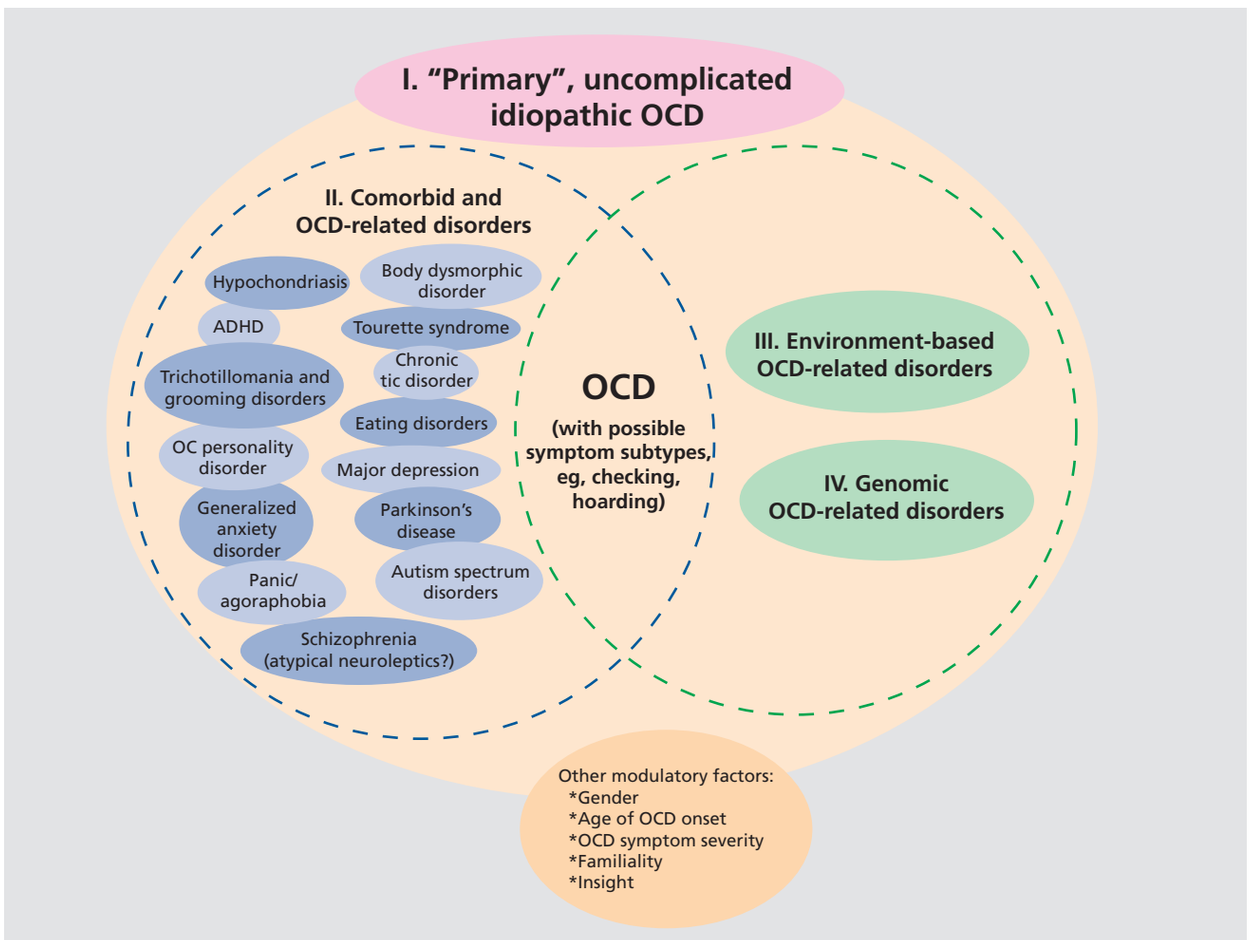

Figure 3. OCD and related disorders: update 2010.
Adapted from ref 12: Hollander E, Kim S, Braun A, Simeon D, Zohar J. Cross-cutting issues and future directions for the OCD spectrum. *Psychiatry Res*. 2009;170:3-6. Copyright © Elsevier/North-Holland Biomedical Press 2009, ref 19: Mataix-Cols D, Rosario-Campos 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

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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

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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

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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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REFERENCES

1. Angst J, Gamma A, Endrass J, et al. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:156-164.
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
3. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science*. 1996;274:740-743.
4. Altman SE, Shankman SA. What is the association between obsessive-compulsive disorder and eating disorders? *Clin Psychol Rev*. 2009;29:638-46.
5. Fallon BA, Qureshi AI, Laje G, Klein B. Hypochondriasis and its relationship to obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;23:605-616.
6. Ferrao YA, Miguel E, Stein DJ. Tourette's syndrome, trichotillomania, and obsessive-compulsive disorder: how closely are they related? *Psychiatry Res*. 2009;170:32-42.
7. Fineberg NA, Sharma P, Sivakumaran T, Sahakian B, Chamberlain SR. Does obsessive-compulsive personality disorder belong within the obsessive-compulsive spectrum? *CNS Spectr*. 2007;12:467-482.
8. Phillips KA, Pinto A, Menard W, Eisen JL, Mancebo M, Rasmussen SA. Obsessive-compulsive disorder versus body dysmorphic disorder: a comparison study of two possibly related disorders. *Depress Anxiety*. 2007;24:399-409.
9. Hermesh H, Hoffnung RA, Aizenberg D, Molcho A, Munitz H. Catatonic signs in severe obsessive compulsive disorder. *J Clin Psychiatry*. 1990;51:259.
10. Hutton J, Goode S, Murphy M, Le Couteur A, Rutter M. New-onset psychiatric disorders in individuals with autism. *Autism*. 2008;12:373-390.
11. Castle DJ, Phillips KA. Obsessive-compulsive spectrum of disorders: a defensible construct? *Aust N Z J Psychiatry*. 2006;40:114-120.
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.
13. Lochner C, Seedat S, Stein DJ. Chronic hair-pulling: phenomenology-based subtypes. *J Anxiety Disord*. 2009.
14. Storch EA, Abramowitz J, Goodman WK. Where does obsessive-compulsive disorder belong in DSM-V? *Depress Anxiety*. 2008;25:336-347.
15. Hollander E, Wong CM. Obsessive-compulsive spectrum disorders. *J Clin Psychiatry.* 1995;56 Suppl 4:3-6; discussion 53-55.
16. Hollander E. Obsessive-compulsive spectrum disorders: an overview. *Psychiatric Annals*. 1993;23:355-358.
17. Lochner C, Hemmings SM, Kinnear CJ, et al. Cluster analysis of obsessive-compulsive spectrum disorders in patients with obsessive-compulsive disorder: clinical and genetic correlates. *Compr Psychiatry*. 2005;46:14-19.
18. Durdle H, Gorey KM, Stewart SH. A meta-analysis examining the relations among pathological gambling, obsessive-compulsive disorder, and obsessive-compulsive traits. *Psychol Rep*. 2008;103:485-498.
19. Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry*. 2005;162:228-238.
20. Potenza MN, Koran LM, Pallanti S. The relationship between impulse-control disorders and obsessive-compulsive disorder: a current understanding and future research directions. *Psychiatry Res*. 2009;170:22-31.
21. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *Lancet*. 2009;374:491-499.
22. Regier DA. Obsessive-compulsive behavior spectrum: refining the research agenda for DSM-V. *Psychiatry Res*. 2009;170:1-2.
23. Hollander E, Kim S, Khanna S, Pallanti S. Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. *CNS Spectr*. 2007;12:5-13.
24. Mataix-Cols D, van den Heuvel OA. Common and distinct neural correlates of obsessive-compulsive and related disorders. *Psychiatr Clin North Am*. 2006;29:391-410, viii.
25. McKay D, Abramowitz JS, Calamari JE, et al. A critical evaluation of obsessive-compulsive disorder subtypes: symptoms versus mechanisms. *Clin Psychol Rev*. 2004;24:283-313.
26. Miguel EC, Leckman JF, Rauch S, et al. Obsessive-compulsive disorder phenotypes: implications for genetic studies. *Mol Psychiatry*. 2005;10:258-275.
27. Leckman JF, Bloch MH, King RA. Symptom dimensions and subtypes of obsessive-compulsive disorder: a developmental perspective. *Dialogues Clin Neurosci*. 2009;11:21-33.
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
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.
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.
31. Abramowitz JS, Wheaton MG, Storch EA. The status of hoarding as a symptom of obsessive-compulsive disorder. *Behav Res Ther*. 2008;46:1026-1033.
32. Pertusa A, Fullana MA, Singh S, Alonso P, Menchon JM, Mataix-Cols D. Compulsive hoarding: OCD symptom, distinct clinical syndrome, or both? *Am J Psychiatry*. 2008;165:1289-1298.
33. Wu KD, Watson D. Hoarding and its relation to obsessive-compulsive disorder. *Behav Res Ther*. 2005;43:897-921.
34. Rettew DC, Swedo SE, Leonard HL, Lenane MC, Rapoport JL. Obsessions and compulsions across time in 79 children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992;31:1050-1056.
35. Mataix-Cols D, Rauch SL, Baer L, et al. Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. *Am J Psychiatry*. 2002;159:263-268.
36. Rufer M, Grothusen A, Mass R, Peter H, Hand I. Temporal stability of symptom dimensions in adult patients with obsessive-compulsive disorder. *J Affect Disord*. 2005;88:99-102.
37. Hasler G, Pinto A, Greenberg BD, et al. Familiality of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD Collaborative Genetics Study. *Biol Psychiatry*. 2007;61:617-625.
38. Samuels J, Shugart YY, Grados MA, et al. Significant linkage to compulsive hoarding on chromosome 14 in families with obsessive-compulsive disorder: results from the OCD Collaborative Genetics Study. *Am J Psychiatry*. 2007;164:493-499.
39. Wendland JR, Moya PR, Timpano KR, et al. A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2009;66:408-416.
40. Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. *Am J Psychiatry*. 2004;161:1038-1048.

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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.

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

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

43. Janet P. *Les Obsessions et la Psychasthenie*. 2nd ed. Paris, France: Bailliere; 1904.

44. Rasmussen SA, Eisen JL. The epidemiology and differential diagnosis of obsessive compulsive disorder. *J Clin Psychiatry*. 1994;55(suppl):5-10; discussion 11-14.

45. Pitman RK. Pierre Janet on obsessive-compulsive disorder (1903). Review and commentary. *Arch Gen Psychiatry*. 1987;44:226-232.

46. Coles ME, Heimberg RG, Frost RO, Steketee G. Not just right experiences and obsessive-compulsive features: experimental and self-monitoring perspectives. *Behav Res Ther*. 2005;43:153-167.

47. Ecker W, Gonner S. Incompleteness and harm avoidance in OCD symptom dimensions. *Behav Res Ther*. 2008;46:895-904.

48. Summerfeldt LJ. Understanding and treating incompleteness in obsessive-compulsive disorder. *J Clin Psychol*. 2004;60:1155-1168.

49. Miguel EC, do Rosario-Campos MC, Prado HS, et al. Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. *J Clin Psychiatry*. 2000;61:150-156.

50. Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR, Charney DS. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. *Arch Gen Psychiatry*. 1989;46:36-44.

51. Goodman WK, Price LH, Rasmussen SA, Heninger GR, Charney DS. Fluvoxamine as an antiobsessional agent. *Psychopharmacol Bull*. 1989;25:31-35.

52. Slattery MJ, Dubbert BK, Allen AJ, Leonard HL, Swedo SE, Gourley MF. Prevalence of obsessive-compulsive disorder in patients with systemic lupus erythematosus. *J Clin Psychiatry*. 2004;65:301-306.

53. Catapano F, Perris F, Fabrazzo M, et al. Obsessive-compulsive disorder with poor insight: A three-year prospective study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:323-330.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 146

54. Eichstedt JA, Arnold SL. Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? *Clin Psychol Rev*. 2001;21:137-157.
55. de Mathis MA, Diniz JB, Shavitt RG, et al. Early onset obsessive-compulsive disorder with and without tics. *CNS Spectr*. 2009;14:362-370.
56. Janowitz D, Grabe HJ, Ruhrmann S, et al. Early onset of obsessive-compulsive disorder and associated comorbidity. *Depress Anxiety*. 2009;26:1012-1017.
57. Carmin C, Wiegartz PS, Wu KD. Obsessive-Compulsive disorder with poor insight. In: Abramowitz JS, McKay D, Taylor S, eds. *Clinical Handbook of Obsessive-Compulsive Disorder and Related Problems*. Baltimore, MD: Johns Hopkins University Press; 2008:109-125.
58. Lochner C, Kinnear CJ, Hemmings SM, et al. Hoarding in obsessive-compulsive disorder: clinical and genetic correlates. *J Clin Psychiatry*. 2005;66:1155-1160.
59. Storch EA, Lack CW, Merlo LJ, et al. Clinical features of children and adolescents with obsessive-compulsive disorder and hoarding symptoms. *Compr Psychiatry*. 2007;48:313-318.
60. Nestadt G, Di CZ, Riddle MA, et al. Obsessive-compulsive disorder: subclassification based on co-morbidity. *Psychol Med*. 2008:1-11.
61. Hollander E, Braun A, Simeon D. Should OCD leave the anxiety disorders in DSM-V? The case for obsessive-compulsive-related disorders. *Depress Anxiety*. 2008;25:317-329.
62. McKay D, Neziroglu F. Methodological issues in the obsessive-compulsive spectrum. *Psychiatry Res*. 2009;170:61-65.
63. Mataix-Cols D, Pertusa A, Leckman JF. Issues for DSM-V: how should obsessive-compulsive and related disorders be classified? *Am J Psychiatry*. 2007;164:1313-1314.
64. Demal U, Lenz G, Mayrhofer A, Zapotoczky HG, Zitterl W. Obsessive-compulsive disorder and depression. A retrospective study on course and interaction. *Psychopathology*. 1993;26:145-150.
65. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. *J Affect Disord*. 2002;68:1-23.
66. Masi G, Perugi G, Toni C, et al. Obsessive-compulsive bipolar comorbidity: focus on children and adolescents. *J Affect Disord*. 2004;78:175-183.
67. Hantouche EG, Angst J, Demonfaucon C, Perugi G, Lancrenon S, Akiskal HS. Cyclothymic OCD: a distinct form? *J Affect Disord*. 2003;75:1-10.
68. Wheaton M, Timpano KR, Lasalle-Ricci VH, Murphy D. Characterizing the hoarding phenotype in individuals with OCD: associations with comorbidity, severity and gender. *J Anxiety Disord*. 2008;22:243-252.
69. Hollander E, Greenwald S, Neville D, Johnson J, Hornig CD, Weissman MM. Uncomplicated and comorbid obsessive-compulsive disorder in an epidemiologic sample. *Depress Anxiety*. 1996;4:111-119.
70. Huppert JD, Simpson HB, Nissenson KJ, Liebowitz MR, Foa EB. Quality of life and functional impairment in obsessive-compulsive disorder: a comparison of patients with and without comorbidity, patients in remission, and healthy controls. *Depress Anxiety*. 2009;26:39-45.
71. LaSalle VH, Cromer KR, Nelson KN, Kazuba D, Justement L, Murphy DL. Diagnostic interview assessed neuropsychiatric disorder comorbidity in 334 individuals with obsessive-compulsive disorder. *Depress Anxiety*. 2004;19:163-173.
72. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15:53-63.
73. Geller DA. Obsessive-compulsive and spectrum disorders in children and adolescents. *Psychiatr Clin North Am*. 2006;29:353-3570.
74. Fornaro M, Gabrielli F, Albano C, et al. Obsessive-compulsive disorder and related disorders: a comprehensive survey. *Ann Gen Psychiatry*. 2009;8:13.
75. Hantouche EG, Lancrenon S. [Modern typology of symptoms and obsessive-compulsive syndromes: results of a large French study of 615 patients]. *Encephale*. 1996;22 Spec No 1:9-21.
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.
77. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. *Psychol Med*. 2001;31:481-487.
78. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
79. Miguel EC, Ferrao YA, Rosario MC, et al. The Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders: recruitment, assessment instruments, methods for the development of multicenter collaborative studies and preliminary results. *Rev Bras Psiquiatr*. 2008;30:185-196.
80. Geller D, Petty C, Vivas F, Johnson J, Pauls D, Biederman J. Examining the relationship between obsessive-compulsive disorder and attention-deficit/hyperactivity disorder in children and adolescents: a familial risk analysis. *Biol Psychiatry*. 2007;61:316-321.
81. Geller D, Petty C, Vivas F, Johnson J, Pauls D, Biederman J. Further evidence for co-segregation between pediatric obsessive compulsive disorder and attention deficit hyperactivity disorder: a familial risk analysis. *Biol Psychiatry*. 2007;61:1388-1394.
82. Asbahr FR, Garvey MA, Snider LA, Zanetta DM, Elkis H, Swedo SE. Obsessive-compulsive symptoms among patients with Sydenham chorea. *Biol Psychiatry*. 2005;57:1073-1076.
83. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med*. 2003;9:914-920.
84. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155:264-271.
85. Alvarenga PG, Hounie AG, Mercadante MT, et al. Obsessive-compulsive symptoms in heart disease patients with and without history of rheumatic fever. *J Neuropsychiatry Clin Neurosci*. 2006;18:405-408.
86. de Alvarenga PG, Floresi AC, Torres AR, et al. Higher prevalence of obsessive-compulsive spectrum disorders in rheumatic fever. *Gen Hosp Psychiatry*. 2009;31:178-180.
87. Hounie AG, Pauls DL, Mercadante MT, et al. Obsessive-compulsive spectrum disorders in rheumatic fever with and without Sydenham's chorea. *J Clin Psychiatry*. 2004;65:994-999.
88. Mercadante MT, Busatto GF, Lombroso PJ, et al. The psychiatric symptoms of rheumatic fever. *Am J Psychiatry*. 2000;157:2036-2038.
89. Hounie AG, Pauls DL, do Rosario-Campos MC, et al. Obsessive-compulsive spectrum disorders and rheumatic fever: a family study. *Biol Psychiatry*. 2007;61:266-272.
90. Seixas AA, Hounie AG, Fossaluza V, et al. Anxiety disorders and rheumatic fever: is there an association? *CNS Spectr*. 2008;13:1039-1046.
91. Hounie AG, Cappi C, Cordeiro Q, et al. TNF-alpha polymorphisms are associated with obsessive-compulsive disorder. *Neurosci Lett*. 2008;442:86-90.
92. Ramasawmy R, Fae KC, Spina G, et al. Association of polymorphisms within the promoter region of the tumor necrosis factor-alpha with clinical outcomes of rheumatic fever. *Mol Immunol*. 2007;44:1873-1878.
93. Snider LA, Swedo SE. PANDAS: current status and directions for research. *Mol Psychiatry*. 2004;9:900-907.
94. Swedo SE, Grant PJ. Annotation: PANDAS: a model for human autoimmune disease. *J Child Psychol Psychiatry*. 2005;46:227-234.
95. Hoffman KL, Hornig M, Yaddanapudi K, Jabado O, Lipkin WI. A murine model for neuropsychiatric disorders associated with group A beta-hemolytic streptococcal infection. *J Neurosci*. 2004;24:1780-1791.
96. Lougee L, Perlmutter SJ, Nicolson R, Garvey MA, Swedo SE. Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *J Am Acad Child Adolesc Psychiatry*. 2000;39:1120-1126.
97. Shulman ST. Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS): update. *Curr Opin Pediatr*. 2009;21:127-130.
98. Kurlan R, Johnson D, Kaplan EL. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. *Pediatrics*. 2008;121:1188-1197.
99. Lin H, Williams KA, Katsovich L, et al. Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. *Biol Psychiatry*. 2010;67:684-691.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 147

100. Rizzo R, Gulisano M, Pavone P, Fogliani F, Robertson MM. Increased antistreptococcal antibody titers and anti-basal ganglia antibodies in patients with Tourette syndrome: controlled cross-sectional study. *J Child Neurol*. 2006;21:747-753.
101. Termine C, Uggetti C, Veggiotti P, et al. Long-term follow-up of an adolescent who had bilateral striatal necrosis secondary to Mycoplasma pneumoniae infection. *Brain Dev*. 2005;27:62-65.
102. Budman C, Sarcevic A. An unusual case of motor and vocal tics with obsessive-compulsive symptoms in a young adult with Behcet's syndrome. *CNS Spectr*. 2002;7:878-881.
103. Bode L, Durrwald R, Rantam FA, Ferszt R, Ludwig H. First isolates of infectious human Borna disease virus from patients with mood disorders. *Mol Psychiatry*. 1996;1:200-212.
104. Cheyette SR, Cummings JL. Encephalitis lethargica: lessons for contemporary neuropsychiatry. *J Neuropsychiatry Clin Neurosci*. 1995;7:125-134.
105. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G. Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. *J Child Neurol*. 2008;23:338-340.
106. Yaramis A, Herguner S, Kara B, Tatli B, Tuzun U, Ozmen M. Cerebral vasculitis and obsessive-compulsive disorder following varicella infection in childhood. *Turk J Pediatr*. 2009;51:72-75.
107. Berthier ML, Kulisevsky J, Gironell A, Lopez OL. Obsessive-compulsive disorder and traumatic brain injury: behavioral, cognitive, and neuroimaging findings. *Neuropsychiatry, Neuropsychol Behav Neurol*. 2001;14:23-31.
108. Coetzer R, Stein DJ, Du Toit PL. Executive function in traumatic brain injury and obsessive-compulsive disorder: an overlap? *Psychiatry Clin Neurosci*. 2001;55:83-87.
109. Grados MA. Obsessive-compulsive disorder after traumatic brain injury. *Int Rev Psychiatry*. 2003;15:350-358.
110. Silver JM, Kramer R, Greenwald S, Weissman M. The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. *Brain Injury*. 2001;15:935-945.
111. McKeon J, Roa B, Mann A. Life events and personality traits in obsessive-compulsive neurosis. *Br J Psychiatry*. 1984;144:185-189.
112. Kant R, Smith-Seemiller L, Duffy JD. Obsessive-compulsive disorder after closed head injury: review of literature and report of four cases. *Brain Inj*. 1996;10:55-63.
113. Roth RM, Jobst BC, Thadani VM, Gilbert KL, Roberts DW. New-onset obsessive-compulsive disorder following neurosurgery for medication-refractory seizure disorder. *Epilepsy Behav*. 2009;14:677-680.
114. Kurlan R. Disabling repetitive behaviors in Parkinson's disease. *Mov Disord*. 2004;19:433-437.
115. Maia AF, Pinto AS, Barbosa ER, Menezes PR, Miguel EC. Obsessive-compulsive symptoms, obsessive-compulsive disorder, and related disorders in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2003;15:371-374.
116. Correia S, Hubbard E, Hassenstab J, et al. Basal ganglia MR relaxometry in obsessive-compulsive disorder: T2 depends upon age of symptom onset. *Brain Imag Behav*. In press.
117. Ruta L, Mugno D, D'Arrigo VG, Vitiello B, Mazzone L. Obsessive-compulsive traits in children and adolescents with Asperger syndrome. *Eur Child Adolesc Psychiatry*. 2010;19:17-24.
118. Zandt F, Prior M, Kyrios M. Similarities and differences between children and adolescents with autism spectrum disorder and those with obsessive compulsive disorder: executive functioning and repetitive behaviour. *Autism*. 2009;13:43-57.
119. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: is there evidence for a schizo-obsessive subtype of schizophrenia? *J Psychiatry Neurosci*. 2005;30:187-193.
120. Poyurovsky M, Koran LM. Obsessive-compulsive disorder (OCD) with schizotypy vs. schizophrenia with OCD: diagnostic dilemmas and therapeutic implications. *J Psychiatr Res*. 2005;39:399-408.
121. Sa AR, Hounie AG, Sampaio AS, Arrais J, Miguel EC, Elkis H. Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol. *Compr Psychiatry*. 2009;50:437-442.
122. Jeste DV, Dolder CR. Treatment of non-schizophrenic disorders: focus on atypical antipsychotics. *J Psychiatr Res*. 2004;38:73-103.
123. Eisen JL, Beer DA, Pato MT, Venditto TA, Rasmussen SA. Obsessive-compulsive disorder in patients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 1997;154:271-273.
124. Poyurovsky M, Fuchs C, Weizman A. Obsessive-compulsive disorder in patients with first-episode schizophrenia. *Am J Psychiatry*. 1999;156:1998-2000.
125. Dowling FG, Pato MT, Pato CN. Comorbidity of obsessive-compulsive and psychotic symptoms: a review. *Harv Rev Psychiatry*. 1995;3:75-83.
126. Fontenelle LF, do Rosario-Campos MC, De Mathis MA, et al. "Post-traumatic" obsessive-compulsive disorder: a neglected psychiatric phenotype? Inaugural Scientific Meeting of the International College of Obsessive Compulsive Spectrum Disorders. Barcelona, Spain; 2008.
127. Gershuny BS, Baer L, Radomsky AS, Wilson KA, Jenike MA. Connections among symptoms of obsessive-compulsive disorder and post-traumatic stress disorder: a case series. *Behav Res Ther*. 2003;41:1029-1041.
128. Dias-Ferreira E, Sousa JC, Melo I, et al. Chronic stress causes frontostriatal reorganization and affects decision-making. *Science*. 2009;325:621-625.
129. Guillem F, Satterthwaite J, Pampoulova T, Stip E. Relationship between psychotic and obsessive compulsive symptoms in schizophrenia. *Schizophr Res*. 2009;115:358-362.
130. Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genet C Semin Med Genet*. 2008;148C:133-139.
131. Nicolini H, Arnold P, Nestadt G, Lanzagorta N, Kennedy JL. Overview of genetics and obsessive-compulsive disorder. *Psychiatry Res*. 2009;170:7-14.
132. Samuels JF. Recent advances in the genetics of obsessive-compulsive disorder. *Curr Psychiatry Rep*. 2009;11:277-282.
133. Grados M, Wilcox HC. Genetics of obsessive-compulsive disorder: a research update. *Expert Rev Neurother*. 2007;7:967-980.
134. Bloch MH, Landeros-Weisenberger A, Sen S, et al. Association of the serotonin transporter polymorphism and obsessive-compulsive disorder: systematic review. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B:850-858.
135. Wendland JR, DeGuzman TB, McMahon F, Rudnick G, Detera-Wadleigh SD, Murphy DL. SERT Ileu425Val in autism, Asperger syndrome and obsessive-compulsive disorder. *Psychiatr Genet*. 2008;18:31-39.
136. Zhang H, Leckman JF, Pauls DL, Tsai CP, Kidd KK, Campos MR. Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette syndrome. *Am J Hum Genet*. 2002;70:896-904.
137. Shugart YY, Samuels J, Willour VL, et al. Genomewide linkage scan for obsessive-compulsive disorder: evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. *Mol Psychiatry*. 2006;11:763-770.
138. Samuels JF, Bienvenu OJ, Grados MA, et al. Prevalence and correlates of hoarding behavior in a community-based sample. *Behav Res Ther*. 2008;46:836-844.
139. Samuels JF, Bienvenu OJ, Pinto A, et al. Sex-specific clinical correlates of hoarding in obsessive-compulsive disorder. *Behav Res Ther*. 2008;46:1040-1046.
140. Grisham JR, Brown TA, Liverant GI, Campbell-Sills L. The distinctiveness of compulsive hoarding from obsessive-compulsive disorder. *J Anxiety Disord*. 2005;19:767-779.
141. Frost RO, Steketee G, Williams LF, Warren R. Mood, personality disorder symptoms and disability in obsessive compulsive hoarders: a comparison with clinical and nonclinical controls. *Behav Res Ther*. 2000;38:1071-1081.
142. Gothelf D, Presburger G, Zohar AH, et al. Obsessive-compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2004;126:99-105.
143. Feinstein C, Eliez S, Blasey C, Reiss AL. Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biol Psychiatry*. 2002;51:312-318.
144. Papolos DF, Faedda GL, Veit S, et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry*. 1996;153:1541-1547.
145. Pulver AE, Nestadt G, Goldberg R, et al. Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. *J Nerv Ment Dis*. 1994;182:476-478.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 148

146. Saunders-Pullman R, Shriberg J, Heiman G, et al. Myoclonus dystonia: possible association with obsessive-compulsive disorder and alcohol dependence. *Neurology*. 2002;58:242-245.
147. Doheny D, Danisi F, Smith C, et al. Clinical findings of a myoclonus-dystonia family with two distinct mutations. *Neurology*. 2002;59:1244-1246.
148. Marechal L, Raux G, Dumanchin C, et al. Severe myoclonus-dystonia syndrome associated with a novel epsilon-sarcoglycan gene truncating mutation. *Am J Med Genet B Neuropsychiatr Genet*. 2003;119:114-117.
149. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat Genet*. 2001;29:66-69.
150. Verkerk AJ, Mathews CA, Joosse M, Eussen BH, Heutink P, Oostra BA. CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics*. 2003;82:1-9.
151. Boghosian-Sell L, Comings DE, Overhauser J. Tourette syndrome in a pedigree with a 7;18 translocation: identification of a YAC spanning the translocation breakpoint at 18q22.3. *Am J Hum Genet*. 1996;59:999-1005.
152. Petek E, Windpassinger C, Vincent JB, et al. Disruption of a novel gene (IMMP2L) by a breakpoint in 7q31 associated with Tourette syndrome. *Am J Hum Genet.* 2001;68:848-858.
153. Diaz-Anzaldua A, Joober R, Riviere JB, et al. Association between 7q31 markers and Tourette syndrome. *Am J Med Genet A*. 2004;127:17-20.
154. Bihari K, Hill JL, Murphy DL. Obsessive-compulsive characteristics in patients with idiopathic spasmodic torticollis. *Psychiatry Res*. 1992;42:267-272.
155. Bihari K, Pigott TA, Hill JL, Murphy DL. Blepharospasm and obsessive-compulsive disorder. *J Nerv Ment Dis*. 1992;180:130-132.
156. Defazio G, Livrea P. Epidemiology of primary blepharospasm. *Mov Disord*. 2002;17:7-12.
157. Marks WA, Honeycutt J, Acosta F, Reed M. Deep brain stimulation for pediatric movement disorders. *Semin Pediatr Neurol*. 2009;16:90-98.
158. Hoehn-Saric R, Ninan P, Black DW, et al. Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch Gen Psychiatry*. 2000;57:76-82.
159. Matsumoto R, Ichise M, Ito H, et al. Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: a [11C]DASB PET study. *Neuroimage*. 2010;49:121-126.
160. MacMaster FP, O'Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2008;47:1262-1272.
161. Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2004;61:564-576.
162. Chamberlain SR, Menzies L. Endophenotypes of obsessive-compulsive disorder: rationale, evidence and future potential. *Expert Rev Neurother*. 2009;9:1133-1146.
163. Hajcak G, Franklin ME, Foa EB, Simons RF. Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *Am J Psychiatry*. 2008;165:116-123.
164. Bedard MJ, Joyal CC, Godbout L, Chantal S. Executive functions and the obsessive-compulsive disorder: on the importance of subclinical symptoms and other concomitant factors. *Arch Clin Neuropsychol*. 2009;24:585-598.
165. Joshi G, Wilens T. Comorbidity in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am*. 2009;18:291-319.
166. Welch JM, Lu J, Rodriguiz RM, et al. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature*. 2007;448:894-900.
167. Zuchner S, Wendland JR, Ashley-Koch AE, et al. Multiple rare SAPAP3 missense variants in trichotillomania and OCD. *Mol Psychiatry*. 2009;14:6-9.

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The genetics of obsessive-compulsive disorder: a review

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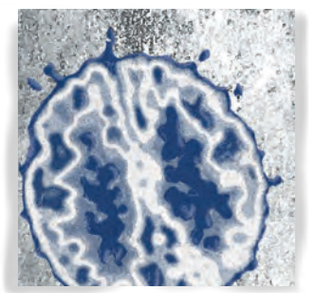

Obsessive-compulsive disorder (OCD) is a serious psychiatric disorder that affects approximately 2% of the populations of children and adults. Family aggregation studies have demonstrated that OCD is familial, and results from twin studies demonstrate that the familiality is due in part to genetic factors. Only three genome-wide linkage studies have been completed to date, with suggestive but not definitive results. In addition, over 80 candidate gene studies have been published. Most of these studies have focused on genes in the serotonergic and dopaminergic pathways. Unfortunately, none have achieved genome-wide significance, and, with the exception of the glutamate transporter gene, none have been replicated. Future research will require the collaboration of multidisciplinary teams of investigators to (i) achieve sufficiently large samples of individuals with OCD; (ii) apply the state-of-the-art laboratory techniques; and (iii) perform the bioinformatic analyses essential to the identification of risk loci.

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Keywords: *obsessive-compulsive disorder; genetics, family study; twin study; linkage study; candidate gene study*

Obsessive-compulsive disorder (OCD) is a prevalent psychiatric disorder that is characterized by disabling obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors).[1] OCD was originally thought to be rare, but a number of studies have reported a lifetime prevalence that ranges between approximately 1% to 3% worldwide.[2-3] Thus, it is one of the more common and serious mental conditions.[4]

Twin and family studies provide convincing evidence for the importance of genetic factors for the expression of OCD. The author has previously reviewed these data.[5] In this paper, the historic evidence is again summarized and updated with recent results. Thus, sections of this manuscript will be similar to those previously published reviews. Supporting results from twin and family aggregation studies, functional neuroimaging, pharmacological, and molecular genetic studies provide compelling data that suggest that biochemical/biological factors are important for the manifestation of OCD.

Twin studies

Twin studies are useful in determining whether genetic factors are important in the etiology of complex disorders. The difference in concordance rates between monozygotic and dizygotic twins can be used to estimate the percentage of the phenotypic variance observed for a specific trait that can be accounted for by genetic factors.

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There are a number of published twin studies for OCD. Results from the early studies should be interpreted with caution, given the limitations of those studies: most are case reports, others have small sample sizes, still others used different criteria to diagnose individuals, and in most cases the investigator evaluating the cotwin was not blind to the diagnosis of the index twin.

In the most comprehensive review to date, van Grootheest et al[6] summarized all published twin studies from 1929 through 2005 *(Table I)*. Of note is that five of the six twin studies with adequate sample sizes[32-36] (~100 twin pairs or more) attempted to estimate the heritability of obsessive-compulsive (OC) symptoms, not OCD. Only two studies[29-30] were able to estimate the heritability of OCD as determined by DSM diagnostic criteria.

There have been only two additional twin study OCD published since 2005.[29-30] The first study[29] included 854 6-year-old twins who had been identified in a community sample and subsequently diagnosed using *DSM-IV* criteria with information obtained in a maternal-informant

Study type	No of twin pairs	MZ concordance	DZ concordance
Case studies			
Lange[7]	3	1/2	-
Le Gras[8,9]	1	1/1	-
Lewis[10]	3	2/3	-
Tarozzi[11]	1	1/1	-
Rüdin[12]	1	-	0/1
Tienari[13]	11	10/11	-
Parker[14]	2	0/2	-
Wooddruff & Pitts[15]	1	1/1	-
Inouye[16]	14	8/10	1/4
DSM-III/DSM-III-R OCD			
Marks et al[17]	1	1/1	-
Tarsh[18]	1	-	1/1
Hoaken & Schurr[19]	1	0/1	-
McGuffin & Mawson[20]	2	2/2	-
Carey & Gottesman[21]	30	13/15	7/15
Torgerson[22]	12	0/3	0/9
McKeon et al[23]	1	0/1	-
Mahgroub et al[24]	1	1/1	-
Kim et al[25]	1	1/1	-
Andrews et al[26]	48	0/18	0/30
Lewis et al[27]	3	3/3	-
Cryan et al[28]	1	1/1	-
DSM-IV		MZ tetrachoric r	DZ tetrachoric r
Bolton et al[29]	854	0.57 (0.24-0.80)	0.22 (-0.02-0.43)
Tambs et al[30]			
OC behaviors		**h^2**	
Young et al[31]	32	0	
Torgerson[32]	99	0.18 (men); 0.23(women)	
Clifford et al[33]	419	0.44(traits); 0.47(symptoms)	
Jonnal et al[34]	527	0.33(obsessions); 0.26(compulsions)	
Eley et al[35]	4 564	0.65 (OC behavior)	
Hudziak et al[36]	4 246	0.45 – 0.61	

Table I. Twin studies of OCD.

Adapted from ref 5: Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genetics C: Sem Med Genet*. 2008;148:133-139. Copyright © Wiley-Liss 2008

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interview. This was the first study with sufficient sample size to adequately evaluate the influence of genetic factors on OCD, not just OC symptoms in the general population of twins. The Bolton et al[29] findings are consistent with the majority of studies with sufficient sample sizes *(Table I)* in that the results support the hypothesis that genetic factors play a significant role in the etiology of OC behaviors as well as OCD.

In addition, these investigators also examined the relation between OCD and two commonly occurring comorbid disorders: tic disorder and anxiety disorders. Their findings support the hypothesis that there are shared etiologic factors for OCD and tics, as well as OCD and other anxiety disorders, and are consistent with the hypothesis that there may be different subtypes of OCD that may have different underlying risk factors.[37-41] This hypothesis will be discussed in more depth in the Family Studies section below.

The second study, published in 2009,[30] obtained data from 2801 young-adult Norwegian twins by means of the Composite International Diagnostic Interview (CIDI). This study examined the heritability of five anxiety disorders (Generalized Anxiety Disorder, Panic Disorder, Phobias, Obsessive-Compulsive Disorder, and Post-Traumatic Stress Disorder.) Valid anxiety data were available for 1385 twin pairs; however, there were only 57 pairs where one twin had a diagnosis of OCD. Because the prevalence of OCD was so low in this sample, the investigators included individuals who met criteria or subthreshold OCD (the number of pairs where at least one had a diagnosis of OCD or subthreshold OCD was 165). The estimate of heritability was 29%. However, these investigators reported that 55% of this heritability was due to a common factor shared by all five anxiety disorders. On the other hand, 45% appear to be due to factors that were specific to OCD.

In summarizing the studies published prior to 2006, van Grootheest and colleagues[6] concluded that "in children, obsessive-compulsive (OC) symptoms are heritable, with genetic influences in the range of 45% to 65%. In adults, studies are suggestive for a genetic influence on OC symptoms, ranging from 27% to 47%..." The findings from the two most recent studies[29,30] are remarkably similar when cotwins who met criteria for subclinical OCD were included in the analyses. Both studies reported that additive genetic effects accounted for 29% of the variance for OCD and subclinical OCD. In the Bolten study,[29] familial aggregation due to combined additive genetic and shared environmental effects accounted for 47% of the phenotypic variance. Unfortunately, these investigators were unable to estimate the effects of additive genetic and shared environmental separately.[29]

Family studies

Numerous family studies on OCD and obsessional neurosis have been published since 1930 *(Table II)*. Results from the majority of these studies demonstrate that at least some forms of OCD are familial, and the findings from twin studies summarized above provide evidence that this familiality is due in part to genetic factors. However, it is also evident that environmental/cultural factors influence OC behaviors and are also transmitted within families.[29] These nongenetic factors unquestionably influence the manifestation of OC behaviors as evidenced from twin studies that consistently demonstrate that the concordance rate of MZ twins for OC behaviors and OCD is always less than 1.0. Understanding the impact of these environmental/cultural factors will be critical to the eventual elucidation of the risk factors important for the manifestation of complex disorders such as OCD. However, while it is clear that genes alone will not explain all of the observed inheritance of OCD, demonstrating familiality is an important step for the eventual determination of the importance of genetic risk factors.

Family history studies

Studies in which all diagnostic data about family members are obtained from one or two informants are referred to as family history studies. Prior to 1987, all studies of the familiality of OC illness and/or OC features relied on family history data. It has been shown that, in general, family history data yields underestimates of the true rates of illness within families.[42-43] Hence, it is significant that these early family history studies reported findings suggesting that OC illness and/or OC features were familial *(Table II)*. An important shortcoming of all of these early studies was that no control samples were obtained to estimate the rate of OC illness or OC features in the general population. Thus, all of these data need to be interpreted with that caveat in mind.

In only one study,[49] results were reported that were not consistent with OC illness and/or features being familial. In this study, a relative was considered affected only

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if they had been hospitalized for OC illness. Using this criterion, no significant increase of OC illness among first-degree relatives of 144 obsessional neurotics was observed, although an increased rate of psychiatric illness among these relatives was reported. Unfortunately, no information about OC symptomatology among relatives who were not hospitalized was provided.

Direct interview family studies

Subsequent to 1986, all family studies collected direct interview from at least some of the relatives in the family. With the exception of one study,[52] all available relatives were directly interviewed. In the study by McKeon and Murray[52] all family members of adult probands with OCD were given the Leyton Obsessional Inventory (LOI), and only those relatives who scored high on the LOI were directly interviewed. Only one of the interviewed relatives met criteria for OC neurosis, suggesting that the disorder is not familial.

It is possible that some relatives with OCD may not have been identified with this ascertainment scheme. Low scores on the LOI can be observed in individuals having only a few obsessions and/or compulsions which consume significant time and cause considerable distress and result in a diagnosis of OCD. Thus, it is possible that some of the noninterviewed relatives could have scored low on the LOI yet still met criteria for a diagnosis of OCD. In should be noted, however, that these investigators did observe an increased rate of mental illness overall among the relatives of these OCD probands.

The remaining 15 family studies of OCD interviewed all

Family history studies	Obsessive-compulsive illness	Obsessive-compulsive features	Controls	
Luxenburger[44]	0.08	0.08	---	
Lewis[45]	---	0.327	---	
Brown[46]	0.073	---	---	
Rüdin[47]	0.040	0.070	---	
Kringlen[48]	0.198		---	
Rosenburg[49]	0.004	---	---	
Insel et al[50]	0	0.150	---	
Rasmussen & Tsuang[51]	0.045	0.114	---	
Adult family studies	**OCD**	**Subclinical OCD**	**OCD**	**Subclinical OCD**
Mckeon & Murray[52]	0.007	---	0.007	
Bellodi et al[53]	0.034	---	---	---
Black et al[54]	0.025	0.156	0.023	0.029
Nicolini et al[55]	0.049	---	---	---
Pauls et al[38]	0.103	0.079	0.019	0.020
Nestadt et al[56]	0.117	0.046	0.027	0.030
Albert et al[57]	0.035	---	---	---
Fyer et al[58]	0.062	0.084	0	0
Lipsitz et al[59]*	0.026	0.057	0.013	0.013
Grabe et al[60]**	0.064	0.055	0.012	0.030
Child family studies	**OCD**	**Subclinical OCD**	**OCD**	**Subclinical OCD**
Lenane et al[61]	0.170	---	---	---
Riddle et al[62]	0.095	---	---	---
Leonard et al[63]	0.130	---	---	---
Reddy et al[64]	0.050	---	0	---
Chabane et al[65]	0.170	---	---	---
Hanna et al[40]	0.225	---	0.026	---
Rosario-Campos et al[41]	0.227	0.065	0.009	0.015

Table II. Family studies of OCD. The rates shown refer to the frequency of these conditions among first-degree relatives.
Adapted from ref 5: Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genetics C: Sem Med Genet*. 2008;148:133-139. Copyright © Wiley-Liss 2008

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available first-degree relatives with structured psychiatric interviews.[38,40-41,53-65] In some of these studies, additional information was obtained from all interviewed relatives about the presence of OCD in all of their first-degree relatives; even those relatives that had been directly interviewed. Thus, both direct interview data and family history data were available for all interviewed individuals in those family studies.

While there were some inconsistent results, most of these studies provided data that are consistent with the hypothesis that some forms of OCD are familial *(Table II)*. In seven studies ascertainment was through children and/or adolescents with OCD *(Table II)*. In the remaining eight studies, ascertainment was through adults with OCD *(Table II)*.

Studies of families ascertained through child/adolescent probands

In all of the studies in which all available relatives of children and/or adolescents with OCD were interviewed,[40-41,61-65] the rates of OCD and subclinical OCD were significantly higher than the population prevalence and/or the rate obtained in controls assessed in the same way. While the frequency of OCD and subclinical OCD differed within families across studies, the overall conclusion was the same: OCD and subclinical OCD are familial. Furthermore, the recurrence risks within these families were considerably higher than the rates observed in families ascertained through adults (see below). While the rate of OCD among relatives of adults with OCD was approximately two times that among controls, the rate of OCD among relatives of children and adolescents with OCD was increased approximately 10-fold in those studies where comparison with controls was possible.

Studies of families ascertained through adult probands

The results from studies of families ascertained through adults with OCD in which all available relatives were interviewed were not as consistent as those family studies of child and/or adolescent probands summarized above. As noted above, the study by McKeon and Murray[52] did not observe an increased rate of OCD among relatives of adult OCD probands. In addition, Black et al[54] reported results of a study examining 120 first-degree relatives of 32 adult OCD probands and 129 relatives of 33 psychiatrically age-matched normal controls. This was the first controlled study of OCD in which all relatives were assessed using structured interviews and all interviewers were blind to the diagnostic status of the proband. *DSM-III* criteria were used to assign all diagnoses from the direct interview data. While family history data had been obtained from all interviewed relatives about other first-degree relatives, none of those data were included in the diagnostic process. These investigators reported an age-corrected rate of *DSM-III* OCD of 2.5% among relatives of probands compared with 2.3% in controls. These data suggest that OCD is not familial. However, when a more broadly defined OCD was used in the analyses the rate among parents of OCD probands was 15.6%. In contrast to the rate among the parents of control individuals was 2.9%. It is noteworthy that these investigators also reported an increased rate of non-OCD anxiety among the relatives. It is possible that, since in this study only direct interview data were used in the diagnostic process, the estimated recurrence risks could have been biased. Lipsitz et al[59] examined whether using informant information influenced the recurrence risk estimates. In most family studies of OCD diagnoses are based on all direct interview and family history data collected from informants in the family. When only data from the direct interviews were used to assign diagnoses, there was not a significant increase in the occurrence of OCD among the relatives. The rate of OCD and subclinical OCD for interviewed relatives when no informant information was used in the diagnostic process was 5.4% compared with 1.7% among controls (P=0.17). On the other hand, the rate of OCD and subclinical OCD among interviewed relatives when additional informant data were used was 8.9% compared with only 1.7% among controls (P=0.02). These investigators concluded that "evidence of familial transmission of OCD was found only when diagnoses were made using information from the proband about the relative." As an explanation for these differences, these authors suggest that since individuals with OCD can be quite secretive about their symptoms, it is possible that upon direct interview, they might deny OC symptomatology. This could be particularly important in the case when the individual being interviewed has never sought treatment for their OC symptoms. On the other hand, it is also possible that an affected relative who has sought treatment or proband may "over-report" symptoms in their relatives. In the Lipsitz et al[59] study, family history informa-

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tion was only collected from the affected probands, all of whom had sought treatment, so it is possible that there was "projection" of their own behaviors onto their relatives, resulting in over-reporting of affected status. However, in other studies where family history data were collected from all interviewed relatives,[3,8,56] information was collected from both affected and unaffected relatives, and therefore it is less likely that there would be over-reporting of OC symptomatology, since unaffected relatives would not be "projecting" their own behavior onto their relatives. Of note is that in the study of Lipsitz et al,[59] an increased rate of other non-OCD anxiety disorders was observed. Finally, Black and colleagues did report that a number of family members were reported to have OC symptomatology by their relatives. Thus, it is possible that, if all available information had been used to assign diagnoses, the recurrence risk for OCD among first-degree relatives could have been higher than reported.

All of the remaining studies of families ascertained through adult individuals with OCD provide evidence that OCD is a familial disorder.[38,53,55-58,60] In these studies, the rate of OCD among relatives of affected individuals was significantly higher than either the estimated population prevalence or rate among controls. In the most recently published study,[60] the investigators ascertained affected individuals from both a population sample and a clinic sample. They observed a significant increase in both relatives of individuals who were ascertained through an OCD clinic and individuals who were identified through a population study of OCD. The study by Grabe et al was the first controlled study of OCD in Europe, and confirmed the results of earlier studies completed in the US[38,56,58] with families ascertained through treatment facilities. The finding that relatives of both clinic patients and individuals identified in a population based study is important. As the authors nicely summarize, "the finding of a comparable familial aggregation of definite OCD and a higher familial aggregation of subclinical OCD in relatives of never treated persons with OCD from the community strongly supports the impact of familial-genetic factors in OCD."

Associated conditions

As noted in the discussion of twin studies, a number of investigators have examined family data to test the hypothesis that other disorders may be significantly increased among relatives of OCD probands. Additional analyses of the Hopkins OCD Family Study[56] were reported.[66-67] Bienvenu et al[66] explored OC-spectrum disorders among proband relatives and found significantly higher rates of BDD (OR=5.4), somatoform disorders (OR 3.9), grooming disorders (OR=1.8), and all spectrum disorders combined (OR=2.7). Similarly, Grados et al[67] explored OCD comorbidity and found an increased prevalence of tic disorders among proband relatives versus control relatives. There was also an association between earlier age of OCD onset and tic comorbidity. These findings are consistent with those reported earlier.[29,38,,41] These findings suggest that there may be at least three different types of OCD: (i) one that is inherited and related to TS; (ii) one that is inherited and not related to TS but possibly related to anxiety; and (iii) one that is not familial.

In sum, these studies of OCD probands and their relatives cumulatively provide strong evidence that some but possibly not all forms of OCD are familial. This was confirmed in a meta-analysis of five family studies of OCD probands published prior to 2001 involving 1209 first-degree relatives[68] in which a significantly increased risk of OCD among relatives of probands was observed (Mantel-Haenszel summary OR=4.0 (95% CI=2.2-7.1)). The unadjusted aggregate risk for relatives of OCD probands was 8.2%, compared with 2.0% for relatives of relatives. Although these family study findings are consistent with a genetic etiology of OCD, by themselves they only demonstrate that OCD is familial; not that genetic factors are necessary for the manifestation of the illness. However, taken together with the evidence from twin studies, there is compelling evidence that genetic factors play an important role in the manifestation of some forms of OCD.

Segregation analyses

Given that the majority of studies demonstrated that OCD is familial, and twin studies suggest that this familiality is in part due to genetic factors, the next step has been to examine whether the mode of transmission in these families can be explained by specific genetic models. Complex segregation analyses allow an examination of specific genetic models by estimating the "goodness-of-fit" of the pattern of transmission specified by an hypothesized genetic model to that of the observed patterns of transmission within families. While complex segregation analyses do not prove the existence of genes

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that are associated with OCD, results of these analyses can reveal patterns of transmission within families that may be helpful in future molecular genetic studies.

To date, four complex segregation analyses of OCD transmission in families ascertained through OCD probands have been reported.[69-72] All studies provided evidence that the transmission of OCD within families is consistent with genetic transmission. However, the genetic model that best explained the transmission within families differed from study to study. Given the variability of recurrence risks observed in the family studies and the clinical heterogeneity that is evident in OCD, this result is not surprising. Nevertheless, it is noteworthy that the conclusions of the authors in all of these reports were that there are some genes of major effect important for the manifestation of OCD. Given the variability in the estimates of recurrence risks in the reported studies, it is quite likely that OCD is an oligogenic disorder (ie, a number of genes are important for the expression of the disorder).

In addition to advances in understanding regarding familiality and genetic mechanisms that are likely to be involved in OCD, there have also been dramatic gains in our understanding of the phenotype of OCD. Perhaps most important for genetic research are new ways to assess the phenotype dimensionally, moving beyond traditional categorical diagnostic classifications. Over the last decade, results from a number of independent studies have demonstrated that there are different clusters of symptoms that comprise the OCD phenotype[73-77] and that they appear to be heritable.[73,76] It follows then that there may be several genes that could influence the different components of OCD.

Candidate gene studies

Given current theoretical understanding of mechanisms that may be implicated in the emergence and maintenance of OCD symptoms and the treatment of the disorder, a number of investigators have pursued genetic studies of specific genes that are known to be involved in systems implicated in the pathogenesis of OCD. In particular, because of the efficacy of serotonin reuptake in treating OCD,[78-79] a number of genes important in the serotonergic system have been examined. In addition, genes in the dopaminergic, glutamatergic, and opioid systems have also been studied to determine if they also contribute to the risk of OCD.[80]

Over 80 candidate gene studies have been published over the last decade *(Table III)*. As noted above, association studies have examined candidate genes that function within the serotonergic and dopaminergic systems and more recently the glutamatergic system based on knowledge of the pathophysiology and pharmacology of OCD. However, with the exception of the glutamate transporter gene *SLCL1A1*,[81-84] none have been consistently replicated. While some of the more recent published studies have larger sample sizes, all have inadequate sample sizes to achieve genome-wide significance (ie, $5x10^{-8}$). Some recent studies have moved beyond simply documenting that individuals with OCD are more likely to have a specific allele or candidate gene that other nonaffected individuals (ie, association studies) and have begun to explore the function of some of the genes being studied. Preliminary results suggest that may be a promising approach.[85] However, none of these studies have yet been replicated, so it is too early to reach any definite conclusions.

Given the complexity of the OCD phenotype, it is highly unlikely that any of the candidate genes examined to date will be significant, unique risk factors for OCD. Thus, although they may truly be associated with the onset, severity, or persistence of OCD symptoms, they are unlikely to cause OCD without the presence of other risk genes. On the other hand, since most current effective pharmacologic agents target the serotonergic and dopaminergic systems, it is possible that some of the genes in those systems could play a role in treatment response. Knowing which genes impact treatment response would be a major advance in the treatment of OCD and is consistent with the primary goal of the emerging field of pharmacogenetics. However, it would not necessarily demonstrate that those genes are involved in the etiology of OCD. Genes involved in response to treatment may not be involved in the etiology of a disorder.

Genetic linkage studies

Only three genome-wide linkage studies of OCD have been completed to date.[135-137] No study yielded genome-wide significance; however all studies suggested regions of interest for future research. Hanna et al[136] completed a genome scan on seven families which included 66 individuals. All families had been identified through childhood OCD probands. All but one of the relatives were

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Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
Serotonin transporter			Cases	Controls	Families		
	McDougle et al[86]	FB	---	---	35	*P*<0.03	L allele
	Bengel et al[87]	CC	75	397	---	*P*=0.023	LL genotype
	Frisch et al[88]	CC	75	172	---	ns	---
	Kinnear et al[89]	CC	54	82	---	ns	---
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
	Saiz et al[92]	CC	99	420	--	ns	---
	Wendland et al93	CC	347	749	---	ns	---
	Wendland et al[84]	CC	295	657	--	*P*<0.018	3 marker haplotype
Serotonin transporter promoter							
	Kinnear et al[94]	CC	129	479	---	ns	---
	Camarena et al[95]	CC/FB	115	136	43	ns	---
	Cavallini et al[96]	CC	180	112	---	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Chabane et al[99]	CC/FB	106	171	86	ns	---
Serotonin receptor 2A							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Enoch et al[101]	CC	62	144	---	*P*<0.05	A allele
	Enoch et al[102]	CC	101	138	---	*P*=0.015	A allele
	Frisch et al[88]	CC	75	172	---	ns	---
	Walitza et al[103]	CC	55	223	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
	Tot et al[105]	CC	??	??	---	ns	---
	Hemmings et al[106]	CC	58	83	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	*P*<0.00007	C - Allele
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
	Saiz et a[92]	CC	99	420	---	*P*=0.02	---
Serotonin receptor 2C							
	Cavallini et al[107]	CC	109	107	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Cavallini et al[107]	CC	109	107	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
Serotonin receptor 1B (1Dβ)							
	Mundo et al[108]	FB	---	---	32	*P*<0.006	G allele
	Mundo et al[109]	FB	---	---	121	*P*=0.023	G allele
	DiBella et al[110]	FB	---	---	48	ns	---
	Hemmings et al[104]	CC	77	129	---	ns	---
	Camarena et al[111]	FB	---	---	47	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---

Table III. Candidate gene studies of OCD. *Association with the hoarding phenotype

Adapted from ref 134 (and updated through 11/2009): Hanna GL, Veenstra-VanderWeele J, Cox NJ, et al. Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet*. 2002;114:541-552. Copyright © Wiley-Liss 2002

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Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
			Cases	Controls	Families		
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
Tryptophan hydroxylase							
	Frisch et al[88]	CC	75	172	---	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---
	Mössner et al[112]	FB	---	---	71	*P*=0.035	G-C Haplotype
Dopamine receptor 4							
	Cruz et al[113]	CC	12	49	---	*P*= 0.018	
	Billet et al[114]	CC	118	118	---	*P*= 0.021	
	Frisch et al[88]	CC	75	172	---	*P*=0.04	7 allele less frequent
	Millet et al[115]	CC/FB	49	63	34	*P*=0.03	2 allele protective
	Hemmings et al[104]	CC	71	129	---	ns	---
	Hemmings et al[106]	CC	95	85	---	*P*=0.013	early vs late onset
Dopamine receptor 2							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	110	110	---	*P*=0.014	CC genotype
Dopamine receptor 3							
	Catalano et al[116]	CC	97	97	---	ns	---
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	103	103	---	ns	---
Dopamine transporter							
	Billet et al[114]	CC	103	103	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
Dopamine receptor 2							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	110	110	---	*P*=0.014	CC genotype
Dopamine receptor 3							
	Catalano et al[116]	CC	97	97	---	ns	---
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	103	103	---	ns	---
Dopamine transporter							
	Billet et al[114]	CC	103	103	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
Monamine oxidase A							
	Karayiorgou et al[117]	FB	---	---	110	*P*=0.019 (males)	G allele
	Camarena et al[95]	CC/FB	122	124	51	CC: *P*=0.024 FB: *P*=0.022	T allele
	Hemmings et al[104]	CC	71	129	---	ns	---
Catechol O-methyl transferase							
	Karayiorgou et al[118]	CC	73	148	---	*P*=0.0002	L allele in males
	Karayiorgou et al[117]	FB	---	---	110	*P*=0.0079	L allele
	Schindler et al[119]	FB	---	---	67	*P*=0.006	L allele

Table III. Continued

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directly assessed with structured psychiatric interviews and 32 received diagnosis of lifetime OCD.

Three hundred forty-nine microsatellite markers were genotyped on these families. Twenty-four additional markers included in the fine-mapping subsequent to the initial genome scan. In the initial analyses a LOD score of 2.25 for marker D9S288 on chromosome 9p was observed. However, after finemapping the LOD score dropped to 1.97. In general, LOD scores above 3.6 are considered to be genome-wide significant.

In an attempt to replicate these findings, Willour et al[138] genotyped microsatellite markers on all available relatives in 50 pedigrees which had been ascertained through persons with OCD. The largest LOD scores observed in this study were for markers D9S1792 (HLOD=2.26) D9S1813 (NPL=2.52, *P*=0.006). D9S1813 and D9S1792 are within 350 kb of marker D9S288, the marker yielding the largest LOD score reported by Hanna et al.

The second genome-wide linkage study included a total of 219 families. Both affected sib-pair and multigenerational families were genotyped.[136] Suggestive evidence was observed for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. The strongest linkage evidence was obtained for markers on chromosome 3q27-28 when both definite and probable cases of OCD were considered affected. The maximum overall Kong and Cox LODall score (2.67) occurred with markers D3S1262

Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
			Cases	Controls	Families		
	Niehaus et al[120]	CC	54	54	---	*P*=0.0017	HL genotype
	Alsobrook et al[121]	FB	---	---	56	*P*=0.048	L allele in females
	Ohara et al[122]	CC	17	35	---	ns	---
	Erdal et al[123]	CC	59	114	---	ns	---
	Azzam et al[124]	CC	144	337	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Katerberg et al[125]	CC	373	462	---	ns	---
Glutamate receptor subtype 2B	Arnold et al[126]	FB	---	---	130	*P*=0.002	5072G-5988T haplotype
Kainite glutamate receptor 2	Delorme et al[127]	CC/FB	156	156	141	CC: ns FB: *P*=0.03	867I allele undertransmitted
Gamma-Amino-butyric acid type B receptor 1	Zai et al[128]	FB	---	---	159	*P*=0.006	A-7265G
Brain-derived neurotropic factor							
	Hall et al[129]	FB	---	---	164	*P*<0.020	Multiple SNPs
	Dickel et al[91]	FB	---	---	54	ns	---
	Wendland et al[93]	CC	347	749	---	ns	---
Myelin oligo-dendrocyte							
	Zai et al[130]	FB	---	---	160	*P*=0.022	MOG4 2-repeat allele
Glutamate transporter							
	Arnold et al[81]	FB	---	---	157	*P*=0.006	2 marker haplotype (males)
	Dickel et al[82]	FB	---	---	71	*P*=0.030	2 marker haplotype (males)
	Stewart et al[83]	FB	---	---	66	*P*=0.0015	3 marker haplotype
	Wendland et al[84]	CC	325	662	---	*P*<0.001	3 marker haplotype
Oligo-dendrocyte lineage transcription factor 2	Stewart et al[131]	FB	---	---	66	*P*=0.004	5 marker haplotype
Neurotrophin-3 receptor gene (NTRK3)*	Muiños-Gimeno et al[132]	CC	153	324	---	*P*=0.005	---
Extraneuronal monoamine transporter, EMT (SLC22A3)	Lazar et al[133]	CC	84	204		ns	---

Table III. Continued

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(*P*=0.0003) and D3S2398 (*P*=0.0004). The method proposed by Kong and Cox estimates the degree of allele sharing between affected individuals and provides using a maximum likelihood approach. When there is no linkage there should be no allele sharing greater than expected by chance.

In a second set of analyses of 219 families, Samuels et al[139] examined whether compulsive hoarding behavior was linked to different markers across the genome. These investigators reported suggestive evidence for linkage for D14S588 (KAC(all)=2.9) on chromosome 14. When families which included two or more hoarding relatives were analyzed separately, the Kong and Cox LODall score increased to 3.7.

In the third genome-wide linkage study,[137 121] individuals in 26 multigenerational families were genotyped with markers with an average spacing of 10 centimorgans (cM). (Note: a centimorgan is defined as the distance on a chromosome in which 1% crossing over occurs. Given the success of the human genome project, this metric is rarely used any more, since it is now possible to determine precisely the number of base pairs between markers.) As in the first study published by these investigators,[135] all relatives were assessed with a semistructured psychiatric interview, and best estimate lifetime psychiatric diagnoses were made using data from these interviews and all other available sources of information. The maximum nonparametric LOD (NLOD) score observed was 2.43 for markers on chromosome 10p15. When data from Hanna et al's first genome scan were analyzed together with the current marker data, the maximum NLOD score in the 10p15 region was decreased to 1.79. These investigators followed up the linkage findings with a family-based association analysis which examined 35 single-nucleotide polymorphisms (SNPs) in this 10p15 region. Association was detected on 10p15 with three adjacent SNPs, including the amino acid variant rs2271275 in the 3' region of adenosine deaminase acting on RNA 3 (ADAR3) (*P*<.05).

All of these findings should be interpreted with caution. The sample sizes in all three studies were quite small. Nevertheless, given that Willour et al[138] observed suggestive linkage to the same chromosome 9p region as reported by Hanna et al is noteworthy. In addition, as discussed above, four independent studies have reported an association of OCD and the glutamate transporter which is located in this region on 9p. Thus, the findings from the two studies by Hanna and colleagues[135,137] and the one reported by Willour et al[138] suggest that there may be a susceptibility locus in this region of 9p. Unfortunately, this region did not show any evidence for linage in the study completed by Shugart et al.[136]

Future work

The twin and family studies summarized in this review demonstrate that at least some forms of OCD have a genetic basis. However, given that none of the linkage studies and essentially all of the candidate genes studies provide only suggestive evidence for risk genes of moderate-to-large effect, whole-genome association studies of OCD are warranted as the next step in our understanding of the genetic basis of the disorder. Whole-genome association studies are preferred over more traditional linkage studies or candidate gene studies because they provide more power to identify risk genes of relatively small effect. The primary difference between genome-wide linkage studies and genome-wide association studies (GWASs) is that with linkage the investigator is looking for cotransmission of a specific DNA marker within a family, while in a genome-wide association study the investigator is looking for a population association between a DNA marker and disease. Linkage studies are better suited to identifying genes that have large effects, and GWASs are better when attempting to identify genes that have relatively small effects on the phenotype. These GWASs should examine both common markers as well a copy number variants and other rare genetic events. It is becoming evidence that complex disorders may be "caused" by both rare genes of major effect and a combination of common genes of lesser effect.

Given the limited state of knowledge about the pathophysiological pathways important for the manifestation of OCD, it is premature at this time to restrict focus on the association of specific candidate genes with OCD. Instead, a GWAS with a sample of sufficient size is the most promising approach for the identification of genomic regions that most likely harbor OCD risk genes. Once these regions have been identified, then more informed candidate gene studies could be undertaken.

Given the variability of recurrence risks and the results from the most recent twin study, it is clear that, like other neuropsychiatric conditions, OCD is etiologically heterogeneous. Given this high likelihood of etiologic heterogeneity, it is critical to study a sufficiently large sam-

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ple of affected individuals so that homogeneous clinical subgroups more likely to be etiologically homogenous can be identified from within the larger sample.[140-141] In order to obtain these large samples, it is imperative that investigators interested in the genetics of OCD collaborate. A collaboration of this type (the International OCD Foundation Genetics Collaborative) is currently conducting a GWAS of OCD on samples contributed from 21 different research sites from around the world. ❑

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REFERENCES

1. Calvocoressi L, Libman D, Vegso SJ, McDougle CJ, Price LH. Global functioning of inpatients with obsessive-compulsive disorder, schizophrenia, and major depression. *Psychiatric Services*. 1998;49:379-381.
2. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five U.S. communities. *Arch Gen Psychiatry*. 1988;45:1084-1099.
3. Weissman MM, Bland RC, Canino GJ, et al. The cross national epidemiology of obsessive compulsive disorder. *J Clin Psychiatry*. 1994;55:5-10.
4. Eaton WW, Martins SS, Nestadt GO, Bienvenu OJ, Clarke D, Alexandre P. The burden of mental disorders. *Epidemiol Rev*. 2008;30:1–14.
5. Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genetics C: Sem Med Genet*. 2008;148:133-139.
6. van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive-compulsive disorder: a review. *Twin Res Hum Genet*. 2005:450-458.
7. Lange J. Leistungen der Zwillingpathologie für die Psychiatrie [The importance of twin pathology for psychiatry]. *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medicin*. 1929;90:122–142.
8. Le Gras AM. Psychose en criminaliteit bij tweelingen [Psychosis and criminality in twins]. Unpublished doctoral dissertation, Rijksuniversiteit Utrecht, the Netherlands. 1932
9. Le Gras AM. Psychose und Kriminalität bei Zwillingen [Psychosis and criminality in twins]. *Zeitschrift für die gesamte Neurologie und Psychiatrie*. 1933;198–222.
10. Lewis A. Problems of obsessional illness. *Proc Roy Soc Med*. 1935; XXIX:325–336.
11. Tarozzi G. Über Zwillingspsychosen [About twin psychoses]. *Zentralblatt für die Gesamte Neurologie und Psychiatrie*. 1939;92: 82.
12. Rüdin E. Ein Beitrag zur Frage der Zwangskrankheit, insbesondere ihrer hereditären beziehungen [A contribution to questions about obsessional illness, especially its heredity]. *Archiv fur Psychiatrie und Nervenkrankheiten*. 1953;191:14–54.
13. Tienari P. Psychiatric illnesses in identical twins. *Acta Psych Scand*. 1964;39(suppl 171):1–195.
14. Parker N. Close identification in twins discordant for obsessional neurosis. *Br J Psychiatry*. 1964;110:496–504.
15. Woodruff R, Pitts FN Jr. Monozygotic twins with obsessional illness. *Am J Psychiatry*. 1964;120:1075–1080.
16. Inouye E. Similar and dissimilar manifestations of obsessive–compulsive neuroses in monozygotic twins. *Am J Psychiatry*. 1965;121:1171–1175.
17. Marks IM, Crowe M, Drewe E, Young J, Dewhurst WG. Obsessive compulsive neurosis in identical twins. *Br J Psychiatry*. 1969;115:991–998.
18. Tarsh MJ. Severe obsessional illness in dizygotic twins treated by leukotomy. *Comp Psychiatry*. 1978;19:165–169.
19. Hoaken, PC, Schnurr, R. Genetic factors in obsessive–compulsive neurosis? A rare case of discordant monozygotic twins. *Can J Psychiatry*. 1980;25: 167–172.
20. McGuffin P, Mawson D. Obsessive–compulsive neurosis: two identical twin pairs. *Br J Psychiatry*. 1980;137:285–287.
21. Carey G, Gottesman II. Twin and familiy studies of anxiety, phobic, and obsessive disorders. In Klein DF, Rabkin J. eds. *Anxiety: New research and changing concepts*. New York, NY: Raven Press; 1981:117-136.
22. Torgersen S. Genetic factors in anxiety disorders. *Arch Gen Psychiatry*. 1983;40:1085–1089.
23. McKeon J, McGuffin P, Robinson P. Obsessive–compulsive neurosis following head injury. A report of four cases. *Br J Psychiatry*. 1984;144:190–192.
24. Mahgroub OM, Ahmed MAM, Al-Suhaibani MO. Identical Saudi twins concordant for obsessive–compulsive disorder. *Saudi Medical Journal.* 1988;9:641–643.
25. Kim SW, Dysken, MW, Kline MD. Monozygotic twins with obsessive–compulsive disorder. *Br J Psychiatry*. 1990;156:435–438.
26. Andrews G, Stewart G, Allen R, Henderson AS. The genetics of six neurotic disorders: a twin study. *J Aff Disord*. 1990;19:23–29.
27. Lewis SW, Chitkara, B, Reveley, AM. Obsessive–compulsive disorder and schizophrenia in three identical twin pairs. *Psychol Med*. 1991;21:135–141.
28. Cryan EM, Butcher GJ, Webb MG. Obsessive–compulsive disorder and paraphilia in a monozygotic twin pair. *Br J Psychiatry*. 1992;161:694–698.
29. Bolton D, Rijsdijk F, O'connor TG, Perrin S, Eley TC. Obsessive–compulsive disorder, tics and anxiety in 6-year-old twins. *Psychol Med*. 2007;37:39–48
30. Tambs K, Czajkowsky N, Røysamb E, et al. Structure of genetic and environmental risk factors for dimensional representations of DSM–IV anxiety disorders. *Br J Psychiatry*. 2009;195:301–307.
31. Young JP, Fenton, GW, Lader MH. The inheritance of neurotic traits: A twin study of the Middlesex Hospital Questionnaire. *Br J Psychiatry*. 1971;119:393–398.
32. Torgersen S. The oral, obsessive, and hysterical personality syndromes. A study of hereditary and environmental factors by means of the twin method. *Arch Gen Psychiatry*. 1980;37:1272–1277.
33. Clifford CA, Murray RM, Fulker DW. Genetic and environmental influences on obsessional traits and symptoms. *Psychol Med*. 1984;14:791–800.
34. Jonnal AH, Gardner CO, Prescott CA, Kendler KS. Obsessive and compulsive symptoms in a general population sample of female twins. *Am J Med Genet*. 2000:96:791–796.
35. Eley TC, Bolton D, O'Connor TG, Perrin S, Smith, P, Plomin R. A twin study of anxiety related behaviours in pre-school children. *J Child Psychol Psychiatry Allied Disciplines*. 2003;44:945–960.
36. Hudziak JJ, van Beijsterveldt CEM, Althoff RR, et al. Genetic and environmental contributions to the Child Behavior Checklist Obsessive–Compulsive Scale: a cross-cultural twin study. *Arch Gen Psychiatry*. 2004;61:608–616.
37. Pauls DL, Raymond CL, Stevenson JM, Leckman JF. A family study of Gilles de la Tourette syndrome. *Am J Hum Genet*. 1991;48:154-163.
38. Pauls DL, Alsobrook J 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive compulsive disorder. *Am J Psychiatry*. 1995;152:76-84.
39. Grados MA, Riddle MA, Samuels JF, et al. The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biological Psychiatry*. 2001;50:559-565.
40. Hanna GL, Veenstra-VanderWeele J, Cox NJ, et al. Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet (Neuropsychiatr Genet).* 2002;114:541-552.
41. do Rosario-Campos MC, Leckman JF, Curi M, et al. A family study of early-onset obsessive-compulsive disorder. *Am J Med Genet (Neuropsychiatr Genet).* 2005;136:92-97.
42. Thompson WD, Weissman MM. Quantifying lifetime risk of psychiatric disorder. *J Psychiatr Res*. 1981;16:113-26.
43. Gershon ES, Guroff JJ. Information from relatives. Diagnosis of affective disorders. *Arch Gen Psychiatry*. 1984;41:173-80.
44. Luxenburger H. Heredität und Familientypus der Zwangsneurotiker. *Arch Psychiatr*. 1930;91:590-594.

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La genética del trastorno obsesivo-compulsivo: una revisión

El trastorno obsesivo-compulsivo (TOC) es un serio trastorno psiquiátrico que afecta aproximadamente al 2% de la población de niños y adultos. Los estudios de agregación familiar han demostrado que el TOC es familiar y los resultados de los estudios en gemelos demuestran que el carácter familiar se debe en parte a factores genéticos. A la fecha se han terminado sólo tres estudios del ligamiento de genoma completo, con resultados sugerentes, pero no definitivos. Además, se han publicado más de 80 estudios de genes candidatos. La mayoría de estos estudios se han focalizado en genes de las vías serotoninérgica y dopaminérgica. Lamentablemente, ninguno de ellos ha logrado una significación para el genoma completo y, con excepción del gen del transportador de glutamato, ninguno ha sido replicado. La investigación a futuro requerirá de la colaboración de equipos multidisciplinarios para: 1) conseguir muestras suficientemente grandes de individuos con TOC, 2) aplicar las técnicas de laboratorio más actualizadas y 3) realizar los análisis bioinformáticos esenciales para la identificación de los loci de riesgo.

Génétique du trouble obsessionnel compulsif : revue de la littérature

Le trouble obsessionnel compulsif (TOC) est un trouble psychiatrique grave affectant environ 2 % de la population enfant et adulte. Des études d'agrégation familiale ont montré que le TOC est d'origine familiale, le résultat d'études sur les jumeaux ayant mis en évidence que le caractère familial serait dû en partie à des facteurs génétiques. Seules trois études de liaison du génome entier sont terminées à ce jour, avec des résultats évocateurs mais pas définitifs. De surcroît, plus de 80 études sur les gènes candidats ont été publiées. La plupart des études se sont intéressées aux gènes des voies sérotoninergiques et dopaminergiques. Malheureusement, aucune n'a pu être significative sur génome entier et, mis à part le gène transporteur du glutamate, aucune n'a pu être reproduite. La recherche ultérieure nécessitera la collaboration d'équipes pluridisciplinaires d'investigateurs pour 1) obtenir des échantillons suffisamment importants de sujets atteints de TOC ; 2) appliquer des techniques de laboratoires optimales ; et 3) réaliser des analyses bio-informatiques essentielles à l'identification des loci à risque.

45. Lewis A. Problems of obsessional illness. *Proc R Soc Med*. 1936;29:325-336.
46. Brown FW. Heredity in the psychoneuroses. Paper presented at: Royal Society of Medicine;1942.
47. Rüdin E. Beitrag zur Frage der Zwangskrankheit, insbesondere ihrer hereditaren Beziehungen. *Arch Psychiatr Nervenkrankh*. 1953;191:14-54.
48. Kringlen E. Obsessional neurotics: a long term follow-up. *Br J Psychiatry*. 1965;111:709-722.
49. Rosenberg CM. Familial aspects of obsessional neurosis. *Br J Psychiatry*. 1967;113:405-413.
50. Insel T, Hoover C, Murphy DL. Parents of patient with obsessive-compulsive disorder. *Psychol Med*. 1983;13:807-8111.
51. Rasmussen SA, Tsuang MT. Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. *Am J Psychiatry*. 1986;143:317-322.
52. McKeon P, Murray R. Familial aspects of obsessive-compulsive neurosis. *Br J Psychiatry*. 1987;151:528-534.
53. Bellodi L, Sciuto G, Diaferia G, Ronchi P, Smeraldi E. Psychiatric disorders in the families of patients with obsessive-compulsive disorder. *Psychiatry Res*. 1992;42:111-120.
54. Black DW, Noyes R, Jr, Goldstein RB, Blum N. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:362-368.
55. Nicolini H, Weissbecker K, Mejia JM, Sanchez de Carmona M. Family study of obsessive-compulsive disorder in a Mexican population. *Arch Med Res.* 1993;24:193-198.
56. Nestadt G, Samuels J, Riddle MA, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:358-363.
57. Albert U, Maina G, Ravizza L, Bogetto F. An exploratory study on obsessive-compulsive disorder with and without a familial component: are there any phenomenological differences? *Psychopathology*. 2002;35:8-16.
58. Fyer AJ, Lipsitz JD, Mannuzza S, Aronowitz B, And Chapman TF. A direct interview family study of obsessive–compulsive disorder I. *Psychol Med*. 2005;35:1611–1621.
59. Lipsitz JD, Manuzza S, Chapman TF, et al. A direct interview family study of obsessive–compulsive disorder. II. Contribution of proband informant information. *Psychol Med*. 2005;35:1623–1631.
60. Hans Joergen Grabe HJ, Stephan Ruhrmann S, Susan Ettelt S, et al. Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. *Am J Psychiatry*. 2006; 163:1986–1992.
61. Lenane MC, Swedo SE, Leonard H, Pauls DL, Sceery W, Rapoport JL. Psychiatric disorders in first degree relatives of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1990;29:407-412.
62. Riddle MA, Scahill L, King R, et al. Obsessive compulsive disorder in children and adolescents: phenomenology and family history. *J Am Acad Child Adolesc Psychiatry*. 1990;29:766-772.
63. Leonard H, Lenane MC, Swedo SE, Rettew DC, Gershon ES, Rapoport JL. Tics and Tourette's disorder: a 2- to 7-year follow-up of 54 obsessive-compulsive children. *Am J Psychiatry*. 1992;149:1244-1251.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 162

64. Reddy PS, Reddy YC, Srinath S, Khanna S, Sheshadri SP, Girimaji SR. A family study of juvenile obsessive-compulsive disorder. *Can J Psychiatry*. 2001;46:346-351.
65. Chabane N, Delorme R, Millet B, Mouren MC, LeBoyer M, Pauls DL. Early-onset obsessive-compulsive disorder: a subgroup with a specific clinical and familial pattern? *J Child Psychol Psychiatry*. 2005;46:881-887.
66. Bienvenu OJ, Samuels JF, Riddle MA, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. *Biological Psychiatry*. 2000;48:287-293.
67. Grados MA, Riddle MA, Samuels JF, et al. The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biol Psychiatry*. 2001;50:559-565.
68. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry*. 2001;158:1568-1578.
69. Nicolini H, Hanna GL, Baxter L, Schwartz J, Weissbecker K, Spence MA. Segregation analysis of obsessive compulsive disorders. *Preliminary results*. Ursus Medicus. 1991;1:25-28.
70. Alsobrook JP, II, Leckman JF, Goodman WK, Rasmussen SA, Pauls DL. Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. *Am J Med Genet*. 1999;88:669-675.
71. Cavallini MC, Bertelli S, Chiapparino D, Riboldi S, Bellodi L. Complex segregation analysis of obsessive-compulsive disorder in 141 families of eating disorder probands, with and without obsessive-compulsive disorder. *Am J Med Genet (Neuropsychiatric Genet).* 2000;96:384-391.
72. Nestadt G, Lan T, Samuels J, et al. Complex segregation analysis provides compelling evidence for a major gene underlying obsessive-compulsive disorder and for heterogeneity by sex. *Am J Hum Genet*. 2000;67:1611-1616.
73. Leckman JF, Grice DE, Boardman J, et al. Symptoms of obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:911-917.
74. Summerfeldt LJ, Richter MA, Antony MM, Swinson RP. Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analytic study. *Behav Res Ther*. 1999;37:297-311.
75. Stewart SE, Rosario MC, Brown TA, et al. (). Principal components analysis of obsessive-compulsive disorder symptoms in children and adolescents. *Biol Psychiatry*. 2007;61:285-291.
76. Hasler G, Pinto A, Greenberg BD, Samuels J, et al. Familiality of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD Collaborative Genetics Study. *Biol Psychiatry*. 2007;61:617-625.
77. Pinto A, Greenberg BD, Grados MA, et al. Further development of YBOCS dimensions in the OCD Collaborative Genetics study: symptoms vs. categories. *Psychiatry Res*. 2008;160:83-93.
78. Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry*. 1990;51(supplement):36-43.
79. Goodman WK, Price LH, Delgado PL, et al. Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1990;47:577-585.
80. Arnold PD, Richter MA, Mundo E, McBride J, Kennedy J. Quantitative and qualitative traits in obsessive-compulsive disorder: association with a glutamate receptor gene. *Int J Neuropsychopharmacol*. 2002;5(S1):S116.
81. Arnold PD, Sicard T, et al. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. *Arch Gen Psychiatry*; 2006;63:769-776.
82. Dickel, DE, Veenstra-VanderWeele J, et al. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2006;63:778-785.
83. Stewart SE, Fagerness JA, Platko J, et al. Association of the SLC1A1 glutamate transporter gene and obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144:1027-1033.
84. Wendland JR, Moya PR, Timpano KR, et al. A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2009;66:408-416.
85. Wendland JR, Moya PR, Kruse MR, et al. A novel, putative gain-of-function haplotype at SLC6A4 associates with obsessive-compulsive disorder. *Hum Mol Genet*. 2008; 17:717-723.
86. McDougle CJ, Epperson CN, Price LH, et al. Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder. *Mol Psychiatry.* 1998;3:270–273.
87. Bengel D, Greenberg BD, Cora-Locatelli G, et al. Association of the serotonin transporter promoter regulatory region polymorphism and obsessive-compulsive disorder. *Mol Psychiatry*. 1999;4:463–466.
88. Frisch A, Michaelovsky E, Rockah R, et al. Association between obsessive-compulsive disorder and polymorphisms of genes encoding components of the serotonergic and dopaminergic pathways. *Eur Neuropsychopharmacol*. 2000;10:205–209.
89. Kinnear CJ, Niehaus DJ, Moolman-Smook JC, et al. Obsessive-compulsive disorder and the promoter region polymorphism (5-HTTLPR) in the serotonin transporter gene (SLC6A4): a negative association study in the Afrikaner population. *Int J Neuropsychopharmacol*. 2000;3:327–331.
90. Damiaan Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HGM. ssociation between serotonergic candidate genes and specific phenotypes of obsessive compulsive disorder. *J Aff Disord*. 2006;91:39–44.
91. Dickel DE, Veenstra-VanderWeele J, Bivens NC, et al. Association studies of serotonin system candidate genes in early-onset obsessive-compulsive disorder. *Biol Psychiatry.* 2007;61:322–329.
92. Pilar A. Saiz PA, Garcia-Portilla MP, Arango C, et al. Association study between obsessive–compulsive disorder and serotonergic candidate genes. *Progr Neuro-Psychopharmacol Biol Psychiatry*. 2008;32:765–770.
93. Wendland JR, Kruse MR, Cromer KC, Murphy DL. A large case–control study of common functional SLC6A4 and BDNF variants in obsessive–compulsive disorder. *Neuropsychopharmacology*. 2007;32:2543-2551.
94. Kinnear CJ, Niehaus DJ, Moolman-Smook JC, et al. Obsessive-compulsive disorder and the promoter region polymorphism (5-HTTLPR) in the serotonin transporter gene (SLC6A4): a negative association study in the Afrikaner population. *Int J Neuropsychopharmacol.* 2000;3:327–331.
95. Camarena B, Rinetti G, Cruz C, et al. Association study of the serotonin transporter gene polymorphism in obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2001;4:269–272.
96. Cavallini MC, Di Bella D, Siliprandi F, Malchiodi F, Bellodi L. Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. *Am J Med Genet*. 2002;114:347-353.
97. Walitza S, Wewetzer C, Gerlach M, et al. Transmission disequilibrium studies in children and adolescents with obsessive-compulsive disorders pertaining to polymorphisms of genes of the serotonergic pathway. *J Neural Transm*. 2004;111:817–825.
98. Meira-Lima I, Shavitt RG, Miguita K, et al. Association analysis of the catechol-omethyltransferase (COMT), serotonin transporter (5-HTT) and serotonin 2A receptor (5HT2A) gene polymorphisms with obsessive-compulsive disorder. *Genes Brain Behav*. 2004;3:75–79.
99. Chabane N, Millet B, Delorme R, et al. Lack of evidence for association between serotonin transporter gene (5-HTTLPR) and obsessive-compulsive disorder by case control and family association study in humans. *Neurosci Lett*. 2004;363:154–156.
100. Nicolini H, Cruz C, Camarena B, et al. DRD2, DRD3and 5HT2A receptor genes polymorphisms in obsessive-compulsive disorder. *Mol Psychiatry*. 1996;1:461–465.
101. Enoch MA, Kaye WH, Rotondo A, et al. 5–HT2A promoter polymorphism -1438G/A, anorexia nervosa, and obsessive-compulsive disorder. *Lancet*. 1998;351:1785–1786.
102. Enoch MA, Greenberg BD, Murphy DL, et al. Sexually dismorphic relationship of a 5-HT2A promoter polymorphism with obsessive-compulsive disorder. *Biol Psychiatry*. 2001;49:385–388.
103. Walitza S, Wewetzer C, Warnke A, et al. 5-HT2A promoter polymorphism -1438G/A in children and adolescents with obsessive-compulsive disorders. *Mol Psychiatry*. 2002;7:1054–1057.
104. Hemmings SM, Kinnear CJ, Niehaus DJ, et al. Investigating the role of dopaminergic and serotonergic candidate genes in obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2003;13:93–98.
105. Tot S, Erdal ME, Yazici K, et al. T102C and -1438 G/A polymorphisms of the 5-HT2A receptor gene in Turkish patients with obsessive-compulsive disorder. *Eur Psychiatry*. 2003;18:249–254.
106. Hemmings SM, Kinnear CJ, Lochner C, et al. Early- versus late-onset obsessive-compulsive disorder: investigating genetic and clinical correlates. *Psychiatry Res*. 2004;128:175–182.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 163

107. Cavallini MC, Di Bella D, Pasquale L, et al. 5HT2C CYS23/SER23 polymorphism is not associated with obsessive-compulsive disorder. *Psychiatry Res*. 1998;77:97–104.
108. Mundo E, Richter MA, Sam F, et al. Is the 5-HT(1Dbeta) receptor gene implicated in the pathogenesis of obsessive-compulsive disorder? *Am J Psychiatry*. 2000;157:1160–1161.
109. Mundo E, Richter MA, Zai G, et al. 5HT1Dbeta receptor gene implicated in the pathogenesis of obsessive-compulsive disorder: further evidence from a family-based association study. *Mol Psychiatry.* 2002;7:805–809.
110. Di Bella D, Cavallini MC, Bellodi L. No association between obsessive-compulsive disorder and the 5-HT(1Dbeta) receptor gene. *Am J Psychiatry.* 2002;159:1783–1785.
111. Camarena B, Aguilar A, Loyzaga C, et al. A family-based association study of the 5-HT-1Dbeta receptor gene in obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2004;7:49–53.
112. Mössner R, Walitza S, Geller F, et al. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2005;9:1–6.
113. Cruz C, Camarena B, King N, et al. Increased prevalence of the seven-repeat variant of the dopamine D4 receptor gene in patients with obsessive-compulsive disorder with tics. *Neurosci Lett*. 1997;231:1–4.
114. Billet EA, Richter MA, Sam F, et al. Investigation of dopamine system genes in obsessivecompulsive disorder. *Psychiatr Genet*. 1998;8:163–169.
115. Millet B, Chabane N, Delorme R, et al. Association between the dopamine receptor D4 (DRD4) gene and obsessive-compulsive disorder. *Am J Med Genet Br.* 2003;116:55–59.
116. Catalano M, Sciuto G, Di Bella D, et al. Lack of association between obsessive-compulsive disorder and the dopamine D3 receptor gene: some preliminary considerations. *Am J Med Genet.* 1994;54:253–255.
117. Karayiorgou M, AltemusM, Galke BL, et al. Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder. *Proc Natl Acad Sci U S A*. 1997;94:4572–4575.
118. Karayiorgou M, Sobin C, Blundell ML, et al. Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessivecompulsive disorder. *Biol Psychiatry.* 1999;45:1178–1189.
119. Schindler KM, Richter MA, Kennedy JL, et al. Association between homozygosity at the COMT gene locus and obsessive compulsive disorder. *Am J Med Genet*. 2000;96:721–724.
120. Niehaus DJ, Kinnear CJ, Corfield VA, et al. Association between a catechol-o-methyltransferase polymorphism and obsessive-compulsive disorder in the Afrikaner population. *J Affect Disord.* 2001;65:61–65.
121. Alsobrook JP, Zohar AH, Leboyer M, et al. Association between the COMT locus and obsessive-compulsive disorder in females but not males. *Am J Med Genet.* 2002;114:116–120.
122. Ohara K, Nagai M, Suzuki Y, et al. No association between anxiety disorders and catechol-O-methyltransferase polymorphism. *Psychiatry Res*. 1998;80:145–148.
123. Erdal ME, Tot S, Yazici K, et al. Lack of association of catechol-O-methyltransferase gene polymorphism in obsessive-compulsive disorder. *Depress Anxiety*. 2003;18:41–45.
124. Azzam A, Mathews CA. Meta-analysis of the association between the catecholamine-Omethyl-transferase gene and obsessive-compulsive disorder. *Am J Med Genet B*. 2003;123:64–69.
125. Katerberg H, Cath D, Denys D, et al. An association study of the COMT Val158Met genotype with factor-analysed Y-BOCS symptom category scores: preliminary findings. *Am J Med Genet B*. 2009 Jun 11. [Epub ahead of print].
126. Arnold PD, Rosenberg DR, Mundo E, et al. Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. *Psychopharmacology (Berl).* 2004;174:530–538.
127. Delorme R, Krebs MO, Chabane N, et al. Frequency and transmission of glutamate receptors GRIK2 and GRIK3 polymorphisms in patients with obsessive compulsive disorder. *Neuroreport*. 2004;15:699–702.
128. Zai G, Arnold P, Burroughs E, Barr CL, et al. Evidence for the gamma-amino-butyric acid type B receptor 1 (GABBR1) gene as a susceptibility factor in obsessive-compulsive disorder. *Am J Med Genet B*. 2005;134:25–29.
129. Hall D, Dhilla A, Charalambous A, et al. Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder. *Am J Hum Genet*. 2003;73:370–376.
130. Zai G, Bezchlibnyk YB, Richter MA, et al. Myelin oligodendrocyte glycoprotein (MOG) gene is associated with obsessive-compulsive disorder. *Am J Med Genet*. 2004;129B:64–68.
131. Stewart SE, Platko J, Fagerness J, et al. A genetic family-based association study of OLIG2 in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2007;64:209-214.
132. Muiños-Gimeno M, Guidi M, Kagerbauer B, et al. Allele variants in functional MicroRNA target sites of the neurotrophin-3 receptor gene (NTRK3) as susceptibility factors for anxiety disorders. *Hum Mutat*. 2009;30:1062-1071.
133. Lazar A, Walitza S, Jetter A, et al. Novel mutations of the extraneuronal monoamine transporter gene in children and adolescents with obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2008;11:35-48.
134. Hemmings SM, Stein DJ. The current status of association studies in obsessive-compulsive disorder. *Psychiatr Clin N Am*. 2006; 29:411-444 .
135. Hanna GL, Veenstra-VanderWeele J, Cox NJ, et al. Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet*. 2002;114:541-552.
136. Shugart YY, Samuels J, Willour VL, et al. Genomewide linkage scan for obsessive-compulsive disorder: evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. *Mol Psychiatry*. 2006;11:763-770.
137. Hanna GL, Veenstra-Vanderweele J, Cox NJ, et al. Evidence for a susceptibility locus on chromosome 10p15 in early-onset obsessive-compulsive disorder. *Biol Psychiatry*. 2007;62:856-862.
138. Willour VL, Yao Shugart Y, Samuels J, et al. Replication study supports evidence for linkage to 9p24 in obsessive-compulsive disorder. *Am J Hum Genet*. 2004;75:508-513.
139. Samuels J, Shugart YY, Grados MA, et al. Significant linkage to compulsive hoarding on chromosome 14 in families with obsessive-compulsive disorder: results from the OCD Collaborative Genetics Study. *Am J Psychiatry*. 2007;164:493-499.
140. Greenberg DA, Abreu P, Hodge SE. The power to detect linkage in complex disease by means of simple LOD-score analyses. *Am J Hum Genet*. 1998;63:870-879.
141. Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J. Psychiatric genetics: search for phenotypes. *Trends Neurosci.* 1998;21:102-105.

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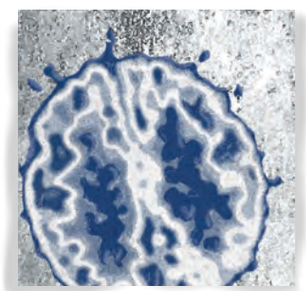
Translational neuroimaging research in pediatric obsessive-compulsive disorder

Frank P. MacMaster, PhD



Obsessive-compulsive disorder (OCD) is a significant public health problem. Selective serotonin reuptake inhibitors (SSRIs) are the only FDA-approved medications for OCD. However, SSRIs are of limited efficacy in clinical practice. Given the persistence of symptoms and levels of treatment response, it is clear that the serotonin paradigm of OCD does not fully account for the neurobiology of the disorder, and that further translational research is needed. In this review, the glutamate hypothesis of pediatric OCD is explored, the neuroimaging evidence reviewed, and the translational impact highlighted. The traditional strategy of going from pharmacology to pathophysiology has failed to show real progress in our understanding of the neurobiology of psychiatric illness and, while still in the early stages, this work demonstrates the clear benefit of approaching psychiatric illness from the opposite direction.

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Obsessive-compulsive disorder (OCD) is a major public health problem. OCD is a severe and chronically debilitating disorder, affecting over 3 million people in the United States alone. People afflicted with OCD have distressing obsessions and compulsions that cripple their functioning in everyday life.[1,2] According to the World Health Organization, OCD is among the ten most disabling medical conditions worldwide.[3] The National Comorbidity Survey Replication found that, in anxiety disorders, OCD has the highest percentage (50.6%) of serious cases.[4] The estimates of its lifetime prevalence in pediatric and adult populations range from 1% to 3%.[4-6]

Why focus on pediatric OCD?

The clinical phenomenology, nosology, and treatment of pediatric OCD have been well described, making the illness a leading candidate for new and innovative neurobiological study. The two reasons to focus on pediatric OCD are, first, that OCD commonly has its onset during the developmental period,[7] and second, that pediatric OCD is continuous with adult OCD. The National Institutes of Mental Health considers OCD to be a neurodevelopmental disorder.[8] Estimates of the mean age at onset of OCD children range from 9 to 11 years in boys to 11 to 13 years in girls.[9,10] Evidence indicates that an early age of onset in OCD is associated with a poor outcome.[11,12] There is a strong genetic component to the illness, with estimates of the heritability of obsessive-compulsive symptoms in children and adolescents ranging from 45% to 65%.[13] Pediatric OCD is chronic and unremitting in up to 87% of cases.[12] Children with OCD are also at higher risk for other psychiatric disorders in adulthood.[9,14]

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Why is translational research into pediatric OCD needed?

The biggest obstacles for people with OCD are getting a proper diagnosis and access to effective treatment.[15] Selective serotonin reuptake inhibitors (SSRIs) are the only FDA-approved medications for OCD. Treatment of OCD with SSRIs, while considered effective, has proven limited in practice. SSRIs are typically only effective in 40% to 60% of patients.[16] This leaves a substantial number still ill.[16] Indeed, many patients who are classed as "responders" are still markedly symptomatic after treatment; as studies define treatment response as a 20% to 40% reduction in symptoms.[16] In fact, typical OCD symptom severity scores, as measured by the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), post-treatment are 15 to 20 (test score range 0 to 40), indicating mild-to-moderate impairment.[17] In addition to medication, cognitive behavioral therapy (CBT) is also considered an effective treatment for OCD.[18] However, even the combination of CBT and medication still leaves approximately one third of pediatric patients markedly ill.[18] Furthermore, an earlier onset of OCD may be more associated with the illness being treatment-refractory.[18] Given the persistence of symptoms and limited levels of response to treatment, especially medication, it is clear that the serotonin paradigm of understanding OCD does not fully account for the neurobiology of the illness. In fact, our understanding of the biology of the disorder has been limited, until now.

How can brain imaging inform translational approaches?

The traditional, but not exclusive, strategy in psychiatry has been to go from the pharmacology to the pathophysiology of a given disorder. The development of the serotonin hypothesis of OCD is an example of this approach, where medications were applied first and a physiological explanation shaped around that. This approach has failed to show real progress in our understanding of the neurobiology of psychiatric illness.[19] However, developing an understanding of the physiology of psychiatric disorders has been difficult. That is, until the development of brain imaging methodologies that have allowed for the in vivo examination of the living brain. Postmortem work, while informative, does have its limits, and samples in pediatric populations with psychiatric illness are rare. There have been 2 decades since the application of brain imaging to the study of OCD, and tremendous progress has been made. Bringing these advances from the "bench" however, has been difficult.

Translational research has in two basic hurdles to jump.[20] The first hurdle is in transferring new understandings of the mechanisms of the disorder into novel treatments, diagnostic tools, and prevention. The second hurdle is in taking these novel therapies, diagnostic and preventative methods, and implementing these protocols in the actual clinic *(Figure 1)*. As out-

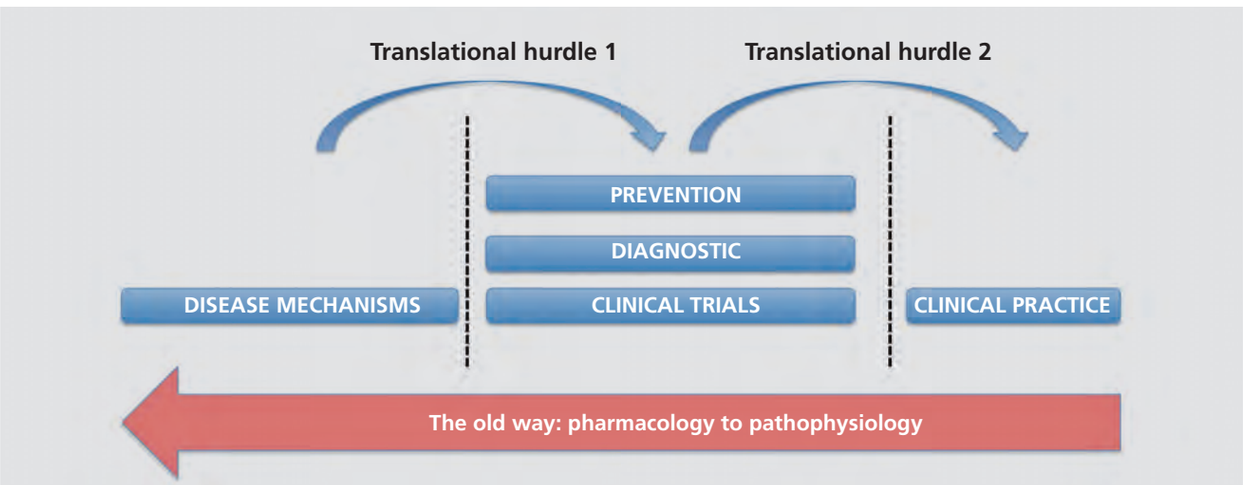

Figure 1. Basic pathway of translational research and the two main hurdles that need to be crossed to make research clinically relevant. The standard method in psychiatry has been to move from pharmacology in clinical practice to theories of pathophysiology.

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lined in the following section, significant progress has been made in increasing our understanding of the neurobiological substrates of pediatric OCD. These advances have directly led to the novel application of agents to treat pediatric OCD. This is one of the rare instances in psychiatric research where knowledge has indeed moved from the "bench" and closer to the "bedside."

Basic neurobiological model of pediatric OCD

In this section, we will outline the basic neurobiological model of OCD *(Figure 2)*. The cortical-striatal-thalamic circuit has been the most consistently implicated in OCD.[21,22] In the striatum, 80% of all synapses are cortical inputs.[23] The cortical regions projecting to the striatum can be divided into "motor" and "limbic associative." Motor projections include somatosensory, motor, and premotor cortex. More pertinent to OCD, the "limbic associative" projections are derived from the amygdala, hippocampus, orbital, frontal, cingulate, parietal, temporal, entorhinal, and association cortex.[24] One can subdivide the cortical-striatal connections into circuit loops. There are sensorimotor, oculomotor, dorsal cognitive, ventral cognitive, affective/motivational loops that extend from the cortex to the striatum to the thalamus and back to the cortex.[22] The anatomy and organization of the cortical-striatal circuits have been reviewed in depth elsewhere.[25-30] These circuits progress through distinct parts of the frontal cortex, basal ganglia, substantia nigra, and the thalamus in a self-repeating loop.[25] Two of the pathways act to regulate output from frontal cortex to insure appropriate behavioral responses to stimuli.[25] The "direct" pathway facilitates thalamic stimulation of the cortex. The "indirect" pathway acts to inhibit the thalamus—thus permitting the cortex to shift sets and respond to novel stimuli. OCD may result from excessive neural tone in the direct pathway relative to the indirect pathway.

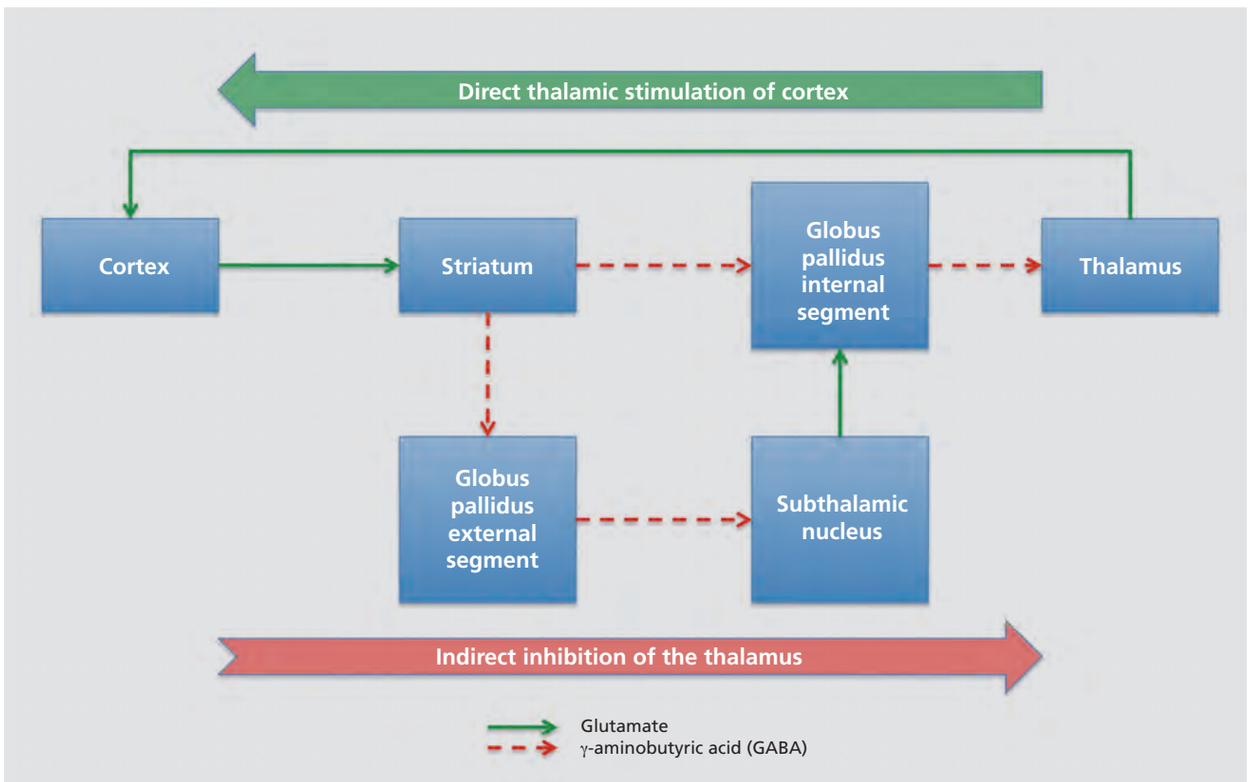

Figure 2. Basic schematic of the cortical-striatal-thalamic-cortical loop pertinent to pediatric obsessive-compulsive disorder.

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Neuroimaging studies of pediatric OCD

Below is a brief review of neuroimaging studies of pediatric OCD. The aim is provide enough background to highlight the move to a translational approach from an investigative one. Reports relevant to the translational research approach are in the following section.

Frontal cortex

Rosenberg et al[31] did not find any significant difference in prefrontal cortex (PFC) volume between pediatric OCD patients and age- and sex-matched controls. However, the measurement of total PFC volume may have been too gross a measure, and more subtle abnormalities in specific subregions lost. Indeed, the genu of the corpus callosum, which connects aspects of PFC across the hemispheres, was found to be larger in pediatric OCD subjects.[32] Larger anterior cingulate volumes were also noted, consonant with the larger genu finding.[33] Anterior cingulate volume was correlated with OCD symptom severity (r=0.73, obsessive subscale). This was replicated in a second sample.[34] This is noteworthy as replication is rare in psychiatric research. Developmentally, the normal increase in anterior cingulate volume with age (r=0.45) was absent in patients with OCD (r=-0.12). Rosenberg and Keshavan[33] hypothesized that increased anterior cingulate volumes correlating with reduced basal ganglia volumes (r=-0.46) in pediatric patients with OCD is suggestive of neural network dysplasia—characterized by alterations in postnatal pruning. Developmentally, the greater anterior cingulate volume and lack of a correlation with age in pediatric patients with OCD may reflect delayed or reduced neural pruning, while reduced striatal volume might reflect increased pruning. No differences in posterior cingulate or dorsolateral prefrontal cortex (DLPFC) volume were noted.[33]

Subcortical and other regions

Smaller basal ganglia volumes have been reported in treatment-naïve pediatric OCD patients.[31] Furthermore, greater ventricular brain ratios have been observed in adolescent patients with OCD compared with healthy controls, which would be expected with decreased basal ganglia volume.[35] The thalamus was found to be larger in pediatric OCD patients as compared with controls, a difference that resolved with SSRI treatment[36] but not cognitive behavioral therapy.[37] Also in the thalamus, greater medial but not lateral thalamic choline was observed in pediatric patients with OCD compared with both healthy controls and patients with major depressive disorder (MDD).[38] The choline resonance is derived primarily from membrane lipid compounds, and the increase may be related to the volumetric alteration noted earlier.[36] Greater creatine concentration was also noted[39] in patients, perhaps reflecting a greater metabolic demand in the medial thalamus. Amygdala volume decreased with effective SSRI treatment in pediatric OCD patients.[40] Interestingly, the change in amygdala volume was not related to a change in OCD symptom severity, but correlated with SSRI dosage. Pituitary gland volume was significantly smaller in pediatric OCD patients as compared to matched controls.[41] This was especially apparent in males, highlighting a possible sex difference in OCD.

Glutamate and pediatric OCD proton magnetic resonance spectroscopy studies (1H-MRS)

The core excitatory neurotransmitter of this cortical-striatal-thalamic circuit mentioned earlier is glutamate. It was in 1998 that Rosenberg and Keshavan[33] first hypothesized a role for glutamate in pediatric OCD, and evidence of glutamate abnormalities in OCD has been mounting since. In the first report on glutamate in OCD, Rosenberg et al,[42] using proton magnetic resonance spectroscopy (1H-MRS), observed above-normal striatal glutamate + glutamine (Glx) concentrations in psychotropic-naive pediatric OCD patients as compared with controls, which normalized after effective treatment with an SSRI. This decrease in striatal Glx may endure after SSRI discontinuation.[43] Interestingly, the other treatment considered effective for OCD, CBT, did not alter caudate Glx concentrations in pediatric OCD patients despite a reduction in symptoms.[44] Conversely, in the anterior cingulate, a single-voxel 1H-MRS study found lower Glx concentrations in pediatric OCD patients than in healthy controls.[45] This was replicated in adults with OCD, where below normal anterior cingulate Glx was observed in female patients.[46] Lower anterior cingulate glutamate correlated with symptom severity in this sample. Again in adult OCD patients, Whiteside et al[47] observed elevated Glx/PCr+Cr (crea-

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tine) levels in the orbital frontal white matter in patients as compared with controls. These effects appear to be regionally specific, with no effect noted in the occipital cortex, an area not typically implicated in the pathophysiology of OCD.[42] In conclusion, in vivo studies of the cortical-striatal-thalamic circuit in OCD have implicated glutamate directly. It is important to note, however, that correlation does not indicate causation and the overall weight of the evidence implicating glutamate should be considered.

Animal models and peripheral marker studies

These neuroimaging findings have been bolstered by studies using other methods and models. Chakrabarty et al[48] studied cerebral spinal fluid (CSF) concentration of glutamate in 21 psychotropic-naïve adults with OCD and 18 healthy controls. CSF glutamate concentration was significantly greater in OCD patients as compared with control subjects. Indirect support for glutamate involvement in OCD has also been provided by rodent models of obsessive-compulsive[49,50] and stereotypic behaviors.[51]

Glutamate transporter polymorphisms

Three independent groups have found that the 3' region of *SCL1A1* may contain a susceptibility allele for OCD, predominantly in male offspring.[52-54] The protein product is the high-affinity neuronal and epithelial transporter (EAAT3, EAAC1) for L-glutamate, L- and D-aspartate, and cysteine.[55,56] EAAT3/EAAC1 is found in cortex, basal ganglia, and hippocampus, and has been detected in all parts of the neuron.[57] In the adults, glutamate transport helps to keep extracellular glutamate below neurotoxic concentrations.[58] EAAT3/EAAC1 exhibits rather low expression and makes a minor contribution to the removal of synaptic glutamate as compared with EAAT1 and EAAT2.[59] During early brain development, it is expressed before astrocytes are functional. This is suggestive that EAAT3/EAAC1 is involved in the developmental role of glutamate.[59] A critical role of EAAT3/EAAC1 in neurodevelopment is consistent with the linkage and association findings supporting *SLC1A1* as a primary candidate gene in not only pediatric OCD,[52-54] but also in autistic spectrum disorders.[60] Testosterone and prolactin regulate the expression of EAAT3/EAAC1.[56] The increase in expression of EAAT3/EAAC1 by testosterone is consistent with the association of OCD with *SLC1A1* being strongest in males.[52,53] As for the possible function of the polymorphism, mice deficient in EAAC1 develop impaired self-grooming.[55] This suggests that EAAT3/EAAC1 knockouts in pediatric OCD may be associated with increased rather than with decreased EAAT3 expression.

Glutamate receptor polymorphisms

In addition to the glutamate transporter, the 5072T/G variant of NMDA subunit 2B gene (*GRIN2B*) has been associated with OCD in pediatric patients.[61] Specifically, the 5072G–5988T haplotype was associated with OCD. GRIN2B, on chromosome 12p, encodes for the NR2B subunit of the ionotropic glutamate receptor. It is expressed mainly in the striatum and the prefrontal cortex.[62] This consistent with regions demonstrating glutamatergic abnormalities in pediatric OCD patients.[42,45] Furthermore, GRIN2B has been linked to schizophrenia,[63] attention deficit hyperactivity disorder[64] and bipolar disorder.[65] During cortical development, GRIN2B is thought to play a role in plasticity.[66] In addition, neurotoxic levels of glutamate during the neonatal period increase the expression of NMDA NR2B in the striatum and cortex.[67] Functionally, the increased expression of GRIN2B in reaction to excess glutamate[68] suggests that pediatric OCD is associated with greater GRIN2B expression in the striatum. Most recently, a significant association was identified between the rs1019385 polymorphism of *GRIN2B* and decreased anterior cingulate cortex Glx but not with occipital Glx in pediatric OCD patients.[69]

Limitations to the glutamate hypothesis of obsessive-compulsive disorder

Clearly, a solitary neurochemical hypothesis of a psychiatric disorder is limited, as neurotransmitters do not operate in a vacuum. The preferential response of OCD patients to SSRIs has spawned the "serotonin" hypothesis of OCD. There is also neurobiological evidence to substantiate that assertion. For example, the serotonin transporter protein (5-HTPR) capacity indexed in platelets by 3H-paroxetine is reduced in pediatric OCD patients compared with controls.[70] However, the persistence of symptoms despite targeting serotonin pharma-

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cologically indicates limits of the serotonin hypothesis of OCD.[16,17] Indeed, glutamate and serotonin interact on a number of levels in the frontal striatal circuit. For instance, Becquet et al[71] found that glutamate exerts a potent inhibitory effect on serotonin release in the caudate nucleus. In addition, the orbitofrontal cortex sends projections to dorsal raphe nuclei, which in turn sends serotonergic input to the striatum. The orbitofrontal cortex also has direct glutamate projections to the striatum, which play a role in the release and turnover of serotonin and regulation of serotonin receptor number in the striatum. Given the above evidence, we believe that glutamate is a logical choice for a biomarker and possible translational focus, as it may play a role in the pathophysiology of the disorder, the mechanism of action of the proposed medication, and its interplay with serotonin, the target of currently approved OCD medications.

Translational impact

Indeed, the glutamate hypothesis and consequent evidence have lead to the application of glutamate-modulating agents for the treatment of pediatric OCD *(Figure 3)*. Given the previously mentioned limitations of SSRI treatment for OCD, the search for novel medica-

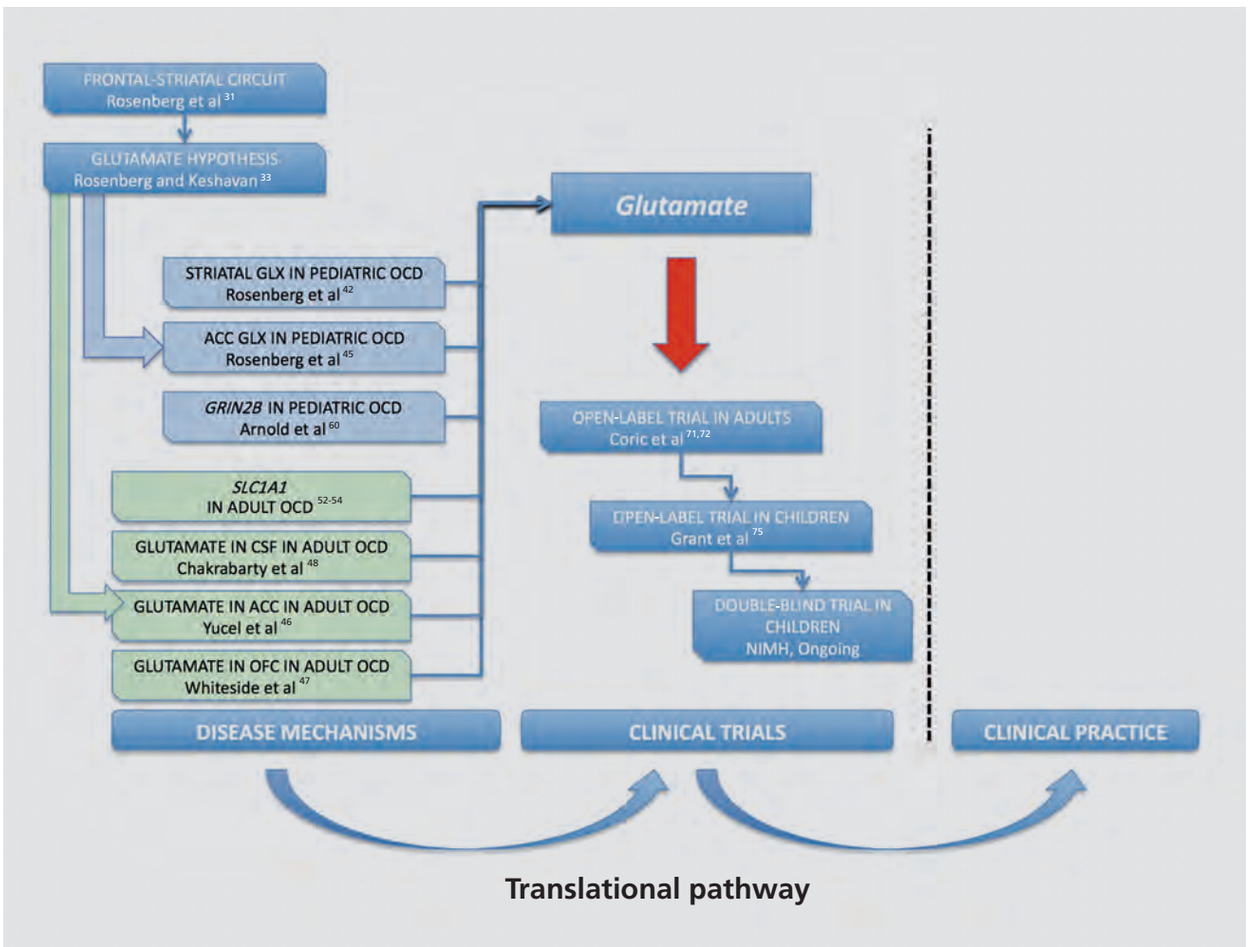

Figure 3. From initial findings to hypothesis to evidence and impact. The first hurdle in translational research has been crossed with neurobiological evidence being translated to clinical trials. ACC = anterior cingulate, Glx = glutamate + glutamine, *GRIN2B* = glutamate receptor gene, OCD = obsessive-compulsive disorder, *SLC1A1* = glutamate transporter gene

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tions/applications and drug combinations is warranted. Recently, the glutamate modulating agent riluzole (1-amino-6-trifluoromethoxybenzothiazole) has shown promise in psychiatric disorders.[72-76] Riluzole is typically well tolerated by patients and is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS).[77-79] The mechanism of action of riluzole is not entirely clear. Riluzole can act in three ways: (i) as an inhibitor of glutamate release; (ii) inactivating voltage dependant sodium channels in cortical neurons; and (iii) acting to block γ-aminobutyric acid (GABA) reuptake.[80-82] In both a case report and an open-label trial in adults with OCD,[72,73] riluzole demonstrated an ability to reduce the symptoms of OCD. More recently, an open-label trial in pediatric OCD patients (8 to 16 years) found that riluzole was both beneficial and well tolerated.[76] Currently, a National Institutes of Mental health-sponsored large double-blind clinical trial is under way. Given the above neurobiological findings and clinical reports, glutamate modulating agents like riluzole offer particular promise as an anti-OCD therapies.

Other glutamate and GABA-modulating agents have shown some promise as well. For example, topiramate has shown some promise in treating OCD in adults.[83-85] However, there are case reports indicating that some glutamate modulating medications (lamotrigine, topiramate) have induced OCD-like behaviors.[86-88] Furthermore, the occurrence of skin rash with lamotrigine treatment is also a concern.[89] Aside from safety, the mechanism of action is also important in choosing which glutamatergic agent. While topiramate enhances GABA activity and lamotrigine is a sodium channel blocker, riluzole acts primarily to inhibit glutamate. Given the above neurobiological findings and clinical reports, glutamate modulating agents like riluzole, offer particular promise as an anti-OCD therapies.

Conclusions

There is converging biological evidence indicating a role for glutamate in the symptoms of OCD.[42,45,47-49,52-54,61,90] Additionally, pharmacologically modulating glutamate has been shown to have an effect on OCD symptoms.[72,75,76] Hence, 1H-MRS, CSF, genetic, animal, and clinical studies have all implicated glutamate in OCD, indicating a clear conceptual link between glutamate and OCD symptoms. Indeed, the work on the glutamate hypothesis in pediatric OCD fits with Dr Tomas Insel's call for "rational therapeutics" for psychiatric illness.[91] Considering the large number of nonresponders and residual symptoms in even patients classed as responders to SSRI treatment, there is a pressing need to find better therapies. This work may have high clinical impact as it may stimulate the wider application of glutamate modulating agents for pediatric OCD. As mentioned earlier, the traditional strategy of going from pharmacology to pathophysiology has failed to show real progress in our understanding of the neurobiology of psychiatric illness.[19] New approaches, such as discussed here, may allow for progress that is more substantial. Given the findings regarding glutamate and OCD, and the development of novel safe agents that modulate glutamate, we could be on the cusp of breakthrough. As with any new medication intervention, there is the risk of failure. However, the payoff is enormous, as a much-needed new avenue of treatment will be developed. ❑

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.
2. Piacentini J, Bergman RL, Keller M, McCracken J. Functional impairment in children and adolescents with obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol*. 2003;13(suppl 1):S61-S69.
3. Murray CJL, Lopez AD. *Global Burden of Disease and Injury Series*. Cambridge, Mass: Harvard University Press; 1996.
4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
5. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, et al. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. *J Clin Psychiatry*. 1994;55(suppl):5-10.
6. Valleni-Basile LA, Garrison CZ, Jackson KL, Waller JL, McKeown RE, Addy CL, et al. Frequency of obsessive-compulsive disorder in a community sample of young adolescents. *J Am Acad Child Adolesc Psychiatry*. 1994;33:782-791.
7. Pauls DL, Alsobrook JP, 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. *Am J Psychiatry*. 1995;152:76-84.
8. RFA-MH-09-021. Novel Interventions for Neurodevelopmental Disorders (R21/R33). National Institutes of Health; 2008.
9. Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34:19-27.
10. Riddle MA, Scahill L, King R, et al. Obsessive compulsive disorder in children and adolescents: phenomenology and family history. *J Am Acad Child Adolesc Psychiatry*. 1990;29:766-772.
11. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder [see comments]. *Arch Gen Psychiatry*. 1999;56:121-127.

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La investigación translacional de neuroimágenes en el trastorno obsesivo-compulsivo pediátrico

El trastorno obsesivo-compulsivo (TOC) es un importante problema de salud pública. Los inhibidores selectivos de la recaptura de serotonina (ISRS) son los únicos medicamentos aprobados por la FDA para el TOC. Sin embargo, los ISRS en la práctica clínica son de una eficacia limitada. Considerando la persistencia de los síntomas y los niveles de respuesta terapéutica, es claro que el paradigma serotoninérgico del TOC no da cuenta totalmente de la neurobiología del trastorno y se requiere de más investigación translacional. En esta revisión se explora la hipótesis glutamatérgica del TOC pediátrico, se revisan las evidencias de las neuroimágenes y los impactos translacionales más destacados. La estrategia tradicional de ir desde la farmacología a la fisiopatología no ha podido mostrar el real progreso en nuestra comprensión de la neurobiología de la enfermedad psiquiátrica y, aunque sea en las primeras etapas, este trabajo demuestra el claro beneficio de una aproximación a la enfermedad psiquiátrica en el sentido opuesto.

Recherche translationnelle en neuro-imagerie dans le trouble obsessionnel compulsif de l'enfant

Le trouble obsessionnel-compulsif (TOC) est un important problème de santé publique. Les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) sont les seuls médicaments pour le TOC approuvés par la FDA, bien qu'ils soient peu efficaces en pratique clinique. Étant donné la persistance des symptômes et les taux de réponse au traitement, il est clair que le modèle sérotoninergique du TOC ne rend pas vraiment compte de la neurobiologie du trouble et qu'une recherche translationnelle supplémentaire est nécessaire. Nous examinons dans cet article l'hypothèse glutamatergique du TOC chez l'enfant, nous passons en revue la neuro-imagerie et nous insistons sur l'impact translationnel. La stratégie classique allant de la pharmacologie à la physiopathologie n'a pas réussi à montrer un vrai progrès dans notre compréhension de la neurobiologie de la maladie psychiatrique et, alors qu'il en est encore aux premiers stades, ce travail démontre le véritable bénéfice d'une approche inverse de la maladie psychiatrique.

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

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

14. Bolton D, Luckie M, Steinberg D. Long-term course of obsessive-compulsive disorder treated in adolescence. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1441-1450.

15. Hollander E, Kwon JH, Stein DJ, Broatch J, Rowland CT, Himelein CA. Obsessive-compulsive and spectrum disorders: overview and quality of life issues. *J Clin Psychiatry*. 1996;57(suppl 8):3-6.

16. Jenike MA. Clinical practice. Obsessive-compulsive disorder. *N Engl J Med*. 2004;350:259-265.

17. Geller DA. Psychopharmacology of pediatric obsessive-compulsive disorder. In: Storch E, Geffken G, Murphy T, eds. *Handbook of Child and Adolescent Obsessive-Compulsive Disorder*. London, UK: Lawrence Erlbaum Associates; 2007:243-272.

18. POTS. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292:1969-1976.

19. Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. *Mol Psychiatry*. 2006;11:11-17.

20. Sung NS, Crowley WF, Jr, Genel M, et al. Central challenges facing the national clinical research enterprise. *JAMA*. 2003;289:1278-1287.

21. Rosenberg DR, Mac Master FP, Mirza Y, Easter PC, Buhagiar CJ. Neurobiology, neuropsychology and neuroimaging of child and adolescent obsessive-compulsive disorder. In: In: Storch E, Geffken G, Murphy T, eds. *Handbook of Child and Adolescent Obsessive-Compulsive Disorder*. London, UK: Lawrence Erlbaum Associates; 2007:31-161.

22. Rauch SL, Savage CR. Neuroimaging and neuropsychology of the striatum. In: Miguel EC, Rauch SL, Leckman JF, eds. *Neuropsychiatry of the Basal Ganglia*. Philadelphia: W.B. Saunders Company; 1997:741-768.

23. Pasik P, Pasik T, DiFiglia M. Quantitative aspects in the neurostriatum of the macaque monkey. In: Yahr MD, ed. *The Basal Ganglia*. New York, NY: Raven Press; 1976:57-90.

24. Mello LEAM, Villares J. Neuroanatomy of the basal ganglia. In: Miguel EC, Rauch SL, Leckman JF, eds. *Neuropsychiatry of the Basal Ganglia*. Philadelphia, PA: W.B. Saunders Company; 1997:691-704.

25. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci*. 1990;13:266-271.

26. Alexander GE. Basal ganglia-thalamocortical circuits: their role in control of movements. *J Clin Neurophysiol*. 1994;11:420-431.

27. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986;9:357-381.

28. Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci*. 1992;15:133-139.

29. Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annu Rev Neurosci*. 1992;15:285-320.

30. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci*. 1990;13:244-254.

31. Rosenberg DR, Keshavan MS, O'Hearn KM, et al. Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1997;54:824-830.

32. Rosenberg DR, Keshavan MS, Dick EL, Bagwell WW, MacMaster FP, Birmaher B. Corpus callosal morphology in treatment-naive pediatric obsessive compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997;21:1269-1283.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 173

33. Rosenberg DR, Keshavan MS. A.E. Bennett Research Award. Toward a neurodevelopmental model of of obsessive--compulsive disorder. *Biol Psychiatry*. 1998;43:623-640.

34. Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, et al. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2004;161:1049-1056.

35. Behar D, Rapoport JL, Berg CJ, et al. Computerized tomography and neuropsychological test measures in adolescents with obsessive-compulsive disorder. *Am J Psychiatry*. 1984;141:363-369.

36. Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Arch Gen Psychiatry*. 2000;57:449-456.

37. Rosenberg DR, Benazon NR, Gilbert A, Sullivan A, Moore GJ. Thalamic volume in pediatric obsessive-compulsive disorder patients before and after cognitive behavioral therapy. *Biol Psychiatry*. 2000;48:294-300.

38. Rosenberg DR, Amponsah A, Sullivan A, MacMillan S, Moore GJ. Increased medial thalamic choline in pediatric obsessive-compulsive disorder as detected by quantitative in vivo spectroscopic imaging. *J Child Neurol*. 2001;16:636-641.

39. Mirza Y, O'Neill J, Smith EA, et al. Increased medial thalamic creatine-phosphocreatine found by proton magnetic resonance spectroscopy in children with obsessive-compulsive disorder versus major depression and healthy controls. *J Child Neurol*. 2006;21:106-111.

40. Szeszko PR, MacMillan S, McMeniman M, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. *Neuropsychopharmacology*. 2004;29:826-832.

41. MacMaster FP, Russell A, Mirza Y, et al. Pituitary volume in pediatric obsessive-compulsive disorder. *Biol Psychiatry*. 2006;59:252-257.

42. Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1096-1103.

43. Bolton J, Moore GJ, MacMillan S, Stewart CM, Rosenberg DR. Case study: caudate glutamatergic changes with paroxetine persist after medication discontinuation in pediatric OCD. *J Am Acad Child Adolesc Psychiatry*. 2001;40:903-906.

44. Benazon NR, Moore GJ, Rosenberg DR. Neurochemical analyses in pediatric obsessive-compulsive disorder in patients treated with cognitive-behavioral therapy. *J Am Acad Child Adolesc Psychiatry*. 2003;42:1279-1285.

45. Rosenberg DR, Mirza Y, Russell A, et al. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. *J Am Acad Child Adolesc Psychiatry*. 2004;43:1146-1153.

46. Yucel M, Wood SJ, Wellard RM, et al. Anterior cingulate glutamate-glutamine levels predict symptom severity in females with obsessive-compulsive disorder. *Mol Psychiatry*. In press.

47. Whiteside SP, Port JD, Deacon BJ, Abramowitz JS. A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. *Psychiatry Res*. 2006;146:137-47.

48. Chakrabarty K, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. *Neuropsychopharmacology*. 2005;30:1735-1740.

49. Nordstrom EJ, Burton FH. A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry. *Mol Psychiatry*. 2002;7:617-25, 524.

50. Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, et al. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature*. 2007;448:894-900.

51. Presti MF, Watson CJ, Kennedy RT, Yang M, Lewis MH. Behavior-related alterations of striatal neurochemistry in a mouse model of stereotyped movement disorder. *Pharmacol Biochem Behav*. 2004;77:501-507.

52. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2006;63:769-776.

53. Dickel DE, Veenstra-VanderWeele J, Cox NJ, et al. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2006;63:778-785.

54. Stewart SE, Fagerness JA, Platko J, et al. Association of the SLC1A1 glutamate transporter gene and obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144:1027-1033.

55. Aoyama K, Suh SW, Hamby AM, et al. Neuronal glutathione deficiency and age-dependent neurodegeneration in the EAAC1 deficient mouse. *Nat Neurosci*. 2006;9:119-126.

56. Franklin RB, Zou J, Yu Z, Costello LC. EAAC1 is expressed in rat and human prostate epithelial cells; functions as a high-affinity L-aspartate transporter; and is regulated by prolactin and testosterone. *BMC Biochem*. 2006;7:10.

57. Guillet BA, Velly LJ, Canolle B, Masmejean FM, Nieoullon AL, Pisano P. Differential regulation by protein kinases of activity and cell surface expression of glutamate transporters in neuron-enriched cultures. *Neurochem Int*. 2005;46:337-346.

58. Kanai Y, Smith CP, Hediger MA. A new family of neurotransmitter transporters: the high-affinity glutamate transporters. *FASEB J.* 1993;7:1450-9.

59. Nieoullon A, Canolle B, Masmejean F, Guillet B, Pisano P, Lortet S. The neuronal excitatory amino acid transporter EAAC1/EAAT3: does it represent a major actor at the brain excitatory synapse? *J Neurochem*. 2006;98:1007-1018.

60. Autism Genome Project Consortium. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet*. 2007;39:319-328.

61. Arnold PD, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA. Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. *Psychopharmacology (Berl).* 2004;174:530-538.

62. Loftis JM, Janowsky A. The N-methyl-D-aspartate receptor subunit NR2B: localization, functional properties, regulation, and clinical implications. *Pharmacol Ther*. 2003;97:55-85.

63. Li D, He L. Association study between the NMDA receptor 2B subunit gene (GRIN2B) and schizophrenia: a HuGE review and meta-analysis. *Genet Med*. 2007;9:4-8.

64. Dorval KM, Wigg KG, Crosbie J, et al. Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. *Genes Brain Behav*. 2007;6:444-452.

65. Martucci L, Wong AH, De Luca V, et al. N-methyl-D-aspartate receptor NR2B subunit gene GRIN2B in schizophrenia and bipolar disorder: Polymorphisms and mRNA levels. *Schizophr Res*. 2006;84:214-221.

66. Sheng M, Cummings J, Roldan LA, Jan YN, Jan LY. Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. *Nature.* 1994;368:144-147.

67. Beas-Zarate C, Rivera-Huizar SV, Martinez-Contreras A, Feria-Velasco A, Armendariz-Borunda J. Changes in NMDA-receptor gene expression are associated with neurotoxicity induced neonatally by glutamate in the rat brain. *Neurochem Int*. 2001;39:1-10.

68. Ueda Y, Doi T, Tsuru N, Tokumaru J, Mitsuyama Y. Expression of glutamate transporters and ionotropic glutamate receptors in GLAST knockout mice. *Brain Res Mol Brain Res*. 2002;104:120-126.

69. Arnold PD, Macmaster FP, Richter MA, Hanna GL, Sicard T, Burroughs E, et al. Glutamate receptor gene (GRIN2B) associated with reduced anterior cingulate glutamatergic concentration in pediatric obsessive-compulsive disorder. *Psychiatry Res*. 2009;172:136-139.

70. Sallee FR, Richman H, Beach K, Sethuraman G, Nesbitt L. Platelet serotonin transporter in children and adolescents with obsessive-compulsive disorder or Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1647-1656.

71. Becquet D, Faudon M, Hery F. In vivo evidence for an inhibitory glutamatergic control of serotonin release in the cat caudate nucleus: involvement of GABA neurons. *Brain Res*. 1990;519:82-88.

72. Coric V, Milanovic S, Wasylink S, Patel P, Malison R, Krystal JH. Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. *Psychopharmacology (Berl).* 2003;167:219-220.

73. Coric V, Taskiran S, Pittenger C, Wasylink S, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry*. 2005;58:424-428.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 174

74. Zarate CA, Jr., Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004;161:171-174.
75. Zarate CA, Jr., Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005;57:430-432.
76. Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol*. 2007;17:761-767.
77. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med*. 1994;330:585-591.
78. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet*. 1996;347:1425-1431.
79. Lacomblez L, Bensimon G, Leigh PN, et al. A confirmatory dose-ranging study of riluzole in ALS. ALS/Riluzole Study Group-II. *Neurology*. 1996;47(6 Suppl 4):S242-S250.
80. Jehle T, Bauer J, Blauth E, Hummel A, Darstein M, Freiman TM, et al. Effects of riluzole on electrically evoked neurotransmitter release. *Br J Pharmacol*. 2000;130:1227-1234.
81. Stefani A, Spadoni F, Bernardi G. Differential inhibition by riluzole, lamotrigine, and phenytoin of sodium and calcium currents in cortical neurons: implications for neuroprotective strategies. *Exp Neurol*. 1997;147:115-122.
82. Urbani A, Belluzzi O. Riluzole inhibits the persistent sodium current in mammalian CNS neurons. *Eur J Neuroscience*. 2000;12:3567-3574.
83. Rubio G, Jimenez-Arriero MA, Martinez-Gras I, Manzanares J, Palomo T. The effects of topiramate adjunctive treatment added to antidepressants in patients with resistant obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2006;26:341-344.
84. Hollander E, Dell'Osso B. Topiramate plus paroxetine in treatment-resistant obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2006;21:189-191.
85. Van Ameringen M, Mancini C, Patterson B, Bennett M. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: a retrospective, open-label case series. *Depress Anxiety*. 2006;23:1-5.
86. Ozkara C, Ozmen M, Erdogan A, Yalug I. Topiramate related obsessive-compulsive disorder. *Eur Psychiatry*. 2005;20:78-79.
87. Alkin T, Onur E, Ozerdem A. Co-occurence of blepharospasm, tourettism and obsessive-compulsive symptoms during lamotrigine treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:1339-1140.
88. Thuile J, Even C, Guelfi JD. Topiramate may induce obsessive-compulsive disorder. *Psychiatry Clin Neurosci*. 2006;60:394.
89. Choi H, Morrell MJ. Review of lamotrigine and its clinical applications in epilepsy. *Exp Opin Pharmacother*. 2003;4:243-251.
90. Delorme R, Krebs MO, Chabane N, Roy I, Millet B, Mouren-Simeoni MC, et al. Frequency and transmission of glutamate receptors GRIK2 and GRIK3 polymorphisms in patients with obsessive compulsive disorder. *Neuroreport*. 2004;15:699-702.
91. Insel T. NIH update. *Biol Psychiatry*. 2008;63:34S.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 175

Pathological gambling and compulsive buying: do they fall within an obsessive-compulsive spectrum?

Donald W. Black, MD; Martha Shaw, BA; Nancee Blum, MSW

Both compulsive buying (CB) and pathological gambling (PG) have been proposed as members of a spectrum of disorders related to obsessive-compulsive disorder (OCD). The spectrum hypothesis originated in the early 1990s and has gained considerable support, despite the lack of empirical evidence. Interest in this hypothesis has become critical because some investigators have recommended the creation of a new category that includes these disorders in DSM-5, now under development. In this article, the authors describe the origin of the obsessive-compulsive (OC) spectrum and its theoretical underpinnings, review both CB and PG, and discuss the data both in support of and against an OC spectrum. Both disorders are described in terms of their history, definition, classification, phenomenology, family history, pathophysiology, and clinical management. The authors conclude that: (i) CB and PG are probably not related to OCD, and there is insufficient evidence to place them within an OC spectrum in DSM-V; (ii) PG should stay with the impulse-control disorders (ICDs); and (iii) a new diagnosis of CB should be created and be classified as an ICD.

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In the early 1990s, interest began to grow around the concept of an obsessive-compulsive (OC) spectrum. Hollander and others[1-3] wrote of a spectrum of disorders related to obsessive-compulsive disorder (OCD). Based on his experience as an OCD researcher, Hollander considered OCD to be at the center of the spectrum, and described its breadth and overlap with many other psychiatric disorders. These disorders were considered to lie along orthogonal axes of impulsivity vs compulsiveness, uncertainty vs certainty, and cognitive vs motoric (features). The OC spectrum concept was quickly embraced by other investigators because it offered a new way to think about the relationship among many neglected disorders, and it potentially offered new treatment options.[4,5] Not all investigators have agreed, and several critical reviews have appeared.[6-9]

Despite the criticism, the concept of a group of disorders being related to OCD remains of great theoretical interest. The idea that disorders are related is crucial to classification schemes, and why should a group of disorders *not* be related to OCD? This question is now of singular interest because those responsible for developing the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* must decide whether to create a separate category for OCD and potentially related disorders, or to keep OCD with the anxiety disorders. If

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Selected abbreviations and acronyms

CB	*compulsive buying*
ICD	*impulse-control disorder*
OC	*obsessive-compulsive*
OCD	*obsessive-compulsive disorder*
PG	*pathological gambling*
SSRI	*selective serotonin reuptake inhibitor*

they create a new category for the OC spectrum they will need to determine its breadth.

The OC spectrum's boundaries have expanded or contracted according to the views of the investigator concerned. It has been described as including disorders of impulse control such as pathological gambling (PG), trichotillomania, and kleptomania; Tourette's and other tic disorders; impulsive personality disorders (eg, borderline personality disorder); hypochondriasis and body dysmorphic disorder; eating disorders; and several disorders not currently recognized in *DSM-IV-TR*[10] such as compulsive buying (CB) and sexual addiction.[1-4] Few investigators have offered evidence to validate a relationship among the disorders. Typically, such evidence might include comparisons of phenomenology, natural history, family history, biological markers, and treatment response.[11]

OCD holds an important place at the center of the spectrum. Currently classified in *DSM-IV-TR*[10] as an anxiety disorder, OCD is independent of other anxiety disorders in the International Classification of Diseases (ICD) system,[12] and a strong rationale has been presented by Zohar et al[13] for its separation from these disorders. First, OCD often begins in childhood, whereas other anxiety disorders typically have a later age of onset. OCD has a nearly equal gender distribution, unlike the other anxiety disorders, which are more common in women. Studies of psychiatric comorbidity show that, unlike the other anxiety disorders, persons with OCD generally tend not to have elevated rates of substance misuse. Family studies have not shown a clear association between OCD and the other anxiety disorders. Brain circuitry that mediates OCD appears to be different from that involved in other anxiety disorders. Lastly, OCD is unique with regard to its response to the serotonin reuptake inhibitors (SSRIs), while noradrenergic medications, effective in mood disorders, and somewhat effective in anxiety disorders, are largely ineffective in OCD. On the other hand, the benzodiazepines, which have little effect on OCD, are often effective for the other anxiety disorders. Further, Zohar et al[13] have argued that recognizing the spectrum would contribute to improved classification, thus enabling a more precise description of endophenotype and biological markers that characterize these conditions, and that better classification could lead to more specific treatments.

Apart from the possibility of an OC spectrum, there has been no consistent approach to categorizing impulsive and compulsive disorders. While some have decried the "medicalization" of problematic behaviors such as CB,[14] discussion has mainly focused on how these disorders should be classified, their relationship to other putative OC spectrum disorders, and whether some of them stand alone as independent disorders (eg, CB, compulsive sexual behavior).

Alternative classification schemes have emphasized the relationship of a putative OC spectrum disorder to depression or other mood disorders, to the impulse-control disorders (ICDs), or to the addictive disorders. Recently, it has been suggested that at least some of the disorders included in the OC spectrum be placed within a new diagnostic category that combines behavioral and substance addictions.[15] "Behavioral addictions" include disorders that the National Institute on Drug Abuse (NIDA) considers to be relatively pure models of addiction because they are not contaminated by the presence of an exogenous substance.

With this background in mind, this article will focus on the status of PG and CB. Are these disorders part of an OC spectrum as defined by Hollander and coworkers? Are they more appropriately considered impulse control disorders (ICDs) or addictions? Are they related to one another? These and other questions will be considered as we explore CB, PG, and the OC spectrum.

Compulsive buying

CB has been described in the psychiatric nomenclature for nearly 100 years. German psychiatrist Emil Kraepelin[16] wrote about the uncontrolled shopping and spending behavior called *oniomania* ("buying mania"). He was later quoted by Swiss psychiatrist Eugen Bleuler[17] in his *Lehrbuch der Psychiatrie*:

> As a last category, Kraepelin mentions the buying maniacs (oniomaniacs) in whom even buying is compulsive and leads to senseless contraction of debts with continuous delay of payment until a catastrophe clears the situation a little – a little bit never altogether because they never admit all their debts. …. The particular element is impul-

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> siveness; they cannot help it, which sometimes even expresses itself in the fact that not withstanding a good school intelligence, the patients are absolutely incapable of thinking differently and conceiving the senseless consequences of their act, and the possibilities of not doing it." (p 540).

Kraepelin and Bleuler each considered "buying mania" an example of a *reactive impulse* or *impulsive insanity*, and placed it alongside kleptomania and pyromania. They may have been influenced by French psychiatrist Jean Esquirol's[18] earlier concept of *monomania*, a term he used to describe otherwise normal persons who had some form of pathological preoccupation.

CB attracted little attention until the late 1980s and early 1990s when consumer behavior researchers showed the disorder to be widespread[19-21] and descriptive studies appeared in the psychiatric literature.[22-25] McElroy et al[22] developed an operational definition that encompasses the cognitive and behavioral aspects of CB. Their definition requires evidence of impairment from marked subjective distress, interference in social or occupational functioning, or financial/legal problems. Further, the syndrome could not be attributed to mania or hypomania.

Other definitions have come from consumer behavior researchers or social psychologists. Faber and O'Guinn[26] defined the disorder as "chronic buying episodes of a somewhat stereotyped fashion in which the consumer feels unable to stop or significantly moderate his behavior" (p 738). Edwards,[27] another consumer behaviorist, suggests that compulsive buying is an "abnormal form of shopping and spending in which the afflicted consumer has an overpowering uncontrollable, chronic and repetitive urge to shop and spend (that functions) … as a means of alleviating negative feelings of stress and anxiety." (p 67). Dittmar[28] describes three cardinal features: irresistible impulse, loss of control, and carrying on despite adverse consequences. Some consumer behavior researchers consider CB part of a spectrum of aberrant consumer behavior, which includes pathological gambling, shoplifting, and credit abuse).[29]

CB is not included in either the *DSM-IV-TR*[10] or the World Health Organization *International Classification of Diseases, Tenth Edition*.[12] Whether to include CB in *DSM-5* is being debated.[30] McElroy et al[23] suggest that compulsive shopping behavior might be related to "mood, obsessive-compulsive or impulse control disorders." Lejoyeux et al[31] have linked it to the mood disorders. Some consider CB to be related to the substance use disorders.[32,33] Others suggest classifying CB as a disorder of impulse control[34] or a mood disorder.[35]

Faber and O'Guinn[26] estimated the prevalence of CB at between 1.8% and 8.1% of the general population, based on results from a mail survey in which the Compulsive Buying Scale (CBS) was administered to 292 individuals selected to approximate the demographic makeup of the general population of Illinois. (The high and low prevalence estimates reflect different score thresholds set for CB.) More recently, Koran et al[36] used the CBS to identify compulsive buyers in a random telephone survey of 2513 US adults, and estimated the point prevalence at 5.8% of respondents. Grant et al[37] utilized the MIDI to assess CBD and reported a lifetime prevalence of 9.3% among 204 consecutively admitted psychiatric inpatients.

CB has an onset in the late teens/early 20s, which may correlate with emancipation from the nuclear family, as well as with the age at which people can first establish credit.[34] Research suggests that 80% to 94% of persons with CBD are women.[38] In contrast, Koran et al[36] reported that the prevalence of CBD in their random telephone survey was nearly equal for men and women (5.5% and 6.0%, respectively). Their finding suggests that the reported gender difference may be artifactual, in that women more readily acknowledging abnormal shopping behavior than men. Men are more likely to describe their compulsive buying as "collecting."

Data from clinical studies confirm high rates of psychiatric comorbidity, particularly for the mood (21% to 100%), anxiety (41% to 80%), substance use (21% to 46%), and eating disorders (8% to 35%).[38] Disorders of impulse control are also relatively common (21% to 40%). The frequency of Axis II disorders in individuals with CB was assessed by Schlosser et al[25] using a self-report instrument and a structured interview. Nearly 60% of 46 subjects met criteria for at least one personality disorder through a consensus of both instruments. The most commonly identified personality disorders were the obsessive-compulsive (22%), avoidant (15%), and borderline (15%) types.

A distinctive and stereotyped clinical picture of the compulsive shopper has emerged. Black[39] has described four phases including: (i) anticipation; (ii) preparation; (iii) shopping; and (iv) spending. In the first phase, the person with CB becomes preoccupied either with having a specific item, or with the act of shopping. This is followed by a preparation phase in which plans are made. This

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phase is followed by the actual shopping experience, which many individuals with CB describe as intensely exciting.[25] The act is completed with the purchase, often followed by a sense of let-down or disappointment.[36]

Perhaps the hallmark of CB is preoccupation with shopping and spending. This typically leads the individual to spend many hours each week engaged in these behaviors.[24,25] Persons with CB often describe increasing tension or anxiety that is relieved when a purchase is made. CB behaviors occur all year, but can be more problematic during the Christmas season and other holidays, as well as around the birthdays of family members and friends. Compulsive buyers are mainly interested in consumer goods such as clothing, shoes, crafts, jewelry, gifts, makeup, and compact discs (or DVDs)[24,25] CB has little to do with intellect or educational level, and has been documented in mentally retarded persons.[40] Similarly, income has relatively little to do with CB, because persons with a low income can be as preoccupied with shopping and spending as wealthier individuals.[38,40]

Nataraajan and Goff[42] have identified two independent factors in CB: (i) buying urge or desire, and (ii) degree of control over buying. In their model, compulsive shoppers combine high urge with low control. This view is consistent with clinical reports that compulsive buyers are preoccupied with shopping and spending and will try to resist their urges, often with little success.[24,38]

Cross-sectional studies suggest the disorder is chronic, though fluctuating in severity and intensity.[22,25] Aboujaoude et al[43] reported that persons who responded to treatment with citalopram were likely to remain in remission during a 1-year follow-up, suggesting that treatment can alter the natural history of the disorder. Lejoyeux et al[44] report that CB is associated with suicide attempts, although there are no reports of the disorder leading to completed suicide.

There is some evidence that CB runs in families and that within these families mood, anxiety, and substance-use disorders exceed population rates. Black et al[45] used the family history method to assess 137 first-degree relatives of 31 persons with CB. Relatives were significantly more likely than those in a comparison group to have depression, alcoholism, a drug use disorder, "any psychiatric disorder" and "more than one psychiatric disorder." CB was identified in nearly 10% of the first-degree relatives, but was not assessed in the comparison group.

Neurobiologic theories have centered on disturbed neurotransmission, particularly involving the serotonergic, dopaminergic, or opioid systems. Selective serotonin reuptake inhibitors (SSRIs) have been used to treat CB,[46-50] in part because of hypothetical similarities between CB and OCD, a disorder known to respond to SSRIs. Dopamine has been theorized to play a role in "reward dependence," which has been claimed to foster behavioral addictions, such as CB and PG.[15] Case reports suggesting benefit from the opioid antagonist naltrexone have led to speculation about the role of opioid receptors[51] There is no direct evidence, however, to support the role of these neurotransmitter systems in the etiology of CB.

Because CB occurs mainly in developed countries, cultural and social factors have been proposed as either causing or promoting the disorder.[39] Interestingly, Neuner et al[52] reported that the frequency of CB in Germany increased following reunification, suggesting that societal factors can contribute to the development of CB. These may include the presence of a market-based economy, the availability of goods, easily obtained credit, and disposable income.[14]

There are no standard treatments, and both psychotherapy and medication have been recommended. Several case studies report the psychoanalytic treatment of CB.[53-55] More recently, cognitive-behavioral treatment (CBT) models have been developed for CB, many of them employing group therapy.[56,57] Mitchell et al[57] found that group CBT produced significant improvement compared with a wait-list in a 12-week pilot study. Improvement attributed to CBT was maintained during a 6-month follow-up. Benson[58] has developed a comprehensive self-help program that can be used by both individuals and groups.

Treatment studies employing psychotropic medications have produced mixed results. Early reports suggested the benefit of antidepressants in treating CB[22,23] Black et al[46] reported the results of an open-label trial in which subjects given fluvoxamine showed benefit. Two subsequent randomized controlled trials (RCTs) found fluvoxamine treatment to be no better than placebo.[47,48] Koran et al[51] later reported that subjects with CB improved with open-label citalopram. In a subsequent study, subjects received open-label citalopram; those who were considered responders were randomized to citalopram or placebo. Compulsive shopping symptoms returned in 5/8 subjects (62.5%) assigned to placebo compared with 0/7 who continued taking citalopram. In an identically designed discontinuation trial, escitalopram did not separate from placebo.[52] Because the medication study findings are mixed, no empirically well-sup-

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ported treatment recommendations can be made. Open-label trials have generally produced positive results, but RCTs have not. Interpretation of these study results is complicated by placebo response rates as high as 64%.[47]

Pathological gambling

PG is increasingly being recognized as a major public health problem.[59] PG is estimated to cost society approximately $5 billion per year and an additional $40 billion in lifetime costs for reduced productivity, social services, and creditor losses.The disorder substantially impairs quality of life in addition to its association with comorbid psychiatric disorders, psychosocial impairment, and suicide.[59-61] Family-related problems include financial distress, child and spousal abuse, and divorce and separation.[61]

While problematic gambling behavior has been recognized for centuries, it was often ignored by the psychiatric community. Bleuler,[17] citing Kraepelin,[16] considered PG, or "gambling mania," a *special impulse* disorder. Criteria for PG were first enumerated in 1980 in *DSM-III*.[62] The criteria were subsequently modified, and in *DSM-IV-TR*,[10] are patterned after those used for substance dependencies and emphasize the features of tolerance and withdrawal. PG is defined as "persistent and recurrent maladaptive gambling behavior (criterion A) that disrupts personal, family, or vocational pursuits…" Ten specific maladaptive behaviors are listed, and ≥5 are required for the diagnosis. The criteria focus on loss of control of gambling behavior; progressive deterioration of the disorder; and continuation despite negative consequences. The diagnosis can only be made when mania is ruled out (Criterion B). In an attempt to reconcile nomenclature and measurement methods, Shaffer and Hall[63] developed a generic multilevel classification scheme that is now widely accepted by gambling researchers.

PG is presently classified as a disorder of impulse control in *DSM-IV-TR*.[10] On the one hand, some investigators have suggested that PG is related to OCD,[1,64] yet others argue against such a relationship.[65] On the other hand, PG is widely considered an addictive disorder.[66,67] It has recently been proposed as a candidate for inclusion in a new category for "behavioral addictions."[15]

Recent estimates of lifetime prevalence for PG range from 1.2% to 3.4% in the general population.[68,69] Prevalence rates have risen in areas where gambling availability has increased.[70,71] A national survey showed that the availability of a casino within 50 miles is associated with a nearly twofold increase in PG prevalence.[59] Gambling behavior typically begins in adolescence, with PG developing by the late 20s or early 30s,[72] though it can begin at any age through senescence. Rates of PG are higher in men, but the gender gap may be narrowing.PG has a later onset in women yet progresses more rapidly ("telescoping") than in men,[73] at a rate similar to that observed in alcohol disorders. Populations at risk include adults with mental health or substance-use disorders, persons who have been incarcerated, African-Americans, and persons with low socioeconomic status.[74,75]

Research has not validated PG subtypes, but perhaps the most widely discussed distinction is between "escape-seekers" and "sensation-seekers."[76] Escape-seekers are often older persons who gamble out of boredom, from depression, or to fill time, and choose passive forms of gambling such as slot machines. Sensation-seekers tend to be younger, and prefer the excitement of card games or table games that involve active input.[76] Blaszczynski and Nower[77] have proposed a "pathways" model that integrates biological, developmental, cognitive, and other determinants of disordered gambling. They have identified three subgroups: a) behaviorally-conditioned gamblers; b) emotionally vulnerable gamblers; and c) antisocial, impulsive gamblers. Behaviorally conditioned gamblers have no specific predisposing psychopathology, but make bad judgments regarding gambling. Emotionally vulnerable gamblers suffer premorbid depression or anxiety, and have a history of poor coping. Finally, antisocial, impulsive gamblers are highly disturbed and have features of antisocial personality disorder and impulsivity that suggest neurobiological dysfunction.

Psychiatric comorbidity is the rule, not the exception, in persons with PG. Both community and clinic-based studies suggest that substance use disorders, mood disorders, and personality disorders are highly prevalent in persons with PG.[78] In clinical samples, from 25% to 63% of pathological gamblers meet lifetime criteria for a substance use disorder.[79] Correspondingly, from 9% to 16% of substance abusers are probable pathological gamblers.[79] PG is also associated with increased prevalence of mood disorders, and overall 13% to 78% of persons with pathological gambling are estimated to experience a mood disorder.[79] On the other hand, patients with mood disorders have not been found to have elevated rates of PG.

Rates of other impulse-control disorders (ICDs) appear higher in persons with pathological gambling than in the

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general population. Investigators have reported rates ranging from 18% to 43% for one or more ICD.[79] CB appears to be the most frequent comorbid ICD in persons with PG, perhaps because both disorders share characteristics of focused attention, monetary gratification, and monetary exchange. Subjects with one ICD appear more likely to have another, suggesting considerable overlap among them.

Personality disorders are relatively common among individuals with PG, particularly those in "cluster B." Antisocial personality disorder has been singled out as having a close relationship with PG, perhaps because crime and gambling frequently co-occur, with rates ranging from 15% to 40%.[79,80] At least one study of persons with antisocial personality disorder showed high rates of PG.[81]

PG is widely thought to be chronic and progressive.[82,83] This view is embedded in *DSM-IV-TR*[10] which holds that the essential feature of PG is "persistent and recurrent maladaptive gambling behavior …that disrupts personal, family, or vocational pursuits" (p 671). These views were influenced by the pioneering observations of Custer[84] who described PG as a progressive, multistage illness that begins with a *winning phase*, followed in turn by a *losing phase*, and a *desperation phase*. The final phase, *giving up*, represented feelings of hopelessness.[85] Some contend that many pathological gamblers experience a "big win" early in their gambling careers that leads directly to their becoming addicted. Custer's four phases of PG have gained wide acceptance despite the absence of empirical data.

Recent work is leading to a reconsideration of these views. LaPlante et al[86] reviewed five studies[87-91] that met their criteria of reporting longitudinal data pertaining to gambling that did not involve a treatment sample. LaPlante et al report that, from the four studies that included level 3 gamblers (ie, persons with PG), most gamblers improved, and moved to a lower level, and that rates of classification improvement were "at least significantly greater than 29%." Results were similar for level 2 (ie, "at-risk") gamblers. Those who were level 0 to 1 gamblers at baseline were unlikely to progress to a higher (ie, more severe) level of gambling behavior, and with one exception,[91] the studies suggested that few level 2 gamblers improved by moving to level 1. La Plante et al[86] conclude that these studies challenge the notion that PG is intractable, and suggest that many gamblers spontaneously improve, as do many substance addicted persons. The findings suggest that those who do not gamble or gamble without problems tend to remain problem-free; those with disordered gambling move from one level to another, though the general direction is toward improved classification.

Family history data suggests that PG, mood disorders, and substance-use disorders are more prevalent among the relatives of persons with PG than in the general population.[92,93] Twin studies also suggest that gambling has a heritable component.[94] Functional neuroimaging studies suggest that among persons with PG, gambling cues elicit gambling urges and a temporally dynamic pattern of brain activity changes in frontal, paralimbic, and limbic brain structures, suggesting to some extent that gambling may represent dysfunctional frontolimbic activity.[95]

There is little consensus about the appropriate treatment of PG. Few persons with PG seek treatment,[96] and until recently the treatment mainstay appeared to be participation in Gamblers Anonymous (GA), a 12-step program patterned after Alcoholics Anonymous. Attendance at GA is free and chapters are available throughout the US, but follow-through is poor and success rates disappointing.[97] Inpatient treatment and rehabilitation programs similar to those for substance-use disorders have been developed, and are helpful to some[98,99] Still, these programs are unavailable to most persons with PG because of geography or lack of access (ie, insurance/financial resources). More recently, CBT and motivational interviewing have been become established treatment methods.[100] Self-exclusion programs have also gained acceptance and appear to benefit selected patients.[101] While rules vary, they generally involve voluntary self-exclusion from casinos for a period of time at the risk of being arrested for trespassing. Medication treatment studies have gained momentum, but their results are inconsistent. Briefly, the opioid antagonists naltrexone and nalmefene were superior to placebo in randomized controlled trials (RCTs)[102,103] but controlled trials of paroxetine and bupropion were negative.[104,105] Open-label studies of nefazodone, citalopram, carbamazepine, and escitalopram have been encouraging, but need to be followed up with adequately powered and controlled studies.[106-109]

Putative relationship between CB/PG and OCD

The relationship between CB/PG and OCD remains uncertain. The inclusion of CB and PG within an OC spectrum, while intriguing, rests on hypothesis and not

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empirical data. How these disorders should be classified has been debated for nearly 100 years. Opinion has mainly favored their inclusion among disorders of impulse control. For historical reasons, and because of the lack of empirical data, we believe that the two disorders should remain with the ICDs until convincing evidence is presented to favor their inclusion either with the addictive disorders or an OC spectrum.

The most obvious connection between CB and PG and OCD is phenomenologic. Each disorder involves repetitive behavior that generally occurs in response to overwhelming thoughts and urges; engaging in the behavior—at least temporarily—will satisfy the urge, and/or reduce tension and anxiety that preceded the behavior. Nonetheless, a fundamental distinction between CB/PG and OCD is that the behaviors (shopping, gambling) are considered *ego-syntonic*; that is, they are viewed as pleasurable and desirable, while behaviors associated with OCD never are, and nearly all patients want to be rid of them. Not so with shopping and gambling: the person with CB or PG finds the behaviors highly pleasurable, and only wants to stop the behaviors when their deleterious secondary consequences become overwhelming.

Proponents of the OC spectrum point to the overlap between these disorders and OCD. Comorbidity studies have found that in clinical samples from 3% to 35% of individuals with CB have comorbid OCD.[22,46] In fact, the presence of CB may characterize a specific subset of OCD patients,[110,111] particularly those who hoard. Hoarding is a special symptom that involves the acquisition of and failure to discard, possessions that are of limited use or value.[112] Yet, unlike the items retained by the typical hoarder, the items purchased by the person with CB are not inherently valueless or useless.

CB frequently appears to be comorbid with the ICDs. Black and Moyer[80] and Grant and Kim[72] each reported elevated rates of CB among samples of pathological gamblers (23% and 8%, respectively). Likewise, other impulse control disorders are common among compulsive shoppers.[39] Comorbidity studies of PG are more mixed, although they generally report higher rates of OCD than in the general population. The reverse does not seem to be true. Axis II comparisons show that the predominant disorders associated with OCD are the "cluster C" disorders. While there are no axis II disorders specifically associated with PG or CB, "cluster B" disorders appear overrepresented, particularly antisocial personality disorder.

Direct investigations into OC characteristics of persons with PG found that those with PG scored higher than those without on scales measuring OC traits.[64] CB and PG also share high trait impulsivity.[19,113]

Other evidence could come from family studies of CB, PG, or OCD. There are few family studies regarding these disorders, and none have supported a familial relationship among these disorders. In the only controlled family history study of CB, Black et al[45] did not find a relationship with OCD. In two family studies, one using the family history method, the other using the family interview method, the investigators were unable to establish a connection between PG and OCD.[114,115] Looking at this connection through OCD family studies has also failed to find a connection. Neither Black et al[114] nor Bienvenu et al[115] were able to establish a familial relationship between OCD and PG.

Demographic similarities are often used to suggest that disorders might be linked, for example the fact that both alcohol disorders and antisocial personality disorder are predominantly found in men. Yet, there is no similarity in gender distribution among these disorders. With PG there is a clear male preponderance; with CB a female preponderance; with OCD, the gender distribution is evenly split.

If these disorders were related, their natural history and course might be similar as well. CB and OCD appear to have an onset in the late teens or early 20s. PG appears to have a slightly later onset, with women developing the disorder much later than men, but having a briefer course from onset of gambling to development of a disorder. This is what is seen with alcohol disorders, but not OCD. With CB, PG, and OCD are all considered mostly chronic, but the similarity stops there. For CB and PG, while there are no careful, longitudinal studies, the data suggest that the disorders may be episodic, that is, may remit for varying lengths of time depending on a host of external factors such as fear of consequences, eg, bankruptcy or divorce, or lack of income; OCD rarely remits. In terms of suicide risk, PG has been reported to carry a risk for suicide attempts and completed suicides; with CB, there are anecdotal reports of suicide attempts, but not completed suicides; with OCD, the data is somewhat mixed, but overall, the risk of completed suicide is considered low.

Here, too, when one considers treatment response, OCD is well known to respond well to serotonin reuptake inhibitor antidepressants, and to cognitive behavioral therapy. CB and PG have no clear response to medica-

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tion, and the most robust treatment data suggests that PG may respond to opioid antagonists. Both CB and PG are reported to respond to CBT, but the completeness and quality of the response is unlike that seen with OCD.

The presence of similar biological markers is another way to assess the connection between these disorders. This task is hampered by the fact that none of these disorders has reliable markers. Nonetheless, a functional magnetic resonance imaging (fMRI) study of PG suggests that the disorder shows an abnormal pattern of activation in specific subcortical-frontal regions following cue exposure. Potenza et al[86] interpret these findings as evidence for the similarity of brain pathways in PG and drug addiction, while the opposite direction of higher brain activation is found in OCD. Similarly, Goodriaan et al[116] review the research on neurochemical and molecular genetic data involving PG. They conclude that there is evidence of disturbed neurotransmission involving dopamine (DA), serotonin, and norepinephrine; and "… are in accordance with the findings of abnormal brain activation in reward pathways, where DA is an important transmitter" (p 134). Dopamine is noted to play an important role in craving and withdrawal in the substance use disorders. While the neurotransmission involved in OCD has not been fully elucidated, the central serotonin system has been the most actively studied. This is perhaps due to the robust effect of SSRIs in the treatment of OCD.

On the whole, neuropsychological studies of PG indicate that pathological gamblers have impaired performance in several aspects of executive function including attention, delay discounting, and decision-making.[115-117] With OCD, neuropsychological research is less consistent; there is evidence of impaired response-inhibition and in attentional set-shifting, but little evidence of impaired reversal learning and decision-making.[118] To our knowledge, there are no neuropsychological studies of persons with CB.

Alternate classification schemes

If CB and PG are not part of an OC spectrum, where should they be classified? Because there is almost no evidence suggesting a relationship with the mood disorders, that possibility can probably be eliminated outright. Of the remaining schemes, the most likely candidates are to include PG and CB with the ICDs, or to move them to a category involving the substance-use disorders.

Keeping PG and CB with the ICDs is the easiest option: PG is already classified as an ICD, and while CB is not currently included in *DSM-IV-TR*, it has historically been considered an impulsive disorder. Both PG and CB share similar clinical features involving the presence of irresistible, ego-syntonic urges that prompt a behavioral response. The response (ie, gambling, shopping) satisfies the urge and/or temporarily reduces tension or anxiety, but is often followed by a sense of guilt or shame, and ultimately leads to adverse, secondary consequences. The behaviors are chronic or intermittent, and may spontaneously remit, sometimes in response to external circumstances. Age of onset and gender distribution differ, as discussed earlier. Possibly, CB may be considered the female equivalent of PG, because they tend to have a reverse gender distribution: men predominate among those with PG; women predominate among those with CB. Both appear to respond to CBT, yet neither has a clear response to medication; SSRIs do not produce consistent improvement. Comorbidity studies show overlap among the disorders, as a disproportionate number of pathological gamblers have CB and vice versa.

On the other hand, data suggest many commonalities with the substance use disorders. PG and CB are both associated with cravings that are not unlike those reported by substance abusers; PG is noted to produce "withdrawal" symptoms when the gambler is abstinent,[119] though this has not been studied in CB. Research shows that persons with PG or CB often have comorbid substance use disorders. Conversely, substance abusers have high rates of PG; there are no comparable data for CB. Family studies show that relatives of probands with PG or CB have high rates of psychiatric illness, particularly alcohol and drug use disorders. Further, Slutske et al[94] have reported that, based on twin data, PG appears to be related to the substance-use disorders and antisocial personality disorder. Finally, as noted earlier, the neuroimaging studies, and both neurotransmitters and molecular genetic research on PG suggest a relationship with the substance-use disorders.[116] These data support the inclusion of PG and perhaps CB in a category for "behavioral addictions," possibly comprising a subset of the substance-use disorders, but they do not support a relationship with OCD.

Conclusions

The review suggests that CB and PG are probably not candidates for inclusion in an OC spectrum. The review was not meant to judge the merit of the OC spectrum concept.

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In fact, we have suggested that there appears to be sufficient evidence to support the existence of a limited OC spectrum that might include body dysmorphic disorder, Tourette's disorder, trichotillomania, subclinical OCD, and perhaps the grooming disorders.[8,120] While there are superficial phenomenologic similarities between CB/PG and OCD, other evidence suggests they are not associated: gender distribution, age at onset, and course; comorbidity studies; neuroimaging, neurotransmitter, and neuropsychological studies; and treatment response. We believe that PG and CB are likely related, despite their much different gender distribution. Further, we believe that in the absence of new and convincing evidence, PG ought to remain within the ICD category. Lastly, we believe that CB is an identifiable and distinct disorder that ought to be included in *DSM-5*, and should be included with the ICDs. ❑

REFERENCES

1. Hollander E. *Obsessive Compulsive Related Disorders.* Washington DC: American Psychiatric Press; 1993.
2. Hollander E. Obsessive-compulsive spectrum disorders: an overview. *Psychiatr Ann*. 1993;23:355-358.
3. Hollander E, Wong CM. Introduction: obsessive-compulsive spectrum disorders. *J Clin Psychiatry*. 1995;56(suppl 4):3-6.
4. Koran LM. *Obsessive-Compulsive and Related Disorders in Adults – a Comprehensive Clinical Guide*. New York NY; Cambridge, UK: 1999.
5. Rasmussen SA. Obsessive-compulsive spectrum disorders. *J Clin Psychiatry*. 1994;55:89-91.
6. Castle DJ, Phillips KA. Obsessive-compulsive spectrum of disorders: a defensible construct? *Aust NZ J Psychiatry*. 2006;40:114-120.
7. Tavares H, Gentil V. Pathological gambling and obsessive compulsive disorder: towards a spectrum of disorders of volition. *Rev Brasil Psiquiatria*. 2007;29:107-117.
8. Black DW. The obsessive-compulsive spectrum: fact or fancy? In: Maj M, Sartorius N, Okasha A, Zohar J, eds. *Obsessive-Compulsive Disorder*. New York, NY: Wiley; 2000:233-235.
9. Phillips KA. The obsessive-compusive spectrum: promises and pitfalls. In: Maj M, Sartorius N, Okasha A, Zohar J, eds. *Obsessive-Compulsive Disorder*. New York, NY: Wiley; 2000:225-227.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
11. Robins E. Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry*. 1970;126:983-987.
12. World Health Organization. *International Classification of Diseases*. 9th Revision. Geneva, Switzerland: World Health Organization; 1977.
13. Zohar J. The Cape Town Consensus Group Consensus Statement for Obsessive-Compulsive Spectrum to Obsessive Compulsive Disorder: The Cape Town Consensus Statement. *CNS Spectr* 2007;12:2(suppl 3): 5-13.
14. Lee S, Mysyk A. The medicalization of compulsive buying. *Soc Sci Med*. 2004;58:1709-1718.
15. Holden C. Behavioral addictions: so they exist? *Science*. 2001;294: 980-982.
16. Kraepelin E. *Psychiatrie*. 8th ed. Leipzig, Germany: Verlag Von Johann Ambrosius Barth; 1915:408-409.
17. Bleuler E. *Textbook of Psychiatry*. AA Brill, Trans. New York, NY: Macmillan; 1930.
18. Esquirol JED. *Des maladies mentales*. Paris, France: Baillière; 1838.
19. O'Guinn TC, Faber RJ. Compulsive buying: a phenomenological exploration. *J Consumer Res*. 1989;16:147-157.
20. Elliott R. Addictive consumption: function and fragmentation in postmodernity. *J Consumer Policy*. 1994;17:159-179.
21. Magee A. Compulsive buying tendency as a predictor of attitudes and perceptions. *Adv Consum Res*. 1994;21:590-594.
22. McElroy S, Keck PE, Pope HG, et al. Compulsive buying: a report of 20 cases. *J Clin Psychiatry*. 1994;55:242-248.
23. McElroy S, Satlin A., Pope HG, et al. Treatment of compulsive shopping with antidepressants: a report of three cases. *Ann Clin Psychiatry*. 1991;3:199-204.
24. Christenson GA, Faber RJ, de Zwaan M, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. *J Clin Psychiatry*. 1994;55:5-11.
25. Schlosser S, Black DW, Repertinger S, Freet D. Compulsive buying: demography, phenomenology, and comorbidity in 46 subjects. *Gen Hosp Psychiatry*. 1994;16:205-212.
26. Faber RJ, and O'Guinn TC. A clinical screener for compulsive buying. *J Consumer Res*. 1992;459-469.
27. Edwards EA. Development of a new scale to measure compulsive buying behavior. *Fin Counsel Plan*. 1993;4:67-84.
28. Dittmar H. Understanding and diagnosing compulsive buying. In: Coombs R, ed. *Addictive Disorders. A Practical Handbook*. New York, NY: Wiley; 2004:411-450.
29. Budden MC, Griffin TF. Explorations and implications of aberrant consumer behavior. *Psychol Marketing*. 1996;13:739-740.
30. Hollander E, Allen A. Is compulsive buying a real disorder and is it really compulsive? *Am J Psychiatry*. 2006;163:1670-1672.
31. Lejoyeux M, Andes J, Tassian V, Solomon J. Phenomenology and psychopathology of uncontrolled buying. *Am J Psychiatry*. 1996;152:1524-1529.
32. Glatt MM, Cook CC. Pathological spending as a form of psychological dependence. *Br J Addict*. 1987;82:1252-1258.
33. Goldman R:. Compulsive buying as an addiction. In: Benson A, ed. *I Shop, Therefore I Am: Compulsive Buying and the Search For Self*. New York, NY: Jason Aronson; 2000:245-267.
34. Black DW. Compulsive buying disorder: definition, assessment, epidemiology and clinical management. *CNS Drugs*. 2001;15:17-27.
35. McElroy SE, Pope HG, Keck PE, et al. Are impulse control disorders related to bipolar disorder? *Compr Psychiatry*. 1996;37:229-240.
36. Koran LM, Faber RJ, Aboujaoude E, et al. Estimated prevalence of compulsive buying in the United States. *Am J Psychiatry*. 2006;163:1806-1812.
37. Grant JE, Levine L, Kim SW, Potenza MN. Impulse control disorders in adult psychiatric inpatients. *Am J Psychiatry*. 2005;162:2184-2188.
38. Black DW. Epidemiology and phenomenology of compulsive buying disorder. In: Grant J, Potenza M, eds. *Oxford Handbook of Impulse Control Disorders*. In press.
39. Black DW. Compulsive buying disorder: a review of the evidence. *CNS Spectrums*. 2007;12:124-132.
40. Otter M, Black DW. Compulsive buying behavior in two mentally challenged persons. *Prim Care Companion J Clin Psychiatry*. 2007;9:469-470.
41. Dittmar H. When a better self is only a button click away: associations between materialistic values, emotional and identity-related buying motives, and compulsive buying tendency online. *J Soc Clin Psychol*. 2007;26:334-361.
42. Nataraajan R, Goff BG. Compulsive buying: toward a reconceptualization. *J Soc Behav Person*. 1991;6:307-328.
43. Aboujaoude E, Gamel N, Koran LM. A 1-year naturalistic follow-up of patients with compulsive shopping disorder. *J Clin Psychiatry*. 2003;64:946-950.
44. Lejoyeux M, Tassian V, Solomon J, Ades J. Study of compulsive buying in depressed persons. *J Clin Psychiatry*. 1997;58:169-173.
45. Black DW, Repertinger S, Gaffney GR, Gabel J. Family history and psychiatric comorbidity in persons with compulsive buying: preliminary findings. *Am J Psychiatry*. 1998;155:960-963.

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El juego patológico y el comprar compulsivo: ¿corresponde incluirlos dentro del espectro obsesivo-compulsivo?

Se ha propuesto que el comprar compulsivo (CC) y el juego patológico (JP) se integren en el espectro de los trastornos relacionados con el trastorno obsesivo compulsivo (TOC). La hipótesis del espectro se originó a comienzos de la década de 1990 y ha conseguido bastante apoyo, a pesar de la falta de evidencias empíricas. El interés en esta hipótesis ha llegado a un punto crítico ya que algunos investigadores han recomendado la creación de una nueva categoría que incluya estos trastornos en el DSM-V, que está actualmente en desarrollo. En este artículo los autores describen el origen del espectro obsesivo-compulsivo (OC) y sus fundamentos teóricos, revisan el CC y el JP, y discuten los datos a favor y en contra de un espectro OC. Ambos trastornos son descritos en términos de su historia, definición, clasificación, fenomenología, historia familiar, fisiopatología y manejo clínico. Los autores concluyen que: 1) el CC y el JP probablemente no se relacionan con el TOC y no es suficiente la evidencia para incluirlos en el espectro OC dentro del DSM-V, 2) el JP debiera incluirse dentro de los trastornos del control impulsivo (TCI) y 3) se debe crear un nuevo diagnóstico del CC y clasificarlo como un TCI.

Jeu pathologique et achat compulsif : font-ils partie du spectre des troubles obsessionnels-compulsifs ?

Certains auteurs ont proposé d'intégrer l'achat compulsif (AC) et le jeu pathologique (JP) dans le spectre des troubles obsessionnels-compulsifs (TOC), concept émergeant au début des années 90, et qui a reçu un soutien important en dépit d'un manque de preuves empiriques. L'intérêt pour cette hypothèse est devenu très important en raison de la recommandation de certains experts de créer une nouvelle catégorie incluant ces troubles dans le DSM-5 actuellement en rédaction. Dans cet article, les auteurs décrivent l'origine des troubles obsessionnels-compulsifs (TOC) et de leurs bases théoriques, analysent le JP et l'AC et examinent les arguments pour et contre leur appartenance au spectre des TOC. Les deux pathologies sont décrites en termes d'historique, de définition, de classification, de phénoménologie, d'antécédents familiaux, de physiopathologie et de prise en charge clinique. Les auteurs concluent que : (i) le JP et l'AC ne sont probablement pas liés aux TOC et que les preuves sont insuffisantes pour les placer dans le cadre OC du DSM-V ; (ii) le JP devrait rester au sein des troubles du contrôle de l'impulsion (TCI) ; et (iii) une nouvelle définition de l'AC devrait être créée pour le classer également dans les TCI.

46. Black DW, Monahan P, Gabel J. Fluvoxamine in the treatment of compulsive buying. *J Clin Psychiatry*. 1997;58:159-163.
47. Black DW, Gabel J, Hansen J, et al. A double-blind comparison of fluvoxamine versus placebo in the treatment of compulsive buying disorder. *Ann Clin Psychiatry*. 2000;12:205-211.
48. Ninan PT, McElroy SL, Kane CP, et al. Placebo-controlled study of fluvoxamine in the treatment of patients with compulsive buying. *J Clin Psychopharmacol*. 2000;20:362-366.
49. Koran LM, Chuang HW, Bullock KD, Smith SC. Citalopram for compulsive shopping disorder: an open-label study followed by a double-blind discontinuation. *J Clin Psychiatry* 2003;64:793-798.
50. Koran, LM, Aboujaoude EN, Solvason B, Gamel N, Smith EH. Escitalopram for compulsive buying disorder: a double-blind discontinuation study. *J Clin Psychopharmacol*. 2007;27:225-227. Letter.
51. Grant JE. Three cases of compulsive buying treated with naltrexone. *Int J Psychiatry Clin Prac*. 2003;7:223-225.
52. Neuner M, Raab G, Reisch L. Compulsive buying in maturing consumer societies: an empirical re-inquiry. *J Econ Psychol*. 2005;26:509-522.
53. Krueger DW. On compulsive shopping and spending: a psychodynamic inquiry. *Am J Psychother*. 1988;42:574-584.
54. Lawrence, L. The psychodynamics of the compulsive female shopper. *Am J Psychoanal*. 1990;50:67-70.
55. Winestine, MC. Compulsive shopping as a derivative of childhood seduction. *Psychoanal Q*. 1985;54:70-72.
56. Villarino R, Otero-Lopez JL, Casto R. *Adicion a la compra: Analysis, evaluaction y tratamiento [Buying addiction: Analysis, evaluation, and treatment]*. Madrid, Spain: Ediciones Piramide; 2001.
57. Mitchell JE, Burgard M, Faber R, Crosby RD. Cognitive behavioral therapy for compulsive buying disorder. *Behav Res Ther*. 2006;44:1859-1865.
58. Benson A. *Stopping Overshopping – a Comprehensive Program to Help Eliminate Overshopping*. New York, NY: April Benson; 2006.
59. National Opinion Research Center at the University of Chicago (NORC): Gambling Impact and Behavior Study, Report to the National Gambling Impact Study Commission, April 1, 1999.
60. Petry NM, Kiluk BD. Suicidal ideation and suicide attempts in treatment-seeking pathological gamblers. *J Nerv Ment Dis*. 2002;190:462-469.
61. Shaw M, Forbush K, Schlinder J, et al. The effect of pathological gambling on families, marriages, and children. *CNS Spectr*. 2007;12:615-622.
62. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
63. Shaffer HJ, Hall MN. Estimating the prevalence of adolescent gambling disorders: a quantitative synthesis and guide toward standard gambling nomenclature. *J Gambl Stud*. 1996;12:193-214.
64. Blaszczynski A. Pathological gambling and obsessive-compulsive spectrum disorders. *Psychol Rep*. 1999;84:107-113.
65. Durdle H, Gorey KM, Stewart SH. A meta-analysis examining the relations among pathological gambling, obsessive-compulsive disorder, and obsessive-compulsive traits. *Psychol Rep*. 2008;103:485-498.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 185

66. Shaffer HJ, LaPlante DA, LaBrie RA, et al. Toward a syndrome model of addiction: multiple expressions, common etiology. *Har Rev Psychiatry*. 2004;12:367-374.
67. Wray I, Dickerson MG. Cessation of high frequency gambling and withdrawal symptoms. *Br J Addiction*. 1981;76:401-405.
68. Shaffer HJ, Hall MN. Updating and refining prevalence estimates of disordered gambling behavior in the United States and Canada. *Can J Pub Health*. 2001;92:168-172.
69. Cunningham-Williams R, Cottler LB. The epidemiology of pathological gambling. *Sem Clin Neuropsychiatry*. 2001;6:155-166.
70. Volberg RA. Prevalence studies of problem gambling in the United States. *J Gambling Stud.* 1996;12:111-128.
71. Jacques C, Ladouceur R, Gerland F. Impact of availability on gambling: a longitudinal study. *Can J Psychiatry*. 2000;45:810-815.
72. Grant J, Kim SW. Demographic and clinical features of 131 adult pathological gamblers. *J Clin Psychiatry*. 2001;62:957-962.
73. Tavares H, Zilberman ML, Beites FJ, et al. Gender differences in gambling progression. *J Gambl Stud*. 2001;17:151-159.
74. Potenza, MN, Kosten TR, Rounsaville BJ. Pathological gambling. *JAMA*. 2001;286:141-144.
75. Templer DI, Kaiser G, Siscoe K. Correlates of pathological gambling propensity in prison inmates. *Compr Psychiatry*. 1993;34:347-351.
76. Blaszczynski A, McConaghy N. Anxiety and/or depression in the pathogenesis of addictive gambling. *Int J Addictions*. 1989;24:337-350.
77. Blaszczynski A, Nower L. A pathways model of problem and pathological gambling. *Addiction*. 2002;97:487-499.
78. Crockford ND, el-Guebaly N. Psychiatric comorbidity in pathological gambling: a critical review. *Am J Psychiatry*. 1998;43:43-50.
79. Black DW, Shaw M. Psychiatric comorbidity and pathological gambling. *Psychiatric Times*. 2008;25:14-18.
80. Black DW, Moyer T. Clinical features and psychiatric comorbidity in 30 subjects reporting pathological gambling behavior. *Psychiatr Serv*. 1998;49:1434-1439.
81. Goldstein RB, Powers SI, McCusker J, et al. Lack of remorse in antisocial personality disorder among drug abusers in residential treatment. *J Pers Disord*. 1996;10:321-334.
82. Cartwright C, DeCaria C, Hollander E. Pathological gambling: a clinical review. *J Prac Psychiatr Behav Health*. 1998;5:277-286.
83. DeCaria C, Hollander E, Grossman R et al. Diagnosis, neurobiology, and treatment of pathological gambling. *J Clin Psychiatry*. 1996;57(suppl 8):80-84.
84. Custer R. *When Luck Runs Out*. New York, NY: Facts on File; 1985:232.
85. Rosenthal R. Pathological gambling. *Psychiatr Ann*. 1992;22:72-78.
86. LaPlante DA, Nelson SE, LaBrie RA, Shaffer HJ. Stability and progression of disordered gambling: lessons from longitudinal studies. *Can J Psychiatry*. 2008;53:52-60.
87. Abbott MW, Williams MM, Volberg RA. A prospective study of problem and regular non-problem gamblers living in the community. *Subst Use Misuse*. 2004;39:855-884.
88. DeFuentes-Merillas L, Koeter MW, Schippers GM, van den Brink W. Temporal stability of pathological scratchcard gambling among adult scratchcard buyers two years later. *Addiction*. 2004;99:117-127.
89. Shaffer HJ, Hall MN. The natural history of gambling and drinking problems among casino workers. *J Soc Psychol*. 2002;142:405-424.
90. Slutske W, Jackson KM, Sher KJ. The natural history of problem gambling from age 18 to 29. *J Abnorn Psychol*. 2003;112:263-274.
91. Winters KC, Stinchfield RD, Botzet A, Anderson N. A prospective study of youth gambling behaviors. *Psychol Addict Behav*. 2002;16:3-9.
92. Black DW, Moyer T, Schlosser S. Quality of life and family history in pathological gambling. *J Nerv Ment Dis*. 2003;191:124-126.
93. Black DW, Monahan PO, Temkit M, Shaw M. A family study of pathological gambling. *Psychiatr Res*. 2006:141;295-303.
94. Slutske W, Eisen S, True WR, et al. Common genetic vulnerability for pathological gambling and alcohol dependence in men. *Arch Gen Psychiatry*. 2000;57:666-673.
95. Potenza MN, Steinberg MA, Skudlarski P, et al. Gambling urges and pathological gambling: a functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2003;60:828-836.
96. Cunningham JA. Little use of treatment among problem gamblers. *Psychiatr Serv*. 2005;56:1024-1025.
97. Brown RIF. The Effectiveness of Gamblers Anonymous. In Edington WR (ed), *The Gambling Studies: Proceedings of the Sixth National Conference on Gambling and Risk Taking*. Reno, NV: Bureau of Business and Economic Research, University of Nevada, Reno; 1985.
98. Russo AM, Taber JI, McCormick RA, Ramirez LF. An outcome study of an inpatient program for pathological gamblers. *Hosp Comm Psychiatry*. 1984;35:823-827.
99. Taber JI, McCormick RA, Russo AM et al. A follow-up of pathological gamblers after treatment. *Am J Psychiatry*. 1987;144:757-761.
100. Petry NM. *Pathological Gambling: Etiology, Comorbidity, and Treatment*. Washington DC: American Psychological Association, 2005
101. Ladouceur R, Sylvain C, Gosselin P. Self-exclusion program: a longitudinal evaluation study. *J Gambl Stud.* 2007;23:85-94.
102. Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. *Biol Psychiatry*. 2001;49:914-921.
103. Grant JE, Potenza MN, Hollander E, et al. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am J Psychiatry*. 2006;163:303-312.
104. Black DW, Arndt S, Coryell WH, et al. Bupropion in the treatment of pathological gambling: a randomized, placebo-controlled, flexible-dose study. *J Clin Psychopharmacol*. 2007;27:143-150.
105. Grant JE, Potenza MN, Blanco C, et al. Paroxetine treatment of pathological gambling: a multi-center randomized controlled trial. *Int Clin Psychopharmacol*. 2003;18:243-249.
106. Pallanti S, Rossi NB, Sood E, Hollander E. Nefazodone treatment of pathological gambling: a prospective open-label controlled trial. *J Clin Psychiatry*. 2002;63:1034-1039.
107. Zimmerman M, Breen RB, Posternak MA. An open-label study of citalopram in the treatment of pathological gambling. *J Clin Psychiatry*. 2002;63:44-48.
108. Black DW, Shaw M, Allen J. Extended release carbamazepine in the treatment of pathological gambling: an open-label study. *Prog Neurpsychopharmacol Biol Psychiatry*. 2008;32:1191-1194.
109. Black DW, Shaw M, Forbush KT, Allen J. An open-label study of escitalopram in the treatment of pathological gambling. *Clin Neuropharmacol*. 2007;30:206-212.
110. du Toit PL, van Kradenburg J, Niehaus D, Stein DJ. Comparison of obsessive-compulsive disorder patients with and without comorbid putative obsessive-compulsive spectrum disorders using a structured clinical interview. *Compr Psychiatry*. 2001;42:291-300.
111. Hantouche EG, Lancrenon S, Bouhassira M, et al. Repeat evaluation of impulsiveness in a cohort of 155 patients with obsessive-compulsive disorder: 12 months prospective follow-up. *Encephale*. 1997;23:83-90.
112. Frost RO, Meagher BM, Riskind JH. Obsessive-compulsive features in pathological lottery and scratch-ticket gamblers. *J Gambling Stud*. 2001;17:5-19.
113. Forbush KT, Shaw MC, Graeber, MA, et al. Neuropsychological characteristics and personality traits on pathological gambling. *CNS Spectrums*. 2008;13:306-315.
114. Black DW, Goldstein RB, Noyes R, Blum N. Compulsive behaviors and obsessive-compulsive disorder (OCD): Lack of a relationship between OCD, eating disorders, and gambling. *Compr Psychiatry*. 1994;35:145-148.
115. Bienvenu OJ, Samuels JF, Riddle MA, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. *Biol Psychiatry*. 2000;48:287-293.
116. Goudriaan AE, Oosterlaan J, deBeurs E, van den Brink W. Pathological gambling: A comprehensive review of biobehavioral findings. *Neurosci Biobehav Rev*. 2004;28:123-141.
117. Cavadini P, Riboldi G, Keller R, et al. Frontal lobe dysfunction in pathological gambling patients. *Biol Psychiatry*. 2002;51:334-341.
118. Menzies L, Chamberlain SR, Laird AR, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronta-striatal model revisited. *Neurosci Biobehav Rev*. 2008;525-549.
119. Cunningham-Williams RM, Gattis MN, Dore PM, et al. Towards DSM-V: considering other withdrawal-like symptoms of pathological gambling disorder. *Int J Methods Psychiatr Res*. 2009;18:13-22.
120. Black DW, Gaffney GR. Subclinical obsessive-compulsive disorder in children and adolescents: additional results from a "high-risk" study. *CNS Spectrums*. 2008;9(suppl 14):54-61.

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Drug treatment of obsessive-compulsive disorder

Michael Kellner, MD, PhD

Knowledge of pharmacotherapeutic treatment options in obsessive-compulsive disorder (OCD) has grown considerably over the past 40 years. Serotonergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are the established pharmacologic first-line treatment of OCD. Medium to large dosages and acute treatment for at least 3 months are recommended until efficacy is assessed. In case of significant improvement, maintenance treatment is necessary. Unfortunately, about half of the patients do not respond sufficiently to oral serotonergic antidepressants; augmentation with atypical antipsychotics is an established second-line drug treatment strategy. Alternatives include intravenous serotonergic antidepressants and combination with or switch to cognitive behavioral psychotherapy. Remarkably, a considerable proportion of OCD patients still do not receive rational drug treatment. Novel research approaches, such as preliminary treatment studies with glutamatergic substances, and trials with further drugs, as well as needed aspects of future research, are reviewed.

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Keywords: *obsessive-compulsive disorder; OCD; pharmacotherapy; drug; treatment; SSRI; antipsychotic; psychotherapy; glutamate*

While only a few decades ago "obsessive neurosis" had been regarded as a psychiatric condition that was mostly treatment-refractory, several effective therapeutic strategies for obsessive-compulsive disorder (OCD)—both psychotherapeutic drugs and behavioral psychotherapeutic techniques—began to evolve during the last third of the 20th century.

In terms of modern pharmacotherapy, the first hints of the efficacy of clomipramine, a tricyclic antidepressant (TCA), which inhibits serotonin reuptake, date back about 40 years.[1-3] In the 1970s, research with more stringent designs in this area began, and soon placebo-controlled trials showed the antiobsessive and anticompulsive action of clomipramine.[4-6] Interestingly, specific anti-OCD effects were even observed when comorbid depression was rigorously excluded. Treatment of OCD patients may require relatively high doses for an extended period of time, which may be accounted for by a greater delay of effect in the orbitofrontal cortex, which is thought to be implicated in OCD.[7] A possible role of serotonergic neurotransmission in the pathophysiology of OCD was surmised by the results of the studies with clomipramine, by later numerous investigations showing the therapeutic action of different selective serotonin reuptake inhibitors (SSRIs) in OCD, and by additional findings, such as the provocation of OCD symptoms by the serotonergic agent m-chlorophenylpiperazine.[8-10] Interestingly, predominantly noradrenergic drugs, such as the TCAs desipramine[11] and nortriptyline[4] were less

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effective than clomipramine. The additional importance of dopamine[12,13] and glutamate dysfunction[14,15] in the pathophysiology of OCD has been established, and led to pharmacotherapeutic applications beyond serotonergic drugs.

Notwithstanding the progress of pharmacotherapy of OCD, even nowadays a high percentage of patients with OCD obviously do not receive adequate drug treatment: upon admission to a northwest European university psychiatric centre, more than one third never had received any pharmacotherapy, one in seven had received inappropriate drugs, and half of the patients had never been treated with an adequate dose of a serotonin reuptake inhibitor (SRI).[16] An interesting side aspect of pharmacotherapy of OCD is that patients with OCD show a considerably lower placebo response than subjects with other anxiety disorders, which is not caused by differential expectancy.[17] This phenomenon, and data about the rarity of spontaneous remission of OCD in all age groups,[18] add evidence for the necessity of administering effective therapeutic approaches to try to reduce long-term morbidity.

In this brief review, current pharmacotherapeutic treatment options for OCD in adults will be highlighted, beginning with established first-line treatments. Then, special emphasis will be given on worthwhile, but still preliminary, strategies for treatment-refractory patients. Finally, a short perspective of potential future aspects of pharmacotherapy of OCD will be discussed.

First-line agents in OCD: SSRIs and clomipramine

SSRIs and the SRI clomipramine are recommended as first-line agents for drug treatment of OCD due to the convincing database from numerous published randomized controlled trials (RCTs), according to several meta-analyses,[19] current expert guidelines, and consensus statements.[20-24] Rather than citing the ample single and mostly equivocal research papers, reference to some of the latter articles will primarily be given in this section.

The current guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) for the pharmacological treatment of OCD[24] grant the highest category of evidence ("A", ie, full evidence from several RCTs) for the SSRIs escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline, as well as for the TCA clomipramine, but not for any other drug. Because clomipramine is less well tolerated than the SSRIs, it was given a recommendation grade of 2 (moderate risk benefit ratio), while the SSRIs received the highest recommendation grade 1 (good risk:benefit ratio). As for citalopram, only one positive double-blind, placebo-controlled study was published, and only a recommendation grade of 3 (limited evidence from controlled studies) was given.

This WFSBP guideline mentions that usually lower response rates are achieved in OCD in comparison with other anxiety disorders, and that sometimes only partial remission is achieved. As a rule, somewhat higher doses are used for these drugs in OCD than for other anxiety disorders, higher doses being associated with greater efficacy in some, but not all, evaluations. In several long-term and relapse-prevention studies, SRIs were shown to be superior to placebo, pointing to the requirement of long-term treatment of OCD. According to a systematic review on all long-term, placebo-controlled trials with SSRIs in OCD,[25] the likelihood of relapse during 24 to 52 weeks of treatment was significantly lower on an SSRI than with placebo. Thus, successful treatment with SSRIs should be maintained at the maximal effective dose for at least 12 months.

An extensive display of the many acute treatment studies on SSRIs versus placebo, different doses of SSRIs, SSRIs versus other SSRIs, clomipramine versus placebo, SSRIs versus clomipramine, SSRIs versus placebo, or clomipramine for continuation treatment and SSRIs vs placebo or clomipramine for relapse-prevention treatment can also be found in the guidelines on core interventions in the treatment of OCD of the National Institute for Health and Clinical Excellence (NICE) of the British Psychological Society and the Royal College of Psychiatrists.[21] According to these guidelines, the initial pharmacological treatment in adults with OCD should be one of the following SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram. Of note, studies on the efficacy of escitalopram in OCD were published only later.[26]

A current Cochrane review of placebo-controlled SSRI trials in OCD, comprising 17 studies with 3097 participants, also showed efficacy for all SSRIs included (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).[27] The authors detected no statistical differences in short-term therapeutic action among the individual SSRIs. For a reliable estimation of potential differences in tolerability between the different SSRIs, further study is needed.

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Treatment of OCD patients refractory to serotonergic antidepressants

Despite the proven efficacy of SSRIs and clomipramine in OCD, as shown above, about 40% to 60% of patients show no or just partial symptom improvement to a treatment with a first-line drug.[28] Therefore, the search for effective second-line treatment strategies in drug-refractory OCD patients is of great clinical importance. However, most of the following options still stand on considerably weaker empirical grounds than the well-established first–line recommendations described above.

Modification of serotonergic drug therapy with first-line agents

Intravenous clomipramine was shown to be more effective than oral clomipramine in two double-blind placebo-controlled trials,[29,30] and thus was considered a recommendation grade 3 strategy for treatment-resistant OCD patients (limited evidence from controlled studies).[24] Regarding citalopram, an open trial showed a beneficial and relatively rapid response in OCD patients resistant to previous oral therapy.[31] However, more sophisticated studies are still needed.

High-dose treatment with serotonergic drugs is another strategy worth considering. Greater improvement with higher vs lower doses of SSRI was reported using 250 to400 mg/d vs 200 mg/d of sertraline[32] and with escitalopram after an increase of dose from 20 up to 50 mg/d.[33] However, two recent studies with escitalopram contradict the notion that a positive response requires higher doses of treatment. A similar response after 24 weeks of 10 mg/d vs 20 mg/d was shown in a double-blind placebo-controlled study.[26] In an open study, a superior reduction in OCD symptoms was found with 30 mg/d vs 20 mg/d of escitalopram, which, however, disappeared when initial comorbid depression and anxiety were considered as analysis covariates.[34]

Whether switching from one first-line drug to another may be advisable, is still an unresolved issue. In one open study, switching from one SSRI to another resulted in a lower response rate (0% to 20%) than switching from one SSRI to clomipramine (33% to 40%).[35] Although meta-analyses have reported a larger treatment effect of oral clomipramine than for SSRIs, head-to-head comparator studies do not support this evidence.[36]

Some open-label studies suggest that combined treatment of clomipramine and an SSRI is effective and well tolerated. Positive results have been reported with long-term augmentation with citalopram (up to 60 mg/d) in 20 treatment-resistent OCD patients on clomipramine.[37] In smaller samples, encouraging data have also been reported with the combination of clomipramine with fluoxetine[38] or with sertraline.[39]

Augmentation with antipsychotics

The combination of the antipsychotics risperidone, haloperidol, olanzapine, or quetiapine with an SSRI was shown to be more effective than SSRI monotherapy in treatment-resistant cases and is recommended (grade 3, ie, limited evidence from controlled studies) by the WFSBP guidelines.[24] In most studies, response occurred within 1 month of augmentation. After such treatment, which should be initiated only after at least 3 months of maximally tolerated therapy of an SSRI, about one third of treatment-refractory OCD patients show a clinically meaningful amelioration.

In several meta-analyses positive acute effects of antipsychotic augmentation were demonstrated.[40-42] Despite their recommendation, the WFSBP guideline[24] mentions that evidence for the efficacy of quetiapine and olanzapine was still inconclusive according to respective systematic review.[40] Further meta-analyses about quetiapine showed equivocal results.[43,44] A recent double-blind augmentation study with quetiapine in severe OCD patients failed to show an effect of quetiapine.[45] In contrast, superior effects of quetiapine versus ziprasidone as an adjunct to SSRI were found in treatment-resistant OCD patients in a retrospective study.[46] Interestingly, (primary!) addition of quetiapine to citalopram was more effective than citalopram alone in reducing OCD symptoms in a large double-blind study in treatment-naïve or medication-free OCD patients,[47] although extrapolation of these results to augmentation studies sensu stricto may be problematic. Regarding olanzapine, a single-blind study comparing risperidone versus olanzapine augmentation of SSRIs showed positive responses without differences between the two treatment groups.[48] The long-term effectiveness of atypical antipsychotics in the augmentation of SSRIs has so far not sufficiently been studied and was not supported in a trial using olanzapine, quetiapine, and risperidone.[49]

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Several further atypical neuroleptics are promising new candidates for augmentation therapies of serotonin reuptake inhibitors according to various case reports and open studies. In a 12-week, open-label, flexible-dose trial of aripiprazole, significant improvement of OCD symptoms was demonstrated.[50] Some respective case reports with aripiprazole had been published before.[51] Even as monotherapy, a case series suggests that aripiprazole holds promise for treating OCD.[52] Also for amisulpride augmentation, an open study has shown promising results.[53] Augmentation with perospirone resulted in beneficial effects in a case report.[54]

Augmentation with or switch to cognitive-behavioral psychotherapy

Preliminary evidence supports the usefulness of cognitive-behavioral therapy (CBT) as a nonpharmacological augmentation treatment. In a randomized controlled trial in patients who were on a therapeutic dose of SSRI for at least 12 weeks, and continued to display clinically significant OCD symptoms, the augmentative effect of exposure and ritual prevention versus stress management training was compared; after 8 weeks significantly more patients with exposure and response prevention showed a decrease of symptom severity of at least 25% and achieved minimal symptoms.[55] In a naturalistic setting, the usefulness of CBT (including exposure and ritual prevention) in nonresponders to at least one adequate trial with a serotonergic antidepressant was shown, while pharmacologic treatment underwent no changes under the trial.[56] In patients responding to 3 months of drug treatment, but showing residual symptoms of OCD, a greater improvement of OCD symptoms after addition of behavior therapy for 6 months versus continuation of drug treatment alone was shown, and significantly more patients achieved remission.[57] However, no control condition for behavior therapy was used.

Also, a switch to CBT should be considered. In a wait-list-controlled open trial, patients with a history of an inadequate response to multiple serotonin reuptake medications in adequate doses were treated with 15 sessions of outpatient CBT, incorporating exposure and ritual prevention.[58] OCD symptoms decreased significantly and gains were maintained over 6 months. Further studies with more elaborate designs are needed. Although a meta-analysis of psychotherapy and pharmacotherapy for OCD[59] found highest effect sizes for combined treatment, no clear advantage for the combination of serotonergic antidepressants and CBT was detected in the individual controlled trials published so far.[60]

Augmentation with or switch to other drugs

Numerous further drugs have been studied for augmentation or in monotherapy for the treatment of OCD, but so far, none of these approaches described below has reached sufficient empirical evidence to become recommended in treatment guidelines.[24] However, some of these drugs seem promising for further study and may be attempted in OCD patients, who were refractory to treatments with superior current evidence.

Glutamatergic agents are among the most exciting new candidates in the treatment of OCD.[14,15] In an open-label augmentation trial with memantine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, a meaningful improvement of symptoms was seen in nearly half of the patients, who had failed to respond to treatment with an SSRI for at least 3 months.[61] Case reports of refractory OCD patients successfully treated with an augmentation of memantine were published previously.[62,63] Interestingly, adjunctive glycine (an NMDA glutamate receptor agonist) was also tested in a small double-blind placebo-controlled trial and approached efficacy for treatment of OCD symptoms.[64] For the glutamate-modulating agent riluzole, which was added to existing psychopharmacotherapy in treatment-resistant OCD patients, significant antiobsessional effects were observed in an open-label trial.[65] Also, amantadine (another NMDA antagonist) could be a useful drug for the treatment of OCD according to preclinical findings,[66] but human studies are so far missing. Augmentation with topiramate, among other actions an α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptor antagonist, in treatment-resistant OCD patients may be beneficial.[67,68] Respective double-blind studies with topiramate are on their way (ClinicalTrials.gov Identifiers: NCT00211744 and NCT00182520). Also for pregabalin, which can indirectly inhibit glutamate release via blockade of calcium channels, beneficial effects on OCD symptoms in combination with serotonergic antidepressants have been reported in case reports.[69,70] A double-blind placebo-controlled study with pregablin in SSRI-refractory OCD is being conducted (ClinicalTrials.gov Identifier: NCT00994786). For aug-

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mentation of fluoxetine in a treatment refractory patient with glutamate modulator N-acetylcysteine, a marked decrease of OCD symptoms was observed.[71] A double-blind study with this agent is currently recruiting patients with OCD (ClinicalTrials.gov Identifier: NCT00539513). Another interesting development with a glutamatergic agent involves D-cycloserine, a partial agonist at the NMDA receptor, which was found to facilitate fear extinction learning in preclinical and human studies when administered before or shortly after exposure to fearful cues.[72] D-cycloserine augmentation of psychotherapy with exposure and response prevention in OCD has so far been investigated in three randomized, double-blind, placebo-controlled studies. A study with ten exposure sessions and drug intake 4 hours before each session failed to support the use of D-cycloserine (250 mg).[73] In contrast, significantly greater decreases in obsession-related distress after four exposure sessions under D-cycloserine (125 mg, given 2 hours before each session) were reported.[74] However, the placebo group tended to catch up after additional sessions. Both the number of therapy dropouts and the number of sessions needed to achieve "clinical milestones" were decreased by active treatment. In another study, OCD patients were reported to be significantly more improved under D-cycloserine at mid-treatment (ten behavior therapy sessions in total, dose of 100 mg 1 hour before each session), but not at later time points.[75] Dosage and timing of D-cycloserine as well as the number of combined intervensions are critical parameters. So far, just a short-term acceleration of response to exposure therapy under D-cycloserine was shown, but no significant differences in the further course due to floor effects of exposure therapy.

Several antidepressants other than SSRIs or clomipramine have been tested, as mentioned for noradrenergic tricyclics above. For the alpha-2 receptor and serotonin $(5\text{-HT})_{2/3}$ receptor antagonist mirtazapine an open trial showed negative results.[76] However, in a double-blind discontinuation period of 8 weeks (after an open trial) superiority of to placebo was demonstrated.[77] Addition of mirtazapine to citalopram did not result in increased efficacy when compared with addition of placebo, but was associated with an accelerated onset of action in a single-blind study.[78] Preclinical experiments suggest that blockade of 5-HT_{2C} receptors may have an anticompulsive effect in OCD.[79] Therefore, agomelatine, a melatonin agonist and 5-HT_{2C} antagonist, would be worth studying in OCD as well, but so far no reports have been published. The monoaminooxidase inhibitor phenelzine was shown to be as effective as clomipramine in a double-blind trial in OCD patients,[80] while in another one it was no better than placebo.[81] A double-blind study with St John's wort (*hypericum perforatum*) failed to support efficacy for OCD.[82] Trazodone, a 5-HT_2 receptor antagonist and SRI, had shown symptomatic improvements in case series in clomipramine-resistant OCD patients[83] and in augmentation of SSRIs.[84] However, a double-blind study indicated that trazodone in monotherapy lacks substantial antiobsessive effects.[85] For selective serotonin-norepinephrine reuptake inhibitors venlafaxine and duloxetine, reliable placebo-controlled trials are still absent. In a double-blind comparison of venlafaxine and paroxetine in primary OCD patients no significant differences with regard to response or responder rates were shown.[86] In a single-blind study, venlafaxine was as efficacious as clomipramine in the acute treatment of OCD.[87] In an open retrospective investigation in treatment-resistant OCD beneficial effects of venlafaxine were demonstrated.[88] According to case series and reports switching from SSRI to duloxetine in treatment-resistant OCD patients may be helpful.[89,90] For the selective noradrenaline reuptake inhibitor reboxetine, successful augmentation of citalopram was reported in a single case.[91]

For augmentation of SSRIs with pindolol, a 5-HT_{1A} and β-adrenergic antagonist, a double-blind placebo-controlled trial found significant improvement of OCD symptoms in treatment resistant patients,[92] while an open trial only showed such effects after supplemental addition of tryptophan.[93] After double-blind primary addition of pindolol versus placebo to fluvoxamine, the latency of antiobsessional response to the SSRI was not shortened.[94] A double-blind study of adjuvant buspirone, a 5-HT_{1A} partial agonist, in OCD patients, who had shown to some extent an effect of clomipramine, did not yield significant further clinical improvement.[95] For lithium two double-blind augmentation studies have been published that do not support its usefulness in OCD. In fluvoxamine-refractory patients, a small though statistically significant reduction of OCD symptoms was reported, but the authors doubted the clinical meaningfulness of these findings.[96] A crossover study with adjuvant lithium or thyroid hormone in clomipramine-treated patients showed no significant change of OCD symptoms after either treatment.[97]

Benzodiazepine and opioid receptor ligands have been tested in OCD. A double-blind combination study of

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clonazepam with sertraline did not reveal significant effects during 12 weeks of treatment.[98] While in a double-blind crossover study clonazepam in monotherapy produced a significant decrement in OCD symptoms during the first 3 weeks of treatment,[99] it was found to be without effect in a 10-week double-blind placebo-controlled trial.[100] A case of rapid remission of OCD with tramadol was reported,[101] but so far no controlled studies have been published. In treatment resistant OCD patients, who had failed two to six SRI trials, double-blind addition of once-weekly morphine resulted in a significant reduction of OCD symptoms at week two versus placebo, while lorazepam as another control condition was undistinguishable from placebo.[102] Augmentation with the opoid antagonist naltrexone did not show efficacy for OCD symptoms in a double-blind placebo-controlled study in SSRI or clomipramine refractory patients.[103]

For several other drugs preliminary interesting findings mostly from short-term open studies or case reports exist. Addition of gabapentin seems to shorten the time of onset of fluoxetine's antiobsessive effect.[104] Restarting of previously untolerated serotonergic antidepressants after valproate pretreatment was reported to lead to better tolerance and reduction of OCD symptoms in a case series.[105] Valproate monotherapy was successful in an SRI-intolerant OCD patient.[106] The 5-HT_3 receptor antagonist ondansetrone may have promise both as monotherapy[107] and as an augmentation strategy for some OCD patients.[108] Amelioration of refractory OCD on treatment with clozapine was described in a few case reports.[109-111] Antiandrogenic treatment with cyproterone acetate[112] and the long-acting gonadotropin-releasing hormone analogue triptorelin[113] was reported to result in considerable improvement of symptoms of OCD. Marked decreases of symptoms were observed shortly after single-dose exposures to the psychedelic drug psilocybin in patients with OCD.[114] Nicotine treatment was reported to display a favorable response, both in monotherapy as well as for augmentation,[115-117] while inositol augmentation of SSRIs led to a clinically significant response in some OCD patients in an open study[118]; in a small double-blind crossover study no significant improvement by this second messenger precursor was seen.[119] Acute significant antiobsessional effects for a single dose of dextroamphetamine were reported in a double-blind crossover study in patients with severe OCD.[120] Improvement of OCD was seen in treatment-resistant patients to serotonergic antidepressants after augmentation with both dextroamphetamine and caffeine in a double-blind study without placebo arm.[121]

Future prospects

Despite the considerable current knowledge that has been accumulated about evidence-based drug treatment of adults with OCD, as given account of above, and as summarized in *Table I*, several important clinical issues are still unresolved and need further research. There is still a paucity of long-term trials (especially for treatment with SRIs for more than 1 year and for augmentation with antipsychotics). Furthermore, there are as yet few switching studies, data on functional outcome parameters, combination studies of drug and cognitive behavior therapy, and randomized controlled trials with novel agents, such as glutamatergic drugs and further atypical antipsychotics.

Because of the relatively high rate of nonresponders, prediction of response to different therapeutic approaches in OCD and a further understanding of the neurobiological underpinnings of successful treatment of OCD is another important area of further research.

First-line pharmacological treatment:
• Selective serotonin reuptake inhibitors (eg, escitalopram, fluvoxamine, fluoxetine, paroxetine or sertraline) or clomipramine
• Administration of medium to high doses
• Acute treatment of at least 3 months
• If efficacious, maintenance treatment of at least 1 year
Treatment options for patients refractory to first-line pharmacological treatment:
• Modification of first-line treatment (eg, intravenous clomipramine, further dose increase, switch to other or combination of first-line drugs)
• Augmentation with antipsychotics (eg, risperidone, haloperidol, quetiapine, olanzapine, or aripiprazole)
• Augmentation with (or switch to) cognitive-behavior therapy
• Trials with other drugs (please see text)

Table I. Algorithm for drug treatment of patients with obsessive-compulsive disorder.

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Currently, psychopathological or clinical parameters are not very helpful in predicting response to pharmacotherapy, not to mention in providing us with differential therapeutic support regarding which drug or therapy to choose. For treatment with SSRIs, severity and duration of OCD, psychosocial disability, earlier age at onset, older age, comorbidity with depression and personality disorder, absence of a positive family history for OCD, and poor insight, as well as neurological soft signs, were identified to predict poorer outcome.[122-129] Studies on the impact of different symptom dimensions of OCD on response to SSRIs have been equivocal, eg, while compulsive hoarding was associated with poorer response to different SSRIs in some studies,[130,131] hoarding symptoms were reported to improve as much as other symptoms of OCD after paroxetine.[132]

Concerning neurobiological markers of response and nonresponse to medication in OCD, preliminary results using endophenotyping or brain imaging have been reported. Functional polymorphisms in the serotonin system and their impact on the response to serotonergic antidepressants have yielded inconsistent results. No differences on the total OCD score in fluvoxamine response were detected in the genotype groups of the promoter region of the serotonin transporter gene *(5-HTTLPR)*,[133] as well as on treatment with different SRIs.[134] In contrast, it was reported that a significant majority of responders to paroxetine and venlafaxine carried the s/l genotype of the *5-HTTLPR* polymorphism; in OCD patients successfully treated with paroxetine response was associated with the G/G genotype of the 5-HT_{2A} receptor polymorphism.[135] Using single photon emission computed tomography (SPECT), higher pretreatment thalamus-hypothalamus serotonin transporter availability in OCD patients was found to significantly predicted better treatment response to clomipramine.[136] In a positron emission tomography (PET) study in OCD patients, local cerebral metabolic rate for glucose was significantly decreased in the head of the right caudate nucleus compared with pretreatment values in responders to fluoxetine; percentage change in OCD symptoms correlated significantly with the percent of right caudate/ipsilateral hemisphere change.[137] In another PET study, higher pretreatment regional glucose metabolism in the right caudate nucleus was shown to significantly correlate with antiobsessional response to paroxtine.[138] A significant correlation between the amelioration of OCD on treatment with serotonin reuptake inhibitors and the changes of the dopamine transporter binding ratio in the right basal ganglia was found in a SPECT study, suggesting a role in the improvement of OCD patients.[139] Distinct biological characteristics were shown in OCD patients who respond to SSRI (higher pretreatment glucose metabolism in the right caudate nucleus) and in SSRI-refractory patients, who benefit from adjunctive risperidone (higher pretreatment glucose metabolism in the right orbitofrontal cortex and bilateral thalamus).[140] Using proton magnetic resonance spectroscopy to measure N-acetyl-aspartate (NAA), a putative marker of neuronal viability, significantly lower NAA was observed in the anterior cingulate only in OCD patients who responded to the combination therapy of SSRI plus atypical antipsychotic.[141]

Whether these exciting new developments will ultimately further advance our understanding of the neurobiology and effective psychopharmacology of OCD, and whether some of them will eventually enter clinical practice to serve our OCD patients, still needs to be established. ❑

REFERENCES

1. Fernandez-Cordoba E, Lopez-Ibor Alino J. La monoclorimipramina en enfermos psiquiatricos resistentes a otros tratamientos. *Acta Luso-Esp Neurol Psiquiatr Ciene Afines*. 1967;26:119-147.
2. Van Renynghe de Voxvrie G. Anafranil (G34586) in obsessive neurosis. *Acta Neurol Psychiatr Belg*. 1968;68:787-792.
3. Rack M, Chir D. Experience with intravenous clomipramine. In: *Obsessional States and their Treatment with Anafranil*. Manchester, UK: Geigy; 1970.
4. Thoren P, Asberg M, Cronholm B, Jornestedt L, Traskman L. Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. *Arch Gen Psychiatry*. 1980;22:667-687.
5. Marks IM, Stern RS, Mawson D, et al. Clomipramine and exposure for obsessive-compulsive rituals: i. *Br J Psychiatry*. 1980;136:1-25.
6. Montgomery SA. Clomipramine in obsessional neurosis: a placebo-controlled trial. *Pharmacol Med*. 1980;1:189-192.
7. El Mansari M, Blier P. Mechanisms of action of current and potential pharmacotherapies of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:362-373.
8. Winslow JT, Insel TR. Neurobiology of obsessive compulsive disorder: a possible role for serotonin. *J Clin Psychiatry*. 1990;51(suppl):27-31.
9. Barr LC, Goodman WK, Price LH, McDougle CJ, Charney DS. The serotonin hypothesis of obsessive compulsive disorder: implications of pharmacologic challenge studies. *J Clin Psychiatry*. 1992;53(suppl):17-28.
10. Goddard AW, Shekhar A, Whiteman AF, McDougle CJ. Serotonergic mechanisms in the treatment of obsessive-compulsive disorder. *Drug Discov Today*. 2008;13:325-332.
11. Zohar J, Insel TR. Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. *Biol Psychiatry*. 1987;22:667-687.
12. Denys D, Zohar J, Westenberg HG. The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *J Clin Psychiatry*. 2004;65(suppl 14):11-17.

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Tratamiento farmacológico del trastorno obsesivo-compulsivo

En los últimos 40 años ha habido un importante aumento del conocimiento de las opciones de farmacoterapia para el trastorno obsesivo-compulsivo (TOC). Los antidepresivos serotoninérgicos, como los inhibidores selectivos de la recaptura de serotonina (ISRS) y la clomipramina, se consideran los tratamientos farmacológicos de primera línea en el tratamiento del TOC. Se recomienda el empleo de dosis intermedias o altas y un tratamiento agudo de al menos tres meses antes de evaluar la eficacia. En el caso de una mejoría significativa es necesario el tratamiento de mantenimiento. Es lamentable que cerca de la mitad de los pacientes no responda suficientemente a antidepresivos serotoninérgicos orales, por lo que la potenciación con antipsicóticos atípicos es una estrategia de tratamiento farmacológico de segunda línea. Otras alternativas incluyen los antidepresivos serotoninérgicos intravenosos y la combinación con una psicoterapia cognitivo conductual o un cambio a esta última. Es destacable que un porcentaje considerable de pacientes con TOC aun no recibe un tratamiento farmacológico racional. Se revisan aproximaciones novedosas de la investigación, como los estudios terapéuticos preliminares con sustancias glutamatérgicas, y los ensayos con otros fármacos, al igual que algunos aspectos de la investigación futura.

Traitement pharmacologique des troubles obsessionnels compulsifs

Ces 40 dernières années ont vu s'améliorer de manière importante la connaissance du traitement pharmacologique du trouble obsessionnel compulsif (TOC).. Les antidépresseurs sérotoninergiques, comme les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) et la clomipramine, représentent le traitement pharmacologique de première ligne reconnu pour les TOC. Des posologies moyennes à fortes sont nécessaires, avec une phase aiguë d'au moins 3 mois pour obtenir des résultats et en cas d'amélioration significative, un traitement d'entretien est nécessaire. Malheureusement, environ la moitié des patients ne répondent pas suffisamment aux antidépresseurs sérotoninergiques oraux. La stratégie thérapeutique de deuxième intention consiste alors à additionner des antipsychotiques atypiques. L'administration d'antidépresseurs sérotoninergiques intraveineux et l'association ou le passage à la psychothérapie cognitivocomportementale sont des alternatives possibles. Étonnamment, un pourcentage considérable de patients atteints de TOC ne reçoit pas encore de traitement adapté. Nous analysons dans cet article les nouvelles démarches concernant la recherche, comme les études thérapeutiques préliminaires avec des substances glutamatergiques, les essais avec d'autres médicaments ainsi que certaines perspectives nécessaires à la recherche future.

13. Harsányi A, Csigó K, Demeter G, Németh A. New approach to obsessive-compulsive disorder: dopaminergic theories. *Psychiatr Hung*. 2007;22:248-258.
14. Pittenger C, Krystal JH, Coric V. Glutamate-modulating durgs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. *NeuroRx*. 2006;3:69-81.
15. Bhattacharyya S, Chakraborty K. Glutamatergic dysfunction – newer targets for anti-obsessional drugs. *Recent Pat CNS Drug Discov*. 2007;2:47-55.
16. Denys D, van Megen H, Westenberg H. The adequacy of pharmacotherapy in outpatients with obsessive-compulsive disorder. *Int J Clin Psychopharmacol*. 2002;17:109-115.
17. Huppert JD, Schultz LT, Foa EB, et al. Differential response to placebo among patients with social phobia, panic disorder, and obsessive compulsive disorder. *Am J Psychiatry*. 2004;161:1485-1487.
18. Bland RC, Newman SC, Om H. Age and remission of psychiatric disorders. *Can J Psychiatry*. 1997;42:722-729.
19. Stein DJ, Ipser JC, Baldwin DS, Bandelow B. Treatment of obsessive-compulsive disorder. *CNS Spectr*. 2007;12(suppl 3):28-35.
20. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines fort he pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2005;19:567-596.
21. NICE clinical guideline 31. Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. 2005. Available at: www. Nice.org.uk.
22. Canadian Psychiatric Association. Clincial Practice Guidelines: management of anxiety disorders. *Can J Psychiatry*. 2006;51(suppl 2):S9-S91.
23. American Psychiatric Association: Practice guidelines for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2007;164 (suppl 1):1-56.
24. Bandelow B, Zohar J, Hollander E, et al. World federation of societies of biological psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. *W J Biol Psychiatry*. 2008;9:248-312.
25. Fineberg NA, Pampaloni I, Pallanti S, Ipser J, Stein DJ. Sustained response versus relapse: the pharmacotherapeutic goal for obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2007;22:313-322.
26. Stein DJ, Andersen EW, Tonnoir B, Fineberg N. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-references, fixed-dose, 24-week study. *Curr Med Res Opin*. 2007;23:701-711.
27. Soomro GM, Altmann DG, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008;1:CD001765.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 195

28. McDougle CJ, Goodman WK, Leckman JF, Price LH. The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. *Psychiatr Clin North Am*. 1993;16:749-766.
29. Fallon BA, Liebowitz MR, Campeas R, et al. Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry*. 1998;55:918-924.
30. Koran LN, Sallee FR, Pallanti S. Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:396-401.
31. Pallanti S, Quercioli L, Koran LM. Citalopram intravenous infusion in resistant obsessive-compulsive disorder: an open trial. *J Clin Psychiatry*. 2002;63:796-801.
32. Ninan PT, Koran LM, Kiev A, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. *J Clin Psychiatry*. 2006;67:15-22.
33. Rabinowitz I Baruch Y, Barak Y. High-dose escitalopram for the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2008;32:49-53.
34. Dougherty DD, Jamesson M, Deckersbach T, et al. Open-label study of high (30 mg) and moderate (20 mg) dose escitalopram for the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2009;24:306-311.
35. Koran LM, Saxena S. Issues and strategies in treating refractory obsessive-compulsive disorder. *CNS Spectr*. 2002;5:24-31.
36. Fineberg NA, Gale TM. Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2005;8:107-129.
37. Marazziti D, Golia F, Consoli G et al. Effectiveness of long-term augmentation with citalopram to clomipramine in treatment-resistant OCD patients. *CNS Spectr*. 2008;13:971-976.
38. Browne M, Horn E, Jones TT. The benefits of clomipramine-fluoxetine combination in obsessive-compulsive disorder. *Can J Psychiatry*. 1993;38:242-243.
39. Ravizza L, Barzega G, Bellino S, Bogetto F, Maina G. Drug treatment of obsessive compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors (SSRIs). *Psychopharmacol Bull*. 1996;32:167-173.
40. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11:622-632.
41. Ipser JC, Carey P, Dhansay Y, Fakier N, Seedat S, Stein DJ. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. *Cochrane Database Syst Rev*. 2006;DC005473.
42. Skapinakis P, Papatheodorou T, Mavreas V. Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials. *Eur Neuropsychopharmacol*. 2007;17:79-93.
43. Fineberg N, Stein DJ, Carey P, et al. Adjunctive quetiapine for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: a meta-analysis of randomized controlled treatment trials. *Int Clin Psychopharmacol*. 2006;21:337-343.
44. Denys D, Fineberg N, Carey PD, Stein DJ. Quetiapine addition in obsessive-compulsive disorder: is treatment outcome affected by type and dose of serotonin reuptake inhibitors? *Biol Psychiatry*. 2007;61:412-414.
45. Kordon A, Wahl K, Koch, et al. Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive-compulsive disorder: a double-blind, randomized, placebo-controlled trial. *J Clin Psychopharmacol*. 2008;28:550-554.
46. Savas HA, Yumru M, Ozen ME. Quetiapine and ziprasidone as adjuncts in treatment-resistant obsessive-compulsive disorder: a retrospective comparative study. *Clin Drug Investig*. 2008;28:439-442.
47. Vulnik NC, Denys D, Fluitman SB, Meinardi JC, Westenberg HG. Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients. *J Clin Psychiatry*. 2009;70:1001-1008.
48. Maina G, Pessina E, Albert, Bogetto F. 8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2008;18:364-372.
49. Matsunaga H, Nagata T, Hayashida K, Ohya K, Kiriike N, Stein DJ. A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 2009;70:863.868.
50. Pessina E, Albert U, Bogetto F, Maina G. Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a 12-week open-label preliminary study. *Int Clin Psychopharmacol*. 2009:24:265-269.
51. Figee M, Denys D. New pharmacotherapeutic approaches to obsessive-compulsive disorder. *CNS Spectr*. 2009;14(suppl 3):13-23.
52. Connor KM, Payne VM, Gadde KM, Zhang W, Davidson JR. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. *J Clin Psychiatry*. 2005;66:49-51.
53. Metin O, Yazici K, Tot S, Yazici AE. Amisulpride augmentation in treatment resistant obsessive-compulsive disorder: an open trial. *Hum Psychopharmacol*. 2003;18:463-467.
54. Otsuka T, Togo T, Sugiyama N, et al. Perspirone augmentation of paroxetine in treatment of refractory obsessive-compulsive disorder with depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;32:564-568.
55. Simpson HB, Foa EB, Liebowitz MR, et al. A randomized, controlled trial of cognitive behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165:621-630.
56. Tundo A, Salvati L, Busto G, DI Spigno D, Falcini R. Addition of cognitive-behavioral therapy for nonresponders to medication for obsessive-compulsive disorder: a naturalistic study. *J Clin Psychiatry*. 2007;68:1552-1556.
57. Tenneij NH, van Megen HJ, Denys DA, Westenberg HG. Behavior therapy augments response of patients with obsessive-compulsive disorder responding to drug treatment. *J Clin Psychiatry*. 2005;66:1169-1175.
58. Tolin DF, Maltby N, Diefenbach GJ, Hannan SE, Worhunsky P. Cognitive-behavioral therapy for medication nonresponders with obsessive-compulsive disorder: a wait-list-controlled open trial. *J Clin Psychiatry*. 2004;65:922-931.
59. Eddy KT, Dutra L, Bradly R; Westen D. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev*. 2004;24:1011-1030.
60. Rothbaum BO. Critical parameters for D-cycloserine enhancement of cognitive-behavioral therapy for obsessive-compulsive disorder. *Am J Psychiatry*. 165;165:293-296.
61. Aboujaoude E, Barry JJ, Gamel N. Memantine augmentation in treatment-resistant obsessive-compulsive disorder: an open label trial. *J Clin Psychopharmacol*. 2009;29:51-55.
62. Poyurovsky M, Weizman R, Weizman A, Koran L. Memantine for treatment-resistant OCD. *Am J Psychiatry*. 2005;162:2191-2192.
63. Pasquini M, Biondi M. Memantine augmentation for refractory obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:1173-1175.
64. Greenberg WM, Benedict MM, Doerfer J, et al. Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults. *J Psychiatr Res*. 2009;43:664-670.
65. Coric V, Taskiran S, Pittenger C, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry*. 2005;58:424-428.
66. Egashira N, Okuno R, Harada S, et al. Effects of glutamate-related drugs on marble-burying behavior in mice: implications for obsessive-compulsive disorder. *Eur J Pharmacol*. 2008;586:164-170.
67. Hollander E, Dell'Osso B. Topiramate plus paroxetine in treatment-resistant obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2006;21:189-191.
68. Van Ameringen M, Mancini C, Patterson B, Bennett M. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: a retrospective, open-label case series. *Depress Anxiety*. 2006;23:1-5.
69. Oulis P, Masdrakis VG, Karapoulios E, et al. Pregabalin augmentation to sertraline-risperidone combination in the treatment of obsessive-compulsive disorder. Prim Care Companion *J Clin Psychiatry*. 2008;10:249.
70. Roebel M, Nenadic I, Sauer H. Pregablin as a successful pharmacotherapeutic option in OCD – a case report. *Nervenarzt*. 2009;80(suppl 2):P-043-007.
71. Lafleur DL, Pittenger C, Kelmendi B, et al. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. *Psychopharmacology*. 2006;184:254-256.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 196

72. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry*. 2008;63:1118-1126.

73. Storch EA, Merlo LJ, Bengtson M, et al. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2007;22:230-237.

74. Kushner MG, Kim SW, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry*. 2007;15:835-838.

75. Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with D-cycloserin for obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165:335-341.

76. Koran LM, Quirk T, Lorberbaum JP, Elliott M. Mirtazapine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2001;21:537-539.

77. Koran LM, Gamel NN, Choung HW, Smith EN, Aboujaoude EN. Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry*. 2005;66:515-520.

78. Pallanti S, Quercioli L, Bruscoli M. Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. *J Clin Psychiatry*. 2004;65:1394-1399.

79. Flaischer-Grinberg S, Klavir O, Joel D. The role of 5-HT2A and 5-HT2C receptors in the signal attenuation rat model of obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2008;11:811-825.

80. Vallejo J, Olivares J, Marcos T, Bulbena A, Mechón JM. Clomipramine versus phenelzine in obsessive-compulsive disorder. A controlled clinical trial. *Br J Psychiatry*. 1992;161:665-670.

81. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obesessive-compulsive disorder. *Am J Psychiatry*. 1997;154:1261-1264.

82. Kobak KA, Taylor LV, Bystritsky A, et al. St John's wort versus placebo in obsessive-compulsive disorder: results from a double-blind study. *Int Clin Psychopharmacol*. 2005;20:299-304.

83. Hermesh H, Aizenberg D, Munitz H. Trazodone treatment in clomipramine-resistant obsessive-compulsive disorder. *Clin Neuropharmacol*. 1990;13:322-328.

84. Marazziti D, Gemignani A, Dell'osso L. Trazodone augmentation in OCD: a case series report. *CNS Spectr*. 1999;4:48-49.

85. Pigott TA, L'Heureux F, Rubenstein CS, Bernstein SE, Hill JL, Murphy DL. A double-blind, placebo-controlled study of trazodone in patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:156-162.

86. Denys D, van der Wee N, van Megen JH, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2003;23:568-575.

87. Albert U, Aguglia E, Maina G, Bogetto F. Venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12 week, controlled study. *J Clin Psychiatry*. 2002;63:1004-1009.

88. Hollander E, Friedberg J, Wasserman S, Allen A, Birnbaum M, Koran LM. Venlafaxine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64:546-550.

89. Dell'Osso B, Mundo E, Marazziti D, Altamura AC. Switching from serotonin reuptake inhibitors to duloxetine in patients with resistant obsessive compulsive disorder: a case series. *J Psychopharmacol*. 2008;22:210-213.

90. Yeh YW, Chen CH, Kuo SC, Wang SC, Chen CK, Feng HM. High-dose duloxetine for treatment-resistant obsessive-compulsive disorder: a case report with sustained full remission. *Clin Neuropharmacol*. 2009;32:174-176.

91. Fontenelle LF, Mendlowicz MV, Miguel EC, Versiani M. Citalopram plus reboxetine in treatment-resistant obsessive-compulsive disorder. *World J Biol Psychiatry*. 2005;6:57-59.

92. Dannon PN, Sasson Y, Hirschmann S, Iancu I, Grunhaus LJ, Zohar J. Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. *Eur Neuropsychopharmacol*. 2000;10:165-169.

93. Blier P, Bergeron R. Sequential administration of augmentation strategies in treatment-resistant obsessive-compulsive disorder: preliminary findings. *Int Clin Psychopharmacol*. 1996;11:37-44.

94. Mundo E, Guglielmo E, Bellodi L. Effect of adjuvant pindolol on the antiobsessional response to fluvoxamine: a double-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 1998;13:219-224.

95. Pigott TA, L.Heureux F, Hill JL, Bihari K, Bernstein SE, Murphy DL. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:11-8.

96. McDougle CJ, Price LH, Goodman WK, Charney DS, Heninger GR. A controlled trail of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. *J Clin Psychopharmacol*. 1991;11:175-184.

97. Pigott TA, Pato MT, L'Heureux F, et al. A controled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1991;11:242-248.

98. Crockett BA, Churchill E, Davidson JR. A double-blind combination study of clonazepam with sertraline in obsessive-compulsive disorder. *Ann Clin Psychiatry*. 2004;16:127-132.

99. Hewlett WA, Vinogradov S, Agras WS. Clomipramine, clonazepam, and clonidine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol.* 1992;12:420-430.

100. Hollander E, Kaplan A, Stahl SM. A double-blind, placebo-controlled trial of clonazepam in obsessive-compulsive disorder. *World J Biol Psychiatry*. 2003;4:40-34.

101. Goldsmith TB, Shapira NA, Keck PE. Rapid remission of OCD with tramadol hydrochloride. *Am J Psychiatry*. 1999;156:660-661.

102. Koran LM, Aboujaoude E, Bullock KD, Franz B, Gamel N, Elliott M. Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2005;66:353-359.

103. Amiaz R, Fostick L, Gershon A, Zohar J. Naltrexone augmentation in OCD: a double-blind placebo-controlled cross-over study. *Eur Neuropsychopharmacol*. 2008;18:455-461.

104. Onder E, Tural U, Gökbakan M. Does gabapentin lead to early symptom improvement in obsessive-compulsive disorder? *Eur Arch Psychiatry Clin Neurosci*. 2008;258:319-323.

105. Deltito JA. Valproate pretreatment for the difficult-to-treat patient with OCD. *J Clin Psychiatry*. 1994;55:500.

106. Corá-Locatelli G, Greenberg BD, Martin JD, Murphy DL. Valproate monotherapy in an SRI-intolerant OCD patient. *J Clin Psychiatry*. 1998;59:82.

107. Hewlett WA, Schmid SP, Salomon RM. Pilot trial of ondansetron in the treatment of 8 patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64:1025-1030.

108. Pallanti S, Bernardi S, Antonini S, Singh N, Hollander E. Ondansetron augmentation in treatment-resistant obsessive-compulsive disorder: a preliminary, single-blind, prospective study. *CNS Drugs*. 2009;23:1047-1055.

109. Young CR, Bostic JQ, McDonald CL. Clozapine and refractory obsessive-compulsive disorder: a case report. *J Clin Psychopharmacol*. 1994;14:209-211.

110. Steinert T, Schmitt-Michel PO, Kaschka WP. Considerable improvement in a case of obsessive-compulsive disorder in an emotionally unstable personality disorder, borderline type under tretment with clozapine. *Pharmacopsychiatry*. 1996;29:111-114.

111. Poyurovsky M. Clozapine in treatment-refractory obsessive-compulsive disorder with comorbid schizotypal personality disorder. *Isr J Psychiatry Relat Sci*. 2008;45:219-220.

112. Casas M, Alvarez E, Duro P, et al. Antiandrogenic treatment of obsessive-compulsive neurosis. *Acta Psychiatry Scand*. 1986;73:221-222.

113. Eriksson T. Anti-androgenic treatment of obsessive-compulsive disorder: an open-label clinical trial of long-acting gonadotropin-releasing hormone analogue triptorelin. *Int Clin Psychopharmacol*. 2007;22:57-61.

114. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2006;67:1735-1740.

115. Salin-Pascual RJ, Basanez-Villa E. Changes in compulsion and anxiety symptoms with nicotine transdermal patches in non-smoking obsessive-compulsive disorder patients. *Rev Invest Clin*. 2003;55:650-654.

116. Lundberg S, Carlsson A, Norfeldt P, Carlsson ML. Nicotine treatment of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:1195-1199.

117. Pasquini M, Garvini A, Biondi M. Nicotine augmentation for refractory obsessive-compulsive disorder. A case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:157-159.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 197

118. Seedat S, Stein DJ. Inositol augmentation of serotonin reuptake inhbitors in treatment-refractory obsessive-compulsive disorder: an open trial. *Int Clin Psychopharmacol*. 1999;14:353-356.
119. Fux M, Benjamin J, Belmaker RH. Inositol versus placebo augmentation of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: a double-blind cross-over study. *Int J Neuropsychopharmacol*. 1999;2:193-195.
120. Insel TR, Hamilton JA, Guttmacher LB, Murphy DL. D-amphetamine in obsessive-compulsive disorder. *Psychopharmacology*. 1983;80:231-235.
121. Koran LM, Aboujaoude E, Gamel NN. Double-blind study of dextroamphetamine versus caffeine augmentation for treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2009;70:1530-1535.
122. Ravizza L, Barzega G. Bellino S, Gogetto F, Maina G. Predictors of drug treatment response in obsessive-compulsive disorder. *J Clin Psychiatry*. 1995;56:368-373.
123. Erzegovesi S, Cavallini MC, Cavedini P, Diaferia G, Locatelli M, Bellodi L. Clinical predictors of drug response in obesessive-compulsive disorder. *J Clin Psychopharmacol*. 2001;21:488-492.
124. Stein DJ, Montgomery SA, Kasper S, Tanghoy P. Predictors of response to pharmacotherapy with citalopram in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2001;16:357-361.
125. Denys D, Burger H, van Megen H, de Geus F, Westenberg H. A score for predicting response to pharmacotherapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2003;18:315-322.
126. Hollander E, Kaplan A, Schmeidler J, et al. Neurological soft signs as predictors of treatment response to selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 2005;17:427-477.
127. Shetti CN, Reddy YC, Kandavel T, et al. Clinical predictors of drug nonresponse in obsessive-compulsive disorder. *J Clin Psychiatry*. 2005;66:1517-1523.
128. Storch EA, Larson MJ, Shapira NA, et al. Clinical predictors of early fluoxetine treatment response in obsessive-compulsive disorder. *Depress Anxiety*. 2006;23:429-433.
129. Tükel R, Bozkurt O, Polat A, Genc A, Atli H. Clinical predictors of response to pharmacotherapy with selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *Psychiatry Clin Neurosci*. 2006;60:404-409.
130. Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 1999;156:1409-1416.
131. Stein DJ, Andersen EW, Overo KF. Response to symptom dimensions in obsessive-compulsive disorder to treatment with citalopram or placebo. *Rev Bras Psiquiatr*. 2007;29:303-307.
132. Saxena S, Brody AL, Maidment KM, Baxter LR. Paroxetine treatment of compulsive hoarding. *J Psychiatry Res*. 2007;41:481-487.
133. Di Bella D, Erzegovesi S, Cavallini MC, Bellodi L. Obsessive-compulsive disorder, 5-HTTLPR polymorphism and treatment response. *Pharmacogenomics J*. 2002;2:176-181.
134. Billett EA, Richter MA, King N, Heils A, Lesch KP, Kennedy JL. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. *Mol Psychiatry*. 1997;2:403-406.
135. Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HG. Prediction of response to paroxetine and venlafaxine by serotonin-related genes in obsessive-compulsive disorder in a randomized, double-blind trial. *J Clin Psychiatry*. 2007;68:747-753.
136. Zitterl W, Aigner M, Stompe T, et al. Changes in thalamus-hypothalamus serotonin transporter availability during clomipramine administration in patients with obsessive-compulsive disorder. *Neuropsychopharmacology*. 2008;33:3126-3134.
137. Baxter LR, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:681-689.
138. Saxena S, Brody AL, Ho ML, Zohrabi M, Maidment KM, Baxter LR. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry*. 2003;160:522-532.
139. Kim CH, Cheon KA, Koo MS, et al. Dopamine transporter density in the basal ganglia in obsessive-compulsive disorder, measured with [123I]IPT SPECT before and after treatment with serotonin reuptake inhibitors. *Neuropsychobiology*. 2007;55:156-162.
140. Hurley RA, Saxena S, Rauch SL, Hoehn-Saric R, Taber KH. Predicting treatment response in obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 2002;14:249-253.
141. Sumitani S, Harada M, Kubo H, Ohmori T. Proton magnetic resonance spectroscopy reveals an abnormality in the anterior cingulate of a subgroup of obsessive-compulsive disorder patients. *Psychiatry Res*. 2007;154:85-92.

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Cognitive behavioral therapy of obsessive-compulsive disorder

Edna B. Foa, PhD

Until the mid-1960s, obsessive-compulsive disorder (OCD) was considered to be treatment-resistant, as both psychodynamic psychotherapy and medication had been unsuccessful in significantly reducing OCD symptoms. The first real breakthrough came in 1966 with the introduction of exposure and ritual prevention. This paper will discuss the cognitive behavioral conceptualizations that influenced the development of cognitive behavioral treatments for OCD. There will be a brief discussion of the use of psychodynamic psychotherapy and early behavioral therapy, neither of which produced successful outcomes with OCD. The main part of the paper will be devoted to current cognitive behavioral therapy (CBT) with an emphasis on variants of exposure and ritual or response prevention (EX/RP) treatments, the therapy that has shown the most empirical evidence of its efficacy.

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Obsessive-compulsive disorder (OCD) was considered until the mid-1960s to be resistant to treatment with both psychodynamic psychotherapy and medication. The first significant breakthrough came in the form of exposure and ritual prevention. This, along with other forms of cognitive behavioral therapy (CBT), and earlier behavioral therapy, will be discussed below.

Cognitive behavioral conceptualization of OCD

Several cognitive behavioral theories about the development and maintenance of OCD symptoms have been put forward. Dollard and Miller[1] adopted Mowrer's two-stage theory[2,3] to explain the development and maintenance of fear/anxiety and avoidance in OCD. Mowrer's theory maintains that a neutral event stimulus (conditioned stimulus, CS) comes to elicit fear when it is repeatedly presented together with an event that by its nature causes pain/distress (unconditioned stimulus; UCS). The CS can be a mental event, such as a thought, and/or a physical object, such as a bathroom or trash cans. After fear/anxiety/distress to the CS is acquired, escape or avoidance behaviors are developed to reduce the anxiety. In OCD, the behavioral avoidance and escape take the form of repeated compulsions or rituals. Like other avoidance behaviors, compulsions are maintained because they indeed reduce the distress. Not only does Mowrer's theory adequately explain fear acquisition,[4] it is also consistent with observations of how rituals are maintained. In a series of experiments, Rachman and colleagues demonstrated that obsessions increase obsessional distress and compulsions reduce this distress.[5,6] This conceptualization of a functional relationship between obsessions and compulsions influenced the

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definitions of OCD in *DSM-III*[7] and its successors.

Foa and Kozak[8] proposed that OCD is characterized by erroneous cognitions. First, OCD sufferers assign a high probability of danger to situations that are relatively safe. For example, an individual with OCD will believe that if he or she touches a public doorknob without washing his or her hands thoroughly, the germs on the doorknob will cause serious disease to him or her and/or to people whom he or she touched with dirty hands. Second, individuals with OCD exaggerate the severity of the bad things that they think can happen. For example, contracting a minor cold is viewed as a terrible thing. Foa and Kozak also pointed out that individuals with OCD conclude that in the face of lack of evidence that a situation or an object is safe, it is dangerous, and therefore OCD sufferers require constant evidence of safety. For example, in order to feel safe, an OCD sufferer requires a guarantee that the dishes in a given restaurant are extremely clean before eating in this restaurant. People without OCD, on the other hand, conclude that if they do not have evidence that a situation is dangerous, then it is safe. Thus, a person without OCD would eat from the dishes in the restaurant unless he or she has clear evidence that they are dirty.

Salkovskis[9] offered a cognitive theory of OCD. He proposed that five assumptions are characteristic of OCD: (i) thinking about an action is the same as doing it; (ii) failing to prevent harm is morally equivalent to causing harm; (iii) responsibility for harm is not diminished by extenuating circumstances; (iv) failing to ritualize in response to a thought about harm is the same as an intention to harm; and (v) one should exercise control over one's thoughts (p 579). Therefore, while the patient may feel their obsessions are unacceptable, the compulsions used to reduce the anxiety are deemed acceptable.

Traditional psychotherapy

OCD was initially viewed as intractable. Psychoanalytic and psychodynamic theories of unconscious drives and wishes produced several formulations of OCD and descriptions of case studies, but did not lead to treatments that reliably resulted in significant reduction of OCD symptoms. Nonetheless, due to lack of alternatives, psychodynamic psychotherapy continued to be administered to patients with OCD despite limited clinical benefit.[10]

Salzman and Thaler[11] in their review of the literature concluded that the traditional approaches to the treatment of OCD "require drastic revision because they have added nothing to the comprehension or resolution of these disorders." The authors proposed that treatment should be focused on the here and now, and refrain from using psychodynamic interpretations of past experiences.

In his 1983 psychiatric review of OCD, Jenike[12] lamented that psychology had little to offer people suffering from OCD. He noted that "OCD is generally easy to diagnose but extremely difficult to treat successfully. The abundance of therapeutic approaches available suggests that none is clearly effective in the majority of cases. Psychotherapy and electroconvulsive therapy are ineffective treatments for pure OCD." [12]

At present it is widely recognized that, for OCD, psychodynamic approaches have little evidence base to justify their use. With regard to psychodynamic therapy and psychoanalysis, one of the most current expert guidelines notes that "there is doubt as to whether it has a place in mental health services for OCD" at all.[13]

Early behavior therapy

Several behavioral interventions were developed to alleviate OCD-related distress, with varying degrees of success. The goal was to reduce obsessional anxiety/distress by exposing the patient to the very events that evoked that distress—and are therefore avoided—until the patient adapted, or habituated, to the situation. Systematic desensitization, developed by Wolpe,[14] for phobias, was applied in the treatment of OCD. This approach involved applied relaxation during gradual exposure to feared items and situations. The goal of desensitization was to eliminate the patient's obsessional anxiety, which in turn was thought to eliminate compulsions or rituals. The important components of treatment are to create a hierarchy of anxiety-provoking stimuli, to train the patient in relaxation techniques, and to present items from the hierarchy to the patient while in a relaxed state. The theory was that the presentation of the fear stimuli together with relaxation will dissipate the fear. Compulsions are not addressed directly because, according to the theory, once the anxiety dissipates, the patient will not need to perform the rituals. Systematic desensitization had only limited success with OCD and its use with this disorder has been extensive.

Aversion therapy, another behavioral therapy that was used in OCD, consists of punishment for an undesirable response. The idea behind this therapy is that an activity

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that is repeatedly paired with an unpleasant experience will be extinguished. Aversive experiences that have been used to change behaviors include drugs that induce nausea (eg, disulfiram for alcohol dependence, electrical shocks for paraphilias or addictions), or any other stimuli aversive to the patient. The most common application of aversive therapy in OCD has been the "rubber-band snapping technique," whereby the patient wears a rubber band on the wrist and is instructed to snap it every time he or she has an obsessive thought, resulting in a sharp pain; thus the pain and obsession become connected.[15] This method was not very effective.[16] A variant of aversive therapy is thought-stopping, in which the therapist or patient shout "Stop" immediately after an obsessional thought had been elicited, but this was also not effective in reducing OCD symptoms.[17]

The breakthrough: exposure and ritual prevention

As noted above, systematic desensitization, as well as operant-conditioning procedures aimed at blocking or punishing obsessions and compulsions, were used in OCD with limited or no success. The first real breakthrough came in 1966, when Meyer described two patients successfully treated with a behavioral therapy program that included prolonged exposure to distressing objects and situations, combined with strict prevention of rituals—exposure and ritual prevention (EX/RP).[18] Meyer and his colleagues continued to implement EX/RP with additional OCD patients, and found that the treatment program was highly successful in 10 of 15 cases, and partially effective in the remaining patients. Moreover, 5 years later, only two of the patients in the case series had relapsed.[19] All patients were hospitalized during their EX/RP treatment.

Description of EX/RP components

As noted above, treatment programs vary with respect to the components that they include. For example, Meyer and colleagues included exposure in vivo and ritual prevention only. Foa and colleagues include imaginal exposure, in vivo exposure, ritual prevention, and processing. Below are descriptions of each component.

Exposure in vivo (ie, exposure in real life), involves helping the patient confront cues that trigger obsessive thoughts. Cues include objects, words, images, or situations. For example, touching water faucets in a public restroom might trigger germ obsessions. Cues were presented in a hierarchical manner, beginning with the moderately distress-provoking ones and progressing to more distressing cues.

Imaginal exposure involves asking the patient to imagine in detail the distressing thoughts or situations. It is used primarily to help patients confront the disastrous consequences that they fear will happen if they do not perform the rituals. For example, imaginal exposure may involve the patient imagining contracting a sexually transmitted disease because they did not wash their hands sufficiently after using a public bathroom and consequently being shunned by friends and family. Obviously these feared consequences cannot and should not be created in reality.

Ritual prevention involves instructing the patient to abstain from the ritualizing that they believe prevents the feared disaster or reduces the distress produced by the obsession (eg, washing hands after touching the floor and fearing contracting a disease). By practicing ritual prevention the patient learns that the anxiety and distress decrease without ritualizing and that the feared consequences do not happen.

Processing involves discussing the patient's experience during or after exposure and response prevention, and how this experience confirms or disconfirms the patient's expectation (eg, you touched the floor and you did not wash your hands for about 1 hour; is your level of distress as high as in the beginning of the exposure? How strong are your urges to wash? Are they as strong as you expected? If not, what have you learned from this experience?)

The efficacy of EX/RP

The successful outcome described by Meyer and his colleagues,[19] prompted clinical researchers to conduct controlled studies, which indeed lent support to Meyer's case reports.
In 1971, Rachman et al[20] conducted a controlled treatment study of 10 inpatients with chronic OCD. All patients received 15 sessions of relaxation control treatment prior to EX/RP. The patients were then assigned

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randomly to intensive treatment of 15 daily sessions of either modeling in vivo or flooding in vivo. Results indicated significantly more improvement in OCD symptoms in EX/RP compared with the relaxation treatment, and the patients maintained their gains at 3 months' follow-up. At a 2-year follow-up with the 10 original and 10 additional patients, three quarters of the 20 patients were much improved.[21]

Influenced by the research of Rachman, Marks, and Hodgson, Foa and Goldstein[22] studied a series of OCD patients, using a quasi-experimental design. Patients' OCD symptom severity was assessed before and after 2 weeks, in which the therapists collected information about their OCD, history, and type of symptoms, but no treatment was conducted. Patients were then treated with EX/RP and their symptom severity was assessed again. This treatment differed in several ways from previous studies. First, for the majority of patients, treatment was conducted as outpatients rather than as inpatients. Second, exposure and ritual prevention involved 10 rather than 15 daily sessions. Third, influenced by reports about the efficacy of imaginal exposure with phobias (see ref 23). Foa and Goldstein[22] included *imaginal* exposure in addition to in-vivo exposure in the EX/RP treatment. During imaginal exposure, therapists described the patients' feared "disasters" that might result from not performing the rituals and asked them to immerse themselves in imagining the scenario described. The treatment program proved quite effective. During the information-gathering stage, no improvement was evident. In contrast, during the 2-week EX/RP, a marked and highly significant improvement was found. At follow-up, 66% of patients were very much improved and 20% partially improved. Only three patients did not benefit from the treatment program, which was attributed to overvalued ideation, ie, poor insight. The treatment program in this study, as well as in all the treatment studies by Foa and colleagues to date, comprised the components described below.

The bulk of the treatment program involves the practice of exposure and ritual prevention exercises, both in session and as homework assignments, working through more difficult exposures as treatment progresses. During the last few sessions, emphasis is placed on relapse prevention and future maintenance of gains. These sessions can be conducted either once a week, twice a week, or daily in an intensive treatment program, depending on symptom severity and logistical considerations.

The relative efficacy of EX/RP treatment components

After the efficacy of EX/RP and its durability in reducing OCD symptom severity had been established, Foa and colleagues embarked on investigating the relative contribution of the different components of the treatment program. To this end, they conducted a series of dismantling studies to ascertain the separate effects of: in-vivo exposure, imaginal exposure, and ritual prevention.

Imaginal exposure compared with in-vivo exposure and their combination

In order to examine the effect of adding imaginal exposure to EX/RP, Foa et al[24] conducted a study that included OCD outpatients with checking rituals who were randomized to two treatments. The first consisted of 10 sessions of a 90-minute uninterrupted imaginal exposure, which focused on the patients' feared consequences if they did not perform their checking rituals; this was followed by a 30-minute in-vivo exposure to situations which give rise to an urge to perform checking rituals. The second treatment consisted of 120-minute in-vivo exposure; no imaginal exposure was conducted. Both groups were asked to refrain from performing checking rituals. At the end of treatment both groups showed equal improvement, but at follow-up those who received only the in-vivo exposure showed some relapse, whereas those receiving both imaginal and in-vivo exposure maintained their gains. Thus, imaginal exposure seemed to contribute to the maintenance of treatment gains.

In a second study, Foa et al[25] compared the efficacy of imaginal exposure with that of in-vivo exposure. OCD outpatients with checking rituals were randomly assigned to one of two treatment conditions: imaginal or in-vivo exposure. Ritual prevention was not included in the treatments. Both treatments involved 15 120-minute sessions over 3 weeks, and two home visits in the fourth week. Patients improved significantly in their OCD symptoms and continued to improve at follow-up (an average of 10 months post-treatment). No significant differences between treatments emerged at post-test or follow-up. The authors concluded that both imaginal and in-vivo exposure offered clinically significant and lasting benefits to patients with OCD.

In sum, although imaginal exposure does not appear essential for immediate outcome, it may enhance long-

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term maintenance and can be used as an adjunct to in-vivo exposure for patients who manifest fear of "disastrous consequences" such as burglary in the absence of checking door locks and windows.

The relative effects of exposure and ritual prevention

To examine the relative effects of exposure and ritual prevention, Foa et al[26] randomly assigned patients with contamination obsessions and washing rituals to treatment by exposure only (EX), ritual prevention only (RP), or their combination (EX/RP). Each treatment was conducted intensively (15 daily, 120-minute sessions conducted over 3 weeks) followed by a home visit. Patients in all conditions improved at both post-treatment and follow-up. However, patients in the EX/RP treatment (combining EX and RP) showed superior outcome on almost every symptom measure compared with EX-only or RP-only treatments. This superior outcome of the combined treatment was found at both post-treatment and follow-up. When comparing the outcome of EX only with that of RP only, patients who received EX reported lower anxiety when confronting feared contaminants than patients who had received RP, whereas the RP group reported greater decreases in urges to ritualize than did the EX patients. Thus, it appeared that EX and RP differentially affected OCD symptoms. The findings from this study clearly suggest that exposure and ritual prevention should be implemented concurrently; treatments that do not include both components yield inferior outcome.

The relative efficacy of medication, EX/RP, and their combination

Parallel to the development of effective cognitive behavioral therapy for OCD, there was a development of medication treatment for the disorder. Clomipramine was the first medication that showed efficacy in reducing OCD symptoms.[27] While it is outside of this article's scope to discuss the literature on the efficacy of pharmacotherapy on OCD symptoms, the relative effects of medication, EX/RP, and their combination will be described, as well as the effect of augmenting the benefit from medication by adding EX/RP.

Several studies examined the effects of medication, EX/RP, and their combination. The first study that used a straightforward design to compare the relative and combined efficacy of clomipramine, intensive EX/RP, their combination, and placebo (PBO) was a two-site study conducted by Foa et al and Leibowitz et al. The EX/RP program included an intensive phase (15 2-hour sessions conducted over 4 weeks) and a follow-up phase (6 brief sessions delivered over 8 weeks). EX/RP alone was compared with 12 weeks of CMI alone, combination of EX/RP+CMI, and PBO. At post-treatment all three active treatments were superior to placebo, and EX/RP was found to be superior to CMI. EX/RP+CMI was superior to CMI alone, but the combined therapy did not enhance outcome achieved by EX/RP alone.[28] Moreover, rate of relapse was higher following the discontinuation of CMI treatment compared with that of EX/RP alone or the combined treatment.[29]

Augmenting medication treatment with EX/RP

Most OCD patients who seek EX/RP treatment are already taking medication, primarily a serotonin uptake inhibitor (SRI). However, as noted earlier, most patients suffer from residual OCD symptoms even when treated with an adequate dose of medication; they seek psychological intervention to further reduce their symptoms. To examine the augmenting effects of EX/RP, Foa et al and Simpson et al conducted a two-site randomized control trial (RCT). Patients on a stable and therapeutic dose of SRI medication, but who experienced only partial response, were randomized to either EX/RP or stress management training (SMT) while continuing with their medication. At of the 8-week acute treatment phase, EX/RP was significantly superior to SMT in further reducing symptoms in OCD patients who are on medication.[30]

Summary

Results from numerous studies demonstrate the efficacy of EX/RP in reducing OCD symptoms; moreover, most patients maintain their gains following treatment. A number of RCTs have found that EX/RP is superior to a variety of control treatments, including placebo medication, relaxation, and anxiety management training. Furthermore, recent studies have indicated that these successful outcomes for EX/RP are not limited to highly selected samples of OCD patients.[31,32]

Abramowitz[33] conducted a meta-analysis to determine

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the degree of symptom improvement associated with four different variations of EX/RP. The meta-analysis revealed that therapist-supervised exposure was more effective than self-exposure. Complete response prevention during exposure therapy yielded superior outcome to that of partial or no response prevention. The combination of in-vivo and imaginal exposure was superior to in-vivo exposure alone in reducing anxiety. There was no significant difference between treatments that included gradual exposure and those that included flooding.

With regard to the effects of combining medication to EX/RP treatment, two studies failed to detect an enhanced reduction in OCD symptoms by adding medication to EX/RP, two studies found a small but temporary effect, and one study found an advantage for combined treatment over EX/RP alone on obsessions but not on compulsions. On the other hand, the addition of EX/RP to medication enhances the efficacy of the medication and OCD symptoms can be reduced further by adding EX/RP to medication treatment.

Cognitive therapy

OCD patients are distressed about their thoughts, or obsessions, because they interpret them as warnings of events that are dangerous and likely to occur. Cognitive therapy (CT) is designed to help patients identify these automatic unrealistic thoughts and change their interpretations of the meaning of the thoughts, resulting in decreased anxiety and decreased compulsions.

In the first stage of CT, patients are taught to develop an awareness of their worries as obsessions and their rituals as compulsions. The patient keeps a daily diary of obsessions, called a thought record. In the thought record, patients write down their obsessions and the interpretations associated with the obsessions. Important details to record may include what the patient was doing when the obsession begin, the content of the obsession, the meaning attributed to the obsession, and what the patient did in response to the obsession (usually a compulsion).

The therapist will review the thought record with the patient and how the obsession was interpreted. Using gentle reasoning and Socratic questioning, the therapist will verbally challenge an unrealistic belief. This helps the patient to identify the cognitive distortion, typically a faulty assessment of danger, an exaggerated sense of responsibility, or fears that thinking something negative will make it come true (thought-action fusion).

Once patients are able to quickly identify their obsessions and compulsions as symptoms of OCD, the therapist will initiate a few behavioral experiments to disprove errors in thinking about cause and effect. For example, if a patient believes that smoking four cigarettes will prevent her family from being harmed in an auto accident, the therapist may instruct the patient to smoke only three cigarettes and then wait to see if family members are actually harmed that day in an auto accident. The therapist may then use the results of this experiment as material for discussion about other types of magical thinking. Over time, patients learn to identify and re-evaluate beliefs about the potential consequences of engaging in or refraining from compulsive behaviors and subsequently begin to eliminate compulsions (see ref 34).

Cognitive therapy compared to in-vivo exposure with ritual prevention

Van Oppen et al[35] conducted a treatment study comparing CT with EX/RP. Seventy-one Dutch OCD patients were randomly assigned to either CT or in-vivo exposure. Sixteen 45-minute sessions were administered. In the CT condition, treatment focused on "overestimation of danger and inflated personal responsibility," and after session 6, behavioral experiments were included to test the basis of unrealistic beliefs. The exposure condition consisted of EX/RP working up a hierarchy of feared and avoided situations, with no discussion of feared consequences until after session 6. Patients in both groups improved significantly. No differences between the two treatments emerged. It should be noted that the behavioral experiments in the CT condition introduced in-vivo exposure and ritual prevention. On the other hand, the processing component of EX/RP was omitted. Thus, it is difficult to interpret the results of the study.

Cottraux et al[36] conducted a study involving 62 French patients who received 20 sessions of CT or EX/RP for OCD. Treatment included 4 weeks of intensive treatment (16 hours) and 12 weeks of maintenance (4 hours). EX/RP and CT produced equal improvements in OCD symptoms after 4 weeks, although EX/RP patients showed greater improvement on a measure of intrusive thoughts and CT patients were more improved in anxi-

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ety and depression. By week 52, most of the differences had disappeared, but the EX/RP group had lower OCD symptoms and the CT group had lower depression. Notably, here too CT included some in vivo exposure in the form of behavioral experiments to test unrealistic fears and cognitive schemas; no processing of cognitive techniques were included in EX/RP.

In another dismantling study of CT and exposure for OCD,[37] patients with OCD were randomly assigned to receive exposure plus relaxation, exposure plus cognitive therapy, or waitlist. The CBT portion of the treatment consisted of 2-hour sessions held twice a week for 6 weeks using EX/RP along with either CT or relaxation; this was followed by 10 more sessions of in-vivo and/or imaginal exposure. The two CBT treatments were equally effective, and patients showed significant improvement post-treatment and through 12-month follow-up.

A meta-analysis by Eddy et al[38] examined data from 15 clinical trials. Treatments included EX/RP, CT, and active and passive control conditions. Overall, approximately two thirds of the patients who completed treatment improved, but only a third met recovery criteria. Among the intent-to-treat sample, which included dropouts, about one-half of patients improved and only a quarter recovered. Findings were stronger for EX/RP than CT, and individual therapy was more effective than group therapy.

Rosa-Alcazar et al[39] conducted a meta-analysis examining data from 19 controlled psychotherapy studies for OCD. EX/RP and CT as well as their combination were found to be highly effective, with no significant differences between treatments. The authors noted that the similarity of the findings for EX/RP and CT may have been due to the fact that both treatments included the same techniques. For example, CT most often included behavioral experiments that involved in vivo exposure to obsession-evoking situations to challenge irrational thoughts, thereby incorporating in-vivo exposure and ritual prevention. On the other hand, the application of EX/RP involves processing that help patients question their unrealistic beliefs and irrational thoughts. It is possible that EX/RP is more effective than CT, but the studies that compare EX/RP with CT have taken special care to avoid the use of cognitive elements in EX/RP, resulting in an incomplete application of EX/RP, whereas CT in research studies usually includes elements of exposure.[39]

Conclusion

Over 40 years of published research has led to the wide consensus among researchers and clinicians that CBT is an effective treatment for OCD.[13,40,41] Exposure-based treatments have the largest evidence base to support their use for OCD. EX/RP which includes processing appears to be most effective, whereas exposure without processing and CT produced equivalent improvement. Based on the large empirical evidence for EX/RP it is recommended as the first-line treatment for OCD, with CBT as an alternative.

While EX/RP has strong support for its efficacy in reducing OCD symptom severity, 20% of patients drop out prematurely. Although about 80% of patients respond well to EX/RP, 20% do not; therefore about 40% of patients with OCD are not helped by existing treatments.[42] Clinical researchers should continue to refine CBT programs to maximize improvement and make treatment more palatable to those in need of help.

It is difficult to determine the usefulness of psychological interventions other than EX/RP and CBT because of lack of control studies. There has been one published RCT on an alternative therapy, yogic meditation, in the treatment of OCD,[43] but no RCTs have been published on any other psychological interventions, such as hypnosis, virtual reality therapy, homeopathy, or an integrated psychological approach. Furthermore, no well-designed single case studies have been published on interventions other than CBT.[13] Further work is needed to validate alternative treatments for OCD.

More work also needs to be done to determine how to best tailor treatment to individual needs. Most studies do not have sufficient power to break down treatment response by OCD subtype such as "washers," "checkers," "orderers," and "hoarders." Some subtypes have been studied more than others, and some subtypes are typically excluded from RCTs. Most OCD sufferers have comorbid disorders, but studies typically exclude participants with substance abuse, psychosis, or bipolar disorder; thus we do not know how effective treatments are for comorbid populations. ❑

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Terapia cognitivo conductual del trastorno obsesivo compulsivo

Hasta mediados de la década de 1960 se consideró que el trastorno obsesivo compulsivo (TOC) era resistente al tratamiento, ya que tanto la psicoterapia psicodinámica como la medicación habían sido ineficaces en la reducción significativa de los síntomas del TOC. El primer avance real ocurrió en 1966 con la introducción de terapia de exposición y la prevención de rituales. En este artículo se discuten los conceptos cognitivo conductuales que influyen en el desarrollo de los tratamientos cognitivos conductuales para el TOC. Se efectúa una discusión breve acerca del empleo de la psicoterapia psicodinámica y las primeras terapias conductuales, a pesar que ninguna de ellas produjo un resultado exitoso en el TOC. La parte central del artículo está dedicada a la terapia cognitivo conductual actual, con un énfasis en las variantes de los tratamientos de exposición y prevención de rituales o respuestas, terapia que ha mostrado la mayor evidencia empírica de eficacia.

Thérapie cognitivocomportementale des troubles obsessionnels compulsifs

Jusqu'au milieu des années 60, les TOC (troubles obsessionnels compulsifs) étaient considérés comme résistant à la fois aux psychothérapies psychodynamiques et aux traitements médicamenteux qui n'avaient pas montré de diminution significative de leurs symptômes. La première réelle avancée a pris place en 1966 avec l'introduction de la thérapie par l'exposition et de la prévention des rituels. Cet article analyse les conceptualisations cognitivo-comportementales qui influent sur le développement des traitements cognitivo-comportementaux des TOC. La psychothérapie psychodynamique et les premiers traitements comportementaux sont brièvement passés en revue, n'ayant eu ni l'un ni l'autre de résultats probants avec les TOC. L'article se consacre principalement aux thérapies cognitivo-comportementales (TCC) actuelles en insistant sur les différents traitements par exposition et prévention de la réponse et du rituel (EX/PR), méthode qui a montré la meilleure efficacité empiriquement.

REFERENCES

1. Dollard J, Miller NE. *Personality and Psychotherapy; an Analysis in Terms of Learning, Thinking, and Culture*. New York, NY:McGraw-Hill;1950.
2. Mowrer OH. Stimulus response theory of anxiety. *Psychol Rev*. 1939;46:553-565.
3. Mowrer OH. *Learning Theory and the Symbolic Processes*. New York, NY: Wiley; 1960.
4. Rachman S, Wilson GT. *Effects of Psychological Therapy*. London, England: Pergamon; 1980.
5. Roper G, Rachman S. Obsessional-compulsive checking: experimental replication and development. *Behav Res Ther*. 1976;14:25-32.
6. Roper G, Rachman S, Hodgson R. An experiment on obsessional checking. *Behav Res Ther*. 1973;11:271-277.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
8. Foa EB, Kozak MJ. Treatment of anxiety disorders: implications for psychopathology. In: Tuma AH, Maser JD, eds. *Anxiety and the Anxiety Disorders*. Hillsdale, NJ: Lawrence Erlbaum Associates;1985:421-452.
9. Salkovskis PM. Obsessional-compulsive problems: a cognitive-behavioral analysis. *Behav Res Ther*. 1985;23:571-583.
10. Greist JH, Jefferson JW. Chapter 31, OCD. In: Gabbard, GO, ed. *Gabbard's Treatments of Psychiatric Disorders*. 4th ed. Arlington, VA: American Psychiatric Publishing; 2007.
11. Salzman L, Thaler FH. Obsessive-compulsive disorders: a review of the literature. *Am J Psychiatry*. 1981;138:286-296.
12. Jenike MA. Obsessive compulsive disorder. *Compr Psychiatry*. 1983;24:99-115.
13. National Institute for Health and Clinical Excellence (NICE). Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. The British Psychological Society & The Royal College of Psychiatrists. 2006. Available at: www.nice.org.uk
14. Wolpe J. *The Practice of Behavior Therapy*, First Edition, New York, NY: Pergamon Press; 1969.
15. Mastellone M. Aversion therapy: a new use for the old rubber band. *J Behav Ther Exp Psychiatry*. 1974:5;311-312.
16. Lam JN, Steketee GS. Reducing obsessions and compulsions through behavior therapy. *Psychoanal Inq*. 2001:21;157-182.
17. Stern RS. Obsessive thoughts: the problem of therapy. *Br J Psychiatry*. 1978:133;200-205.
18. Meyer, V. Modification of expectations in cases with obsessional rituals. *Behav Res Ther*. 1966:4;273-280.
19. Meyer V, Levy R, Schnurer A. A behavioral treatment of obsessive-compulsive disorders. In Beech HR, ed. *Obsessional states*. London, UK: Methuen; 1974.
20. Rachman S, Hodgson R, Marks IM. The treatment of chronic obsessive-compulsive neurosis. *Behav Res Ther*. 1971:9;237-247.
21. Marks IM., Hodgson R, Rachman S. Treatment of chronic obsessive-compulsive neurosis by in vivo exposure. *Br J Psychiatry*. 1975:127;349-364.
22. Foa EB, Goldstein AJ. Continuous exposure and complete response prevention in the treatment of obsessive-compulsive neurosis. *Behav Ther*. 1978:9;821-829.
23. Mathews A. Fear-reduction research and clinical phobias. *Psychol Bull*. 1978:85;390-404.
24. Foa EB, Steketee G, Turner RM, Fischer SC. Effects of imaginal exposure to feared disasters in obsessive-compulsive checkers. *Behav Res Ther*. 1980:18;449-455.
25. Foa EB, Steketee G, Grayson JB. Imaginal and in vivo exposure: a comparison with obsessive-compulsive checkers. *Behav Ther*. 1985:16;292-302.
26. Foa EB, Steketee G, Grayson JB, Turner RM, Latimer P. Deliberate exposure and blocking of obsessive-compulsive rituals: Immediate and long-term effects. *Behav Ther*. 1864:15;450-472.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 207

27. Fernandez-Cordoba E, Lopez-Ibor Alino J. Monochlorimipramine in mental patients resisting other forms of treatment. *Actas Luso Esp Neurol Psiquiatr*. 1967;26:119-147.
28. Foa EB, Liebowitz MR, Kozak, MJ, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 2005:162;151-161.
29. Simpson HB, Liebowitz MR, Foa EB, et al. Post-treatment effects of exposure therapy and clomipramine in obsessive-compulsive disorder. *Depress Anxiety*. 2004;19:225-233.
30. Simpson HB, Foa EB, Liebowitz, MR, et al. A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165:621-630.
31. Franklin ME, Abramowitz JS, Kozak MJ, Levitt JT, Foa EB. Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples. *J Consult Clin Psychol*. 2000;68:594-602.
32. Valderhaug L, Götestam P. An open clinical trial of cognitive-behavior therapy in children and adolescents with obsessive-compulsive disorder administered in regular outpatient clinics. *Behav Res Ther*. 2007:45;577-589.
33. Abramowitz JS. Variants of exposure and response prevention in the treatment of obsessive-compulsive disorder: a meta-analysis. *Behav Ther*. 1996;27:583-600.
34. Salkovskis PM. Psychological approaches to the understanding of obsessional problems. In: Swinson RP, Antony MM, Rachman S, Richter MA, eds. *Obsessive-Compulsive Disorder: Theory, Research, and Treatment*. New York, NY: Guilford Press; 1998:33-50.
35. Van Oppen P, de Haan E, Van Balkom AJLM, et al. Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. *Behav Res Ther*. 1995:33;379-390.
36. Cottraux J, Note I, Yao SN, et al. A randomized controlled trial of cognitive therapy versus intensive behavior therapy in obsessive compulsive disorder. *Psychother Psychosom*. 2001:70;288-297.
37. Vogel PA, Stiles TC, Gotestam KG. Adding cognitive therapy elements to exposure therapy for obsessive compulsive disorder: a controlled study. *Behav Cogn Psychother*. 2004:32;275-290.
38. Eddy KT, Dutra L, Bradley R, Westen D. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev*. 2004:24;1011-1030.
39. Rosa-Alcázar, AI, Sánchez-Meca J, Gómez-Conesa A, Marín-Martínez F. Psychological treatment of obsessive-compulsive disorder: a meta-analysis. *Clin Psychol Rev*. 2008:28;1310-1325.
40. Frances A, Docherty JP, Kahn DA. Treatment of obsessive-compulsive disorder. *J Clin Psychiatry*. 1997;58(suppl 4);5-72.
41. Greist JH., Bandelow B, Hollander E, et al. WCA recommendations for the long-term treatment of obsessive-compulsive disorder in adults. *CNS Spectr*. 2003;8(suppl 1):7-16.
42. Abramowitz JS. The psychological treatment of obsessive-compulsive disorder. *Can J Psychiatry*. 2006:51;407-416.
43. Shannahoff-Khalsa DS, Ray LE, Levine S, Gallen CC, Schwartz BJ, Sidorowich JJ. Randomized controlled trial of yogic meditation techniques for patients with obsessive-compulsive disorder. *CNS Spectrums*. 1999:4;34-47.

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How to treat the untreated: effectiveness of a self-help metacognitive training program (myMCT) for obsessive-compulsive disorder

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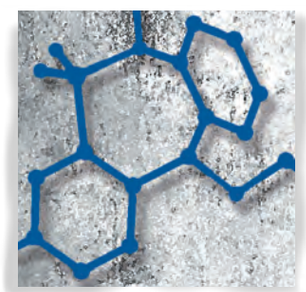

Despite advances in the understanding and treatment of obsessive-compulsive disorder (OCD), many patients undergoing interventions display incomplete symptom reduction. Our research group has developed a self-help manual entitled "My Metacognitive Training for OCD" (myMCT) aimed at raising patients' awareness about cognitive biases that seem to subserve OCD. The training is particularly intended for patients currently unable or unwilling to attend standard therapy, or in cases where such a treatment option is not available. For the present study, 86 individuals suffering from OCD were recruited over the Internet. Following the initial assessment, participants were either immediately emailed the myMCT manual or allocated to a waitlist group. After 4 weeks, a second assessment was performed. The myMCT group showed significantly greater improvement for OCD symptoms according to the Y-BOCS total score compared with the waitlist group (d =.63), particularly for obsessions (d=.69). Medium to strong differences emerged for the OCI-R (d =.70) and the BDI-SF (d =.50). The investigation provides the first evidence for the effectiveness of the myMCT for OCD.

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Efficacy of treatment for obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a severe mental illness characterized by intrusive, repetitive, and bothersome thoughts (ie, obsessions) usually followed by ritualized behavior (ie, compulsions such as excessive hand-washing for fear of transmitting diseases) aimed at neutralizing the obsessive contents.[1] As a consequence of OCD, the majority of patients are confronted with vast economic and social problems; many patients are unable to work, and lack a stable social network. Quality of life is usually very low,[2,3] and comorbid depression is diagnosed in one to two thirds of all patients.[3]

Effective treatment strategies have been at hand for quite some time now. As a rule of thumb, cognitive-behavioral therapy (CBT) has a success rate of around 80% for those who complete treatment.[4,5] Recent reviews assert[6,7] that its core ingredients, behavioral and cognitive techniques, share roughly similar efficacy. The overall effect size for psychological interventions in adult samples is d=1.24 according to a Cochrane review.[6] In adolescents, estimates are similar.[8]

Keywords: *obsessive-compulsive disorder; cognition; metacognition; psychotherapy; association splitting*

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However, several words of caution are necessary in view of studies that find less favorable results.[9,10] For example, when dropout rates are considered, response is typically only seen in every second patient.[1,11] While Pinard[11] concludes in his editorial introduction on Abramowitz' meta-analysis[4] that "OCD therapeutic strategies are […] less than satisfactory for the moment," treatment reality beyond controlled trials, the latter usually being conducted with skilled, trained, and highly motivated therapists, may be even worse. The dropout rate seen under standard clinical conditions is likely to be higher relative to ideal study conditions. For example, a Spanish study[12] reports that of 203 patients (mainly anxiety disorders) seen in a cognitive-behavioral unit 43.8% dropped out mostly at early stages of the intervention.

Treatment gap of OCD: the need for improved interventions

It often takes up to 10 years until OCD patients seek professional help for their problems, and there is a lag of 6 or more years until the diagnosis is correctly determined and appropriate treatment is initiated.[13,14] The rate of untreated cases for OCD is 59.5% (so-called treatment gap) according to a large WHO study.[15] However, the few patients receiving psychiatric or psychological help often do not get optimal, evidence-based treatment. A recent study[16] showed that 65% of adult patients with OCD were treated with an SSRI, whereas only 7.5% of the patients received CBT despite its effectiveness.[7] A recent German study found that less than 50% of all interviewed psychotherapists (CBT and other) performed exposure and response prevention (ERP) mainly owing to lack of experience and insufficient training in this technique.[17] According to patients' reports, the situation is even worse. Approximately 84% of the sample reported that they did not receive exposure and response prevention at all.[18,19]

Importantly, treatment success is usually not defined as full symptom remission, but as a symptom decline of 30% to 35% at least on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[20] which has led to some criticism, for example by Pinard[11] who wrote: "as if reducing rituals from 6 to 4 hours were clinically meaningful." Others[21] have noted that outcome criteria are less strict for OCD than for other disorders for which a remission of 50% of symptoms is considered substantial. Thus, many patients remain severely disabled even after a clinically defined successful therapy. Furthermore, modest symptom decline does not necessarily translate into improved quality of life.[3]

Metacognitive training for OCD (myMCT)

Based on a cognitive tradition of psychotherapy, our group developed a self-help manual called Metacognitive Training for OCD (myMCT).[22] Among other cognitive distortions, it deals with the six cognitive biases identified by the Obsessive-Compulsive Working Group[23-26]: (i) inflated responsibility, (ii) overimportance of thoughts, (iii) excessive concern about the importance of controlling one's thoughts, (iv) overestimation of threat, (v) intolerance of uncertainty, and (vi) perfectionism *(*see *Appendix)*.

Some of its exercises have been derived from a metacognitive training program for schizophrenia first published in 2005.[27] The myMCT pursues three overarching aims: (i) knowledge translation/psychoeducation, that is, to teach patients about core features of OCD (ie, obsessions, compulsions, avoidance, and safety behaviors); (ii) help patients to detect cognitive biases, dysfunctional metacognitive beliefs as well as dysfunctional coping strategies that subserve, maintain, or fuel OCD symptoms; (iii) convey new strategies to reduce and cope with OCD symptoms, particularly obsessions.

The program is eclectic and encompasses theories and strategies derived from other "schools," most notably cognitive-behavioral, metacognitive,[28] and to a lesser degree psychoanalytic accounts,[29] whose theoretical foundations are not mutually exclusive but may in part reflect different sides of the same coin. To illustrate, inflated responsibility plays a central role for most OCD theories. Whereas cognitive intervention would primarily target the content of the belief, dynamic approaches would ask how far responsibility reflects, for example, reaction formation, that is, overcompensation of latent aggression.[30] In a recent study, we indeed found evidence that these seemingly contradictory attitudes—inflated responsibility and high moral standards versus latent aggression and mistrust—coexist in patients.[31] From Wells' metacognitive standpoint, exaggerated responsibility is an epiphenomenon related to fusion beliefs[32]: Patients feel responsible as their thoughts are deemed toxic and potentially harmful to others.

Our self-help manual starts with an introduction which defines core features of OCD symptomatology, demon-

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strates its most prevalent subtypes, and requests patients to identify their own core problems (obsessions, compulsions, avoidance, safety behavior) and dysfunctional coping strategies (eg, thought suppression, rumination). Then, the aims of the program are explicated. The myMCT consists of 14 sections dealing with prevalent cognitive biases in OCD. These are summarized in the *Appendix*.

The present study set out to explore the feasibility and effectiveness of the myMCT as a self-help approach for OCD. Although therapist-guided CBT remains the undisputed treatment of choice for OCD, a large group of patients, as mentioned before, does not actively seek professional help and specialized therapy is not widely available. So far, there is scarce evidence for the effectiveness of self-help programs ("bibliotherapy"). Most studies to date involved at least some contact to therapists.[33] In a recent study by Tolin and coworkers,[34] patients performed an exposure and response prevention, either self- or therapist-directed. This study demonstrated that bibliotherapy is an effective method, although direct treatment led to more favorable results. In this study, therapist contact was minimal (first session).

To reach patients outside the treatment system, for the present study, participants with OCD were recruited over the Internet for the present study. Assessments were also made online. Half of the patients were allocated to a waitlist group and the other half received the myMCT immediately after participation in the initial assessment. The post assessment was performed 1 month later. We expected myMCT to be superior to the waitlist group, especially for the reduction of obsessions. As exposure and response prevention was not included in the manual at that time (this aspect was incorporated later), a negligible improvement on compulsions was expected. However, in view of poor attention, motivation, and slowness in many patients, we expected that not all patients in the experimental (myMCT) arm would read the manual and perform the exercises.

Methods

Recruitment

The first author posted an invitation for an Internet-based self-help trial aimed at reducing OCD symptoms on three Internet forums for OCD. Two sites were hosted by the German and Swiss Societies for Obsessive-Compulsive Disorder which provide help to OCD sufferers and disseminate information about OCD to the public. The third Web site was again solely devoted to OCD. This strategy ensured approaching persons with OCD only. If we had posted the announcement in forums with a broader scope, our invitation might have attracted patients with non-OCD diagnoses. Subjects were asked to refrain from participation if they did not experience obsessive thoughts, did not regard their obsessional worries as at least exaggerated (low illness insight), had no time to perform exercises in the course of the following four weeks, or did not agree to participate in an anonymous (Internet-based) survey before and after the intervention. Further, it was made mandatory that a diagnosis of OCD had to be determined by a health care professional beforehand. No compensation was offered for study participation except for the cost-free delivery of an electronic self-help manual (PDF-converted e-book). A Web link was then provided for those willing to participate.

When accessing the Internet questionnaire, participants were welcomed and the study rationale was repeated. It was made clear that participation would not require personal or telephone contact and that it was strictly anonymous. MyMCT was not described beforehand to avoid recruitment biases.

The Internet-based questionnaire at the preintervention phase consisted of the following sections: introduction, sociodemographic questions (age, gender, school education), and medical history (eg, prior therapies, if therapy was sought at all, profession of person who had diagnosed OCD before). This was followed by a clinical part consisting of the scales described below. At the beginning of the Y-BOCS section, examples for obsessions and compulsions were given to prevent possible misunderstandings (eg, cognitive compulsions such as counting are sometimes confused with obsessive thoughts). Items were worded in the original item format and the survey only proceeded if all items (except for comments) were answered. On the final page, participants were asked to enter their email address and a code word which would be asked for at the post-intervention phase.

Participants who left e-mail addresses were allocated to the experimental or waitlist group according to a random plan. The treatment manual was sent to the participants of the experimental group via e-mail attachment within 24 hours. The other half was informed via e-mail that they

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were allocated to the waitlist group and would receive the manual subsequent to the reassessment 4 weeks later. Patients were provided with the e-mail address of the first author in case of questions. E-mails were responded to within 24 hours. However, only three participants turned to the first author, whereby questions were solely related to the handling of the PDF file.

Four weeks after the dispatch of the manual, participants were e-mailed a second link and requested to take part in the post-assessment. To identify participants, either the code word or e-mail address had to be entered first on the Web page. The second assessment contained the same questionnaires as before (see below: OCI-R, Y-BOCS, BDI-SF) but did not ask again for sociodemographic data or the medical history again. For those participants who affirmed having read the manual, a number of questions were administered including subjective effectiveness of the technique, comprehensibility of the manual, and motivation to administer the technique in the future (4-point likert scale: fully agree, almost agree, somewhat agree, do not agree). In case the intervention was subjectively effective, participants were asked to indicate when improvement had occurred. At the end of the assessment, gratitude for participation was expressed to all subjects. Participants also had the opportunity to download the latest version of the manual. The e-mail address of the first author was provided again in case of questions or remarks. Participants gave informed consent.

Participants

A total of 86 participants completed the questionnaires and left their e-mail addresses (ie, 63% of the 137 different individuals who accessed the first page of the questionnaire). All participants confirmed that a diagnosis of OCD was previously determined by a health care professional.

Questionnaires

Participants had to fill out the Obsessive-Compulsive Inventory-Revised (OCI-R),[35] a self-report scale to evaluate the frequency and distress experienced by OC symptoms across six subscales. The OCI-R has good psychometric properties[35-37] that also apply to the German version,[38,39] and is sensitive to change.[40]

To tap depressive symptoms, the Beck Depression Inventory-Short Form (BDI-SF)[41,42] was administered which is based on the cognitive-affective subscale of the long form, a widely used scale and the gold standard for the subjective assessment of depression. It contains good concurrent validity in medical inpatients.[42]

The primary outcome of the study was the self-report version of the Y-BOCS,[20,43] which measures the severity of obsessions and compulsions. The self-report version of the scale has shown strong convergent validity with the original interview version.[44,45]

For the post-assessment, participants were contacted at the designated date of the reassessment and reminded 3 to 4 days later. Another 3 to 4 days later, a second reminder was sent. If this was not responded to, members of the intervention group were asked via email to state at least whether they had read the myMCT manual in case they did not want to complete the entire assessment.

Strategy for data analysis

We aimed to consider data from all subjects with available baseline data (intention-to-treat analysis, ITT). However, data from participants in the experimental group (myMCT) who after the third and final reminder still did not disclose whether or not they had read the manual were removed from the analyses because in these cases changes across time could not clearly be attributed to the method for certain (in contrast, in clinical studies principal investigators usually know if non-completers have taken at least one pill or participated in one therapeutic session so that the ITT procedure can be applied). To provide a rather conservative estimate for the effectiveness of the approach, we retained patients in the myMCT group who had read (part of) the manual but did not perform any of the exercises according to self-report.

Results

Baseline differences

Table I presents the sociodemographic and psychopathological characteristics of the waitlist and the myMCT group at baseline. As can be seen, no significant differences emerged for any of the variables (no stratification procedure was applied). For the OCI-R washing subscore, waitlist patients achieved somewhat elevated scores (P =.06).

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Group comparisons

Five patients from the waitlist group and seven patients from the myMCT group did not participate in the post assessment, $\chi^2(1) = .39$, $P > .5$. As the rate of noncompletion was both low and similar across groups (14%), this did not impact on between-group analyses.

Of the remaining 36 patients who received the manual, nine stated that they had not read the manual at all. Three of these experienced technical problems with download. Four gave lack of time as the major reason. Two did not provide any reasons. Thus, the per-protocol myMCT group comprised 27 patients.

Figures 1 and 2 show the results of the pre-post assessment calculated for completers. For this analysis, we added subjects from the myMCT group who did not read the manual to the waitlist group. When we removed this subgroup from the waitlist sample, as one could argue that the nonreaders represent a special group, status and level of significance did not change for any of the analyses. For some OCI-R variables, numerical differences in favor of the myMCT emerged even more strongly.

Across all domains, symptom improvements were stronger for the myMCT group. Significant differences were found for the Y-BOCS total score ($t(71)=2.68$, $P<.01$; $d=.63$) which primarily reflected greater symptom decline in the myMCT group for the obsessions subscale ($t(71)=3.00$, $P<.01$; $d=.69$). For the compulsions subscale, no significant difference emerged ($t(71)=.86$, $P>.1$, $d=.20$). The difference on the OCI-R score also achieved significance ($t(71)=2.92$, $P<.001$; $d=.70$), particularly owing to a greater decline on the subscales measuring obsessing and hoarding. The BDI-SF score also declined significantly more strongly in the myMCT in the range of a medium effect size ($t(71)=2.25$, $P<.05$, $d=.5$).

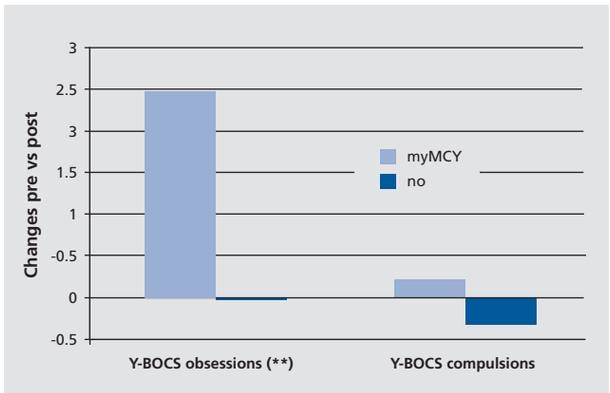

Figure 1. Patients in the myMCT group showed greater improvement on the Y-BOCS total score than the waitlist group who numerically slightly worsened ($P<.01$, $d=.63$). This result was especially owing to a decline on obsessions ($P<.005$, $d=.69$), while symptom decline on the compulsions subscore was marginal and insignificant ($P>.1$, $d=.20$).

Variables	Waitlist (n=43)	myMCT (n=43)	Statistics
Sociodemographic variables			
Sex (male/female)	12/31	16/27	$\chi^2(1)=.85$, $P>.3$
Age	34.09 (9.41)	34.95 (11.87)	t (84)=.37, $P>.7$
School education (high school level, yes vs no)	24/19	22/21	$\chi^2(1)=.19$, $P>.6$
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)			
Obsessions	10.30 (3.51)	10.16 (3.84)	t (84)=.18, $P>.8$
Compulsions	9.67 (4.52)	8.44 (5.09)	t (84)=1.19, $P>.2$
Total	19.98 (5.90)	18.60 (6.86)	t (84)=.99, $P>.3$
Obsessive-Compulsive Inventory-Revised (OCI-R)			
Washing	8.63 (4.25)	6.91 (4.09)	t (84)=1.91, $P=.06$
Obsessing	10.74 (3.51)	10.72 (3.33)	t (84)=.03, $P>.9$
Hoarding	6.26 (3.08)	5.91 (2.77)	t (84)=.55, $P>.5$
Ordering	7.63 (3.62)	7.35 (3.99)	t (84)=.34, $P>.7$
Checking	8.33 (3.37)	8.67 (4.05)	t (84)=.43, $P>.6$
Neutralizing	5.95 (3.13)	6.37 (3.65)	t (84)=.57, $P>.5$
Total	47.54 (12.46)	45.93 (12.79)	t (84)=.59, $P>.5$
BDI-SF total	13.37 (7.68)	12.72 (7.65)	t (84)=.39, $P>.6$

Table I. Baseline differences between the myMCT and waitlist group.

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Completer analyses

We separated the initial sample (*n*=86) into three groups according to completion status and adherence: completers (*n*=65), noncompleters (*n*=12), and completers but nonreaders (*n*=9; ie, allocated to the myMCT group but did not read the manual). Nonreaders had significantly reduced baseline Y-BOCS total scores in comparison to noncompleters (*P*=.04). The difference to completers was in the same direction but only approached trend level (*P*=.07). This result was primarily due to differences in the Y-BOCS obsessions subscale: nonreaders showed significantly lower scores compared with completers (P=.01) and noncompleters (*P*=.03). Further, on the OCI-checking subscale nonreaders had lower scores than noncompleters (*P*=.04). At trend level (*P*=.06), nonreaders had lower scores on the obsessing subscale compared with the completers. To summarize, while noncompleters were indistinguishable from completers, nonreaders showed attenuated symptoms and thus perhaps less *leidensdruck* (psychological distress).

Outcome predictors

Additionally, we investigated which baseline variables best predicted outcome, defined as the pre-post difference on the Y-BOCS total score. Patients with high baseline Y-BOCS total scores benefited most from the training. This variable accounted for 57% of the entire variance (R^2=.57, beta=.75, *t*=6.58, *P*<.001).

Reliability

The re-test reliability of the Y-BOCS (*r*=.82, *P*<.001), OCI-R (*r*=.84, *P*<.001) and BDI-SF (*r*=.84, *P*<.001) were satisfactory (retest reliability was determined with scores from the waitlist only). The two scales correlated significantly at the first point in time (*r*=.56, *P*<.001).

Subjective appraisal

Table II provides data on the patients' subjective appraisal regarding the myMCT. The vast majority found the manual useful and adequate for self-administration; 85% of the patients found the myMCT superior to other self-help programs. Approximately two out of three patients reported a symptom decline due to the myMCT. However, half of the patients stated that they did not find the time to study the manual intensively. 25.9% performed exercises over a timespan of at least 14 days, whereby only two patients (7.4%) performed the exercises every day. The largest group (55.5%) performed the exercises for 7 to 14 days. The rest (18.5%) spend less than seven days performing the exercises.

Patients were also asked why they had not regularly performed the exercises. Lack of time (*n*=6) and that contents were partly known (*n*=5) were noted most frequently. 77% of the sample claimed that they would continue to use the myMCT.

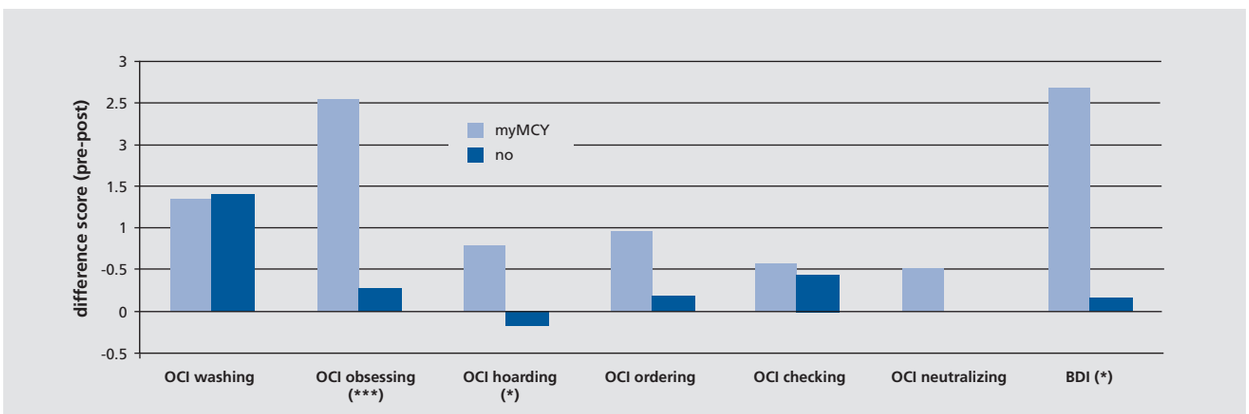

Figure 2. Group differences on the OCI-R and BDI-SF. Patients in the myMCT group showed significantly more decline than the waitlist group on the OCI-R total score (*P*<.001, *d*=.70) as well as BDI-SF (*P*<.05, *d*=.50). Subanalyses showed especially strong improvements for the OCI obsessing subscale. For OCI-R hoarding, the difference also turned out significant, but the improvement in the myMCT group was rather small.

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Discussion

The present trial asserts that myMCT is a feasible and effective self-help approach to treat patients with OCD. Medium to strong effect sizes in favor of myMCT were obtained for the Y-BOCS and OCI-R total scores. A fine-grained analysis showed that the decline was especially owing to a decrement on the Y-BOCS obsessions and the OCI-R obsessing subscales. Depression also declined significantly for those who read the e-book. Benefits for compulsions were small and nonsignificant (d=.20). Since the initial release we expanded the myMCT manual with a chapter on exposure which will likely positively impact on compulsions.

In retrospect, two thirds of the patients reported a symptom decline due to myMCT and the manual was deemed useful and comprehensive. The overwhelming majority (85%) found the myMCT more useful than other self-help books. While these findings are encouraging, they clearly fall behind the response rates obtained in formal clinician-administered psychotherapeutic studies,[5,6] which mirrors prior results on self- versus therapist-directed exposure and response prevention.[34] Patients in the myMCT group who refrained from reading the manual had fewer symptoms and possibly less *leidensdruck*.[46]

Before turning to possible implications, some limitations need to be acknowledged. Firstly, myMCT addresses different cognitive and metacognitive distortions and illness models derived from cognitive therapy (eg, normalizing: demonstrating patients that obsessions are common in the population and not a sign of psychopathology per se[47]), recent basic research on cognitive biases (eg, inflated responsibility, perfectionism), Wells' metacognitive therapy (eg, teaching patients that thoughts are not equivalent to actions and the dysfunctionality of rumination), analytic theorizing (especially latent aggression), and self-developed techniques (eg, association splitting[48,49]). Therefore, it is impossible to identify the most potent and efficacious component of the myMCT. We think, however, that some differences, for example between Wells' metacognitive therapy and CBT, have been overemphasized in the past[28] and that overlaps exist between CBT and analytic approaches[29] as well as between cognitive therapy and behavioral-oriented approaches.[50] Because some views are compatible and possibly complementary, we felt the need to integrate different concepts into a comprehensive treatment program. The result may be considered messy relative to pure programs. However, from the patients' comments we are left with the impression that for different patients different domains and exercises were helpful in line with a multifactorial illness model of OCD claiming that different etiologies may cause similar symptoms.

Secondly, the data relied on self-report rendering its results preliminary. While we acknowledge that external validation is the gold standard, recent studies have shown the reliability of self-report instruments and the compatibility of results obtained with the Y-BOCS self-report scale and the conventional expert rating.[44,45] In addition, the validity of internet relative to conventional research has been increasingly demonstrated,[51-54] even with severely impaired groups.[55,56] In line with these findings, the reliability (all scales r>.8) and validity (r=.56 between Y-BOCS and OCI-R) of the instruments were good in the present study.

MyMCT is not aimed to substitute standard psychotherapies but to reach patients unwilling or unable to undergo such therapies. As we have laid out in the introduction, the majority of patients does not receive (competent) help and if so, only at a very late stage. Low-threshold help and knowledge translation is thus extremely important at ear-

Item	Percentage endorsement
The myMCT is appropriate for self-administration	96%
My OCD symptoms have decreased due to the myMCT	63%
The manual was written comprehensively	100%
I found the manual useful	96%
I was able to regularly perform the exercises	78%
I did not find the time to study the manual intensively	52%
Other persons helped me with the myMCT	4%
I would find the myMCT more helpful in combination with a direct psychotherapy	67%
I found the myMCT more helpful than other self-help approaches	85%

Table II. Subjective appraisal of the myMCT (n=27).

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lier stages, before symptoms become chronic, and psychosocial and work functioning deteriorate, which may further aggravate psychological problems. Presumably, many of the patients participating in the study would not have undergone a formal clinical study. However, in future studies, we will test the utility of myMCT as a complement or add-on of regular psychotherapies.

To conclude, myMCT is a promising novel program targeting common cognitive biases in OCD. Whereas those biases identified by the Obsessive Compulsive Cognitions Working Group[23-26] are at its core, the program additionally incorporates other techniques (association splitting, detached mindfulness). It may not only serve as a self-help e-book, but its exercises, diagrams, and illustrations could also facilitate planning and performing psychotherapies, especially in view of increasing reports about a large number of therapists not adhering to standard therapy guidelines.[19] ❑

Appendix. The myMCT comprises 14 sections which deal with the following themes.

Section	Aim (literature)	Content
1. Bad thoughts are not normal?	Targets the false metacognitive belief that worries relating to contamination, aggression, and magical beliefs are abnormal and "bad" per se[47]	Patients are asked to guess how many of 100 healthy subjects endorse items with typical OCD content. The learning aim is to show that OCD-related worries are common in the general population and are not a sign of illness per se. What is fundamentally different between healthy and OCD participants is the appraisal of such cognitions. A second part deals with negative and aggressive feelings and ways to cope with such attitudes in a socially competent manner.
2. Evil thoughts cause evil actions?	Targets false metacognitive belief that thoughts are not (much) different from actions (thought-action fusion)[28]	Patients are given multiple examples that subjectively evil or bad ideas must not necessarily be translated into actions. Different kinds of fusion beliefs are challenged by behavioral experiments.
3. Thoughts have to obey will?	Targets false metacognitive belief that thoughts must obey will	Examples are presented where thoughts do not obey will (eg, intrusive thoughts, normal slips of the tongue, sudden creative ideas). Patients are encouraged to allow their thoughts some degrees of freedom as surveillance and suppression lead to a paradoxical increase of intrusions.
4. The world is dangerous?	Targets dysfunctional cognitive belief that one is at heightened vulnerability for disaster (ie, overestimation of threat, unrealistic pessimism)[57-59]	Readers are told about the tendency of many patients to overestimate their vulnerability for negative events, to overestimate negative consequences, and to process fear-related stimuli more efficiently than other classes of events. Exercises teach novel strategies to explore the environment (attention splitting: shift to neutral stimuli from the same modality as the feared stimuli) and exercises involving the calculation of base rates emphasizing that every new precondition decreases the likelihood for an event to occur.
5. Bad thoughts should be suppressed?	Targets dysfunctional coping strategy to get rid of thoughts by means of thought suppression[60]	The paradoxical increase of thoughts due to active suppression is demonstrated using a variant of the "white bear" exercise. Alternatively, patients are instructed to exercise detached mindfulness and to work with imaginations to attenuate bothersome thoughts (eg, to imagine a storm from a safe distance, whereby the bypassing thunderclouds stand for the obsessive thoughts).
6. If feelings signal alarm, there is real danger?	Targets dysfunctional metacognitive beliefs about	Strong emotions are often misinterpreted as signals of approaching dangers and resulting emotions often guide perception and appraisal. Patients are

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	the importance and validity of emotional states	shown that strong emotions are prone to false alarms and are often nurtured by peripheral factors (eg, coffee, alcohol etc.). In one exercise, patients are encouraged to actively dramatize their fears to experience that the emotional tension will decrease rather than increase by means of this intervention.
7. OCD poisons my thoughts forever?	Teaches a new technique to attenuate and "decontaminate" OCD cognitions[48,49]	The technique association splitting and its cognitive underpinning, the fan-effect,[61] are explained to patients. Basically, patients learn to associate "toxic" cognitions (eg, cancer=death) with neutral concepts (eg, cancer=zodiac sign) which automatically weakens the connections between an obsessive cognition to negative associations.
8. I am always responsible?	Targets false cognitive belief that negative events are primarily owing to oneself (inflated responsibility)[62]	Patients typically overestimate their share for the occurrence of negative events. Exercises involve the pie-chart technique: Patients first estimate the share that others and circumstances have for a negative event before evaluating their own share/responsibility. Another exercise is to view the same subjectively disastrous event that happened to oneself from the perspective of a good friend. This usually brings double standards to light which are subsequently challenged.
9. Good is not good enough? (Perfectionism)	Targets false cognitive belief that one has to be or act perfectly[23-26]	The disadvantages and dysfuntionality of perfectionist attitudes are brought to the patients' attention. It is made clear that even role models such as actors and political leaders are not perfect if you look behind the façade. In one of the exercises the patient should deliberately commit mistakes in order to experience that feared consequences are minor and largely exaggerated.
10. Seeking for truth	Targets dysfunctional beliefs about intolerance of ambiguity[23-26]	Many patients seek for truth even in areas where judgements are in the eye of the beholder and may vary across time, culture, and between subjects (eg, beauty, intelligence). Patients are encouraged to identify areas where a consensual opinion cannot be reached because they depend on taste (eg, arts), or where resolution would not even be welcome (eg, surprise parties).
11. Rumination helps?	Targets dysfunctional beliefs about the positive effects of rumination[28]	The dysfunctionality of rumination is demonstrated. Exercises are introduced such as the stop-technique, association splitting, and rumination postponement, the latter was inspired by Freeman and DeWolf.[63]
12. OCD as a brain disease?	Questions an overly biologistic illness model	While some patients are relieved by the view that their obsessions are caused by a brain disease, for others this view fuels fatalism and hopelessness. Some patients are convinced that having a brain defect means that their problems can only be alleviated through brain surgery or pills. While obsessive thoughts like all cognitive processes stem from activations in the brain, this does not imply that those activations are the cause for obsessive thoughts. In addition, the positive effects of psychotherapy on brain metabolism are outlined.
13. I am worthless?	Targets dysfunctional beliefs contributing to low self-esteem and depression	The participant is referred to module 8 of our metacognitive training for schizophrenia patients (MCT) which can be obtained cost-free via www.uke.de/mkt in various languages including English. This module presents generic/illness-unspecific exercises on typical depressive cognitions, as one to two thirds of OCD patients fulfill diagnostic criteria for an affective disorder.
14. Am I going insane?	Deals with the exaggerated worry of OCD patients of having or developing schizophrenia[3]	Many OCD patients are worried that they have or might get schizophrenia. Information on delusions and schizophrenia is provided and the core differences between OCD versus schizophrenia are contrasted (eg, doubt vs. conviction, different content).

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¿Cómo tratar lo intratable? Eficacia de un programa de auto-ayuda de entrenamiento metacognitivo (miEMC) para el trastorno obsesivo-compulsivo

A pesar de los avances en la comprensión y tratamiento del trastorno obsesivo-compulsivo (TOC), muchos pacientes que se someten a alguna intervención presentan una reducción incompleta de los síntomas. Nuestro grupo ha desarrollado un manual de auto-ayuda titulado "Mi entrenamiento metacognitivo" (miEMC) orientado a aumentar la conciencia de los pacientes acerca de los prejuicios cognitivos que parecer favorecen el TOC. El entrenamiento está planeado particularmente para pacientes que en ese momento son incapaces o no están dispuestos a asistir a una terapia adecuada, o en casos donde no se dispone de esa opción terapéutica. Para el presente estudio se reclutaron por internet 86 individuos que padecían de un TOC. Después de la evaluación inicial a los participantes se les envió por email el manual miEMC o se los asignó a un grupo en lista de espera. Luego de cuatro semanas se realizó una segunda evaluación. El grupo con miEMC mostró una mejoría significativamente mayor para los síntomas del TOC de acuerdo al puntaje total de la escala de Yale Brown (Y-BOCS) en comparación con el grupo de la lista de espera (d=0,63), especialmente para las obsesiones (d=0,69). Diferencias moderadas o marcadas aparecieron para el inventario obsesivo-compulsivo-revisado (OCI-R) (d=0,70) y el inventario de depresión de Beck en su forma acortada (BDI-SF) (d=0,50). Esta investigación aporta la primera evidencia de la eficacia del miEMC en el TOC.

Comment traiter ce qui ne l'est pas : efficacité d'un programme d'entraînement métacognitif de développement personnel (myMCT) pour le trouble obsessionnel compulsif

Malgré des progrès dans la compréhension et le traitement du trouble obsessionnel compulsif (TOC), de nombreux patients ayant été traités ne présentent qu'une diminution partielle des symptômes. Notre groupe a mis au point un manuel de développement personnel intitulé « Ma formation métacognitive pour le TOC » (« myMCT »), dont le but était de faire prendre conscience au patient des biais cognitifs semblant favoriser le TOC. La formation est particulièrement destinée aux patients actuellement incapables ou réticents à suivre une thérapie adéquate, ou au cas où ce traitement n'est pas disponible. Pour cette étude, 86 patients atteints de TOC ont été recrutés sur internet. Après l'évaluation initiale, les participants ont été répartis en 2 groupes : un qui recevait immédiatement par e-mail le manuel « myMCT », l'autre sur liste d'attente. Après 4 semaines, une seconde évaluation a été réalisée. Les symptômes du TOC ont été améliorés de façon significative dans le groupe « myMCT », selon le score total au Y-BOCS comparé au groupe de la liste d'attente (d = 0,63), en particulier pour les obsessions (d = 0,69). Des différences légères à importantes ont été enregistrées à l'OCI-R (d = 0,70) et au BDI-SF (d = 0.50). Ainsi, ces analyses ont permis de mettre en évidence de premiers éléments en faveur de l'efficacité du « myMCT » pour le TOC.

REFERENCES

1. Abramowitz JS. *Obsessive-Compulsive Disorder: Advances in Psychotherapy—Evidence Based Practice*. Cambridge, MA: Hogrefe & Huber; 2006.
2. Bobes J, García-Portilla M-P, Bascarán M-T, Sáiz P-A, Bobes-Bascarán M-T, Bousoño M. Quality of life in obsessive-compulsive disorder In: Ritsner MS, Awad AG, eds. *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders*. Amsterdam, the Netherlands: Elsevier; 2007:293-303
3. Moritz S. A review on quality of life and depression in obsessive-compulsive disorder. *CNS Spectr*. 2008;13 (suppl 14):16-22.
4. Abramowitz JS. Does cognitive-behavioral therapy cure obsessive-compulsive disorder? A meta-analytic evaluation of clinical significance. *Behav Ther.* 1998;29:339-355.
5. Abramowitz JS. The psychological treatment of obsessive-compulsive disorder. *Can J Psychiatry*. 2006;51:407-416.
6. Gava I, Barbui C, Aguglia E, Carlino D, Churchill R, De Vanna M, et al. Psychological treatments versus treatment as usual for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2007;2 (Art. No.: CD005333).
7. Rosa-Alcazar AI, Sanchez-Meca J, Gomez-Conesa A, Marin-Martinez F. Psychological treatment of obsessive-compulsive disorder: a meta-analysis. *Clin Psychol Rev*. 2008;28:1310-1325.
8. O'Kearney RT, Anstey KJ, von Sanden C. Behavioural and cognitive behavioural therapy for obsessive compulsive disorder in children and adolescents. *Cochrane Database Syst Rev*. 2006(4 (Art. No.: CD004856)).
9. Moritz S, Fricke S, Jacobsen D, Kloss M, Wein C, Rufer M, et al. Positive schizotypal symptoms predict treatment outcome in obsessive-compulsive disorder. *Behav Res Ther*. 2004;42:217-227.
10. Hand I. Out-patient, multi-modal behaviour therapy for obsessive-compulsive disorder. *Br J Psychiatry*. 1998;173:45-52.
11. Pinard G. The pharmacologic and psychological treatment of obsessive-compulsive disorder. *Can J Psychiatry*. 2006;51:405-406.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 219

12. Bados A, Balaguer G, Saldaña C. The efficacy of cognitive–behavioral therapy and the problem of drop-out. *J Clin Psychol*. 2007;63:585–592.
13. Hollander E, Kwon JH, Stein DJ, Broatch J, Rowland CT, Himelein CA. Obsessive-compulsive and spectrum disorders: overview and quality of life issues. *J Clin Psychiatry*. 1996;57(suppl 8):3-6.
14. Stengler-Wenzke K, Angermeyer MC. Inanspruchnahme von professioneller Hilfe durch Patienten mit Zwangserkrankungen [Employment of professional help by patients with obsessive-compulsive disorders]. *Psychiatrische Praxis*. 2005;32:195-201.
15. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bulletin of the World Health Organisation*. 2004;82:858-866.
16. Blanco C, Olfson M, Stein DJ, Simpson HB, Gameroff MJ, Narrow WH. Treatment of obsessive-compulsive disorder by U.S. psychiatrists. *J Clin Psychiatry*. 2006;67:946-951.
17. Kulz AK, Hassenpflug K, Riemann D, Linster HW, Dornberg M, Voderholzer U. Psychotherapeutic care in OCD outpatients - results from an anonymous therapist survey. *Psychother, Psychosom, Med Psychol*. 2009;59:1-8.
18. Böhm K, Förstner U, Külz A, Voderholzer U. Versorgungsrealität der Zwangsstörungen: Werden Expositionsverfahren eingesetzt? [Health care provision for patients with obsessive compulsive disorder: is exposure treatment used?]. *Verhaltenstherapie*. 2008;18:18-24.
19. Shafran R, Clark DM, Fairburn CG, Arntz A, Barlow DH, Ehlers A, et al. Mind the gap: Improving the dissemination of CBT. *Behav Res Ther*. In press.
20. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
21. Eddy KT, Dutra L, Bradley R, Westen D. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev*. 2004;24:1011-1030.
22. Moritz S. *Metacognitive Training for Obsessive-Compulsive Disorder (MyMCT). A Self-Help Book. [Erfolgreich gegen Zwangsstörungen. Metakognitives Training. Denkfallen erkennen und entschärfen.]* Heidelberg, Germany: Springer. 2010.
23. Obsessive Compulsive Cognitions Working Group. Cognitive assessment of obsessive-compulsive disorder. *Behav Res Ther*. 1997;35:667-681.
24. Obsessive Compulsive Cognitions Working Group. Development and initial validation of the obsessive beliefs questionnaire and the interpretation of intrusions inventory. *Behav Res Ther*. 2001;39:987-1006.
25. Obsessive Compulsive Cognitions Working Group. Psychometric validation of the and the Interpretation of Intrusions Inventory: Part I. *Behav Res Ther*. 2003;41:863-878.
26. Obsessive Compulsive Cognitions Working Group. Psychometric validation of the Obsessive Beliefs Questionnaire and the Interpretation of Intrusions Inventory - Part II: Factor analyses and testing of a brief version. *Behav Res Ther*. 2005;43:1527-1542.
27. Moritz S, Woodward TS. Metacognitive training in schizophrenia: from basic research to knowledge translation and intervention. *Curr Opin Psychiatry*. 2007;20:619-625.
28. Fisher P, Wells A. *Metacognitive Therapy*. Hove: Routledge; 2009.
29. Kempke S, Luyten P. Psychodynamic and cognitive-behavioral approaches of obsessive-compulsive disorder: is it time to work through our ambivalence? *Bull Menninger Clin*. 2007;71:291-311.
30. Hall CS. *A Primer of Freudian Psychology*. New York, NY: Mentor Book; 1954.
31. Moritz S, Wahl K, Ertle A, Jelinek L, Hauschildt M, Klinge R, et al. Neither saints nor wolves in disguise: ambivalent interpersonal attitudes and behaviors in obsessive-compulsive disorder. *Behav Mod*. 2009;33:274-92.
32. Myers SG, Wells A. Obsessive-compulsive symptoms: the contribution of metacognitions and responsibility. *Anxiety Disord*. 2005;19:806-817.
33. Mataix-Cols D, Marks IM. Self-help with minimal therapist contact for obsessive-compulsive disorder: a review. *Eur Psychiatry*. 2006;21:75-80.
34. Tolin DF, Hannan S, Maltby N, Diefenbach GJ, Worhunsky P, Brady RE. A randomized controlled trial of self-directed versus therapist-directed cognitive-behavioral therapy for obsessive-compulsive disorder patients with prior medication trials. *Behav Ther*. 2007;38:179-191.
35. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, et al. The Obsessive-Compulsive Inventory: development and validation of a short version. *Psychological Assessment*. 2002;14:485-496.
36. Abramowitz JS, Deacon BJ. Psychometric properties and construct validity of the Obsessive-Compulsive Inventory--Revised: Replication and extension with a clinical sample. *J Anxiety Disord*. 2006;20:1016-1035.
37. Huppert JD, Walther MR, Hajcak G, Yadin E, Foa EB, Simpson HB, et al. The OCI-R: validation of the subscales in a clinical sample. *J Anxiety Disord*. 2007;21:394-406.
38. Gonner S, Leonhart R, Ecker W. The Obsessive-Compulsive Inventory-Revised (OCI-R): validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. *J Anxiety Disord*. 2008;22:734-749.
39. Gönner S, Leonhart R, Ecker W. Das Zwangsinventar OCI-R - die deutsche Version des Obsessive-Compulsive Inventory-Revised: Ein kurzes Selbstbeurteilungsinstrument zur mehrdimensionalen Messung von Zwangssymptomen [The German version of the obsessive-compulsive inventory-revised: a brief self-report measure for the multidimensional assessment of obsessive-compulsive symptoms]. *Psychother, Psychosom, Med Psychol*. 2007;57:395-404.
40. Abramowitz JS, Tolin D, Diefenbach G. Measuring change in OCD: sensitivity of the Obsessive-Compulsive Inventory-Revised. *J Psychopathol Behav Assess*. 2005;27:317-324.
41. Beck AT, Steer RA. Beck *Depression Inventory Manual*. San Antonio: Psychological Corporation; 1993.
42. Furlanetto LM, Mendlowicz MV, Romildo Bueno J. The validity of the Beck Depression Inventory-Short Form as a screening and diagnostic instrument for moderate and severe depression in medical inpatients. *J Affect Disord*. 2005;86:87-91.
43. Baer L, Brown-Beasley MW, Sorce J, Henriques AI. Computer-assisted telephone administration of a structured interview for obsessive-compulsive disorder. *Am J Psychiatry*. 1993;150:1737-1738.
44. Schaible R, Armbrust M, Nutzinger DO. Yale-Brown Obsessive Compulsive Scale: Sind Selbst- und Fremdrating äquivalent? [Yale-Brown Obsessive Compulsive Scale: Are self-rating and interview equivalent measures?]. *Verhaltenstherapie*. 2001;11:298-303.
45. Steketee G, Frost R, Bogart K. The Yale-Brown Obsessive Compulsive Scale: interview versus self-report. *Behav Res Ther*. 1996;34:675-684.
46. Besiroglu L, Cilli AS, Askin R. The predictors of health care seeking behavior in obsessive-compulsive disorder. *Compr Psychiatry*. 2004;45:99-108.
47. Rachman S, de Silva P. Abnormal and normal obsessions. *Behav Res Ther*. 1978;16:233-248.
48. Moritz S, Jelinek L. *Association Splitting - Self-Help Guide for Reducing Obsessive Thoughts*. Hamburg: VanHam Campus Verlag; 2007.
49. Moritz S, Jelinek L, Klinge R, Naber D. Fight fire with fireflies! Association Splitting: a novel cognitive technique to reduce obsessive thoughts. *Behav Cogn Psychotherapy*. 2007;35:631-635.
50. Kozak MJ, Foa EB. *Mastery of Obsessive Compulsive Disorder: a Cognitive Behavioral Approach*. San Antonio: Psychological Corporation; 1997.
51. Coles ME, Cook LM, Blake TR. Assessing obsessive compulsive symptoms and cognitions on the internet: evidence for the comparability of paper and Internet administration. *Behav Res Ther*. 2007;45:2232-2240.
52. Meyerson P, Tryon WW. Validating internet research: a test of the psychometric equivalence of internet and in-person samples. *Behav Res Methods, Instr, Comp*. 2003;35:614-620.
53. Ritter P, Lorig K, Laurent D, Matthews K. Internet versus mailed questionnaires: a randomized comparison. *J Med Internet Res*. 2004;6:e29.
54. Riva G, Teruzzi T, Anolli L. The use of the internet in psychological research: comparison of online and offline questionnaires. *CyberPsychol Behav.* 2003; 6:73-80.
55. Chinman M, Young AS, Schell T, Hassell J, Mintz J. Computer-assisted self-assessment in persons with severe mental illness. *J Clin Psychiatry*. 2004;65:1343-151.
56. Moritz S, Larøi F. Differences and similarities in the sensory and cognitive signatures of voice-hearing, intrusions and thoughts. *Schizophrenia Res*. 2008;102:96-107.
57. Moritz S, Jelinek L. Inversion of the "unrealistic optimism" bias contributes to over-estimation of threat in obsessive-compulsive disorder. *Behav Cogn Psychotherapy.* In press.
58. Moritz S, Pohl RF. Biased processing of threat-related information rather than knowledge deficits contributes to overestimation of threat in obsessive-compulsive disorder. *Behav Mod*. 2009;33:763-777.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 220

59. Moritz S, Pohl RF. False beliefs maintenance for fear-related information in obsessive-compulsive disorder: an investigation with the hindsight paradigm. *Neuropsychol*. 2006;20:737-742.
60. Rassin E. *Thought Suppression*. New York, NY: Elsevier; 1995.
61. Anderson JR. Retrieval of propositional information from long-term memory. *Cogn Psychol*. 1974;6:451-474.
62. Salkovskis PM, Forrester E. Responsibility. In: Frost RO, Steketee G, eds. *Cognitive Approaches to Obsessions and Compulsions - Theory, Assessment, and Treatment*. Amsterdam, the Netherlands: Pergamon; 2002:45-51.
63. Freeman A, DeWolf R. *10 Dumbest Mistakes Smart People Make and How to Avoid Them*. New York, NY: Harper; 1992.

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Body dysmorphic disorder

Andri S. Bjornsson, PhD; Elizabeth R. Didie, PhD; Katharine A. Phillips, MD

Body dysmorphic disorder (BDD) is a relatively common disorder that consists of a distressing or impairing preoccupation with imagined or slight defects in appearance. BDD is commonly considered to be an obsessive-compulsive spectrum disorder, based on similarities it has with obsessive-compulsive disorder. It is important to recognize and appropriately treat BDD, as this disorder is associated with marked impairment in psychosocial functioning, notably poor quality of life, and high suicidality rates. In this review, we provide an overview of research findings on BDD, including its epidemiology, clinical features, course of illness, comorbidity, psychosocial functioning, and suicidality. We also briefly review recent research on neural substrates and cognitive processing. Finally, we discuss treatment approaches that appear efficacious for BDD, with a focus on serotonin-reuptake inhibitors and cognitive-behavioral therapy.

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Body dysmorphic disorder (BDD) is a *DSM-IV* disorder that is characterized by a distressing or impairing preoccupation with slight or imagined defect(s) in one's physical appearance. BDD has been consistently described around the world for more than a century.[1,2] Enrico Morselli, an Italian physician who called this disorder "dysmorphophobia," offered this poignant description in 1891: "The dysmorphophobic patient is really miserable; in the middle of his daily routines, conversations, while reading, during meals, in fact everywhere and at any time, is overcome by the fear of deformity… which may reach a very painful intensity, even to the point of weeping and desperation".[3] BDD was later described by distinguished psychiatrists such as Emil Kraepelin and Pierre Janet[4,5] and, over the years, numerous case studies have been reported from around the world.[6]

Despite its long history, BDD has been researched in a sustained and systematic way for less than two decades. During this time, much has been learned about the disorder, including its clinical features, epidemiology, and treatment. While still very preliminary, data are beginning to emerge on BDD's neurocognitive deficits and underlying neurobiology. BDD is becoming better known, but it remains underrecognized.[7-11] Because BDD causes substantial suffering and impairment in functioning, there is a need for increased recognition of this often-debilitating condition across all specialties.[12]

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Definition and classification of BDD

Here we provide *DSM-IV*'s definition of BDD and briefly comment on each diagnostic criterion.

A) "Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive." The most common preoccupations focus on the skin (eg, scarring, acne, color), hair (eg, going bald, excessive facial or body hair), or nose (eg, size or shape), although any body part can be the focus of concern.[13] "Preoccupation" in criterion A is not operationalized, but it is often defined as thinking about the perceived appearance defect(s) for at least 1 hour a day (similar to obsessive-compulsive disorder [OCD]).[1,14,15]

B) "The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning." As in other disorders, distress and impairment in functioning vary in terms of severity. But typically, patients experience substantial impairment in social, occupational, and academic functioning, as will be discussed later in this review.

C) "The preoccupation is not better accounted for by another mental disorder (eg, dissatisfaction with body shape and size in anorexia nervosa)." This criterion indicates that if a person's only appearance concern is that he/she weighs too much or is too fat, and the person meets diagnostic criteria for anorexia nervosa or bulimia nervosa, then the eating disorder, rather than BDD, is diagnosed. However, BDD and eating disorders are frequently comorbid, in which case both disorders should be diagnosed.[16,17]

DSM first included BDD in the third edition (*DSM-III*), where it was called "dysmorphophobia."[18] In *DSM-III*, it was an example of an atypical somatoform disorder (the "atypical" designation was similar to *DSM-IV*'s "Not Otherwise Specified" category), and diagnostic criteria were not provided. BDD was first given diagnostic criteria, and classified as a separate disorder (a somatoform disorder), in *DSM-III-R*, where it was called "body dysmorphic disorder."[19] In the current edition of *DSM* (*DSM-IV-TR*), BDD is also classified as a somatoform disorder.[15] ICD-10 classifies BDD, along with hypochondriasis, as a type of "hypochondriacal disorder," also in the somatoform section.[20] During the *DSM-IV* development process, consideration was given to moving BDD to the anxiety disorders section of *DSM*, but there were insufficient data at that time to determine whether this change was warranted.[21] Under consideration for *DSM-5* is whether BDD might be included in a section of "Anxiety and Obsessive-Compulsive Spectrum Disorders," although it is not yet known whether such a section will be included in *DSM-5*.[22]

A clinically important issue is how BDD's delusional variant (in which patients are completely convinced that they appear ugly or abnormal) should be classified. In *DSM-IV*, BDD's delusional variant is classified as a type of delusional disorder, somatic type, in the psychosis section of the manual.[15] However, *DSM-IV* allows BDD and its delusional disorder variant to be doublecoded; in other words, patients with delusional BDD can receive a diagnosis of both delusional disorder and BDD.[15] This double coding reflects evidence that BDD's delusional and nondelusional variants may in fact be variants of the same disorder.[7,23,24] Importantly, BDD's delusional variant appears to respond to treatment with serotonin-reuptake inhibitor (SRI) monotherapy, and, although data are very preliminary, treatment with neuroleptics does not appear promising.[25,26] During the *DSM-5* development process, consideration is being given to combining BDD's delusional variant with its nondelusional variant into one disorder (BDD) while specifying degree of insight (with good or fair insight, with poor insight, or with delusional BDD beliefs).[17]

Epidemiology

BDD appears to be relatively common. Epidemiologic studies have reported a point prevalence of 0.7% to 2.4% in the general population.[27-30] These studies suggest that BDD is more common than disorders such as schizophrenia or anorexia nervosa.[15] Investigations in nonclinical adult student samples have yielded higher prevalence rates of 2% to 13%.[31-35]

BDD is commonly found in clinical settings, with studies reporting a prevalence of 9% to 12% in dermatology settings, 3% to 53% in cosmetic surgery settings, 8% to 37% in individuals with OCD, 11% to 13% in social phobia, 26% in trichotillomania, and 14% to 42% in atypical major depressive disorder (MDD).[8,36-49] Studies of psychiatric inpatients have found that 13% to 16% of patients have *DSM-IV* BDD.[9,50] A study of adolescent inpatients found that 4.8% of patients had BDD.[10]

These studies indicate that BDD is relatively common. However, these estimates may underreport its prevalence. Many individuals with BDD feel ashamed of their

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appearance and the fact that they are so focused on it. As a consequence, they may not report their BDD symptoms to clinicians. In one study of psychiatric inpatients, only 15.1% had revealed their body image concerns to their mental health clinicians, and the most common reason for not disclosing their concerns was embarrassment (in 31.3%).[50] Furthermore, in five studies in which adults were systematically screened for BDD, no patient who was found by the researchers to have BDD had the diagnosis of BDD in their medical record.[7-11] The number of patients found to have BDD were as follows: 30 of 30, 11 of 80, 16 of 122, 10 of 208, and 16 of 122.

Demographic characteristics

BDD has been reported to occur in children as young as 5 and in adults as old as 80.[6,51] Regarding gender ratio, the two largest population-based studies of BDD (one conducted in the US; n=2048, and the other conducted in Germany; n=2552) found a point prevalence of 2.5% of women vs 2.2% of men, and 1.9% of women and 1.4% of men, respectively.[28,30] The largest clinical samples of persons ascertained for BDD contained an equal proportion of females and males (49% of 188 participants were female)[52] or a somewhat higher proportion of females (68.5% of 200 participants).[53] Thus, BDD may be somewhat more common in women, but it clearly affects many men as well.

The two population-based studies cited earlier found that individuals with BDD are less likely to be married than those without BDD,[28,30] and are more likely to be divorced. Individuals with BDD are also significantly more likely to be unemployed than the general population.[28,30] In a sample of 200 individuals with BDD, 37.6% were currently unemployed.[54]

Case description

Ms A, a 32-year-old single white female, was referred by her dermatologist to a BDD specialty clinic. She lived alone, was not involved in a romantic relationship, and had no children. Despite having completed college, she was employed as a part-time clerk in a clothing boutique. Ms A attributed her difficulties with obtaining full-time work to interference she experienced from intrusive thoughts and compulsive behaviors related to her appearance concerns.

Ms A looked normal but had been preoccupied with the appearance of her skin (minor blemishes and "uneven" skin tone) since age 13. She reported thinking about her appearance for at least 7 to 8 hours a day, and she worried that other people would notice her or judge her negatively because her skin looked so "ugly." For 5 to 6 hours a day, Ms. A checked her skin in mirrors and other reflecting surfaces, picked her skin, and compared her skin with that of other people. She spent thousands of dollars a year on skin-care products, and she frequently bought special lighting and mirrors to better examine her skin.

Because she was so preoccupied with, and distressed by, her skin, Ms A was often late for work, and her productivity suffered, which resulted in conflicts with her supervisor. She often got "stuck" in the mirror at work, examining her skin. Because Ms A was so embarrassed about how she looked, and feared that other people would judge her negatively (eg, as "abnormal looking" and "hideous"), Ms A avoided all contact with friends and saw her family only on special occasions. Ms A reported feeling anxious and depressed over her skin. She also expressed passive suicidal ideation because she thought her skin looked so ugly.

Ms A had seen several dermatologists for treatment to improve her skin's appearance. Her compulsive skin picking was intended to improve perceived skin flaws by "smoothing" her skin and removing tiny blemishes. However, because her skin picking was difficult to control and occurred for several hours a day, this behavior caused skin irritation and slight redness and scarring. Ms A had undergone three dermatologic procedures but continued to be "obsessed" with improving the quality of her skin. "I just want to look normal!" she stated. Ms A reported that the dermatologic procedures had done little to change her perception of her skin's appearance and made her feel even more anxious and preoccupied. This was the first time Ms A had sought mental health treatment for her skin concerns. In the past, she had been reluctant to discuss her concerns with a mental health clinician for fear that she would be perceived as "superficial" or "vain."

Appearance preoccupations

The most frequent body areas of concern are the skin (73%), hair (56%), and nose (37%).[52,55] However, any body area can be the focus of preoccupation. On aver-

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age, over their lifetime, persons with BDD are preoccupied with 5 to 7 different body parts.[52,55] Some individuals are preoccupied with their overall appearance; this includes the muscle dysmorphia form of BDD which consists of the belief that one's body is too small and inadequately muscular.[56-58]

Approximately 40% of individuals with BDD actively think about the disliked body parts for 3 to 8 hours per day, and 25% report thinking about them for more than 8 hours per day.[6] These preoccupations are almost always difficult to resist or control, and they are intrusive and associated with significant anxiety and distress.[1]

Insight regarding perceived appearance defects

Insight regarding the perceived appearance defects varies. In one sample, 35.6% of participants were classified on the reliable and valid Brown Assessment of Beliefs Scale (BABS[59]) as delusional—that is, completely certain that their beliefs about how they look were accurate.[60] Prior to effective treatment, few patients have good insight. Studies have consistently found that insight is poorer in BDD than in OCD, with 27% to 60% of BDD patients having delusional beliefs versus only 2% of OCD patients.[13,61]

About two thirds of BDD patients have past or current ideas or delusions of reference, believing that other people take special notice of them in a negative way or mock or ridicule them because of how they look.[23] Clinical impressions indicate that such referential thinking may lead to feelings of rejection and to anger (even violence, such as attacking someone they believe is mocking them).[1]

As previously noted, patients with delusional BDD beliefs would receive a *DSM-IV-TR* diagnosis of delusional disorder, or *DSM-IV-TR* diagnoses of both delusional disorder and BDD. Studies comparing delusional and nondelusional BDD patients reveal more similarities than differences between the two groups, and that the primary difference is BDD symptom severity.[23,25,60] Importantly, delusional BDD appears to respond to SRI monotherapy and may not respond to antipsychotic medications, suggesting (from a treatment perspective) that delusional BDD is not a typical psychotic disorder.[26] Thus, it may be more accurate to view insight as existing on a continuum and to consider BDD to encompass both delusional and nondelusional appearance beliefs.[62] Furthermore, some individuals with BDD describe fluctuations in insight, such that they are completely convinced that they are ugly at some times but not convinced at others.[6] As one patient remarked: "Some days I think my skin's not so bad, but other days I'm convinced."[1] Observations such as these offer further support for the view that delusional BDD and nondelusional BDD constitute the same disorder, characterized by a range of insight, rather than being different disorders.

Compulsions, safety behaviors, and avoidance

The *DSM-IV-TR* diagnostic criteria for BDD make no reference to compulsive and safety behaviors that are commonly associated with BDD; during the *DSM-5* development process, consideration is being given to adding these symptoms to BDD's diagnostic criteria.[17] Indeed, nearly everyone with BDD performs specific behaviors—such as mirror checking and skin picking, as illustrated in the above case—that are linked to their appearance preoccupations.[52,55] The relationship between thoughts and behaviors in BDD appears similar to the relationship between obsessions and compulsions in OCD. That is, the compulsive behaviors arise in response to the obsessive thoughts about appearance, and are meant to reduce anxiety and other painful emotions.[13] As in OCD, the behaviors are not pleasurable.[13]

These compulsive behaviors are repetitive, time-consuming (about half of BDD patients spend 3 or more hours per day engaged in them), and hard to control and resist.[63] Some behaviors, such as camouflaging disliked body parts (eg, with a hat, makeup, sunglasses), are called safety behaviors, because their function is to reduce or avoid painful emotions or prevent something bad from happening, such as being humiliated or embarrassed.[1]

Most BDD patients perform multiple compulsive behaviors.[52,55] One common behavior is comparing themselves with other people. Clinical impressions suggest that this usually happens quite automatically, and can cause anxiety and inability to concentrate. About 90% of BDD patients check themselves repeatedly and excessively in mirrors or other reflective surfaces.[1] Typically, they do this in the hope that they look acceptable, but often, after seeing their reflection, they feel worse.[64] Other common repetitive behaviors are excessive grooming (eg, combing their hair or washing their skin repeatedly), tanning (to improve their skin color or skin imperfections), reas-

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surance seeking (asking whether one's appearance is acceptable), excessive shopping for beauty products, changing their clothes repeatedly to find a more flattering outfit, and excessive exercise (eg, weightlifting in the case of muscle dysmorphia).[1,52,55,64-66] Many BDD patients (27% to 45%) pick at their skin in an attempt to improve perceived blemishes or imperfections; however, this behavior sometimes causes observable appearance defects and can even cause severe damage such as skin infections and rupture of blood vessels.[67-69] Many other examples of compulsive behaviors exist, which are often idiosyncratic, such as drinking more than 3 gallons of water a day to make one's face look fuller.[1]

Avoidance is a common behavior in BDD.[70,71] Patients often avoid social situations since they fear being negatively judged by other people because they look "ugly." They may not take a job where they think they will be scrutinized by others. Avoidance may serve a similar purpose as the compulsive behaviors in the short term—that is, to temporarily relieve BDD-related anxiety and distress. However, clinical experience indicates that compulsions and avoidance seldom improve anxiety or reduce the intensity of BDD-related thoughts; rather these behaviors may contribute to the chronicity and severity of BDD.[1,72]

Course of illness

BDD usually begins during adolescence, with two studies reporting a mean age at onset of 16 and a mode of 13.[55,73] Retrospective data indicate that BDD appears to usually have a chronic course, unless it is treated.[52,55] In what is to our knowledge the only prospective study of BDD's course, it was found that the probability of full remission from BDD over 1 year of follow-up was only .09, which is lower than has been reported for mood disorders, most anxiety disorders, and personality disorders in other longitudinal studies.[74] More severe BDD symptoms at intake, longer duration of BDD, and the presence of one or more comorbid personality disorders at intake predicted a lower likelihood of remission from BDD.[75]

Psychosocial functioning and quality of life

BDD is associated with substantial impairment in psychosocial functioning and markedly poor quality of life. In a sample of 200 individuals with BDD (n=200), 36% did not work for at least one week in the past month because of psychopathology, and 11% had permanently dropped out of school because of BDD symptoms.[54] Individuals with BDD have, on average, much poorer mental health, emotional well-being, social functioning, and overall quality of life than the general population, and scores on quality of life measures are poorer than for patients with diabetes or clinical depression.[76,77] In the only prospective study of BDD, overall functioning continued to be poor over 1 to 3 years, and poorer functioning was predicted by more severe BDD and greater delusionality of BDD beliefs at intake.[78] Many patients with more severe BDD are unable to work, be in or attend school, or have relationships.[1,54] In two studies, 27% to 31% of individuals with BDD had been completely housebound for at least 1 week due to BDD symptoms, and more than 40% had been psychiatrically hospitalized.[52,55]

Risk behaviors: suicidality, substance abuse, and violence

Rates of suicidal ideation, suicide attempts, and completed suicide appear markedly elevated.[79] Approximately 80% of individuals with BDD report past or current suicidal ideation, and about one quarter have attempted suicide, which is often attributed to BDD symptoms.[42,50,52,79-81] In the only prospective study of the course of BDD, completed suicide was reported in 0.3% of cases per year.[82] This finding should be considered preliminary, because the sample size was relatively small and the follow-up period was relatively brief; nonetheless, this suicide rate is markedly elevated. While caution should be used in comparing this rate to that of other disorders, the standardized mortality ratio in this study is higher than that reported for nearly any other mental disorder.[83]

Approximately one third of people with BDD report violent behavior that they attribute primarily to BDD symptoms (eg, attacking someone or damaging property).[1,84] Clinical impressions suggest that anger or violence may be fueled by anger about looking "deformed," inability to fix the "defect," delusions of reference (eg, believing that other people are mocking the "defect"), and feeling rejected by others because of the "defect." In addition, anger or even violent behavior may be caused by dissatisfaction with cosmetic procedures. According to one survey, 12% of plastic surgeons said that they had been threatened physically by a dissatisfied BDD patient.[85] There are occasional reports of individuals with probable BDD who attacked and even

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killed their plastic surgeon after being distraught by the outcome of a cosmetic procedure.[2]

Many individuals with BDD abuse alcohol or drugs. In one study,[86] 48.9% of BDD participants were diagnosed with a lifetime substance-use disorder, with 42.6% reporting an alcohol-use disorder and 30.1% reporting a cannabis-use disorder. Onset of BDD preceded onset of a substance-use disorder by at least 1 year in 60% of the participants, followed onset of the substance-use disorder in 19% of the participants, and began in the same year in 21%. When asked about the relationship between substance use and BDD symptoms, 68% said that BDD symptoms contributed to the substance use becoming problematic.[86]

Comorbidity

BDD is often comorbid with other mental disorders. In the two largest phenomenology studies of individuals ascertained for BDD (n=293 and n=200), which assessed all participants with the Structured Clinical Interview for *DSM*,[14] major depressive disorder was the most common comorbid disorder, with a lifetime prevalence of about 75% in both samples.[55,73] The other most common lifetime comorbid disorders were substance-use disorders (30% to 48.9%), OCD (32% to 33%), and social phobia (37% to 39%).[55,73,86]

BDD in children and adolescents

Even though BDD usually begins before age 18, very few studies have systematically examined a broad range of BDD's clinical features in youth.[87,88] Like adults, youth report prominent, distressing, and time-consuming appearance preoccupations as well as prominent appearance-related compulsive behaviors. Nearly all youth experience impairment in psychosocial functioning that is attributed primarily to BDD symptoms. In a study of 33 children and adolescents,[87] 18% had dropped out of elementary school or high school primarily because of BDD symptoms, and in a study of 36 youths, 22% had dropped out of school primarily because of BDD.[88] Such difficulties may be particularly problematic during adolescence, because they may substantially interfere with important adolescent developmental transitions.[1,87,89]

Preliminary findings suggest that BDD appears largely similar in youths and adults; however, in a study that directly compared adolescents with adults, the adolescents had more delusional beliefs about their appearance, and they were significantly more likely to currently have a substance-use disorder (30.6% vs 12.8%) and a history of suicide attempts (44.4% vs 23.8%).[88] In an adolescent inpatient study, adolescents with BDD (n=14) scored significantly higher than those without clinically significant body image concerns (n=140) on the Suicide Probability Scale, which reflects suicide risk.[10,90]

Neural substrates and cognitive processing

Findings from neuropsychological research suggest that those with BDD overfocus on details of visual stimuli rather than global aspects.[91] Similarly, an fMRI study of facial processing found a bias among BDD subjects for using strategies to encode details of stimuli rather than use of holistic visual processing strategies.[92] These findings are consistent with clinical observations that individuals with BDD overly focus on minor details of their appearance, which is theorized to fuel preoccupation with minor or nonexistent appearance flaws.[1,72,92,93] Recent research suggests that other information processing abnormalities are present in BDD, eg, threatening interpretations for nonthreatening scenarios and overestimation of the attractiveness of others' faces.[94] In studies that used photographs showing emotional expressions,[94,95] BDD subjects relative to healthy controls tended to misinterpret neutral emotional expressions as contemptuous and angry in scenarios that were self-referent (ie, when someone was said to be looking at the BDD subject).[94] This finding is consistent with how individuals with BDD often report ideas or delusions of reference (thoughts that they are being judged negatively or rejected because of their appearance). Future research is necessary to examine this important area further and assess implications for treatment.

Additional neuroimaging studies have been done, with some similar results and some dissimilar results across studies; findings should be considered preliminary because sample sizes were small and few studies have been published. A small MRI study found that BDD subjects, compared with healthy control participants, exhibited significantly abnormal asymmetry of the caudate nucleus, with a leftward shift in laterality quotient, as well as greater total white matter volume.[96] A second small study similarly found greater white matter volume in BDD relative to controls, in addition to smaller orbitofrontal cortex and anterior cingulate and larger

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thalamic volumes.[97] However, a third study found no significant volumetric differences in BDD vs healthy controls.[98] A small BDD single proton-emission computed tomography study showed relative perfusion deficits in bilateral anterior temporal and occipital regions and asymmetric perfusion in the parietal lobes.[99] In another study, when viewing a photograph of their own face vs a familiar face, BDD subjects had relative hyperactivity in left orbitofrontal cortex and bilateral head of the caudate compared with controls; frontostriatal activation correlated with aversiveness ratings of faces and BDD severity.[100] These results are similar to those in OCD symptom provocation studies,[101] suggesting that BDD and OCD symptoms may possibly be mediated by the same orbitofrontal-subcortical circuit (although this study did not directly compare BDD and OCD).

Cosmetic treatment for BDD

A majority of individuals with BDD seek (71% to 76%) and receive (64% to 66%) cosmetic treatment (eg, surgical, dermatologic, or dental) for their perceived appearance flaws.[102,103] In a general population sample from Germany, 7.2% of those with BDD had received cosmetic surgery, compared with only 2.8% of those without BDD.[30] However, such treatment appears to only rarely improve overall BDD symptoms. In a study of 200 individuals with BDD, subjects retrospectively reported that only 3.6% of all treatments resulted in overall improvement in BDD.[102] In another study (n=250), only 7% of treatments (retrospectively assessed) led to overall improvement in BDD.[103] Veale et al found that 81% of 50 BDD patients were dissatisfied with past medical consultation or surgery.[81] Such an outcome can have serious negative consequences for both patients and physicians. In the previously noted survey of cosmetic surgeons, 40% of respondents indicated that dissatisfied BDD patients had threatened them physically or legally.[85] It is therefore important for BDD patients and their mental health providers to be aware that non-mental health interventions appear unlikely to successfully treat BDD symptoms.

Pharmacotherapy

Pharmacologic treatment for BDD is described in more detail elsewhere,[1,26] including in a Cochrane review and a guideline from the United Kingdom's National Institute of Clinical Excellence (NICE) on the treatment of OCD and BDD, which recommend SRIs for the treatment of BDD.[104,105] No medication is approved by the FDA for the treatment of BDD; studies that are required for FDA approval have not been conducted in BDD. Currently, SRIs are recommended as the first-line medication for BDD, including delusional BDD.[1,26,104,105] Two controlled studies, four open-label trials, and clinical series have reported on SRI efficacy for BDD. All studies found that these medications are often efficacious for BDD.[106-110] In a randomized double-blind parallel-group study, fluoxetine was more efficacious than placebo (d=.70).[111] In a randomized, double-blind crossover trial, the SRI clomipramine was more efficacious than the non-SRI antidepressant desipramine.[106] Four open-label trials (of fluvoxamine, citalopram, and escitalopram), retrospective studies of a broad range of SRIs, and case series similarly suggest that SRIs are often efficacious for BDD and associated symptoms.[7,107-109,112-115]

SRI antidepressants appear more efficacious for BDD than non-SRI antidepressants or other types of psychotropic medication, although data are limited.[26] Relatively high SRI doses appear to often be needed, and current recommendations are that the SRI should be taken for at least 12 weeks before determining whether it is efficacious.[1,26] At that time, if it is not helpful, the SRI should be augmented with another medication, or the SRI should be switched to a different SRI.[1,115] Successful SRI treatment results in less frequent and intense appearance preoccupations, decreased BDD-related distress, less intense urges and less time spent performing compulsive/safety behaviors, and better control over BDD preoccupations and compulsions.[26] Most studies have found that associated symptoms, such as depressive symptoms, functioning, and quality of life, often improve as well.[26,116] In addition, most studies have found that insight regarding the perceived appearance flaws improves with SRI treatment.[26]

Little data are available on the efficacy of antipsychotic medications for BDD, even though many patients have delusional BDD beliefs. Several case reports indicate successful SRI augmentation with an antipsychotic.[117,118] However, a study that examined the efficacy of augmenting fluoxetine with pimozide versus placebo found that pimozide augmentation was not more efficacious than placebo augmentation.[119] The sample size was small (n=28), raising the possibility of Type II error. However,

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the effect size was small (d=0.23), and only 18.2% of subjects responded to pimozide (versus 17.6% to placebo), suggesting minimal efficacy for pimozide augmentation. In a small case series of olanzapine augmentation of fluoxetine, BDD symptoms were minimally improved in 2 of 6 patients, and no patient experienced more substantial improvement, suggesting that atypical neuroleptics may not be efficacious for BDD.[120] Other augmentation strategies have been preliminarily examined, with data suggesting that buspirone, and occasionally other medications, may be helpful when added to an SRI.[1,26,114,115]

Two open-label studies (n=17 for both studies) suggest that the serotonin-norepinephrine reuptake inhibitor venlafaxine or the antiepileptic medication levetiracetam may be efficacious for some patients with BDD.[121,122] While these findings are promising, the small sample sizes, lack of a control group, and lack of replication indicate that these medications should not be considered first-line treatments for BDD at this time.

Cognitive-behavioral therapy

Available research suggests that cognitive-behavioral therapy (CBT) may be efficacious for BDD.[123-125] Most studies have examined a combination of cognitive components (eg, cognitive restructuring that focuses on changing appearance-related assumptions and beliefs) with behavioral components, consisting mainly of exposure and response prevention (ERP) to reduce avoidance and compulsive and safety behaviors. Findings from neuropsychological research (as reviewed above) support the use of cognitive-behavioral strategies to help patients focus less on minor details of their appearance and to instead view their body more "holistically."[126]

Early case reports indicated that exposure therapy may be effective.[127,128] In a subsequent series, in which BDD patients (n=17) received 20 sessions of daily individual 90-minute CBT, BDD symptom severity significantly decreased.[129] In an open trial of group CBT (n=13), administered in twelve 90-minute sessions, BDD and depressive symptoms significantly improved (from severe to moderate).[124] In a study of ten participants who received thirty 90-minute individual ERP sessions without a cognitive component, and 6 months of relapse prevention, improvement was maintained at up to 2 years.[130]

Two waitlist controlled studies have been published. Veale, Gournay, and colleagues randomized 19 patients to 12 weekly sessions of individual CBT or a 12-week no-treatment waitlist control.[123] Two measures of BDD symptoms showed significant improvement with CBT compared to the waitlist condition. In a randomized controlled trial of group CBT for BDD, 54 women were assigned to a CBT treatment group (provided in 8 weekly 2-hour sessions) or to a no-treatment waitlist control.[131] Subjects who received CBT had significantly greater improvement in BDD symptoms, self-esteem, and depression than those on a waiting list with large effect sizes. Although preliminary, these findings suggest that CBT is very promising for BDD.

One challenge when treating patients with CBT is that many are insufficiently motivated for treatment, because of poor insight (ie, not accepting that they have a treatable psychiatric illness or believing that they need cosmetic treatment rather than mental health treatment). Clinical impressions suggest that use of motivational interviewing techniques may be helpful.[125,132] In addition, certain BDD symptoms may require specialized techniques, such as the use of habit reversal training for compulsive skin-picking or hair-plucking.[126]

At this time it is not known whether medication or CBT are more efficacious for BDD, as no randomized controlled studies have directly compared them. Furthermore, it is not known whether a combination of medication and CBT is more efficacious than either treatment alone. However, based on clinical experience, the authors recommend that all patients with severe BDD, severe depressive symptoms, or active suicidal ideation receive an SRI and ideally both treatments.[1] Future studies are needed to assess these important questions.

Alternative psychosocial treatments

Despite the severe morbidity associated with BDD, there are few effective treatments and a pressing need for more treatment options and more treatment research. Currently, CBT is the only psychosocial treatment with preliminary empirical support. Some patients, however, refuse CBT or terminate prematurely from therapy.[133] Therefore, alternative treatments are needed. Interpersonal psychotherapy (IPT) may offer a promising alternative. Individuals with BDD often have a history of emotional abuse,[134] long-standing interpersonal conflicts,[135] and may suffer from crippling social anxiety and interpersonal problems.[70,71] IPT enables patients to

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develop more effective strategies to reduce interpersonal distress, poor self-esteem, and depressed mood,[136,137] which are hypothesized to maintain body image concerns. Results from a small open trial pilot (n=9) regarding the preliminary efficacy of IPT for BDD are promising,[138] and a randomized controlled trial is currently under way.

Conclusions

Despite BDD's prevalence and severity, this disorder remains underdiagnosed in clinical settings. Given the markedly poor functioning and quality of life, and high rates of suicidality, among these patients, it is important that BDD is recognized and accurately diagnosed.[12,125] Interventional research on BDD is still limited; however, available treatment data are promising and indicate that most patients improve with appropriate treatment that targets BDD symptoms specifically. Limited data exist regarding BDD in children and adolescents or the expression of BDD in other cultures. There is emerging evidence that information processing deficits play an important role in BDD, but very little is known about this important topic. It is hoped that further research on BDD will elucidate the many aspects of this disorder that remain poorly understood, lead to more effective treatments and more treatment options, and ultimately enable prevention of this severe mental disorder. ❑

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REFERENCES

1. Phillips KA. *Understanding Body Dysmorphic Disorder: an Essential Guide*. New York, NY: Oxford University Press; 2009.
2. Phillips KA. Body dysmorphic disorder: the distress of imagined ugliness. *Am J Psychiatry*. 1991;148:1138-1149.
3. Morselli E. Sulla dismorfofobia e sulla tafefobia. *Bolletinno della R Accademia di Genova*. 1891;6:110-119.
4. Kraepelin E. *Psychiatrie*. Oxford, UK: J A Barth; 1896.
5. Janet P. *Les Obsessions et la Psychasthenie*. Paris, France: Felix Alcan; 1903.
6. Phillips KA. *The Broken Mirror: Understanding and Treating Body Dysmorphic Disorder* (2nd ed, revised). New York, NY: Oxford University Press; 2005.
7. Phillips KA, McElroy SL, Keck PE, Jr, Pope HG, Jr, Hudson JI. Body dysmorphic disorder: 30 cases of imagined ugliness. *Am J Psychiatry*. 1993;150:302-308.
8. Phillips KA, Nierenberg AA, Brendel G, Fava M. Prevalence and clinical features of body dysmorphic disorder in atypical major depression. *J Nerv Ment Dis.* 1996;184:125-129.
9. Grant JE, Kim SW, Crow SJ. Prevalence and clinical features of body dysmorphic disorder in adolescent and adult psychiatric inpatients. *J Clin Psychiatry*. 2001;62:517-522.
10. Dyl J, Kittler J, Phillips KA, Hunt JI. Body dysmorphic disorder and other clinically significant body image concerns in adolescent psychiatric inpatients: prevalence and clinical characteristics. *Child Psychiatry Hum Dev.* 2006;36:369-382.
11. Zimmerman M, Mattia JI. Body dysmorphic disorder in psychiatric outpatients: recognition, prevalence, comorbidity, demographic, and clinical correlates. *Compr Psychiatry*. 1998;39:265-270.
12. Thompson CM, Durrani AJ. An increasing need for early detection of body dysmorphic disorder by all specialties. *J R Soc Med*. 2007;100:61-62.
13. Phillips KA, Kaye WH. The relationship of body dysmorphic disorder and eating disorders to obsessive-compulsive disorder. *CNS Spectr*. 2007;12:347-358.
14. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN).* New York, NY: Biometrics Research NYSPI; 2002.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
16. Ruffulo JS, Phillips KA, Menard W, Fay C, Weisberg R. Comorbidity of body dysmorphic disorder and eating disorders: severity of psychopathology and body image disturbance. *Int J Eat Disord*. 2006;39:11-19.
17. Phillips KA, Wilhelm S, Koran LM, et al. Body dysmorphic disorder: Some key issues for DSM-V. *Depress Anxiety*. In press.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987.
20. World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organization; 1992.
21. Phillips KA, Hollander E. Body dysmorphic disorder. In: Widiger TA, Frances AJ, Pincus HA, Ross R, First MB, Davis WW, eds. *DSM-IV Sourcebook*. Washington, DC: American Psychiatric Association; 1996.
22. Phillips KA, Stein DJ, Rauch SL, et al. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? *Depress Anxiety*. In press.
23. Phillips KA, McElroy SL, Keck PE, Pope HG, Hudson JI. A comparison of delusional and nondelusional body dysmorphic disorder in 100 cases. *Psychopharmacol Bull*. 1994;30:179-186.
24. McElroy SL, Phillips KA, Keck PE, Hudson JI. Body dysmorphic disorder: does it have a psychotic subtype? *J Clin Psychiatry*. 1993;54:389-395.
25. Mancuso S, Knoesen N, Castle DJ. Delusional vs nondelusional body dysmorphic disorder. *Compr Psychiatry*. 2010;51:177-182.
26. Phillips KA, Hollander E. Treating body dysmorphic disorder with medication: evidence, misconceptions, and a suggested approach. *Body Image*. 2008;5:13-27.
27. Faravelli C, Salvatori S, Galassi F, Aiazzi L, Drei C, Cabras P. Epidemiology of somatoform disorders: a community survey in Florence. *Soc Psychiatry Psychiatr Epidemiol*. 1997;32:24-29.
28. Koran LM, Abujaoude E, Large MD, Serpe RT. The prevalence of body dysmorphic disorder in the United States adult population. *CNS Spectr*. 2008;13:316-322.
29. Otto MW, Wilhelm S, Cohen LS, Harlow BL. Prevalence of body dysmorphic disorder in a community sample of women. *Am J Psychiatry*. 2001;158:2061-2063.
30. Rief W, Buhlmann U, Wilhelm S, Borkenhagen A, Brahler E. The prevalence of body dysmorphic disorder: a population-based survey. *Psychol Med*. 2006;36:877-885.

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Trastorno dismórfico corporal

El trastorno dismórfico corporal (TDC) es una patología relativamente común que se caracteriza por una preocupación agobiante o limitante relacionada con defectos leves o imaginarios de la apariencia. Habitualmente se considera el TDC como un trastorno del espectro obsesivo-compulsivo, dadas las similitudes que tiene con el trastorno obsesivo-compulsivo. Es importante reconocer y tratar apropiadamente el TDC, ya que este trastorno se asocia con un marcado deterioro del funcionamiento psicosocial, una muy pobre calidad de vida y alta frecuencia de suicidalidad. En esta revisión se entrega una panorámica de los hallazgos de la investigación en el TDC, incluyendo su epidemiología, las características clínicas, el curso de la enfermedad, la comorbilidad, el funcionamiento psicosocial y la suicidalidad. También se revisa brevemente la investigación reciente sobre los sustratos neurales y el procesamiento cognitivo. Finalmente se discuten las aproximaciones terapéuticas que parecen eficaces para el TDC, con un foco en los inhibidores de la recaptura de serotonina y la terapia cognitivo-conductual.

Trouble dysmorphophobique

Le trouble dysmorphophobique est un trouble relativement courant consistant en une préoccupation pénible ou obsédante concernant une imperfection légère ou imaginaire de l'apparence. La dysmorphophobie est considérée couramment comme un trouble du spectre obsessionnel-compulsif (TOC), fondé sur ses ressemblances avec le TOC. Il est important de le reconnaître et de le traiter correctement, ce trouble étant associé à une altération importante du fonctionnement psychosocial, en particulier une mauvaise qualité de vie et un taux élevé de suicides. Cet article présente les travaux sur le trouble dysmorphophobique, incluant son épidémiologie, son tableau clinique, l'évolution de la maladie, la comorbidité, le fonctionnement psychosocial et le taux de suicide. Nous présentons également rapidement les résultats de recherche récente sur les substrats neuraux et les processus cognitifs. Nous abordons finalement les traitements qui semblent efficaces pour cette pathologie, en mettant l'accent sur les inhibiteurs de la recapture de la sérotonine et le traitement cognitivo-comportemental.

31. Biby EL. The relationship between body dysmorphic disorder and depression, self-esteem, somatization, and obsessive-compulsive disorder. *J Clin Psychol*. 1998;54:489-499.
32. Bohne A, Wilhelm S, Keuthen NJ, Florin I, Baer L, Jenike MA. Prevalence of body dysmorphic disorder in a German college student sample. *Psychiatry Res*. 2002;109:101-104.
33. Cansever A, Uzun O, Donmez E, Ozsahin A. The prevalence and clinical features of body dysmorphic disorder in college students: a study in a Turkish sample. *Compr Psychiatry*. 2003;44:60-64.
34. Mayville S, Katz RC, Gipson MT, Cabral K. Assessing the prevalence of body dysmorphic disorder in an ethnically diverse group of adolescents. *J Child Fam Stud*. 1999;8:357-362.
35. Taqui AM, Shaikh M, Gowani SA, et al. Body dysmorphic disorder: Gender differences and prevalence in a Pakistani medical student population. *BCM Psychiatry*. 2008;8:20.
36. Hollander E, Cohen LJ, Simeon D. Body dysmorphic disorder. *Psychiatr Ann*. 1993;23:359-364.
37. Aouizerate B, Pujol H, Grabot D, et al. Body dysmorphic disorder in a sample of cosmetic surgery applicants. *Eur Psychiatry*. 2003;18:365-368.
38. Brawman-Mintzer O, Lydiard RB, Phillips KA, et al. Body dysmorphic disorder in patients with anxiety disorders and major depression: a comorbidity study. *Am J Psychiatry*. 1995;152:1665-1667.
39. Castle DJ, Molton M, Hoffman K, Preston NJ, Phillips KA. Correlates of dysmorphic concern in people seeking cosmetic enhancement. *Aust NZ J Psychiatry*. 2004;38:439-444.
40. Ishigooka J, Iwao M, Suzuki M, Fukuyama Y, Murasaki M, Miura S. Demographic features of patients seeking cosmetic surgery. *Psychiatry Clin Neurosci*. 1998;52:283-287.
41. Kelly KE, Alpert JE, Worthington JJ, et al. Body dysmorphic disorder in outpatients with major depression. *J Affect Disord*. 2002;69:141-148.
42. Perugi G, Giannotti D, Frare F, et al. Prevalence, phenomenology and comorbidity of body dysmorphic disorder (dysmorphophobia) in a clinical population. *Int J Psych Clin Pract*. 1997;1:77-82.
43. Phillips KA, Dufresne RG, Jr, Wilkel CS, Vittorio CC. Rate of body dysmorphic disorder in dermatology patients. *J Am Acad Dermatol*. 2000;42:436-441.
44. Sarwer DB, Wadden TA, Pertschuk MJ, Whitaker LA. Body image dissatisfaction and body dysmorphic disorder in 100 cosmetic surgery patients. *Plast Reconstr Surg*. 1998;101:1644-1649.
45. Soriano JL, O'Sullivan RL, Baer L, Phillips KA, McNally RJ, Jenike MA. Trichotillomania and self-esteem: a survey of 62 female hair pullers. *J Clin Psychiatry*. 1996;57:77-82.
46. Uzun O, Basoglu C, Akar A, et al. Body dysmorphic disorder in patients with acne. *Compr Psychiatry*. 2003;44:415-419.
47. Vargel S, Ulusahin A. Psychopathology and body image in cosmetic surgery patients. *Aesthetic Plast Surg*. 2001;25:474-478.
48. Vindigni V, Pavan C, Semenzin M, et al. The importance of recognizing body dysmorphic disorder in cosmetic surgery patients: do our patients need a preoperative psychiatric evaluation? *Eur J Plast Surg*. 2002;25:305-308.
49. Wilhelm S, Otto MW, Zucker BG, Pollack MH. Prevalence of body dysmorphic disorder in patients with anxiety disorders. *J Anxiety Disord*. 1997;11:499-502.
50. Conroy M, Menard W, Fleming-Ives K, Modha P, Cerullo H, Phillips KA. Prevalence and clinical characteristics of body dysmorphic disorder in an adult inpatient setting. *Gen Hosp Psychiatry*. 2008;30:67-72.
51. Albertini RS, Phillips KA, Guevremont D. Body dysmorphic disorder in a young child (letter). *J Am Acad Child Adolesc Psychiatry*. 1996;35:1425-1426.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 231

52. Phillips KA, Diaz SF. Gender differences in body dysmorphic disorder. *J Nerv Ment Dis*. 1997;185:570-577.
53. Phillips KA, Menard W, Fay C. Gender similarities and differences in 200 individuals with body dysmorphic disorder. *Compr Psychiatry*. 2006;47:77-87.
54. Didie ER, Menard W, Stern AP, Phillips KA. Occupational functioning and impairment in adults with body dysmorphic disorder. *Compr Psychiatry*. 2008;24:26-28.
55. Phillips KA, Menard W, Fay C, Weisberg R. Demographic characteristics, phenomenology, comorbidity, and family history in 200 individuals with body dysmorphic disorder. *Psychosomatics*. 2005;46:317-325.
56. Pope HG, Jr., Gruber AJ, Choi P, Olivardia R, Phillips KA. Muscle dysmorphia: an underrecognized form of body dysmorphic disorder. *Psychosomatics*. 1997;38:548-557.
57. Olivardia R, Pope HG, Jr., Hudson JI. Muscle dysmorphia in male weightlifters: a case-control study. *Am J Psychiatry*. 2000;157:1291-1296.
58. Pope CG, Pope HG, Menard W, Fay C, Olivardia R, Phillips KA. Clinical features of muscle dysmorphia among males with body dysmorphic disorder. *Body Image*. 2005;2:395-400.
59. Eisen JL, Phillips KA, Baer L, Beer DA, Atala KD, Rasmussen SA. The Brown Assessment of Beliefs Scale: reliability and validity. *Am J Psychiatry*. 1998;155:102-108.
60. Phillips KA, Menard W, Pagano ME, Fay C, Stout RL. Delusional versus nondelusional body dysmorphic disorder: clinical features and course of illness. *J Psychiatr Res*. 2006;40:95-104.
61. Eisen JL, Phillips KA, Coles ME, Rasmussen SA. Insight in obsessive compulsive disorder and body dysmorphic disorder. *Compr Psychiatry*. 2004;45:10-15.
62. Phillips KA. Psychosis in body dysmorphic disorder. *J Psychiatr Res*. 2004;38:63-72.
63. Phillips KA, Gunderson CG, Mallya G, McElroy SL, Carter W. A comparison study of body dysmorphic disorder and obsessive-compulsive disorder. *J Clin Psychiatry*. 1998;59:568-575.
64. Veale D, Riley S. Mirror, mirror on the wall, who is the ugliest of them all? The psychopathology of mirror gazing in body dysmorphic disorder. *Behav Res Ther*. 2001;39:1381-1393.
65. Feusner JD, Hembacher E, Phillips KA. The mouse who couldn't stop washing: pathologic grooming in animals and humans. *CNS Spectr*. 2009;14:503-513.
66. Phillips KA, Conroy M, Dufresne RG, et al. Tanning in body dysmorphic disorder. *Psychiatr Q*. 2006;77:129-138.
67. Grant JE, Menard W, Phillips KA. Pathological skin picking in individuals with body dysmorphic disorder. *Gen Hosp Psychiatry*. 2006;28:487-493.
68. O'Sullivan RL, Phillips KA, Keuthen NJ, Wilhelm S. Near-fatal skin picking from delusional body dysmorphic disorder responsive to fluvoxamine. *Psychosomatics*. 1999;40:79-81.
69. Phillips KA, Taub SL. Skin picking as a symptom of body dysmorphic disorder. *Psychopharmacol Bull*. 1995;31:279-288.
70. Kelly M, Walters C, Phillips K. Social anxiety and its relationship to functional impairment in body dysmorphic disorder. *Behav Ther*. 2010;41:143-153.
71. Pinto A, Phillips KA. Social anxiety in body dysmorphic disorder. *Body Image*. 2005;2:401-405.
72. Veale D. Advances in a cognitive behavioural model of body dysmorphic disorder. *Body Image*. 2004;1:113-125.
73. Gunstad J, Phillips KA. Axis I comorbidity in body dysmorphic disorder. *Compr Psychiatry*. 2003;44:270-276.
74. Phillips KA, Pagano ME, Menard W, Stout RL. A 12-month follow-up study of the course of body dysmorphic disorder. *Am J Psychiatry*. 2006;163:907-912.
75. Phillips KA, Pagano ME, Menard W, Fay C, Stout RL. Predictors of remission from body dysmorphic disorder: a prospective study. *J Nerv Ment Dis*. 2005;193:564-567.
76. Phillips KA. Quality of life for patients with body dysmorphic disorder. *J Nerv Ment Dis*. 2000;188:170-175.
77. Phillips KA, Menard W, Fay C, Pagano ME. Psychosocial functioning and quality of life in body dysmorphic disorder. *Compr Psychiatry*. 2005;46:254-260.
78. Phillips KA, Quinn G, Stout RL. Functional impairment in body dysmorphic disorder: a prospective, follow-up study. *J Psychiatr Res*. 2008;42:701-707.
79. Phillips KA. Suicidality in body dysmorphic disorder. *Primary Psychiatry*. 2007;14:58-66.
80. Phillips KA, Coles ME, Menard W, Yen S, Fay C, Weisberg RB. Suicidal ideation and suicide attempts in body dysmorphic disorder. *J Clin Psychiatry*. 2005;66:717-725.
81. Veale D, Boocock A, Gournay K, Dryden W. Body dysmorphic disorder: a survey of fifty cases. *Br J Psychiatry*. 1996;169:196-201.
82. Phillips KA, Menard W. Suicidality in body dysmorphic disorder: a prospective study. *Am J Psychiatry*. 2006;163:1280-1282.
83. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a metaanlysis. *Br J Psychiatry*. 1997;170:205-228.
84. Perugi G, Akiskal HS, Giannotti D, Frare F, Di Vaio S, Cassano GB. Gender-related differences in body dysmorphic disorder (dysmorphophobia). *J Nerv Ment Dis*. 1997;185:578-582.
85. Sarwer DB. Awareness and identification of body dysmorphic disorder by aesthetic surgeons: results of a survey of american society for aesthetic plastic surgery members. *Aesthet Surg J*. 2002;22:531-535.
86. Grant JE, Menard W, Pagano ME, Fay C, Phillips KA. Substance use disorders in individuals with body dysmorphic disorder. *J Clin Psychiatry*. 2005;66:309-316.
87. Albertini RS, Phillips KA. 33 cases of body dysmorphic disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:453-459.
88. Phillips KA, Didie ER, Menard W, Pagano ME, Fay C, Weisberg RB. Clinical features of body dysmorphic disorder in adolescents and adults. *Psychiatry Res*. 2006;141:305-314.
89. Phillips KA, Atala KD, Albertini RS. Case study body dysmorphic disorder in adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1216-1220.
90. Cull J, Gill W. *Suicide Probability Scale*. Los Angeles, CA: WPS; 1982.
91. Deckersbach T, Savage CR, Phillips KA, et al. Characteristics of memory dysfunction in body dysmorphic disorder. *J Int Neuropsychol Soc*. 2000;6:673-681.
92. Feusner JD, Townsend J, Bystritsky A, Bookheimer S. Visual information processing of faces in body dysmorphic disorder. *Arch Gen Psychiatry*. 2007;64:1417-1425.
93. Buhlmann U, Reese HE, Renaud S, Wilhelm S. Clinical considerations for the treatment of body dysmorphic disorder with cognitive-behavioral therapy. *Body Image*. 2008;5:39-49.
94. Buhlmann U, Etcoff NL, Wilhelm S. Emotion recognition bias for contempt and anger in body dysmorphic disorder. *J Psychiatr Res*. 2006;40:105-111.
95. Buhlmann U, McNally RJ, Etcoff NL, Tuschen-Caffier B, Wilhelm S. Emotion recognition deficits in body dysmorphic disorder. *J Psychiatr Res*. 2004;38:201-206.
96. Rauch SL, Phillips KA, Segal E, et al. A preliminary morphometric magnetic resonance imaging study of regional brain volumes in body dysmorphic disorder. *Psychiatry Res*. 2003;122:13-19.
97. Atmaca M, Bingol I, Aydin A, et al. Brain morphology of patients with body dysmorphic disorder. *J Affect Disord.* 2009;123:701-707.
98. Feusner JD, Townsend J, Bystritsky A, McKinley M, Moller H, Bookheimer S. Regional brain volumes and symptom severity in body dysmorphic disorder. *Psychiatry Res*. 2009;172:161-167.
99. Carey P, Seedat S, Warwick J, van Heerden B, Stein DJ. SPECT imaging of body dysmorphic disorder. *J Neuropsychiatry Clin Neurosci*. 2004;16:357-359.
100. Feusner JD, Moody T, Hembacher E. Abnormalities of visual processing and frontostriatal systems in body dysmorphic disorder. *Arch Gen Psychiatry*. In press.
101. Rotge JY, Guehl D, Dilharreguy B, et al. Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry*. 2009;65:75-83.
102. Crerand CE, Phillips KA, Menard W, Fay C. Nonpsychiatric medical treatment of body dysmorphic disorder. *Psychosomatics*. 2005;46:549-555.
103. Phillips KA, Grant J, Siniscalchi J, Albertini RS. Surgical and nonpsychiatric medical treatment of patients with body dysmorphic disorder. *Psychosomatics*. 2001;42:504-510.
104. Ipser J, Sander C, Stein D. Pharmacotherapy and psychotherapy for body dysmorphic disorder. Available at: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005332/abstract.html. *Cochrane Database Syst Rev*. Accessed May 24, 2010.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 232

105. Obsessive compulsive disorder: core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder. Available at: http://www.nice.org.uk/nicemedia/pdf/cg031niceguideline.pdf. National Institute for Health and Clinical Excellence. Accessed May 24, 2010.
106. Hollander E, Allen A, Kwon J, et al. Clomipramine vs desipramine crossover trial in body dysmorphic disorder: selective efficacy of a serotonin reuptake inhibitor in imagined ugliness. *Arch Gen Psychiatry*. 1999;56:1033-1039.
107. Perugi G, Giannotti D, Di Vaio S, Frare F, Saettoni M, Cassano GB. Fluvoxamine in the treatment of body dysmorphic disorder (dysmorphophobia). *Int Clin Psychopharmacol*. 1996;11:247-254.
108. Phillips KA. An open-label study of escitalopram in body dysmorphic disorder. *Int Clin Psychopharmacol*. 2006;21:177-179.
109. Phillips KA, Dwight MM, McElroy SL. Efficacy and safety of fluvoxamine in body dysmorphic disorder. *J Clin Psychiatry*. 1998;59:165-171.
110. Phillips KA, Najar F. An open-label study of citalopram in body dysmorphic disorder. *J Clin Psychiatry*. 2003;64:715-720.
111. Phillips KA, Albertini RS, Rasmussen SA. A randomized placebo-controlled trial of fluoxetine in body dysmorphic disorder. *Arch Gen Psychiatry*. 2002;59:381-388.
112. Hollander E, Cohen LJ, Simeon D, Rosen J, deCaria CM, Stein D. Fluvoxamine treatment of body dysmorphic disorder. *J Clin Psychopharmacol*. 1994;14:75-77.
113. Hollander E, Liebowitz MR, Winchel R, Klumker A, Klein DF. Treatment of body-dysmorphic disorder with serotonin reuptake blockers. *Am J Psychiatry*. 1989;146:768-770.
114. Phillips KA. An open study of buspirone augmentation of serotonin-reuptake inhibitors in body dysmorphic disorder. *Psychopharmacol Bull*. 1996;32:175-180.
115. Phillips KA, Albertini RS, Siniscalchi JM, Khan A, Robinson M. Effectiveness of pharmacotherapy for body dysmorphic disorder: a chart-review study. *J Clin Psychiatry*. 2001;62:721-727.
116. Phillips KA, Rasmussen SA. Change in psychosocial functioning and quality of life of patients with body dysmorphic disorder treated with fluoxetine: a placebo-controlled study. *Psychosomatics*. 2004;45:438-444.
117. Grant JE. Successful treatment of nondelusional body dysmorphic disorder with olanzapine: A case report. *J Clin Psychiatry*. 2001;62:297-298.
118. Nakaaki S, Murata Y, Furukawa TA. Efficacy of olanzapine augmentation of paroxetine therapy in patients with severe body dysmorphic disorder. *Psychiatry Clin Neurosci*. 2008;62:370.
119. Phillips KA. Placebo-controlled study of pimozide augmentation of fluoxetine in body dysmorphic disorder. *Am J Psychiatry*. 2005;162:377-379.
120. Phillips KA. Olanzapine augmentation of fluoxetine in body dysmorphic disorder (letter). *Am J Psychiatry*. 2005;162:1022-1023.
121. Allen A, Hadley SJ, Kaplan A, et al. An open-label trial of venlafaxine in body dysmorphic disorder. *CNS Spectr*. 2008;13:138-144.
122. Phillips KA, Menard W. A prospective pilot study of levetiracetam for body dysmorphic disorder. *CNS Spectr*. 2009;14:252-260.
123. Veale D, Gournay K, Dryden W, et al. Body dysmorphic disorder: a cognitive behavioural model and pilot randomised controlled trial. *Behav Res Ther*. 1996;34:717-729.
124. Wilhelm S, Otto MW, Lohr B, Deckersbach T. Cognitive behavior group therapy for body dysmorphic disorder: a case series. *Behav Res Ther*. 1999;37:71-75.
125. Phillips KA, Didie ER, Feusner J, Wilhelm S. Body dysmorphic disorder: treating an underrecognized disorder. *Am J Psychiatry*. 2008;165:1111-1118.
126. Wilhelm S, Phillips KA, Steketee G. *A Cognitive Behavioral Treatment Manual for Body Dysmorphic Disorder*. New York, NY: Guilford Press. In press.
127. Marks IM, Mishan J. Dysmorphophobic avoidance with disturbed bodily perception: A pilot study of exposure therapy. *Br J Psychiatry*. 1988;152:674-678.
128. Neziroglu F, Khemlani-Patel S. A review of cognitive and behavioral treatment for body dysmorphic disorder. *CNS Spectr*. 2002;7:464-471.
129. Neziroglu F, McKay D, Todaro J, Yaryura-Tobias JA. Effect of cognitive behavior therapy on persons with body dysmorphic disorder and comorbid Axis II diagnosis. *Behav Ther*. 1996;27:67-77.
130. McKay D. Two-year follow-up of behavioral treatment and maintenance for body dysmorphic disorder. *Behav Modif*. 1999;23:620-629.
131. Rosen JC, Reiter J, Orosan P. Cognitive-behavioral body image therapy for body dysmorphic disorder. *J Consult Clin Psychol*. 1995;63:263-269.
132. Miller WR, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York, NY: Guilford Press; 1991.
133. Didie ER, Kurahara L, Menard W, Phillips KA. Adherence to cognitive behavioral therapy and pharmacotherapy recommendations among patients with body dysmorphic disorder. Poster presented at: the annual meeting of the Association for Behavioral and Cognitive Therapies; November; 2008; Orlando, FL.
134. Didie ER, Tortolani CC, Pope CG, Menard W, Fay C, Phillips KA. Childhood abuse and neglect in body dysmorphic disorder. *Child Abuse Negl*. 2006;30:1105-1115.
135. Didie ER, Loerke E, Menard W, Phillips KA. Severity of interpersonal problems in individuals with body dysmorphic disorder. Poster presented at: the annual meeting of the NIMH New Clinical Drug Evaluation Unit; 2008; Phoenix, AZ.
136. Kerman GL, Weismann MM, Rousanville BA, Chevron ES. *Interpersonal Psychotherapy of Depression*. New York, NY: Basic Books; 1984.
137. Fairburn CG. Interpersonal therapy for bulimia nervosa. In: Garner DM, Garfinkel PE, eds. *Handbook of Treatment for Eating Disorders*. New York, NY: Guilford Press; 1997:67-93.
138. Didie ER, Phillips KA. Interpersonal psychotherapy for body dysmorphic disorder: a pilot study. Poster presented at: the annual meeting of the International Society for Interpersonal Psychotherapy; March, 2009; New York, NY.

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Compulsive hoarding: current controversies and new directions

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Compulsive hoarding is a disabling psychological disorder characterized by excessive collecting and saving behavior. This article reviews four key areas of recent advances in hoarding research. First, we provide an overview of the evolving controversy regarding the diagnostic status of hoarding, highlighting accumulating evidence that it may be best conceptualized as a separate syndrome. Second, we describe advances in our understanding of the epidemiology, course, and demographic features of compulsive hoarding. Third, we review the latest findings regarding possible neuropsychological correlates of the disorder. Finally, we discuss ongoing progress and future directions related to the clinical management of compulsive hoarding.

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Compulsive hoarding is a syndrome characterized by excessive collecting and saving behavior that results in a cluttered living space and significant distress or impairment.[1] In the past decade, there has been a notable increase in research on hoarding, including its phenomenology, pathophysiology, and treatment approaches. This surge in interest has been coupled with contention regarding key aspects of the disorder. These controversies have led to exciting new research that has deepened our understanding of this complex syndrome. The aim of this article is to describe some of these debated issues, as well as to highlight recent advances in compulsive hoarding research.

Diagnostic status

An obvious example of a current debate within hoarding research is the question of where hoarding belongs within our diagnostic nosology. The uncertainty regarding the most appropriate classification of compulsive hoarding syndrome has had important consequences for our understanding of hoarding, and in some ways has constituted an obstacle to hoarding research. The lack of clear placement within *DSM* has led to an underestimation of the significance of the burden of disease associated with compulsive hoarding, inconsistencies with respect to an appropriate clinical comparison group in hoarding research, difficulties comparing findings across hoarding studies, and misconceptions regarding which assessment and treatment models are most relevant to hoarding.

In the *DSM-IV-TR*,[2] hoarding is described as difficulty discarding items, and is listed as one of the eight diag-

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nostic criteria for obsessive-compulsive personality disorder (OCPD). Accumulating evidence, however, suggests that it is misleading and invalid to classify hoarding as part of OCPD. When studies examining the prevalence of OCPD in hoarding samples exclude the criterion describing difficulty discarding, most studies suggest that hoarding is no more associated with OCPD than it is with other Axis II disorders.[3,4] In addition, hoarding has been found to have the lowest specificity and predictive criteria of all eight of the diagnostic criteria for OCPD.[5] Based on these findings, Saxena et al[6] argued convincingly that hoarding should be removed from the diagnostic criteria for OCPD. Nevertheless, there is some evidence to suggest a link between hoarding and OCPD. A recent study of hoarding within a collaborative OCPD genetics study found that hoarders had a greater prevalence of certain OCPD traits, particularly miserliness and preoccupation with details.[7] In addition, several previous studies have reported that OCPD is more common in hoarders.[8-10] Thus while the consensus appears to be that hoarding is inappropriately classified as a criterion of OCPD, the broader issue of the relation of hoarding to OCPD, as well as to other Axis II disorders, remains unresolved.

Despite its placement in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV*, clinicians and researchers typically consider hoarding a symptom or subtype of obsessive-compulsive disorder (OCD). For example, the Y-BOCS checklist[11] lists hoarding obsessions and compulsions, and many investigations into hoarding have involved comparing OCD individuals with and without hoarding. This view of hoarding as part of OCD derived from early findings that approximately one third of individuals with OCD have hoarding symptoms.[12-14] More recent studies, however, have found ample evidence that hoarding should not be conceptualized only as an OCD symptom. For example, Wu and Watson[4] found that hoarding correlated more weakly with other symptoms of OCD than these other symptoms correlated with each other. Moreover, Saxena et al[6] found that patients who hoard, compared with other OCD patients, had different functional neuroimaging findings, response to treatment, and clinical profiles. In a large study of hoarding among OCD patients,[7] individuals with hoarding were more likely to have symmetry obsessions and counting, ordering, and repeating compulsions. They also were more likely to have greater illness severity, more difficulty initiating and completing tasks, and problems with indecision.

A recent study by Abramowitz and colleagues[15] provided further evidence that although some individuals with OCD may show hoarding behavior, hoarding is most likely distinct from OCD. Abramowitz and colleagues compared OCD patients, patients with other anxiety disorders, and unscreened undergraduate students. OCD patients scored higher on all OCD symptoms except hoarding, in which the student group scored slightly, but significantly higher than both clinical groups. Similarly to Wu and Watson,[4] Abramowitz and colleagues found that the magnitude of the correlations between hoarding and other OCD symptoms was significantly weaker than the magnitude of the correlations amongst all other OCD symptoms. In addition, the hoarding items loaded weakly on a unitary OCI-R factor. In a second study, Abramowitz et al[15] found that hoarding was correlated weakly with depression, but not with anxiety. Other OCD symptoms showed at least a moderate association with anxiety. Due to these recent findings, there is a growing consensus that hoarding should not be considered as a symptom of OCPD or OCD, but as a separate clinical syndrome.

Several researchers have also examined whether there are important differences between hoarding behavior seen in the context of OCD and hoarding that occurs without any other OCD symptoms.[3,4,16] A recent study conducted by Petrusa et al[3] compared individuals with severe compulsive hoarding who met criteria for OCD (OCD plus hoarding group) with individuals with severe hoarding who did not meet criteria for OCD (monosymptomatic hoarding). Individuals in the OCD plus hoarding group differed from the monosymptomatic hoarding group in several important ways. For example, OCD plus hoarding participants were more likely to hoard bizarre items and more likely to report other obsessions and compulsions related to their hoarding than those in the monosymptomatic hoarding group. In addition, the OCD plus hoarding group endorsed more cluster C personality traits than the monsymptomatic hoarding group.

Given that hoarding can occur in the absence of OCD and that it shares some similarity to impulse control disorders (ICDs) such as pathological gambling, pyromania, and kleptomania, it may have a place within behavioral addiction. Although hoarding behavior is sometimes motivated by a desire to reduce anxiety, it also sometimes appears to be driven by anticipation of pleasure and impaired self-regulation.[16] Since both anx-

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iety and approach behaviors may play a role in compulsive hoarding, a common diathesis may underlie both hoarding and certain impulse control disorders. Samuels et al[14] reported a greater frequency of trichotillomania and skin picking among hoarding compared with non-hoarding individuals with OCD. In addition, Frost et al[17] found that pathological gamblers reported significantly more hoarding symptoms than light gamblers.

Although Grant et al[18] found a low prevalence of ICDs overall among individuals with obsessive-compulsive disorder, obsessive-compulsive disorder participants with a lifetime and current impulse control disorder were more likely to report hoarding symptoms. In a recent study, Hayward and Coles[19] examined the relation of hoarding to OCD and ICDs in an undergraduate sample, and found that hoarding behaviors were related moderately to symptoms of compulsive buying, and more weakly related to pathological gambling, trichotillomania, and kleptomania. The possible association between hoarding and ICDs is consistent with McElroy and colleagues' conceptualization of a compulsive-impulsive spectrum,[20] but requires further exploration.

The nosological issues surrounding hoarding will influence its placement in the next edition of the *DSM*. One position is that compulsive hoarding should be included in our diagnostic system as an independent syndrome, which is sometimes comorbid with OCD. Including hoarding as a separate syndrome has a number of important practical advantages, well-summarized by Rachman and colleagues.[21] For example, it would expand the boundaries of the hoarding population to be consistent with the data showing a high incidence of hoarding not associated with OCD. It would also encourage clinicians and researchers to use hoarding-specific assessment tools rather than measures designed for OCD, and facilitate the development of new treatment methods for hoarding. Another possibility is that hoarding may be listed in DSM-5 as both a separate syndrome and as an OCD symptom.

Epidemiology

Hoarding researchers also have made substantial progress in understanding the prevalence and manifestation of compulsive hoarding in the population. Until very recently, researchers estimated the prevalence of hoarding as a subportion of individuals with OCD in the community.[22] Similarly, information regarding the burden of hoarding was based on anecdotal evidence and small samples. Recent epidemiological studies, however, suggest that compulsive hoarding may be far more prevalent and burdensome in the community than previously thought. Data from the Baltimore Epidemiologic Catchment Area Follow-up survey suggest that 5% of the general population experiences clinically significant hoarding, while data from the National Comorbidity Survey Replication indicate that the lifetime prevalence of compulsive hoarding may be as high as 14%.[23,24] These studies estimated hoarding based upon reports of difficulty discarding, and did not specifically target clutter and excessive acquisition, and thus it is unknown whether cases met criteria for compulsive hoarding as defined by Frost and Hart.[11] A recent twin study that utilized a self-report instrument to assess the broad hoarding phenotype found that 2% of its sample reported clinically significant hoarding symptoms.[25] As symptom severity obtained by self-report tends to be lower than clinician-rated severity, the current prevalence of clinically significant compulsive hoarding may be somewhere between 2% and 5%.

Importantly, a large proportion of individuals who hoard report having at least one first-degree relative who experiences hoarding problems.[3,14] In a sample of individuals with OCD, Samuels and colleagues[14] reported that probands of individuals with hoarding symptoms were four times more likely to experience hoarding symptoms than probands of individuals who did not report hoarding symptoms. Genetic factors and unshared environmental factors may explain this familial connection. In a large sample of female twins, genetic factors accounted for approximately 50% of the variance in compulsive hoarding, while shared environmental factors encountered by twins growing up in the same household did not substantially contribute to the other half.[25]

Recent data suggests that the prevalence of hoarding increases with age. Samuels and colleagues[24] reported that hoarding was almost three times more prevalent in individuals over the age of 54 than it was in individuals aged 34 to 44. This finding most likely is due to compulsive hoarding being a chronic and progressive disorder. Hoarding symptoms often develop during childhood or adolescence, and become clinically significant during middle age.[26,27] Having the means to acquire and accumulate objects as a child may be substantially restricted; therefore, it may take a decade or more for symptoms to

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become clinically significant. In such cases, progression of hoarding symptoms may be slow. In other cases, hoarding may have a sudden onset in adulthood, such as after a traumatic life event or brain injury.[27,28] Fifty-five percent of Grisham and colleagues'[27] sample reported experiencing a stressful life event at the onset of hoarding symptoms, and these individuals had a significantly later age of onset than individuals who did not experience a stressful life event.

Clinical studies have demonstrated that hoarding often co-occurs with other psychological disorders. In a large clinical sample, almost all individuals with a hoarding diagnosis met criteria for another Axis I disorder, and these individuals had significantly more co-occurring disorders than nonhoarding individuals with OCD.[29] Compared with nonhoarding individuals with OCD, hoarders are consistently more likely to meet criteria for social anxiety disorder, bipolar disorder, and pathological grooming behavior.[7,14,29] Hoarders also appear more likely to experience an alcohol-use disorder at some point in their lives.[24,29] A community study has found that the prevalence of co-occurring disorders differs for men and women. In men, hoarding is associated with generalized anxiety disorder and tics, while among women, hoarding is associated with social phobia, post-traumatic stress disorder, body dysmorphic disorder, nail biting, and skin picking.[7] Women and men also may not be affected equally by hoarding symptoms. While clinical samples tend to be predominantly female,[3,30] epidemiological samples have found that hoarding is twice as prevalent in males.[24,25] The identification of a significant prevalence of men who compulsively hoard, and gender-specific comorbidity differences, presents a significant challenge for developing and engaging all individuals in effective treatment.

A growing body of research suggests that hoarding is associated with a lower quality of life. First, hoarding appears to occur more frequently in the unemployed and poor.[24,29] Although longitudinal studies are needed to determine if hoarding is a cause or consequence of financial insecurity, a recent Internet study indicated that hoarding may at least contribute to financial insecurity. Five percent of the Web sample reported they had been fired because of hoarding, and on average, employed individuals reported seven psychiatric work impairment days per month.[31] Second, hoarding has been linked to poorer health status. Individuals who hoard are very likely to be overweight or obese and suffer from a severe medical condition.[31] Third, several clinical and community studies have reported a low rate of marriage among compulsive hoarders.[14,29,32,33] Those who are married or cohabitating tend to have a lower degree of hoarding severity.[31] Fourth, hoarding is associated with high rates of family frustration. Family members who cohabit with hoarders report being embarrassed about the condition of their home, arguing about the clutter, and feeling rejection and hostility toward the hoarder.[31]

In summary, emergent research suggests that the prevalence of compulsive hoarding ranges from 2% to 5%, and men may be more likely to hoard than women. In most cases, hoarding is a chronic disorder. Although some people may experience a gradual rise in symptoms throughout their lifetime, others may develop hoarding symptoms quite quickly after a stressful life event. Men and women who hoard may experience different co-occurring disorders, yet both genders are likely to experience a substantial amount of burden associated with their hoarding.

Neuropsychological impairment

Neuropsychological research into hoarding did not begin to build until the last decade. The initial clues that hoarding was related to frontal-lobe dysfunction came from case reports of pathological collecting and saving that began after a brain injury, typically along with other changes in personality and social functioning.[34-36] In the last decade, two papers presented findings suggesting that hoarding is the result of frontal-lobe lesions. In the first report, Hahm and colleagues[36] described the case of a 46-year-old Korean man who began unusual collecting behavior after he suffered an injury to his left ventromedial prefrontal cortex and caudate. This man had difficulty with social decision-making and judgment processes. In the second report, Anderson et al[37] examined compulsive hoarding behavior within a sample of 86 patients with focal lesions, and found that 13 of these participants exhibited abnormal collecting behavior. Magnetic resonance imaging (MRI) showed that all 13 individuals with hoarding symptoms had damage to the mesial frontal region of the brain, including the right polar sector and anterior cingulate. If excessive collecting and saving behaviors can begin after brain injury, individuals who hoard in the absence of lesions may possess similar deficits in neuropsychological functioning or impaired self-regulation that contribute to compulsive hoarding symptoms.

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Self-report and laboratory studies of neuropsychological functioning in hoarding have highlighted potential areas of subtle impairment. In a study by Hartl et al, hoarding patients reported increased symptoms of attention deficit-hyperactivity disorder (ADHD).[38] They also have been found to perform worse on certain neuropsychological tasks, including measures of attention and nonverbal intelligence,[39] memory,[40] and decision-making.[41] Deficits in executive function marked by inhibition, planning, and decision-making difficulties may limit hoarders' ability to discard and organize their possessions. Although this is an intriguing and rapidly advancing area within hoarding research, there has been some inconsistency with respect to the specific pattern of deficits associated with hoarding.

There is some evidence that individuals who compulsively hoard demonstrate significant difficulty making decisions. They tend to believe a disproportionate number of their possessions are very important, and feel paralyzed by seemingly commonplace decisions about what items to discard and what items to keep, which items are valuable, and how to organize the items they decide to keep. These decision-making problems have been associated with hoarding in several studies using self-report measures.[42-44] With respect to laboratory studies, however, research has provided mixed results regarding decision-making deficits. Grisham et al[39] found that hoarders displayed relatively intact decision making on the Iowa Gambling Task relative to a clinical and community control groups. A recent study in our laboratory has replicated this finding, showing that individuals with compulsive hoarding did not demonstrate decision-making problems on the computerized Cambridge Gambling Task.[45]

However, Lawrence et al[41] found that hoarding symptoms were associated with specific decision making impairments on the same gambling task and that these deficits were related to the severity of the hoarding symptoms. Lawrence et al[41] suggested that hoarders have difficulty deciding whether to save or discard their possession due to general decision-making difficulties. One important difference between the Grisham et al[39] and Lawrence et al[41] studies was the composition of the hoarding group. In the Grisham et al study, the hoarding group comprised participants who met criteria for compulsive hoarding, regardless of whether they had OCD, while the hoarding group in the Lawrence et al study consisted of OCD patients who displayed hoarding behaviors. This difference in the samples may explain the discrepancy on the decision-making task in the two studies. Future studies may compare hoarding patients with and without other OCD symptoms to nonhoarding OCD patients and community controls in order to clarify the source of the decision-making difficulties.

Another area that remains unresolved is the role of proposed categorization problems in hoarding patients.[1,46] Compulsive hoarding patients appear to exhibit problems grouping their possessions into categories, which contributes to the disorganization and clutter that are hallmark features of this disorder.[1] A few studies have investigated these hypothesized differences in the way hoarding patients categorize. Wincze et al[47] contrasted hoarding participants, obsessive-compulsive nonhoarding participants and healthy control participants on categorization tasks. The results of this study suggested that categorization problems occur only when compulsive hoarders sort their own possessions. In contrast, Luchian et al[48] found that nonclinical hoarders also created more categories when categorizing nonpersonal objects. They also took almost twice as long to sort objects, and found sorting to be more difficult and stressful than did nonhoarding participants. Inconsistencies between this study and Wincze et al[47] may be due to differences between nonclinical and clinical hoarding participants or because of methodological differences between the two studies. Thus, the circumstances under which hoarders have categorization difficulties remains unknown due to the lack of systematic comparisons between personal and nonpersonal objects.

Despite recent advances in the study of cognitive functioning among individuals who hoard, many key questions remain to be addressed. While there is some indication of deficits in hoarding patients, it is unclear how reliably these deficits can be identified. It is also uncertain whether these deficits are present to varying degrees in all hoarding patients, or a subset of patients. Future research also should provide greater understanding regarding the specific nature of information processing difficulties and/or cognitive impairment. Finally, it will be important as we gain greater understanding of cognitive difficulties to examine whether these difficulties may be remediated in order to improve treatment outcome.

Treatment

Research on the treatment of hoarding also has advanced significantly in recent years. Several earlier studies found that hoarding symptoms are negative

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treatment predictors for therapies that have demonstrated effectiveness for OCD. In serotonergic medication trials for OCD, individuals with hoarding symptoms typically have poorer outcomes.[49-51] Only one that has examined the effectiveness of selective serotonin reuptake inhibitors in reducing obsessive-compulsive symptoms has demonstrated equivalent outcomes for individuals with and without hoarding symptoms.[52] Although this finding appears promising, the results need to be qualified. The authors only measured obsessive-compulsive symptoms, symptom response was poor in both groups (23% to 24% symptom reduction), and individuals with hoarding symptoms took paroxetine for significantly more days. As with pharmacological approaches, the presence of hoarding symptoms is a negative predictor of cognitive-behavioral treatment outcome for OCD.[53,54] Only one third of hoarders with OCD demonstrate clinically significant improvement in response to exposure and response prevention, while one half to two thirds of nonhoarders with OCD demonstrate such improvement.[53] In response to these disappointing outcomes, researchers have developed psychological treatments for compulsive hoarding that are based on Frost and Hartl's cognitive-behavioral model.[1] Treatments outcomes based on Frost and Hartl's model are encouraging, but suggest that many sessions are required to produce change and that clutter is slow to improve. The first case study reported that approximately 45 sessions were needed to completely reduce clutter.[55] After 20 weeks of treatment, Steketee et al[56] demonstrated a 16% reduction in Y-BOCS scores, while Saxena et al[57] demonstrated a 35% reduction in Y-BOCS scores after 6 weeks of daily intensive treatment. Utilizing Steketee and Frost's[58] cognitive-behavioral treatment manual for compulsive hoarding, Tolin et al[59] offered 26 individual sessions (in-office sessions and at least one home visit) over a 7- to 12-month period to 14 individuals. On average, treatment completers (n=10) demonstrated 25% improvement in their clutter and difficulty discarding, and 35% reduction in acquiring. Following this open trial, Steketee et al[60] made minor modifications to the treatment and examined its efficacy in a randomized controlled trial. Findings from this trial indicated that improvements in hoarding symptoms were greater after receiving 12 sessions of cognitive behavioral therapy (CBT) than after waiting for a comparable period. After 26 sessions of CBT, 68% to 76% of patients were rated as improved by their therapists or themselves, respectively, and 41% of patients met criteria for clinically significant improvement.

Given that changes are slow to occur during the treatment of compulsive hoarding, researchers have been examining alternative delivery models in hopes of increasing the cost-effectiveness of treatment. Using a multiple cohort pretest–post-test design, Muroff and colleagues examined the effectiveness of group CBT using Steketee and Frost's treatment manual.[32] After 16 to 20 sessions and two home visits, patients evidenced a mean reduction of 8.6 points on the Saving Inventory-Revised (SI-R), which is less than that produced from individual treatment using the same manual (18.7 or 16.9).[59,60] After these investigators modified their research procedures to more thoroughly screen group members and utilized a more detailed and structured manual for the group, the mean SI-R reduction in the final group was 14.25.

As access to clinicians trained in CBT for compulsive hoarding is limited, a Web-based self-help group has also been examined for its effectiveness. This Web-based treatment was also based on Steketee and Frost's manual[58] and required individuals to take active steps to reducing their hoarding behavior within 2 months of membership. After 6 months of memberships, SI-R scores decreased by an average of 6 points. These two group studies suggest that highly structured, in-person groups may lead to greater improvements in hoarding outcomes than less-structured groups. Internet treatment approaches are important because they have the potential to expand significantly the number of individuals with hoarding who receive treatment, and thus, ways to improve outcomes achieved from Internet-delivered therapy are much needed.

More effective treatments are warranted for this common and disabling disorder. Novel pharmacotherapies, such as cognitive enhancers and stimulants, should be evaluated for their utility with hoarding patients. Cognitive enhancers may improve memory, attention, and overall cognitive functioning, while stimulants may improve attention, alertness, and information-processing speed. Only one case report has been published describing the effects of a stimulant in an individual with compulsive hoarding. In this case, a combined treatment of fluvoxamine, risperidone, amphetamine salts, and behavior therapy was used to treat a 56-year old man diagnosed with OCD, compulsive hoarding, ADHD, and schizotypal personality disorder. Although the patient reported that after treatment he procrastinated less, kept appointments better, and was less upset when throwing things away, the patient's clutter did

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not significantly decrease.[61] In order to determine if stimulants or cognitive enhancers are effective adjuncts for the treatment of compulsive hoarding, systematic, randomized controlled trials are needed.

Overall, research findings indicate that compulsive hoarders do respond to CBT, although improvements are moderate in comparison with gains observed in nonhoarders with OCD. A number of methodological limitations, however, curtail these findings. First, there is a lack of properly controlled treatment studies that involve random allocation to treatment (CBT or medication) and a placebo group. Also, the lack of specificity of the measures used to index symptoms makes it difficult to determine whether improvements are due to changes in hoarding symptoms or to reductions in nonhoarding OCD symptoms.

Future directions

Despite the increased research on compulsive hoarding in recent years, several avenues still require exploration. Researchers must continue to unravel the complex story of hoarding's etiology and pathogenesis through additional laboratory studies examining the cognitive, emotional, neural, and behavioral features of the disorder. Future research may also help to establish the relation of hoarding symptoms to OCD, anxiety, ADHD, and ICDs. Finally, further treatment studies investigating the efficacy of cognitive rehabilitation, behavioral interventions, Internet applications, and novel medication treatments are essential for improving clinical outcomes. ❑

REFERENCES

1. Frost RO, Hartl T. A cognitive-behavioral model of compulsive hoarding. *Behav Res Ther.* 1996;34:341-350.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
3. Pertusa A, Fullana MA, Singh S, Alonso P, Menchon JM, Mataix-Cols D. Compulsive hoarding: OCD symptom, distinct clinical syndrome, or both? *Am J Psychiatry*. 2008;165:1289-1298.
4. Wu KD, Watson D. Hoarding and its relation to obsessive-compulsive disorder. *Behav Res Ther*. 2005;43:897-921.
5. Grilo CM, McGlashan TH, Gunderson JG, et al. Internal consistency, intercriterion overlap and diagnostic efficiency of criteria sets for DSM-IV schizotypal, borderline, avoidant and obsessive-compulsive personality disorders. *Acta Psychiatrica Scandinavica*. 2001;104:264-272.
6. Saxena S. Is compulsive hoarding a genetically and neurobiologically discrete syndrome? Implications for diagnostic classification. *Am J Psychiatry*. 2007;164:380-384.
7. Samuels JF, Bienvenu Iii OJ, Pinto A, et al. Hoarding in obsessive-compulsive disorder: Results from the OCD Collaborative Genetics Study. *Behav Res Ther*. 2007;45:673-86.
8. Frost RO, Steketee G, Williams LF, Warren R. Mood, personality disorder symptoms, and disability in obsessive-compulsive hoarders: A comparison with clinical and nonclinical controls. *Behav Res Ther*. 2000;38:1071-1081.
9. Mataix-Cols D, Baer L, Rauch S, Jenike MA. Relation to factor analyzed symptom dimensions of obsessive-compulsive disorder to personality disorders. *Acta Psychiatrica Scandinavica*. 2000;102:199-202.
10. Samuels J, Nestadt G, Bienvenu III OJ, Costa PT, Riddle MA, Liang KY. Persoanltiy disorders and normal personality dimensions in obsessive-compulsive disorder: Results from the John Hopkins OCD Family Study. *Br J Psychiatry*. 2000;177:457-462.
11. Goodman WK, Price LH, Rasmussen SA, et al. The Yale–Brown Obsessive–Compulsive Scale. I. Development, use and reliability. *Arch Gen Psychiatry*. 1989;46:1006–1011.
12. Frost RO, Krause MS, Steketee G. Hoarding and obsessive-compulsive symptoms. *Behav Modif*. 1996;20:116-132.
13. Rasmussen SA, Eisen JL. The epidemiology and differential diagnosis of obsessive compulsive disorder. *J Clin Psychiatry*. 1992;53:4-10.
14. Samuels J, Bienvenu III OJ, Riddle MA, et al. Hoarding in obsessive-compulsive disorder: Results from a case-control study. *Behav Res Ther*. 2002;40:517-528.
15. Abramowitz JS, Wheaton MG, Storch EA. The status of hoarding as a symptom of obsessive-compulsive disorder. *Behav Res Ther*. 2008;46:1026-1033.
16. Grisham JR, Brown TA, Liverant G, Campbell LA. The distinctiveness of hoarding from other dimensions of obsessive-compulsive disorder. *J Anxiety Disord*. 2005;19:767-769.
17. Frost RO, Meagher BM, Riskind JH. Obsessive-compulsive features in pathological lottery and scratch ticket gamblers. *J Gambl Stud*. 2001;17:5-19.
18. Grant JE, Mancebo MC, Pinto A, Eisen JL, Rasmussen SA. Impulse control disorders in adults with obsessive compulsive disorder. *J Psychiatr Res*. 2006;40:494-501.
19. Hayward LC, Coles ME. Elucidating the relation of hoarding to obsessive compulsive disorder and impulse control disorders. *J Psychopathol Behav Assess.* 2009;31:220-227.
20. McElroy SL, Keck PE, Phillips KA. Kleptomania, compulsive buying, and binge-eating disorder. *J Clin Psychiatry*. 1995;56:14-26.
21. Rachman SJ, Elliot CM, Shafran R, Radomsky A. Separating hoarding from OCD. *Behav Res Ther*. 2009;47:520-522.
22. Steketee G, Frost RO. Compulsive hoarding: current status of the research. *Clin Psychol Rev*. 2003;23:905-927.
23. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15:53-63.
24. Samuels JF, Bienvenu OJ, Grados MA, et al. Prevalence and correlates of hoarding behavior in a community-based sample. *Behav Res Ther*. 2008;46:836-844.
25. Iervolino AC, Perroud N, Fullana MA, et al. Prevalence and heritability of compulsive hoarding: a twin study. *J Am Acad Child Adolesc Psychiatry*. 2009;166:1156-1161.
26. Ayers CR, Saxena S, Golshan S, Wetherell JL. Age at onset and clinical features of late life compulsive hoarding. *Int J Geriatr Psychiatry*. 2010;25:142-149.
27. Grisham JR, Frost RO, Steketee G, Kim HJ, Hood S. Age of onset of compulsive hoarding. *J Anxiety Disord*. 2006;20:675-686.
28. Cromer KR, Schmidt NB, Murphy DL. An investigation of traumatic life events and obsessive-compulsive disorder. *Behav Res Ther*. 2007;45:1683-1691.
29. Wheaton M, Timpano KR, Lasalle-Ricci VH, Murphy DL. Characterizing the hoarding phenotype in individuals with OCD: associations with comorbidity, severity and gender. *J Anxiety Disord*. 2008;22:243-252.
30. Muroff J, Steketee G, Himle J, Frost R. Delivery of internet treatment for compulsive hoarding (D.I.T.C.H.). *Behav Res Ther*. 2010;48:79-85.
31. Tolin DF, Frost RO, Steketee G, Gray KD, Fitch KE. The economic and social burden of compulsive hoarding. *Psychiatry Res*. 2008;160:200-211.
32. Muroff J, Steketee G, Rasmussen J, Gibson A, Bratiotis C, Sorrentino C. Group cognitive and behavioral treatment for compulsive hoarding: a preliminary trial. *Depress Anxiety.* 2009;26:634-640.

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Acaparamiento compulsivo: controversias actuales y perspectivas

El acaparamiento compulsivo es un trastorno psicológico invalidante, caracterizado por conductas inadecuadas de acumular y guardar. Este artículo revisa cuatro áreas clave de los avances recientes en la investigación del acaparamiento. Primero, se entrega una panorámica de la controversia que se ha desarrollado en relación con la condición diagnóstica del acaparamiento, destacando la evidencia que se ha acumulado en relación con el hecho que sería mejor conceptualizarlo como un síndrome independiente. Segundo, se describen los avances en la comprensión de la epidemiología, el curso y las características demográficas del acaparamiento compulsivo. Tercero, se revisan los últimos hallazgos relacionados con posibles correlatos neuropsicológicos de este trastorno. Finalmente se discute el progreso actual y las perspectivas futuras en relación con el manejo clínico del acaparamiento compulsivo.

Collectionnisme compulsif : controverses actuelles et nouvelles orientations

Le collectionnisme compulsif est un trouble psychologique handicapant caractérisé par un comportement d'épargne et de stockage excessif. Cet article analyse quatre points clés des avancées récentes de la recherche sur ce sujet. Nous débutons premièrement par une synthèse de la controverse en pleine évolution sur le diagnostic de ce trouble : les arguments sont de plus en plus en faveur d'une meilleure conceptualisation du trouble comme syndrome à part. Deuxièmement, nous décrivons les avancées concernant notre compréhension de son épidémiologie, de son évolution et de ses cadres démographiques. Troisièmement, nous analysons les derniers résultats des corrélations neuropsychologiques éventuelles du trouble. Enfin, nous discutons des progrès en cours et des orientations futures de la prise en charge clinique du collectionnisme compulsif.

33. Steketee G, Frost RO, Kim HJ. Hoarding by elderly people. *Health Soc Work*. 2001;26:176-184.
34. Harlow JM. Recovery from the passage of an iron bar through the head. *Proc Counc Mass Med Soc*. 1868;2:327-347.
35. Eslinger PJ, Damasio AR. Severe disturbance of higher cognition after frontal lobe ablation: Patient EVR. *Neurology*. 1985;35:1731-1741.
36. Hahm DL, Kang Y, Cheong SS, Na DL. A compulsive collecting behavior following an A-com aneurismal rupture. *Neurology*. 2001;56:398-400.
37. Anderson SW, Damasio H, Damasio AR. A neural basis for collecting behaviour in humans. *Brain*. 2005;128:201-212.
38. Hartl TL, Duffany SR, Allen GJ, Steketee G, Frost RO. Relationships among compulsive hoarding, trauma, and attention-deficit/hyperactivity disorder. *Behav Res Ther*. 2005;43:269-276.
39. Grisham JR, Brown TA, Savage CR, Steketee G, Barlow DH. Neuropsychological impairment associated with compulsive hoarding. *Behav Res Ther*. 2007;45:1471-1483.
40. Hartl TL, Frost RO, Allen GJ, Deckersbach T, et al. Actual and perceived memory deficits in individuals with compulsive hoarding. *Depress Anxiety.* 2004;20:59-69.
41. Lawrence NS, Wooderson S, Mataix-Cols D, David R, Speckens A, Phillips ML. Decision making and set shifting impairments are associated with distinct symptom dimensions in obsessive-compulsive disorder. *Neuropsychology*. 2006;20:409-419.
42. Frost RO, Gross RC. The hoarding of possessions. *Behav Res Ther*. 1993;31:367-381.
43. Frost RO, Shows DL. The nature and measurement of compulsive indecisiveness. *Behav Res Ther*. 1993;31:683-692.
44. Steketee G, Frost RO, Kyrios M. Cognitive aspects of compulsive hoarding. *Cognit Ther Res.* 2003;27:463-479.
45. Grisham JR, Melissa MM, Williams AD, Certoma SP, Kadib R. Categorization and cognitive deficits in compulsive hoarding. *Behav Res Ther*. In press.
46. Frost RO, Steketee G. Hoarding: clinical aspects and treatment strategies. In: Jenike MA, Baer L, Minichiello WE, eds. *Obsessive-Compulsive Disorder: Practical Management*. 3rd ed. St Louis, MO: Mosby Yearbook Medical; 1998:533-554.
47. Wincze JP, Steketee G, Frost RO. Categorization in compulsive hoarding. *Behav Res Ther*. 2007;45:63-72.
48. Luchian SA, McNally RJ, Hooley JM. Cognitive aspects of nonclinical obsessive-compulsive hoarding. *Behav Res Ther*. 2007;45:1657-1662.
49. Black DW, Monahan P, Gable J, Blum N, Clancy G, Baker P. Hoarding and treatment response in 38 nondepressed subjects with obsessive-compulsive disorder. *J Clin Psychiatry*. 1998;59:420-425.
50. Mataix-Cols D, Rauch S, Manzo P, Jenike M, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 1999;156:1409-1416.
51. Winsberg ME, Cassic KS, Koran LM. Hoarding in obsessive-compulsive disorder: a report of 20 cases. *J Clin Psychiatry*. 1999;60:591-597.
52. Saxena S, Brody AL, Maidment KM, Baxter LRJ. Paroxetine treatment of compulsive hoarding. *J Psychiatry Res*. 2007;41:481-487.
53. Abramowitz JS, Franklin ME, Schwartz SA, Furr JM. Symptom presentation and outcome of cognitive-behavioral therapy for obsessive-compulsive disorder. *J Consult Clin Psychol*. 2003;71:1049-1057.
54. Mataix-Cols D, Marks IM, Greist JH, Kobak KA, Baer L. Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: Results from a controlled trial. *Psychother Psychosom*. 2002;71:255-262.
55. Hartl TL, Frost RO. Cognitive-behavioral treatment of compulsive hoarding: a multiple baseline experimental case study. *Behav Res Ther*. 1999;37:451-461.
56. Steketee G, Frost RO, Wincze J, Greene K, Douglass H. Group and individual treatment of compulsive hoarding: a pilot study. *Behav Cogn Psychother*. 2000;28:259-68.
57. Saxena S, Maidment KM, V, Vapnik T, et al. Obsessive-compulsive hoarding: Symptom severity and response to multimodal treatment. *J Clin Psychiatry*. 2002;63:21-27.
58. Steketee G, Frost RO. *Compulsive Hoarding and Acquiring: Therapist Guide*. New York, NY: Oxford University Press; 2007.
59. Tolin DF, Frost RO, Steketee G. An open trial of cognitive-behavioral therapy for compulsive hoarding. *Behav Res Ther*. 2007;45:1461-1470.
60. Steketee GF, Tolin DF, Rasmussen J, Brown TA. Waitlist-controlled trial of cognitive behavior therapy for hoarding disorder. *Depress Anxiety*. 2010;27:476-484.
61. Kaplan A, Hollander E. Comorbidity in compulsive hoarding: a case report. *CNS Spectr*. 2004;9:71-73.

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Epilepsy and obsessive-compulsive disorder

Peter W. Kaplan, MB, FRCP

Obsessive-compulsive disorder (OCD) has long been associated with epilepsy. The link with temporal lobe (usually refractory) epilepsy (TLE) is particularly prominent. Of TLE patients, 10% to 22% of patients may have OCD, often underdiagnosed in the outpatient clinic. Data on the links include case reports, case series, and controlled studies. Three larger, controlled studies in TLE patients, using comprehensive epilepsy and OCD classifications, in aggregate, have noted the obsessive qualities of washing, symmetry/exactness, and ordering, with a greater preoccupation with certain aspects of religion, compared with controls or patients with idiopathic generalized epilepsy. TLE foci may be either left- or right-sided. Social and neurobiological factors are involved in OCD in TLE. The neurobiology implicates a pathophysiological or structural impairment of the orbitofrontal-thalamic, and fronto-thalamic-pallidal-striatal-anterior cingulate-frontal circuits. Discrete anatomic lesions in these pathways, or their surgical removal, may induce (or conversely) improve OCD in TLE patients.

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Obsessive-compulsive disorder and epilepsy

Obsessive-compulsive disorder (OCD) includes a range of clinical characteristics with two major components. There is firstly the intrusion of thoughts, ideas, or compulsions; and secondly, the resulting triggering of abnormal behaviors or rituals. These actions may serve to resolve the mental imperative of the intrusive thoughts by inducing the person to perform repeated actions or movements that often appear ritualistic. The ritual is composed of sets or sequences of these behaviors, often in order, and may consume much of the patient's waking attention. OCD is not rare, and occurs with a lifetime prevalence of up to 3%.[1] Even with medication as well as behavioral modification, more than one in ten patients are significantly impaired in their activities of daily living.[2] Obsessive-compulsive symptoms (OCS) may be seen in OCD itself, or may appear in other psychiatric conditions,. However, despite a number of case reports, no unifying theory of causation has been clearly established. An increased prevalence of OCS, however, has been noted in refractory epilepsy,[3] particularly with temporal lobe epilepsy (TLE). There is therefore interest in whether these two conditions are causally linked.

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Epilepsy can affect up to 1% of the population, and is one of the commoner groups of neurological disorders in adults.[4,5] This group of disorders is defined as the clinical expression of repeated epileptic seizures occurring spontaneously (unprovoked). There may be many possible causes. These include genetic conditions with onset at various ages and stages of development, and a large spectrum of acquired insults such as conferred by trauma, strokes, neoplasia, inflammation, or infections. Most patients with frequent seizures are offered medical treatments, but even with a wide choice of antiepileptic drugs (AEDs), over one quarter of patients are refractory to medical treatment. Patients with epilepsy may also express a number of patterns of behavioral abnormality and personality characteristics, and experience memory, emotional, behavioral, and social disabilities.[6-9] Up to 40% of epilepsy patients may be so disabled, particularly in the patients with pharmacoresistant seizures.[6] Ertekin and colleagues' review[10] notes that in refractory epilepsy, some 70% had psychiatric disorders[7]; prevalence of axis I psychiatric disorders ranged up to 80%[8]; and that using the Symptom Checklist-90-Revised (SCL-90-R), adults with partial epilepsy had a prevalence of 88% mental health complaints when scoring for symptoms in the index.[9] In epilepsy, mood disorders, including depression and anxiety, are frequent.[10] In over 200 patients, anxiety was found in almost 25%.[11] As part of this behavioral disturbance, patients may present with features of OCD.

This review will examine the links between OCD and epilepsy, and review the evolution of the literature on case reports, case series, and larger retrospective controlled studies. Included will be the components of OCD seen in epilepsy, effects of medical and surgical treatments, and an overview of the theoretical neurobiological underpinnings that might link the two disorders.

Behavioral and thought disturbances in epilepsy

Teasing out the elements, types, and causes of behavioral disturbance in epilepsy presents a challenge. It is not clear whether the behavioral changes that occur following seizures or with epilepsy may, for example: (i) arise from the epilepsy itself; (ii) may appear as a form of forced change induced by the seizure; (iii) might arise from reactive or released behaviors after the seizure (as a postictal phenomenon); or (iv) may be a comorbid psychiatric condition (which often occur in epilepsy). Quite aside from the acute effects of acute seizures, is the possibility that it is the chronic progression of the epileptic disorder that might predispose to the appearance of OCS among the many possible psychiatric consequences of epilepsy. These mechanisms might also apply to the many different types of seizures that exist in the family of epilepsy syndromes, along with the various underlying and differing cerebral insults (both etiological and anatomical) that can cause epilepsy. In looking at possible seizure types that are associated with OCD, it seems that exclusively generalized tonic-clonic seizures are rarely associated with OCS. Psychiatric problems in general were greater in TLE (80%) than in juvenile myoclonic epilepsy (JME), a genetic nonfocal epilepsy.[12] Others have failed to be able to link epilepsy type with psychopathology.[13] There has been a long association between TLE and OCD, as will be explored below.

The association between OCD and TLE

There has been a long-standing observation that patients with various types of epilepsy had a higher incidence of many psychiatric conditions. More specifically, TLE patients occasionally showed clinical features of compulsive behavior. Some examples published as case reports delineate this relationship.[14-19] Many years ago Tizard suggested that epilepsy generated, or was associated with, a number of personality traits that had obsessional characteristics, suggesting that particular types of epilepsy cause certain types of psychopathology.[20] Waxman and Geschwind described an *interictal behavior syndrome* characterizing the religious, hypergraphic, and circumstantiality features in epilepsy patients, and others have noted that such qualities in an epilepsy population leads to a low quality of life.[21,22] There were suggestions that this *TLE syndrome* characterized by religiosity, hyposexuality, hypergraphia, and obsessional features[21] might correspond to a lateralized temporal lobe focus, but patients with OCD were found in some reports or studies to have left- or right-sided epileptic foci.[15,23,24] This was further underscored by the study by Bear and Fedio who isolated some of these psychological features, particularly elements of OCD.[25] Patients with the appearance or resolution of OCD features with the onset or regression of neurological disease strengthened these possible associations. Bear and Fedio suggested that the 2.5% prevalence of OCD in the general

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population would be exceeded in patients with TLE (for example) if there were associative or causative factors to link the two disorders.[25,26]

Individual case reports or small series have led to the suggestion that a right hemisphere proclivity exists for manifestation of OCD in patients with TLE. Furthermore, it had been found that some patients with OCD features had right hemisphere structural abnormalities. There have also been other reports of lateralized abnormalities when TLE patients with OCD had magnetic resonance imaging (MRI) studies which revealed structural abnormalities, or had electroencephalographic (EEG) asymmetries.[27,28] Schmitz and colleagues, however, failed to find that TLE laterality correlated with varying degrees of personality characteristics, or obsessionality.[29]

Although a number of studies with a small number of subjects indicated a link between TLE and OCD, there were few group studies. It awaited the development of better retrospective and prospective studies to explore the similarity noted between the forced thinking seen in some patients with TLE and OCD, and to determine whether there was merely a chance comorbidity, or a clear association. Hence, there was a need to build upon the casual clinical impression and the several case reports of TLE and OCD, and design more systematic investigations in the form of case series or controlled studies. These studies would have to use structured neuropsychological instruments, trained personnel, and a control population to help eliminate biases inherent in many case series.

In order to systematize and lend validity to the association of OCD and epilepsy, Isaacs and colleagues looked at the profile of symptoms in TLE to see if TLE and OCD shared common neural mechanisms, and to facilitate diagnosis and symptom treatment in TLE.[3] To do this, they measured the prevalence of OC features using an Obsessive-Compulsive Inventory and compared their results with those of normative controls. They found that patients with OCD manifested abnormalities on neuropsychological tests that involved nonverbal memory and visuospatial tasks. This has been endorsed by some imaging studies in patients with OCD without epilepsy, but other reports indicate a more bilateral involvement.[3,27,30,31] Hence, from their findings, it is unclear to what degree a right hemisphere predominance of abnormalities prevails in TLE with OCD. The symptoms in the TLE group included *doubting, ordering, hoarding, checking, neutralizing and washing*, emphasizing the more compulsive components rather than the obsessive moiety of this duality.[3] This study thus indicated the possibility that the neurobiological pathways subserving compulsive thought processes may differ from those underlying obsessive traits. Hence, in TLE, compulsions may be particularly favored. Isaacs and colleagues suggest that *doubting, checking*, and *hoarding* in particular might represent the effects of behavioral impairments in patients with TLE, for example related to a problem in memory; while *hoarding* might reflect deficits in organization stemming from frontal lobe problems.[3]

The work by Monaco and colleagues has also been influential in exploring these links.[32] There has been a distinction made between the concept of *traits* (features) of a particular individual, or a state, arising from the role that a disease might play in a patient's life.[32] As Monaco and colleagues have pointed out, this analytical approach has been used with quantitative evaluation techniques that use personality psychometrics, but have been less used with neurological disorders.[32] Several factors may impair the strength of conclusion from older studies. These comprise possible selection bias, the absence of systematic data, and a reliance on self-rating scales without confirmation of validity, and finally an underuse of more prevalent psychometric tools.[32]

In their review of consecutive patients with TLE versus patients with nonfocal idiopathic generalized (genetic) epilepsy (IGE), Monaco and colleagues studied subjects employing investigators who were fully trained in clinical psychology and who used a Structured Clinical Interview for SDM-IV Patient Version for OCD diagnosis and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). They evaluated obsessionality as a trait using a Minnesota Multiphasic Personality Inventory - 2 (MMPI-2) version addressing the Pt clinical scale and OBS content scales that contain evaluations of characteristics of *compulsions, excessive doubts, obsessions, perfectionist personality traits*, and *fear*. The particular OC features investigated included *neutralizing, checking, doubting, ordering, hoarding*, and *washing*. The OBS content scale identifies OCS and behaviors, "maladaptive ruminations," and obsessive thoughts. These scales were supplemented by the Beck Depression Inventory and State-Trait Anxiety Inventory Y1 and Y2. Of the 164 enrolled subjects matched with 82 controls, AEDs, seizure control, age, gender, duration, EEG, and MRI among many items, were evaluated. TLE patients scored higher on the *Pt* and *OBS* scales than IGE and

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normal controls, unrelated to seizure control, severity of epilepsy, medication, or etiology. This indicated that obsessionality is a TLE trait in patients with a biological predisposition, with a prior psychiatric history. In turn, this would suggest that there is a link between mesolimbic regions and particular personality characteristics, a link previously believed to exist in TLE patients. The study further supports the concept that involvement of particular brain areas, by the various epilepsy syndromes will be relevant to the appearance of specific psychopathological expression and psychiatric conditions. Of note was the fact that the results in the normal controls resembled those of IGE patients, differentiating these two groups from TLE. The study also revealed that almost 15% of TLE patients had OCD. Such findings contrasted with the Isaacs study which found that 22% of TLE patients had features of OCD,[3] but which had examined a refractory TLE population. An unsettling finding in the Monaco study is that only one of the nine patients had been previously diagnosed with OCD, indicating that OCD is poorly recognized in an outpatient epilepsy patient population. One reason may well be the relative lack of investigators trained in psychiatry in an outpatient epilepsy clinic setting. Regarding mechanisms, the authors note that the amygdala is involved in OCD, and has major connections with the striatum. Such affective and motivational components facilitate the conduction of automated often ritualistic behavior in response to danger. The reciprocal links to the amygdala, ventral striatum, and stria terminalis may serve the anxiety-modulating effects of rituals and repetitive behaviors.[33]

Ertekin and colleagues built on the prior investigations and constructed a study to evaluate the associations of TLE arising from unilateral mesial temporal sclerosis (MTS), and IGE with psychiatric comorbidities including OCD.[10] They compared 29 TLE patients with 27 IGE patients from an epilepsy clinic population, and with 30 control subjects, they employed investigators experienced in epilepsy and psychiatry. This team evaluated the three groups, and supplemented their evaluations with MRI imaging and EEG. Using a Structured Clinical Interview (SCID-I) and Y-BOCS Symptom Checklist that includes some 50 types of obsessive and compulsive characteristics, they were able to rate severity and type of symptom, including patients with subsyndromal characteristics of OCD. The authors found that about 10% of TLE patients had OCD, 24% had subsyndromal OCD, which was higher than in the matched IGE group (3.7% and 7.4% - not statistically significant). The commonest comorbidity with OCD was depression,[10] and there was a left-sided predominance in this association with TLE.

Overall, psychiatric comorbidity in the epilepsy population probably arises from many sources. Principal among them probably is a combination of social and neurobiological interplay. Lending support to the effect of the chronicity of an enduring condition, is the study by Swinkels and colleagues who noted that both predisposition and brain dysfunction played a part.[8] They speculated that anatomical factors, however, were more important than the chronicity of the disease. Confirming observations by Monaco and colleagues, Ertekin and colleagues found that depression was highly associated with OCD in TLE, also supporting conclusions by Isaacs and colleagues who used an Obsessive Compulsive Inventory (OCI), but not a SCID-IP or Y-BOCS to delineate an OCD diagnosis.[3,10,32] Findings by Ertekin and colleagues also endorse the Isaacs findings. They found that patients with TLE have greater obsessions with contamination and a compulsion to *wash* than do patients with IGE; similarly with *symmetry/exactness* obsessions and *ordering* compulsion; while Isaacs and colleagues found greater *washing, ordering, checking, hoarding, doubting*, and *neutralizing*. Some patients with TLE have greater preoccupation with existential aspects of religion.[3,10,34]

Other epilepsies and OCD

Frontal lobe epilepsy (FLE) is another likely candidate as a fellow traveler with OCD, possibly because of the executive and behavioral functions subserved by this part of the brain. From a neurobiological perspective, dysfunction in this region affects part of the frontal-cingulate-thalamic-limbic circuit, and hence might favor the functional dysregulation of this circuit, thus inducing elements of OCD.[16,18,28]

Another candidate is limbic epilepsy, with its unusual automatisms which may simulate the ritualistic behavior of OCS. Patients may display repetitive movements and types of automatic behavior.

Other rarer conditions may possess both epilepsy and rituals or at least repetitive behaviors as clinical expressions of a particular disease. Examples include the handwringing seen with Rett Syndrome, and other behavioral

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features noted with Angelman syndrome and autism spectrum disorder.

Neurobiology of the association between epilepsy and OCD

There has been an increasing effort to formulate a neurobiological underpinning to OCD. Various theories have been advanced, and have been supported by the findings of OCD triggered by a number of neurological conditions. These include head trauma, brain tumors, cerebral infarction, and seizures. Modell and colleagues suggest that there are two principal loops or circuits underlying control of the behaviors involved in OCD.[34] They are comprised of a thalamo-orbitofrontal connection mediated by glutamate, and a collateral loop that includes striatal-orbitofrontal-thalamic interconnections mediated additionally by serotonin, dopamine, and gamma-aminobutyric acid (GABA). The latter loop controls the activity in the thalamo-orbitofrontal circuit. Normally, orbitofrontal cortex activates the caudate and then the pallidum so as to inhibit the medial thalamic nucleus that then feeds into the frontal cortex. In this manner, medial thalamic inputs would regulate hyperactivity of the orbitofrontal thalamic relays. Dysfunction of these circuits might produce OCD, with increased activity inducing obsessive characteristics and compulsive traits.[34]

However, complicating this paradigm is the paradoxical clinical resolution in some cases of established OCD by the new appearance of one of strokes, tumors, or by deep brain stimulation.[35,36] Nonetheless, such serendipitous associations have spawned a neurobiological underpinning for OCD that includes the malfunctioning of various brain circuits. Abnormally functioning circuits include the thalamus, basal ganglia, anterior cingulate gyrus, and the orbito-frontal cortex.[37,38] It has been postulated that there is an abnormality in the circuit linking frontal regions to the basal ganglia. These circuits pass through the frontal-thalamic-pallidal-striatal areas and back to the frontal regions, transiting via the anterior cingulate gyrus and the internal capsule. To support the concept of this specific circuitry underlying OCD is the finding that disruption of this pathway by surgical anterior internal capsulotomy and anterior cingulotomy enables improvements in OCD.[39] A new model for OCD has been proposed by Huey and colleagues based on studies using functional MRI, MRI, and positron emission tomography.[36] They examined patients with OCD who had other neurological disorders, and compared them to patients with idiopathic OCD. Some patients with "secondary" OCD had undergone surgery or deep brain stimulation believed to decrease hyperactivity in regions thought to provoke OCD. The group postulated that three regions are implicated in both types of OCD: orbitofrontal cortex which directs appropriate behavior, the basal ganglia that acts as a gate in connecting behaviors to subsequent reward, and the anterior cingulate region that modulates perception of which behavioral "choice" will result in reward. Patients with OCD from neurological disease had less anxiety with the compulsion than did those with the idiopathic form. Huey and colleagues postulated that the anxiety and impulse towards particular behaviors are requited only when the behavior is completed.[36]

Theories underlying the particular association between OCD and epilepsy include not only a possible shared mechanism, but an incidental OCD problem in patients with epilepsy.[39] However, a compelling explanation for the OCS-epilepsy association is the interruption of a "pathological shared organization" when certain types of focal brain neurosurgery are performed, with the effect of causing regression of seizures, but also allowing latent OCD traits to appear.[38,40] A sudden cessation of seizures after surgery might be seen as a form of "forced normalization."[41,42] Hence the surgical removal of excitation, and preponderance of inhibition, would enable the occurrence of psychiatric disorders, and have been termed the "forced normalization" concept and the "latent disease theory."[41,42] Of note however, many post-operative TLE seizure patients never develop psychiatric problems.

One of the components of OCD involving the perception of forced thoughts may occur from seizures themselves. In the classification of seizures, those seizures that involve part of the brain and which do not impair vigilance or memory, are termed simple partial seizures. It has long been noted that obsessive thoughts can occur in the preictal period, be caused by simple partial seizures as an ictal phenomenon, or occur in the postictal period.

Kroll and Drummond have suggested that the comorbidity of OCD and TLE might be due to kindling.[15] The theory of kindling is that focal chemical or electrical brain stimulation can later result in a more persistent condition (eg, epilepsy). Some speculate that this might occur in the limbic circuit, and induce OCD problems.

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However, there is little evidence for this theory. Others have suggested that TLE and OCD might share a common mechanism. Problems with this theory are the absence of a single focus of neuronal deficit in OCD. In contrast, several regions have been implicated in OCD, including the basal ganglia, cingulate, and frontal areas,[23,36] with limbic areas involved in OCD and TLE.[16,18,28] The results of studies revealing a right-hemisphere TLE focus predilection, suggested an increased vulnerability to OC in this TLE population.

There may be a role of AEDs in OCD, as they might convey a neuropharmacological susceptibility to OCD. Ertekin and colleagues found in their TLE patients that most were on carbamazepine, while patients with IGE (with less OCD) were on valproate.[10] This suggests that epilepsy syndrome aside, one drug might favor, or the other drug might hinder, the development of OCD.

Because of the finding of depressive comorbidity with OCD in epilepsy, limbic dysfunction might represent an underlying neurobiological underpinning. Clinically, patients with OCD should therefore be assessed and treated for depression.[10]

The effects of surgery on OCD

In contrast to the appearance or the worsening of OCD with temporal lobe surgery as mentioned above, a subgroup of patients with particularly temporal-lobe foci may significantly benefit from resective surgery. Surgery is also sometimes effective in extratemporal foci, or with more widespread epileptic conditions with multiple seizure types (eg, Lennox-Gastaut syndrome), in which partial interruption of the corpus callosum may decrease certain types of seizures, particularly atonic seizures.

Many types of underlying premorbid psychopathology may get worse following epilepsy surgery, even when epilepsy improves.[39,43,44] There are reports of depression and psychosis, and in some cases suicide and death after temporal lobe surgery.[44-47] De novo psychosis may arise,[47] as well as de novo depression in 8%.[45,48] Leinonen and colleagues commented on new-onset schizophrenia in a group of 57 subjects[45] after surgery. Such tendencies can be evaluated before surgery and may well factor in the decision whether to advocate this treatment in affected patients.

Although Kulaksizoglu and colleagues found no particular risk factors for de novo postoperative psychiatric problems, most problems appeared to manifest within the first 2 months after surgery.[40] Six of 74 patients undergoing temporal lobectomy had new-onset psychosis with 6 suicide attempts in the first month.[49,50] In another series, by 6 weeks post-temporal lobectomy, of the previously nonsymptomatic patients for psychiatric disorders, half developed anxiety and depression, and almost half had emotional lability.[51] Other studies suggest that nondominant hemisphere surgery favors the appearance of more severe psychiatric problems,[52,53] even if lesions on either side may induce OCD in nonepileptic patients. Other neurosurgical studies support the involvement of neural loops in OCD in patients with epilepsy, and the subsequent improvement that can occur following surgery.[54] To reinforce the involvement of frontal pathways, Kulaksizoglu and colleagues review the reports on the dysfunction of frontal subcortical circuits, and the abnormalities in visual-spatial and nonverbal tasks that particularly implicate right subcortical frontal circuits in the process.[40]

Future directions in epilepsy/OCD research

There is much work to be done in establishing the causation of OCD, and possible links to epilepsy. Future studies should extend investigation to nonepilepsy neurological groups as well as a psychiatry group with OCD.[3] Multicenter studies would be valuable in looking at the entire severity spectrum of OCD in TLE. In addition, with the findings of greater religiosity and writing compulsions in patients with epilepsy, research into OCD in epilepsy would be enhanced by developing specific tools or scales that measure these parameters.[10] Greater attention might be directed at the comorbidity of depression and anxiety in OCD in patients with epilepsy, with examination of the neurobiological and structural relationships to clinical expression.[10]

As with any implied association, prospective larger studies with optimally trained personnel with experience in psychiatric testing instruments, the development of tailored characterization of OCD subtypes and feature categorization, and the application of these tools and trained personnel to carefully categorized populations of different types of epilepsy, are warranted. Multicenter trials would have a good chance of lending support to the neurobiology, causes, and optimal management in patients with the several types of epilepsies and varieties of OCD. ❑

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Epilepsia y trastorno obsesivo-compulsivo

El trastorno obsesivo-compulsivo (TOC). Es muy importante la vinculación con la epilepsia del lóbulo temporal (ELT), la cual es habitualmente refractaria. De los pacientes con ELT, el 10% a 22% puede tener un TOC, el cual con frecuencia es subdiagnosticado en los pacientes ambulatorios. La información de estas vinculaciones incluye reportes de casos, series de casos y estudios controlados. Tres grandes estudios controlados en pacientes con ELT, utilizando extensas clasificaciones de epilepsia y TOC han mostrado las características obsesivas del lavado, la simetríalexactitud y el orden, como también una mayor preocupación por ciertos aspectos de la religión, en comparación con controles o con pacientes con epilepsia idiopática generalizada. Los focos de la ELT pueden estar al lado izquierdo o derecho. Los factores sociales y neurobiológicos están involucrados en el TOC y en la ELT. La neurobiología implica un deterioro estructural o fisiopatológico de los circuitos tálamo - órbitofrontal y fronto – tálamo – pálido – estriatal - cíngulo anterior - frontal. Discretas lesiones anatómicas en estas vías o su remoción quirúrgica, pueden inducir una mejoría o un empeoramiento en el TOC de los pacientes con ELT.

Épilepsie et trouble obsessionnel compulsif

Le trouble obsessionnel compulsif (TOC) a longtemps été associé à l'épilepsie. Ainsi, le lien avec l'épilepsie du lobe temporal (ELT), habituellement réfractaire, est particulièrement important. Parmi les patients ayant une ELT, 10 % à 22 % peuvent avoir un TOC, souvent sous-diagnostiqué en consultation externe. Des rapports de cas, des séries de cas et des études contrôlées permettent de faire le lien entre ces deux pathologies. Trois plus grandes études contrôlées chez des patients ayant une ELT, utilisant la classification complète de l'épilepsie et des TOC, ont permis au total, en comparaison avec des témoins ou à des patients ayant une épilepsie généralisée idiopathique, de constater des obsessions de lavage, de symétrie/précision et d'ordre, et une préoccupation particulière pour certains aspects de religiosité. Les foyers d'ELT peuvent être localisés à gauche ou à droite. Des facteurs sociaux et neurobiologiques sont impliqués dans les TOC présents au cours de l'ELT. Les études neurobiologiques ont montré une altération physiopathologique ou structurelle des circuits orbitofrontaux-thalamiques et fronto-thalamo-pallido-striatro-antérieur cingulaire-frontal. Des lésions anatomiques discrètes de ces voies, ou leur levée chirurgicale, peuvent améliorer (ou l'inverse) les TOC chez les patients atteints d'ELT.

REFERENCES

1. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45:1094-1099.
2. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1999;56:121-127.
3. Isaacs KL, Philbeck JW, Barr WB, Devinsky O, Alper K. Obsessive-compulsive symptoms in patients with temporal lobe epilepsy. *Epilepsy Behav*. 2004;4:569-74.
4. Annegers JF. The epidemiology of epilepsy. In: Wyllie E, ed. *The Treatment of Epilepsy; Principles and Practice*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:131-138.
5. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain*. 2000;123:665-676.
6. Devinsky O. Psychiatric co-morbidity in patients with epilepsy: implications for diagnosis and treatment. *Epilepsy Behav*. 2003; S2-S10.
7. Tsopelas ND, Saintfort R, Friccione GL. The relationship of psychiatric illnesses and seizures. *Curr Psychiatry Rep*. 2001;3:235-242.
8. Swinkels WAM, Kuyk J, Van Dyck R, Spinhoven PH. Psychiatric comorbidity in epilepsy. *Epilepsy Behav*. 2005;7:37-50.
9. Butterbaugh G, Rose M, Thomson J, et al. Mental health symptoms in partial epilepsy. *Arch Clin Neuropsychol*. 2005;20:647-654.
10. Ertekin BA, Kulaksizoglu IB, Ertekin E, Gurses C, Bebek N, Gokyigit A, Baykan B. A comparative study of obsessive-compulsive disorder and other psychiatric comorbidities in patients with temporal lobe epilepsy and idiopathic generalized epilepsy. *Epilepsy Behav*. 2009;14:634-639.
11. Swinkels WAM, Kuyk J, De Graaf EH, Van Dyck R, Spinhoven PH. Prevalence of psychopathology in Dutch epilepsy inpatients: a comparative study. *Epilepsy Behav*. 2001;2:441-447.
12. Perini GI, Tosin C, Carraro C, et al. Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry*. 1996;61:601-605.
13. Manchanda R, Schaefer B, McLachlan R, Blume WT. Interictal psychiatric morbidity and focus of epilepsy in treatment-refractory patients admitted to an epilepsy unit. *Am J Psychiatry*. 1992;149:1096-1098.
14. Caplan R, Comair Y, Shewmon DA, Jackson L, Chugani HT, Peacock WJ. Intractable seizures, compulsions and coprolalia: a pediatric case study. *J Neuropsychiatry*. 1992;4:315-319.
15. Kroll L, Drummond LM. Temporal lobe epilepsy and obsessive compulsive symptoms. *J Nerv Ment Dis*. 1993;181:457-458.
16. Kwon Js, Kim JJ, Lee DW, et al. Neural correlates of clinical symptoms and cognitive dysfunctions in obsessive-compulsive disorder. *Psychiatry Res Neuroimaging*. 2003;122;37-47.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 248

17. Stern TA, Murray GB. Complex partial seizures presenting as a psychiatric illness. *J Nerv Ment Dis*. 1984;172:625-627.

18. Kanner AM, Morris HH, Stagno S, Chelune G, Luders H. Remission of an obsessive-compulsive disorder following a right temporal lobectomy. *Neuropsychiatry Neuropsychol Behav Neurology*. 1993;6:126-129.

19. Kettl PA, Marks IM. Neurological factors in obsessive-compulsive disorder: two case reports and a review of the literature. *Br J Psychiatry*. 1986;149:315-319.

20. Tizard B. The personality of epileptics: a discussion of the evidence. *Psychol Bull*. 1962;59:196-210.

21. Waxman SG, Geschwind N. The interictal behavior syndrome of temporal lobe epilepsy. *Arch Gen Psychiatry*. 1976;32:1580-1586.

22. Ritaccio AL, Devinsky O. Personality disorders in epilepsy. In: Ettinger AB, Kanner AM, eds. *Psychiatric Issues in Epilepsy*. Baltimore, MD: Lippincott Williams & Wilkins; 2001:147-162.

23. Lacerda AL, Dalgalarrondo P, Caetano D, et al. Elevated thalamic and prefrontal regional cerebral blood flow in OCD: a SPECT study. *Psychiatry Res Neuroimag*. 2003;123:125-134.

24. Kim KW, Lee DY. Obsessive-compulsive disorder associated with a left orbitofrontal infarct. *J Neuropsychiatry Clin Neurosci*. 2002;14:242.

25. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch Neurol*. 1977;34:454-467.

26. Griest JH, Jefferson JW. *OCD Casebook: Obsessive-Compulsive Disorder*. Arlington, VA: American Psychiatric Press; 1995.

27. Garber HJ, Ananth JV, Chiu LC, Griswold VI, Oldendorf QWH. Nuclear magnetic resonance study of obsessive-compulsive disorder. *Am J Psychiatry*. 1989;146:1001-1005.

28. Jenike MA, Brotman AW. The EEG in obsessive-compulsive disorder. *J Clin Psychiatry*. 1984;45:122-124.

29. Schmitz EB, Moriarty J, Costa DC, Ring HA, Ell PJ, Trimble MR. Psychiatric profiles and patterns of cerebral blood flow in focal epilepsy: interactions between depression, obsessionality, and perfusion related to the laterality of the epilepsy. *J Neurol Neurosurg Psychiatry*. 1997;62:458-463.

30. Breiter HC, Rauch SL, Kwong KK, et al. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1996;53:595-606.

31. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry*. 1998;35(suppl):26-37.

32. Monaco F, Cavanna A, Magli E, et al. Obsessionality, obsessive-compulsive disorder and temporal lobe epilepsy. *Epilepsy Behav*. 2005;7:491-496.

33. Alheid GF, Heimer L. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid and corticopetal components of substantia innominata. *Neuroscience*. 1988;27:1-39.

34. Modell JG, Mountz JM, Curtis GC, Greden JF. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 1989;1;27-36.

35. Mula M, Cavanna AE, Critchley H, Robertson MM, Monaco F. Phenomenology of obsessive compulsive disorder in patients with temporal lobe epilepsy or Tourette syndrome. *J Neuropsychiatry Clin Neurosci*. 2008;20:223-226.

36. Huey ID, Zahn R, Krueger F, et al. A psychological and neuroanatomical model of obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 2008;20:390-408.

37. Berthier ML, Kulisevsky J, Gironell A, Heras JA. Obsessive compulsive disorder associated with Brain. lesions: clinical phenomenology, cognitive function and anatomic correlates. *Neurology*. 1996;47:353-361.

38. Liddle PF. Obsessive compulsive disorder. In: Liddle PF, ed. *Disordered Mind and Brain: the Neural Basis of Mental Symptoms*. London, UK: Gaskell; 2001:214-220.

39. Kim CH, Chang JW, Koo MS, et al. Anterior cingulotomy for refractory obsessive-compulsive disorder. *Acta Psychiatr Scand*. 2003;107:283-290.

40. Kulaksizoglu IB, Bebek N, Baykan B, et al. Obsessive-compulsive disorder after epilepsy surgery. *Epilepsy Behav*. 2004;5:113-118.

41. Mace CJ, Trimble MR. Psychosis following temporal lobe surgery: report of six cases. *J Neurol Neurosurg Psychiatry*. 1991;61:82-89.

42. Ferguson SM, Rayport M, Blumer DP, et al. Post operative psychiatric changes. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. New York, NY: Raven Press; 1993:649-661.

43. Blumer D, Wakhlu S, Davies K, Hermann B. Psychiatric outcome of temporal lobectomy for epilepsy: incidence and treatment of psychiatric complications. *Epilepsia*. 1998;39:478-486.

44. Koch-Weser M, Garron DC, Gilley DW, et al. Prevalence of psychologic disorders after surgical treatment of seizures. *Arch Neurol*. 1988;45:1308-1311.

45. Leinonen E, Tuunainen A, Lepola U. Postoperative psychoses in epileptic patients after temporal lobectomy. *Acta Neurol Scand*. 1994;90:394-399.

46. Blumer DP, Davies K. Psychiatric issues in epilepsy surgery. In: Ettinger AB, Kanner AM, eds. *Psychiatric Issues in Epilepsy*. Baltimore, MD: Lippincott Williams & Wilkins; 2001:231-250.

47. Taylor DC. Mental state and temporal lobe epilepsy. *Epilepsia*. 1972;12:727-765.

48. Naylor AS, Rogvi-Hansen B, Kessing L, Kruse-Larsen C. Psychiatric morbidity after surgery for epilepsy: short-term follow up of patients undergoing amydalohippocampectomy. *J Neurol Neurosurg Psychiatry*. 1994;57:1375-1381.

49. Jenson I, Larsen JK. Psychosis in drug resistant temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 1979;42:948-954.

50. Jenson I, Larsen JK. Mental aspects of temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 1979;42:256-265.

51. Ring HA, Moriarty J, Trimble MR. A prospective study of the early post-surgical psychiatric associations of epilepsy surgery. *J Neurol Neurosurg Psychiatry*. 1998;64:601-604.

52. Doval O, Gaviria M, Kanner AM. Frontal lobe dysfunction in epilepsy. In: Ettinger AB, Kanner AM, eds. *Psychiatric Issues in Epilepsy*. Baltimore, MD: Lippincott Williams & Wilkins; 2001:261-271.

53. Stevens J. Psychiatric consequences of temporal lobectomy for intractable seizures: a 20-30 year follow-up of 14 cases. *Psychol Med*. 1990;20:529-545.

54. Guarnieri R, Araujo D, Carlotti CG, et al. Suppression of obsessive-compulsive symptoms after epilepsy surgery. *Epilepsy Behav*. 2005;7:316-319.

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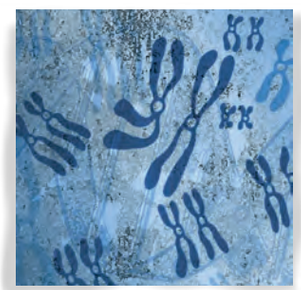
Brief report

Superstitiousness in obsessive-compulsive disorder

Peter Brugger, PhD; Isabelle Viaud-Delmon, PhD



It has been speculated that superstitiousness and obsessive-compulsive disorder (OCD) exist along a continuum. The distinction between superstitious behavior *and superstitious* belief*, however, is crucial for any theoretical account of claimed associations between superstitiousness and OCD. By demonstrating that there is a dichotomy between behavior and belief, which is experimentally testable, we can differentiate superstitious behavior from superstitious belief, or magical ideation. Different brain circuits are responsible for these two forms of superstitiousness; thus, determining which type of superstition is prominent in the symptomatology of an individual patient may inform us about the primarily affected neurocognitive systems.*

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Keywords: belief; magical ideation; contingency/causality detection; habit; stereotypy; basal ganglia; hippocampus

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According to the Merriam-Webster online dictionary (http://www.merriam-webster.com), a superstition is "a belief or practice resulting from ignorance, fear of the unknown, trust in magic or chance, or a false conception of causation." Focusing on one or several aspects of this broad definition, some authors have suggested that superstitions are a fundamental feature of obsessive-compulsive disorder (OCD).[1-5] We first elaborate on the dichotomy between behavior and belief, mentioned in the above definition, and differentiate superstitious *behavior* from superstitious *belief*, or magical ideation. We then propose that different brain circuits may be responsible for these two forms of superstitiousness, and that the type of superstition observed in an individual patient may thus inform investigators about the prominently affected neurocognitive systems.

Superstitious behavior

In its purest form, superstitious behavior was described in the behaviorist literature as a consequence of response-independent reinforcement. Skinner's experiments with pigeons are legendary[6]; the birds were offered food at random intervals and behavior incidentally displayed at times of food delivery was continuously reinforced, such that idiosyncratic behavioral stereotypies were established. Noting that the birds behaved *as if* they assumed a causal relation between the appearance of food and their behavior, Skinner coined the term "superstitious behavior" for this type of response-reinforcement association. This was later criticized with statements that the inference regarding the animals' beliefs about a nonexistent causality was not necessarily warranted, and attributes like "mediating" and "collateral" were suggested to describe their behavior in a more parsimonious way (see ref 7 for the liter-

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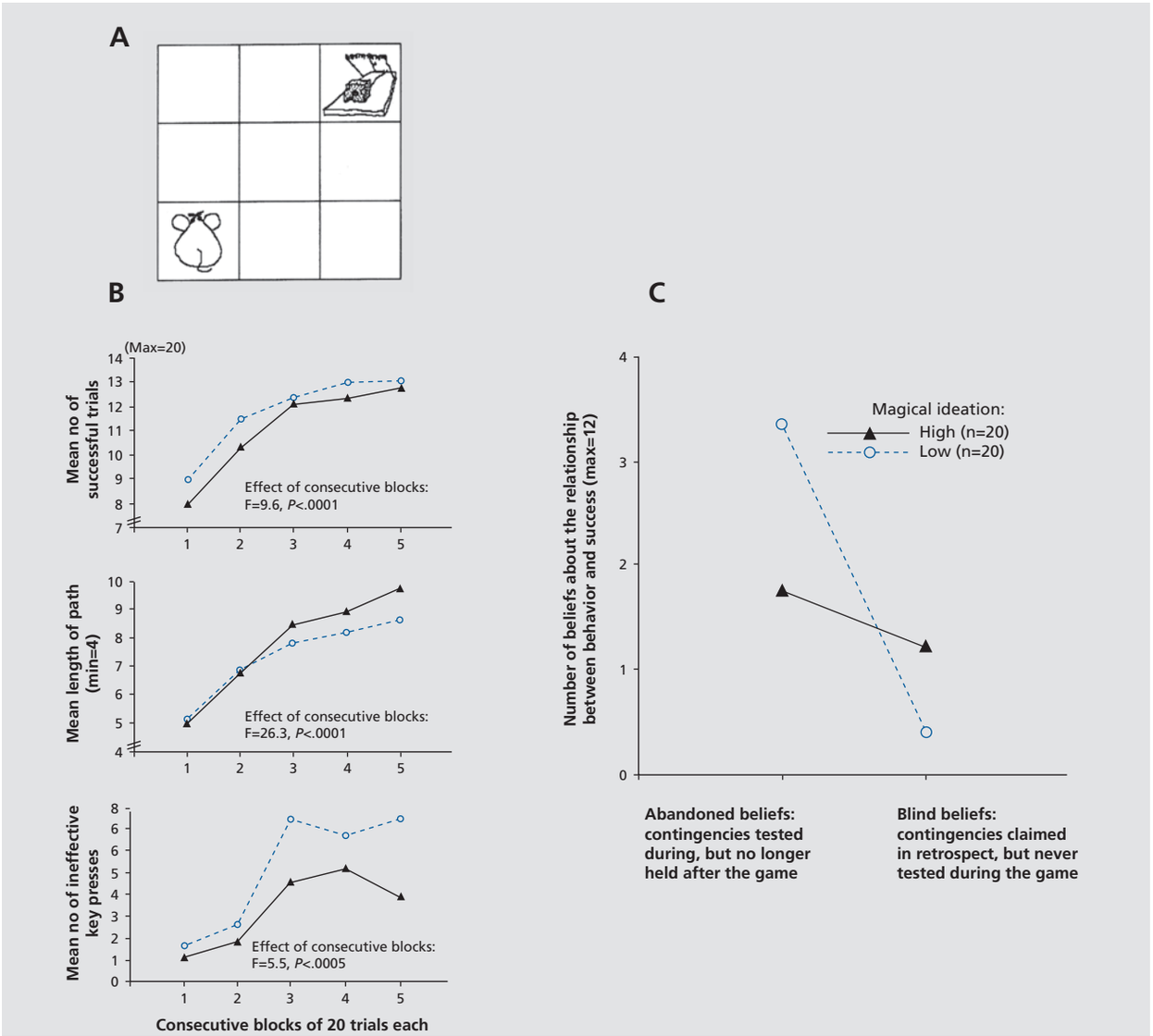

Figure 1. A computer game differentiating superstitious behavior and superstitious belief.[7] **A:** The screen as it was presented to 40 healthy subjects. They were instructed to move the mouse from the lower left corner onto the field containing the trap (using the cursor keys in the 4 cardinal directions). The final move was either "rewarded" with the cheese or "punished" by the closing of the trap. The type of feedback depended on the amount of time the participant took to reach the target field; times faster than 4 sec were punished and slower times were rewarded with the cheese. Subjects were unaware of these contingencies and were instructed to find out, during 100 trials, "how the game worked." Beliefs about the contingencies that determined success in the task were carefully assessed after completion of the task. **B:** Aspects of motor behavior for 20 subjects low on magical beliefs (MI scale[9] scores 0 to 9; dashed lines) and for 20 high scorers (scores 10 to 20; solid lines). Top panel: across consecutive blocks, all subjects learned to get the cheese with increasing frequency (without noticing the critical contingency). Middle panel: all subjects increased the number of key presses per trial ("superstitious behavior"), to reach the field with the cheese. Bottom panel: another indicator of superstitious behaviour, the number of ineffective key presses (eg, pressing the UP key when already in the uppermost row), also increased over the task and independent of a subject's MI scores. **C:** Superstitious beliefs about task contingencies: subjects with low MI scores started out with many hypotheses, but most were abandoned in the course of the game and "blind" beliefs were virtually absent. Conversely, subjects with high MI scores tested fewer hypotheses during the game, but were not disinclined to believe in forms of contingencies they had never tested.

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ature). In fact, some of the behavioral sequences shown by human subjects in a situation of response-independent reinforcement are more reminiscent of a desperate attempt to explore the nature of the schedule of reinforcement than of any "superstitiousness" in the sense of a fixed belief. We may cite the particularly illustrative example of a healthy woman seated in a test booth with a response lever on a table in front of her and a signal light and point counter mounted on the wall.[8]

About 5 min into the session, a point delivery occurred after she had stopped pulling the lever temporarily and had put her right hand on the lever frame. This behavior was followed by a point delivery, after which she climbed on the table and put her right hand to the counter. Just as she did so, another point was delivered. Thereafter she began to touch many things in turn, such as the signal light, the screen, a nail on the screen, and the wall. About 10 min later, a point was delivered just as she jumped to the floor, and touching was replaced by jumping. After five jumps, a point was delivered when she jumped and touched the ceiling with her slipper in her hand. Jumping to touch the ceiling was continued repeatedly and was followed by points until she stopped about 25 min into the session, perhaps because of fatigue (p 265).

Unfortunately, as introspective reports have never been seriously considered in the behaviorist literature, this subject had not been explicitly asked about her thoughts and beliefs while apparently obsessed with touching and jumping.

Superstitious belief

As "false conceptions of causation," superstitious beliefs are conceptually removed from the touching and jumping behavior described above. They usually lack a direct motor manifestation. In fact, most characteristic of modern superstitious beliefs are rather abstract ideas about a paranormal causation of coincidences (telepathy, clairvoyance, precognition). These ideas are cross-culturally universal and, within a society, largely resistant to education. Designated as "magical ideation" (MI), they are a core element of positive symptoms in schizotypy,[9] equivalent to the delusions of reference in schizophrenia. While magical or superstitious beliefs can be conceived as the cognitive equivalents of superstitious behaviors, it is important to note that each type of superstition can occur without the other. In the pigeon, there is clear evidence, obtained from well-designed studies, for a dissociation between motor and cognitive superstitions. It was shown, for instance, that the same birds, whose pecking superstitions were based on temporal contiguity instead of contingency, were well able to distinguish between events elicited by chance and those controlled by their own behavior.[10] In human subjects, a similar dissociation was demonstrated when studying the relationship between superstitious behavior and superstitious belief.[7] In a computer game, high and low scorers on the MI scale,[9] an instrument designed to quantify superstitious beliefs in everyday life, displayed superstitious behavior to a comparable degree. However, the subjects believing in paranormal forms of causation were more inclined than the disbelievers to assume a causal relationship between their (irrelevant) behavior and success in the game (see *Figure 1* for more details).

Superstitious behavior and superstitious belief in OCD

The distinction between superstitious behavior and superstitious belief is crucial for any theoretical account of claimed associations between superstitiousness and OCD. As indicated above, in healthy individuals superstitious motor behavior can occur without accompanying beliefs in nonexistent causative forces. Conversely, the formation of superstitious beliefs may take place without direct mediation by the motor system. We suggest, therefore, that different neural circuits are involved in the genesis of the two forms of superstitiousness. Specifically, we propose that the origin of superstitious rituals in OCD primarily involves the basal ganglia "habit system,"[11] including its connections with the (orbito)frontal cortex. Dysfunction of this neural circuitry is prominent in patients with OCD and OC-spectrum disorders. It is responsible for behavioral routines, whose stereotypy and irrationality is typically recognized by the patient. Nonetheless, recognition of the senselessness of the repetitive motor displays does not enable a patient to break the routine. Significantly, whether superstitiously motivated or not, perseveration is an almost defining feature of an obsessive-compulsive ritual *(Figure 2)*.[12]

Another region of interest in connection with OCD comprises medial temporal lobe structures, in particular the hippocampus.[13] According to one model,[11,12] a "limbic memory system" coordinates those subordinate brain circuits controlling inflexible habits and fixed action

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Figure 2. The hallmark of superstitiousness in OCD is stereotyped, repetitive behavioral routines, not necessarily accompanied by superstitious beliefs in false causal attributions.

sequences. It states that one prominent task of the hippocampus is to enhance behavioral variability, and OCD symptoms are thought to emerge from the failure of the hippocampal complex to curb the subcortical-frontal "habit system" (see ref 14 for an alternative view of the hippocampus in OCD). In the literature on superstitious behavior and belief, the important role of the hippocampus was early recognized. Hippocampectomized rats were found to display exaggerated superstitious behavior[15,16] that was not simply a consequence of enhanced perseverative tendencies, but reflected the crucial role played by the hippocampus "in adapting economically to a loss of positive contingency and in averting the burden of superstition when reinforcers never bear causal relation to behavior (p 274)".[16] In human clinical neuropsychology, medial temporal lobe pathology has been implicated in the emergence of superstitious beliefs. Patients suffering from temporal lobe epilepsy often show a "syndrome of sensory-limbic hyperconnection,"[17] which is characterized by a preoccupation with mystical, religious, and paranormal themes and an exaggerated belief in an extrasensory causation of coincidences (ref 18 for the literature). In patients with OCD who manifest marked magical ideation,[5] limbic dysfunction might also predominate. It remains to be determined whether these patients would represent a proper "schizotypy subtype" of OCD.[19]

Conclusion

To conclude with a word of caution: we doubt that, over and beyond an exaggeration of normal patterns of behavior and thought, superstitions are a genuine element of OCD. However, disentangling components of superstitious motor behavior from those of superstitious beliefs may not only help the clinician, but might provide insights into the mechanisms underlying the disorder. ❑

REFERENCES

1. Leonard HL, Goldberger EL, Rapoport JL, Cheslow DL, Swedo SE. Childhood rituals: normal development or obsessive-compulsive symptoms? *J Am Acad Child Adolesc Psychiatry*. 1990;29:17-23.
2. Frost RO, Krause MS, MacMahon MJ, Peppe J, Evans M, McPhee AE, Holden M. Compulsivity and superstitiousness. *Behav Res Ther*. 1993;31:423-425.
3. Amir N, Freshman M, Ramsey B, Neary E, Brigidi B. Thought-action fusion in individuals with OCD symptoms. *Behav Res Ther*. 2001;39:765-776.
4. Evans DW, Milanak ME, Medeiros B, Ross JL. Magical beliefs and rituals in young children. *Child Psychiatry Hum Develop*. 2002;33:43-58.
5. Einstein DA, Menzies RG. The presence of magical thinking in obsessive compulsive disorder. *Behav Res Ther*. 2004;42:539-549.
6. Skinner BF. Superstition in the pigeon. *J Exp Psychol*. 1948;38:168-172.
7. Brugger P, Graves RE. Testing vs. believing hypotheses: magical ideation in the judgment of contingencies. *Cog Neuropsychiatry*. 1997;2:251-272.
8. Ono K. Superstitious behavior in humans. *J Exp Analysis Behav*. 1987;47:261-271.
9. Eckblad M, Chapman L. Magical ideation as an indicator of schizotypy. *J Cons Clin Psychol*. 1983;51:215-225.
10. Killeen PR. Superstition: a matter of bias, not detectability. *Science*. 1978;199:88-90.
11. Pitman RK. Animal models of compulsive behavior. *Biol Psychiatry*. 1989;26:189-198.
12. Eilam D, Zor R, Szechtman H, Hermesh H. Rituals, stereotypy and compulsive behavior in animals and humans. *Neurosci Biobehav Rev*. 2006;30:456-471.
13. Atmaca M, Yildirim H, Ozdemir H, et al. Hippocampus and amygdalar volumes in patients with refractory obsessive-compulsive disorder. *Prog Neuro-Psychopharm Biol Psychiatry*. 2008;32:1283-1286.
14. Gray JA, McNaughton N. *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System*. 2nd ed. Oxford, UK: Oxford University Press; 2003.
15. Devenport LD. Superstitious bar-pressing in hippocampal and septal rats. *Science*. 1979;205:721-723.
16. Devenport LD, Holloway FA. The rat's resistance to superstition: role of the hippocampus. *J Comp Physiol Psychol*. 1980;94:691-705.
17. Bear DM. Temporal lobe epilepsy – a syndrome of sensory-limbic hyperconnection. *Cortex*. 1979;15:357-384.
18. Brugger P, Dowdy MA, Graves RE. From superstitious behavior to delusional thinking: the role of the hippocampus in misattributions of causality. *Med Hyp*. 1994;43:397-402.
19. Sobin C, Blundell ML, Weiller F, Gavigan C, Haiman C, Karayiorgou M. Evidence of a schizotypy subtype in OCD. *J Psychiatry Res*. 2000;34:15-24.

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Brief report

Superstición en el trastorno obsesivo-compulsivo

Se ha especulado que la superstición y el trastorno obsesivo-compulsivo (TOC) se dan en un continuo. La distinción entre conducta supersticiosa y creencia supersticiosa; sin embargo, es crucial para cualquier tipo de teoría acerca de las asociaciones entre superstición y TOC. Existe una dicotomía entre la conducta y la creencia, que se puede demostrar experimentalmente, lo que nos permite diferenciar la conducta supersticiosa de la creencia supersticiosa o la ideación mágica. Diferentes circuitos cerebrales son responsables de estas dos formas de superstición. Conocer el tipo de superstición que predomina en la sintomatología de un paciente afectado de un TOC permite comprender mejor el papel de los principales sistemas neurocognitivos implicados en la patología.

Superstitiosité dans le cadre du trouble obsessionnel compulsif

Il est souvent proposé que la superstitiosité et le trouble obsessionnel compulsif feraient partie d' un même continuum. La distinction entre le comportement superstitieux et la croyance superstitieuse est néanmoins cruciale pour toute théorie s'intéressant aux associations entre superstitiosité et TOC. Il existe une dichotomie, démontrable expérimentalement, entre le comportement et les croyances superstitieuses, qui permet de différencier les comportements des croyances superstitieuses, et de la pensée magique. Des réseaux neuronaux distincts sont responsables de ces deux formes de superstitiosité. Ainsi, la connaissance du type de superstition dominante dans la symptomatologie d'un patient atteint de TOC pourrait permettre de mieux comprendre le rôle des principaux systèmes neurocognitifs impliqués dans cette pathologie.

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Free paper

SPECT assessment of brain activation induced by caffeine: no effect on areas involved in dependence

Astrid Nehlig, PhD; Jean-Paul Armspach, PhD; Izzie J. Namer, MD, PhD

The methylxanthine, caffeine, is the most widely used psychoactive substance in the world. Most of the caffeine consumed comes from dietary sources such as coffee, tea, soft drinks, and chocolate. The content of caffeine of these food items ranges from 70 to 220 mg/150 mL for coffee to 30 to 40 mg/150 mL for tea, 15-35 mg/150 mL for cola drinks, and 4 mg/150 mL for chocolate drinks.[1] World caffeine consumption from all sources can be estimated as 76 mg/person/day, but reaches about 220 mg/day in the United States and Canada, and more than 400 mg/person/day in Sweden and Finland.[1,2]

Caffeine acts as a psychostimulant and exerts numerous effects on the brain. These include stimulant effects on

Caffeine is not considered addictive, and in animals it does not trigger metabolic increases or dopamine release in brain areas involved in reinforcement and reward. Our objective was to measure caffeine effects on cerebral perfusion in humans using single photon emission computed tomography, with a specific focus on areas of reinforcement and reward. Two groups of nonsmoking subjects were studied, one with a low (8 subjects) and one with a high (6 subjects) daily coffee consumption. The subjects ingested 3 mg/kg caffeine or placebo in a raspberry-tasting drink, and scans were performed 45 min after ingestion. A control group of 12 healthy volunteers receiving no drink was also studied. Caffeine consumption led to a generalized, statistically nonsignificant perfusion decrease of 6% to 8%, comparable in low and high consumers. Compared with controls, low consumers displayed neuronal activation bilaterally in inferior frontal gyrus-anterior insular cortex and uncus, left internal parietal cortex, right lingual gyrus, and cerebellum. In high consumers, brain activation occurred bilaterally only in hypothalamus. Thus, on a background of widespread low-amplitude perfusion decrease, caffeine activates a few regions mainly involved in the control of vigilance, anxiety, and cardiovascular regulation, but does not affect areas involved in reinforcing and reward.

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Keywords: *caffeine; cerebral blood flow; dependence; SPECT*

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motor behavior, modulation of mood states and levels of anxiety, effects on vigilance and sleep, on information processing and performance.[3] In the periphery, the effects of coffee/caffeine have been studied, but at moderate doses, they do not appear to exert harmful effects on cardiovascular function.[4]

The issue of a possible dependence on caffeine has been debated for many years.[5-8] Caffeine acts as a mild reinforcer (ie, maintaining its self-administration or being preferentially chosen over placebo), although not consistently in both humans and animals.[6] In humans, the widely recognized behavioral stimulant and mildly reinforcing properties of caffeine are probably responsible for the maintenance of caffeine self-administration.[7,9] The possible physical dependence to the methyxanthine has been considered for about two decades,[5,9,10] but appears to be quite low compared with common drugs of abuse, such as cocaine, amphetamine, morphine, and nicotine.

The critical role of the mesolimbic dopamine system has been emphasized as underlying drug dependence.[11,12] This system consists of the dopaminergic neurons originating in the ventral tegmental area, projecting to the nucleus accumbens, and ending in the frontal and prefrontal cortex. Drugs of abuse selectively activate the shell of the nucleus accumbens, which belongs to the mesolimbic dopaminergic system and is currently recognized as a critical target of drugs of abuse.[13-15] The shell of the nucleus accumbens plays a role in emotion, motivation, and reward functions. The laterodorsal core part of the nucleus accumbens regulates somatomotor functions. The drugs of abuse specifically increase dopamine release and functional activity (glucose utilization and blood flow) in the shell of the nucleus accumbens without affecting the core of the nucleus.[13,14] These drug-induced changes in the shell of the nucleus accumbens have been hypothesized to relate to the general abuse liability of these drugs independently from their specific mechanism of action.[12]

In a previous study, we investigated the effects of 1 to 10 mg/kg caffeine on local cerebral glucose utilization in rats. We showed that 1 to 5 mg/kg caffeine in the rat (70 to 350 mg for a 70-kg individual) which are in the range of normal human daily consumption[1,2] failed to increase metabolic levels in the shell of the nucleus accumbens.[15] Likewise, caffeine did not induce a release of dopamine in the shell of the nucleus accumbens when injected over a large spectrum of doses ranging from 0.5 to 30.0 mg/kg.[16,17] However, the high dose of 10 mg/kg caffeine in rats, no longer representative of human consumption—7 large cups of coffee in one sitting—led to unspecific metabolic increases in the shell and the core of the nucleus accumbens, together with the activation of most motor, limbic, thalamic, and cortical regions.[15]

The objective of the present study was to extend these approaches to the human situation and to measure the effects of caffeine on cerebral perfusion in human subjects using single photon emission computed tomography (SPECT). We measured caffeine-induced perfusion changes in a large number of brain areas, including the areas involved in the circuit of dependence and reward, mainly the nucleus accumbens and prefrontal cortex. Moreover, two groups of subjects were studied, one with a low daily coffee consumption and one with a high daily coffee consumption. They were compared with a control group not exposed to any drink to account for the intraindividual variations of perfusion between two consecutive scans.

Methods

Subjects

A total number of 26 normal human subjects (10 men and 16 women), ranging in age from 19 to 47 (mean age, 29.9 + 7.9 years; median, 28 years) with no history or clinical evidence of medical, neurological, or psychiatric disease participated in this study. The subjects were recruited among the healthy nonsmoking population, and met the following additional criteria: no night shift-work, no use of any medication except for birth control, and no report of any history of alcohol or drug abuse. To exclude any morphological abnormality, cerebral magnetic resonance imaging (MRI) was performed in all cases. All subjects gave their informed written consent before the study, which was approved by the local ethical committee.

Caffeine groups

Within the caffeine groups, the first subgroup of eight subjects consisted of a population of very low caffeine consumers or abstainers (0 to 1 cup of coffee per day, ie, less than 100 mg/day, low-consumption, LC group); the second one included six subjects who consumed elevated

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quantities of coffee (more than 4 cups per day, ie, over 500 mg/day) and reported feeling "dependent" on coffee (high-consumption, HC group). This was only based on the subjects' own feelings and not on any *DSM-IV* criteria. The subjects were told that they were entering a study on the effects of caffeine on cerebral circulation, but were not informed about the exact purpose of the study, ie, the study of the specific effect of caffeine on the brain areas involved in drug dependence.

The subjects were asked to observe a 12-hour abstinence from caffeine-containing foods and beverages prior to the measurement of cerebral blood flow. Blood samples were taken at arrival at the hospital to reinforce compliance. The subjects ingested 3 mg/kg body weight caffeine or a placebo in a raspberry-tasting drink. The drinks were prepared by the pharmacy of the University Hospitals and were administered in a double-blind, randomized, counterbalanced design. The blood pressure and heart rate were measured and the mood and anxiety profiles of the subjects assessed with a specific questionnaire before and after caffeine ingestion. The questionnaire used was the State-Trait Anxiety Inventory (STAI) for adults which is the most widely used self-report measure of tension and anxiety.

Control group

To allow group analysis and evaluation of the inter- and intraindividual variations of cerebral perfusion, a control group of 12 healthy volunteers was included in the study. Within this group of twelve healthy volunteers (low consumers of 0 to 2 cups of coffee daily) not receiving any drink before the two SPECT examinations, eight and six were randomly selected for comparison with the LC and HC caffeine group, respectively, while the whole caffeine-consuming group was compared with the totality of the control group.

SPECT procedure

The caffeine groups subjects were subjected to two separate morning examinations upon arrival at the hospital: (i) one SPECT study after the placebo beverage; and (ii) one SPECT study after the caffeine containing beverage. The two beverages were given on two different days at 7-day interval, in a double-blind randomized counterbalanced design. Upon arrival at the clinic, the subjects were invited to relax in a comfortable armchair in a quiet and pleasant room. A venous catheter for tracer injection was immediately inserted into the left arm, and a first blood sample was taken to measure caffeine levels to check for compliance to 12 h caffeine abstinence. Heart rate and blood pressure measurements were then performed and the subjects filled in the STAI questionnaire. Then, subjects received the caffeine or placebo drink and were asked to rest in the same surrounding for 45 min. This time was chosen since caffeine reaches peak values in the brain between 45 and 60 min postingestion.[3] Thereafter, the subjects underwent the same procedure for the measurement of plasma caffeine levels, cardiovascular parameters, and filled in the STAI questionnaire again. Immediately afterwards, the tracer, 640-925 MBq ^{99m}Tc-ethyl cysteinate dimer (ECD, Neurolite, Bristol-Myers Squibb Medical Imaging), was injected into the already inserted venous catheter. The subjects were not allowed to read, write, or talk for 5 min, including the fixation period of the radiotracer.

The control group subjects were also subjected to two separate morning SPECT examinations at 7-day intervals, in the same conditions, without any beverage. This procedure was used to evaluate the intrasubject variability between two examinations and to avoid the consequences of variable spontaneous mental activity and/or possible perfusion changes induced by the stressful environment related to SPECT examination.

SPECT imaging studies were realized with a low-energy, high-resolution, double-head camera (Helix, Elscint). The camera was operated in the "stop and shoot" mode, with acquisitions at 3° intervals and a total acquisition time of 25 min (120 projections, 642 matrix). The total number of counts was superior to 6 million. Slices were reconstructed by filtered back-projection using a Metz filter (FWMH of 8 mm). Slices were acquired 30 min after the injection of ECD.

Image analysis and statistics

Images were realigned with each other using affine algorithm in MEDIMAX software,[18] transformed into the standard anatomic space corresponding to the atlas of Talairach, and normalized in statistical parametric mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London) using MATLAB (Mathworks Inc, Massachusetts) for calculations and image matrix manipulations.

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After the preprocessing of SPECT images, all the statistical analysis was performed by multigroup analysis with SPM2. A voxel-by-voxel comparison according to the general linear model and I statistics was used to calculate the differences in cerebral perfusion between the two conditions (caffeine vs placebo) of caffeine groups and the differences between two conditions (rest vs rest) of the control group (LC group vs control group, HC group vs control group, and LC + HC groups vs control group). The resulting statistical parametric map was subsequently used to assign probability values (to voxels and clusters), which were corrected for multiple comparisons applied for the whole brain. Significant differences were defined at a corrected value of $P \leq 0.001$ and size ≥10 voxels (80 mm^3).

Results

Clinical data

Two groups of subjects were studied, including eight subjects (seven females and one male) and seven subjects (two females and five males) belonging to the LC and HC groups, respectively *(Table I)*. All clinical data including age, arterial blood pressure, heart rate, electrocardiographic recording, and other current physiological parameters (plasma potassium level and hepatic enzyme activities) were in the physiological range and identical in both groups. None of these parameters was significantly affected by caffeine or placebo. In addition, the clinical surroundings had no significant influence on anx-

		Low consumption (0-1 cup/day) N = 8	Heavy consumption (>4 cups/day) N = 6
Baseline data	Age (y)	27.6 ± 6.1	30.0 ± 5.1
	Arterial BP (mm Hg)		
	Systolic	109.5 ± 13.3	115.1 ± 10.6
	Diastolic	63.1 ± 4.5	64.5 ± 5.9
	Heart rate (beats/min)	70.6 ± 4.8	68.1 ± 8.2
Placebo	Arterial BP (mm Hg)		
	Systolic before placebo	118.1 ± 11.3	117.1 ± 12.5
	Systolic after SPECT	117.5 ± 20.5	115.7 ± 12.7
	Arterial BP (mm Hg)		
	Diastolic before placebo	75.6 ± 9.8	71.3 ± 13.6
	Diastolic after SPECT	77.1 ± 12.5	75.7 ± 12.7
	Heart rate (beats/min)		
	before placebo	78.0 ± 9.0	69.1 ± 10.8
	after SPECT	74.0 ± 10.7	70.9 ± 9.2
	Plasma caffeine level (mg/L)		
	before placebo	0.28 ± 0.24	0.21 ± 0.15
	after SPECT	0.25 ± 0.27	0.14 ± 0.13
Caffeine	Arterial BP (mm Hg)		
	Systolic before caffeine	115.0 ± 7.6	120.0 ± 14.1
	Systolic after SPECT	116.3 ± 13.0	125.0 ± 18.9
	Arterial BP (mm Hg)		
	Diastolic before caffeine	69.4 ± 6.8	77.1 ± 12.5
	Diastolic after SPECT	68.8 ± 9.9	77.1 ± 17.0
	Heart rate (beats/min)		
	before caffeine	73.5 ± 9.6	69.1 ± 10.5
	after SPECT	71.3 ± 8.9	64.6 ± 8.8
	Plasma caffeine level (mg/L)		
	before caffeine	0.20 ± 0.14	1.64 ± 0.80
	after SPECT	0.16 ± 0.12	2.15 ± 1.06

Table I. Clinical data of the subjects undergoing SPECT examinations for the effects of caffeine on cerebral blood flow.

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iety levels, as assessed upon arrival, and neither did the dose of caffeine ingested and the insertion of the catheter for ECD injection, as assessed 45 min later. Subjects had a tendency to feel more alert after the ingestion of the caffeine-containing drink. The low level of caffeine before SPECT analysis confirmed that the patients had omitted the methylxanthine from their food and beverage for 12 h. Circulating levels of caffeine were increased by a factor of 8 to 13 at about 1 h after caffeine ingestion.

SPECT data

The consumption of caffeine led to a generalized decrease in perfusion levels of 6% to 8% which was of similar amplitude in both LC and HC groups *(Table II)*. Compared with intraindividual variations of control subjects, these changes were not statistically significant.
On the other hand, discrete perfusion increases corresponding to specific neuronal activation were found in specific regions. Indeed, when the LC caffeine group was compared with the control group *(Figure 1)*, increases in perfusion occurred bilaterally in the inferior frontal gyrus-anterior insular cortex (predominantly on the right side) and in the uncus, on the left side in the internal parietal cortex, on the right side in the lingual gyrus and cerebellum. In the HC group compared with the control group, perfusion increases were located bilaterally in hypothalamus. When both caffeine groups were pooled and compared with the whole control group, significant perfusion increases occurred bilaterally in the inferior frontal gyrus-anterior insula, hypothalamus, right cerebellum, and left uncus *(Figure 1)*.

Discussion

The main findings of this study were the lack of significant differences in perfusion between caffeine-exposed subjects and controls, whether they were HC or LC, the lack of effects of the methylxanthine on the areas of reinforcing and reward and only very discrete changes in perfusion in areas mediating mainly anxiety, attention and vigilance, and cardiovascular function.
The vasoconstrictive properties of caffeine in the brain have been known for a long time, and caffeine has been

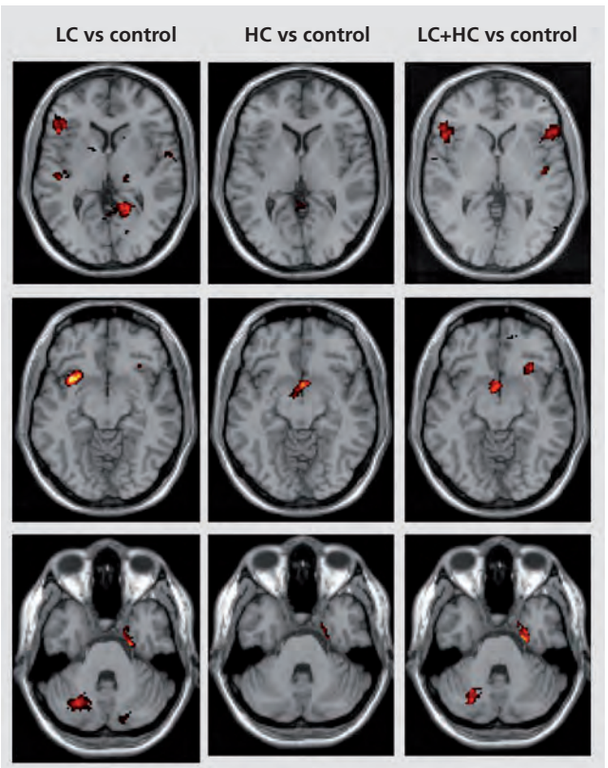

Figure 1. Caffeine-induced perfusion changes superimposed on transaxial slices of a standard MRI surface: left column: Low consumption (LC) group (n=8) vs control group (n=8); middle column: High consumption (HC) group (n=6) vs control group (n=6); right column: LC+HC group (n=14) vs control group (n=12).

	Low consumption (0-1 cup/day) n = 8	Heavy consumption (>4 cups/day) n = 6	Student's t-test
Frontal cortex	-6%	-6%	NS
Median cingular gyrus	0	-6%	NS
Anterior insula	-7%	-7%	NS
Amygdala and temporal lobe	-6%	-8%	NS
Thalamus - hypothalamus	-6%	-6%	NS
Nucleus accumbens	0	0%	NS
Vermis	0	-8%	NS

Table II. Caffeine-induced changes in cerebral perfusion calculated as follows: (SPECT CAFFEINE - SPECT PLACEBO) / SPECT PLACEBO using SISCOM.

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shown to decrease cerebral blood flow in humans.[19-23] Previous studies used the 133Xe-xenon inhalation technique,[22] positron emission tomography,[19] inversion recovery perfusion MR technique [20] and blood oxygenation level-dependent (BOLD) signal intensity changes in functional MRI (fMRI).[22,23] Recent papers studied the effects of caffeine on cerebral circulation since caffeine ingestion might be a source of errors in functional brain imaging experiments.[20,21,23]

The present study showed a 6% to 8% statistically nonsignificant caffeine-induced decrease in perfusion. Several other studies reported caffeine-induced cerebral blood flow decreases ranging from 3.4% to 18%[19,20,22,24,25] but not consistently in all subjects.[22] The reasons for the discrepancies may have various origins. First, the hemodynamic response measured by different techniques (cerebral blood flow, BOLD contrast, or perfusion changes) is not directly comparable. Second, in most if not all studies, the same dose of caffeine was given to the subjects independently of body weight. Conversely, in the present study, the dose of caffeine ingested was adjusted to body weight, ie, 3 mg/kg. The third factor differing amongst the studies is the period of abstinence from caffeine. The latter was similar to the one applied here, ie, about 12 h in several studies,[19,23] very short, 2 to 3 hours in other studies,[22,24] or much longer, ie, 30 hours.[20,21] The period of abstinence may be an important factor in the effect of caffeine on cerebral blood flow, and has been a matter of concern in imaging studies over the last few years.[20,21] Indeed, the cerebral blood flow rates and velocities are increased during the withdrawal state, mainly in high users[20,26] and go back to baseline values after about 2 h.[26] Therefore the widespread lack of significance in the perfusion values recorded in the present study with and without caffeine may partly reflect the withdrawal state induced by the overnight caffeine deprivation imposed on the subjects. On the other hand, the discrete changes recorded in some brain areas after caffeine indicate the specific changes due to the methylxanthine.

In the present study, on a background of widespread statistically nonsignificant perfusion decrease, discrete increases in perfusion corresponding to specific neuronal activation could be identified. Brain activation was mostly seen in the LC group. In this group, significant activation was recorded in regions known to mediate anxiety like the inferior frontal gyrus-anterior insular cortex, the uncus, the lingual gyrus, and the cerebellum.[27,28] Simultaneously, many other regions involved in the regulation of anxiety levels, such as the amygdala, cingulate and orbitofrontal cortex, thalamus, and striatum, were not activated by caffeine. The inferior frontal gyrus-anterior insular cortex seems to play a role in anticipating aversive stimuli and in anxiety and emotion regulation.[29] Its activation was observed in different anticipatory anxiety induction protocols,[30-32] and was totally different from the claustrum-posterior insular cortex activation observed in pharmacologically induced panic attacks with cardiovascular and visceral symptomatology.[32-34] Caffeine is known to be anxiogenic, at low doses in a subset of individuals and at quite large doses in most of the population.[35] The activation recorded only in a limited number of areas may reflect the fact that the subjects did not report increased anxiety after ingestion of the caffeinated drink. They could also imply that caffeine may specifically act at some given steps of the anxiety process, for example, at the anterior insular cortex for integration of internal state, parietal cortex for spatially specific associations, but does not reach, at this dose, the sensory-motor integration in thalamus and the initiation of action—since there is no defensive action required—depending on the anterior cingulate cortex.[28,36]

Brain activation was observed in the internal parietal cortex of LC subjects and in the hypothalamus of HC subjects. These activations relate to changes in vigilance and attention. The parietal cortex is critical for attention and spatial updating. It is involved in visual representations of space in an eye-centered coordinate frame, and in providing a signal for directing the eyes towards these objects.[28,37] The hypothalamus mediates many vegetative functions as well as attention and vigilance. In our experience, hypothalamic activations were often associated with changes in attention and vigilance. These activations are in line with the known effects of caffeine on vigilance. Indeed, the pattern of consumption of caffeine throughout the day shows that caffeine is mostly consumed to increase the level of vigilance,[35] and caffeine is well known to impair sleep.[3,38] Likewise, caffeine focuses available attention and energy on the task to complete, mostly by limiting distracting external stimuli.[39]

Finally, the anterior insular cortex, which was activated by caffeine, regulates cardiovascular function and respiratory rhythms. Numerous epidemiologic studies have focused on the effects of coffee and caffeine on cardiovascular risk, cholesterol, and blood pressure (for review see ref 40). The data currently available indicate that a

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moderate caffeine intake does not adversely affect cardiovascular function. However, a recent meta-analysis on the relationship between coffee, caffeine, and blood pressure reported that caffeine consumption increases blood pressure by a mean value of 4.2 mm for systolic and 2.0 mm Hg for diastolic blood pressure.[41] In the present study, the values of systolic blood pressure slightly increased after caffeine, especially in the HC group, but because of the large interindividual variability, this slight change was not significant. In the present study, the main difference in caffeine-induced brain activation between LC and HC subjects was the involvement of hypothalamus which was the single region affected in HC, while perfusion was not affected in hypothalamus when the same amount of caffeine was given to LC. When both groups were pooled, the caffeine-induced brain activation was significant in all areas involved in the two groups.

In the present study, we did not record any brain activation or inhibition in the different components of the brain circuit of dependence. In the presurgical follow-up of a 20-year-old male epileptic patient with right temporal lobe epilepsy and seizures induced by compulsive smoking, we were incidentally able to show that nicotine induced clear focal brain activation in the nucleus accumbens, the key area involved in addiction and reward, while caffeine (3.5 mg/kg) did not induce change in brain activation in the nucleus accumbens (Marescaux, Namer, and Nehlig, unpublished data). Therefore, these earlier data plus the present data reflect that caffeine at doses representing about two cups of coffee in one sitting does not activate the circuit of dependence and reward and especially not the main target area, the nucleus accumbens.[10-12] This lack of effect is present both in light and heavy coffee drinkers who had claimed that they felt "dependent" on coffee. This data is in agreement with our previous data on rats in which the doses of 2.5 and 5.0 mg/kg also failed to activate the circuit of dependence and reward.[15] It is also in good agreement with recent reviews reporting that caffeine acts as a mild stimulant that is able to restore mental alertness and wakefulness, mainly in situations with low alertness level.[8,42] Therefore, caffeine appears to be different from drugs of dependence like cocaine, amphetamine, morphine, and nicotine, and does not fulfil the common criteria or the scientific definitions to be considered an addictive substance.[42] ❑

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REFERENCES

1. Debry G, ed. *Coffee and Health*. London, UK: John Libbey; 1994.
2. Barone JJ, Roberts HR. Caffeine consumption. *Food Chem Toxicol*. 1996;34:119-126.
3. Fredholm BB, Bättig K, Holmen J, Nehlig A, Zvartau E. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev*. 1999;51:83-133.
4. Higdon JV, Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr*. 2006;46:101-123.
5. Griffiths RR, Woodson PP. Caffeine physical dependence, a review of human and laboratory animal studies. *Psychopharmacology*. 1988;94:437-451.
6. Juliano L. M, Griffiths RR, A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features, *Psychopharmacology*. 2004;176:1-29.
7. Nehlig A, Are we dependent on coffee and caffeine? A review on human and animal data. *Neurosci Biobehav Rev*. 1999;23:563-576.
8. Nehlig A. Are we dependent on coffee and caffeine: an update. in Nehlig A, ed. *Coffee, Tea, Chocolate and the Brain*. Boca Raton, FL: CRC Press; 2004:133-146.
9. Griffiths RR, Mumford GK. Caffeine reinforcement, discrimination, tolerance and physical dependence in laboratory animals and humans. In: Schuster, CR, Kuhar MJ, eds. *Handbook of Experimental Pharmacology*. Vol 118. Heidelberg, Germany: Springer Verlag; 1996:315-341.
10. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci*. 1992;13:177-184.
11. Self DW, Nestler EJ. Molecular mechanisms of drug reinforcement and addiction. *Annu Rev Neurosci*. 1995;18:463-495.
12. Di Chiara G. The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug Alcohol Depend*. 1995;38:95-137.
13. Pontieri FE, Tanda G, Di Chiara G. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. *Proc Natl Acad Sci U S A*. 1995;92:12304-12308.
14. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*. 1996;382:255-257.
15. Nehlig A, Boyet S. Dose-response study of caffeine effects on cerebral functional activity with a specific focus on dependence. *Brain Res*. 2000;858:71-77.
16. Acquas E, Tanda G, Di Chiara G. Differential effects of caffeine on dopamine and acetylcholine transmission in brain areas of drug-naive and caffeine-pretreated rats. *Neuropsychopharmacology*. 2002;27:182-193.
17. De Luca MA, Bassareo V, Bauer A, Di Chiara G. Caffeine and accumbens shell dopamine. *J Neurochem*. 2007;103:157-163.
18. Nikou C, Heitz F, Armspach JP, Namer IJ, Grucker D. Registration of MR/MR and MR/SPECT brain images by fast stochastic optimization of robust voxel similarity measures. *NeuroImage*. 1998;8:30-43.
19. Cameron OG, Modell JG, Hariharan M. Caffeine and human cerebral blood flow: a positron emission tomography study. *Life Sci*. 1990;47:1141-1146.
20. Field AS, Laurienti PJ, Yen YF, Burdette JH, Moody DM. Dietary caffeine consumption and withdrawal: confounding variables in quantitative cerebral perfusion studies? *Radiology*. 2003;227:129-135.

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Evaluación con SPECT de la activación cerebral inducida por cafeína: ausencia de efecto en áreas involucradas en la dependencia

No se considera que la cafeína sea adictiva y en animales no provoca aumento del metabolismo ni liberación de dopamina en las áreas que participan en los mecanismos de refuerzo y recompensa. Nuestros objetivos fueron medir los efectos de la cafeína en la perfusión cerebral utilizando la tomografía computada de emisión de fotón único con un foco específico en las áreas de refuerzo y recompensa. Se estudiaron dos grupos de sujetos no fumadores, uno con bajo consumo diario de café (8 sujetos) y otro con alto consumo (6 sujetos). Los sujetos ingirieron 3mg/kg de cafeína o placebo en una bebida con sabor a frambuesa y los escáners se realizaron 45 minutos post-ingesta. También se estudió un grupo control de 12 voluntarios sanos que no recibió ninguna bebida. El consumo de cafeína determinó una disminución generalizada del 6% al 8% de la perfusión, sin significación estadística, comparable tanto en los sujetos con bajo como con alto consumo. En comparación con los controles, los sujetos de bajo consumo mostraron actividad neuronal bilateral en el giro frontal inferior-corteza insular anterior y en el uncus, la corteza parietal interna izquierda, el giro lingual derecho y el cerebelo. En los sujetos de alto consumo la activación cerebral ocurrió bilateralmente sólo en el hipotálamo. Por lo tanto, la cafeína -aunque provoca de fondo una extensa disminución de la perfusión de baja amplitud- activa unas pocas regiones involucradas principalmente en el control de la vigilancia, la ansiedad y la regulación cardiovascular, sin afectar áreas que participan en el refuerzo y la recompensa.

Évaluation par SPECT de l'activité cérébrale induite par la caféine : aucun effet sur les aires impliquées dans la dépendance

La caféine n'engendre pas de dépendance et ne déclenche pas d'augmentation du métabolisme ou de libération de dopamine dans les aires cérébrales impliquées dans le renforcement ou la récompense chez les animaux. Notre but était de mesurer les effets de la caféine sur la perfusion cérébrale humaine en utilisant la tomographie par émission monophotonique, en insistant sur les aires du renforcement et de la récompense. Deux groupes de sujets non fumeurs ont été étudiés, l'un ayant une faible (8 sujets) et l'autre une forte (6 sujets) consommation quotidienne de café. Les sujets ont pris 3 mg/kg de caféine ou un placebo dans une boisson au goût de framboise et des scanners ont été réalisés 45 min après l'ingestion, un groupe témoin de 12 volontaires sains ne prenant aucune boisson étant également étudié. La consommation de caféine a conduit à une réduction généralisée du débit statistiquement non significative de 6 % à 8 %, comparable chez les petits ou gros consommateurs. Les petits consommateurs, par rapport aux témoins, ont présenté une activation neuronale bilatérale dans le gyrus frontal inférieur, le cortex insulaire antérieur et l'uncus, dans le cortex pariétal interne gauche, le gyrus lingual droit et le cervelet. Chez les gros consommateurs, l'activation cérébrale est apparue de façon bilatérale seulement dans l'hypothalamus. Ainsi, sur un fond de diminution étendue du débit de faible amplitude, la caféine activerait quelques régions principalement impliquées dans le contrôle de la vigilance, de l'anxiété et de la régulation cardiovasculaire, mais n'affecterait pas les aires impliquées dans le renforcement et la récompense.

21. Laurienti PJ, Field AS, Burdette JH, Maldjian JA. et al. Relationship between caffeine-induced changes in resting cerebral perfusion and blood oxygenation level-dependent signal. *Am J Neuroradiol*. 2003;24:1607-1611.
22. Mathew RJ, Wilson WH. Caffeine induced changes in cerebral circulation. *Stroke*. 1985;16:814-817.
23. Mulderink TA, Gitelman DR, Mesulam MM, Parrish TB. On the use of caffeine as a contrast booster for BOLD fMRI studies. *NeuroImage*. 2002;15:37-44.
24. Mathew RJ, Wilson WH. Behavioral and cerebrovascular effects of caffeine in patients with anxiety disorders. *Acta Psychiatr Scand*. 1990;82:17-22.
25. Ragab S, Lunt M, Birch A, Thomas P, Jenkinson DF. Caffeine reduces cerebral blood flow in patients recovering from an ischaemic stroke. *Age Ageing*. 2004;33:299-303.
26. Couturier EG. M, Laman DM, van Duijn M. AJ, van Duijn H. Influence of caffeine and caffeine withdrawal on headache and cerebral blood flow velocities. *Cephalalgiae*. 1997;17:188-190.

PAGES_11_AG_1009_BA.qxd:DCNS#45 9/06/10 10:27 Page 263

27. Kilts CD, Kelsey JE, Knight B, Ely TD, et al. The neural correlates of social anxiety disorder and response to pharmacotherapy. *Neuropsychopharmacology*. 2006;31:2243-2253.
28. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry*. 2006;60:383-387.
29. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev*. 1996;22:229-244.
30. Chua P, Krams M, Toni I, Passingham R, Dolan RA functional anatomy of anticipatory anxiety. *NeuroImage*. 1999;9:563-571.
31. Nitschke JB, Sarinopoulos I, Mackiewicz KL. Schaefer HS, Davidson RJ. Functional neuroanatomy of aversion and its anticipation. *NeuroImage*. 2006;29:106-116.
32. Schunck T, Erb G, Mathis A, Gilles C, et al. Functional magnetic resonance imaging characterization of CCK-4-induced panic attack and subsequent anticipatory anxiety. *NeuroImage*. 2006;31:1197-1208.
33. Reiman EM, Raichle ME, Robins E, Mintun MA, et al. Neuroanatomical correlates of a lactate-induced anxiety attack. *Arch Gen Psychiatry*. 1989;46:493-500.
34. Cameron OG, Zubieta JK, Grunhaus L, Minoshima S. Effects of yohimbine on cerebral blood flow, symptoms, and physiological functions in humans. *Psychosom Med*. 2000;62:549-559.
35. Brice CF, Smith AP. Effects of caffeine on mood and performance: a study of realistic consumption. *Psychopharmacology (Berlin).* 2002;164:188-192.
36. Wardak C, Duhamel JR. Le rôle du cortex pariétal (Gaze control: role of the parietal cortex). *Med Sci (Paris).* 2004;20:89-97.
37. Hubbard EM, Piazza M, Pinel P, Dehaene S. Interactions between number and space in parietal cortex. *Nat Rev Neurosci*. 2005;6:435-448.
38. Jacobson KA, Gao ZG. Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov*. 2006;5:247-264.
39. Ruijter J, Lorist MM, Snel J, De Ruiter MB. The influence of caffeine on sustained attention: an ERP study. *Pharmacol Biochem Behav*. 2000;66:29-37.
40. Nawrot P, Jordan S, Eastwood J, Rotstein J, et al. Effects of caffeine on human health. *Food Addit Contam*. 2003;20:1-30.
41. Noordzij M, Uiterwaal CS, Arends LR, Kok FJ, et al. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens*. 2005;23:921-928.
42. Satel S, Is caffeine addictive?--a review of the literature. *Am J Drug Alcohol Abuse*. 2006;32:493-502.

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