# Review

# SHOULD OCD BE CLASSIFIED AS AN ANXIETY DISORDER IN DSM-V?

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> In DSM-III, DSM-III-R, and DSM-IV, obsessive-compulsive disorder (OCD) was classified as an anxiety disorder. In ICD-10, OCD is classified separately from the anxiety disorders, although within the same larger category as anxiety disorders (as one of the "neurotic, stress-related, and somatoform disorders"). Ongoing advances in our understanding of OCD and other anxiety disorders have raised the question of whether OCD should continue to be classified with the anxiety disorders in DSM-V. This review presents a number of options and preliminary recommendations to be considered for DSM-V. Evidence is reviewed for retaining OCD in the category of anxiety disorders, and for moving OCD to a separate category of obsessive-compulsive (OC)-spectrum disorders, if such a category is included in DSM-V. Our preliminary recommendation is that OCD be retained in the category of anxiety disorders but that this category also includes OC-spectrum disorders along with OCD. If this change is made, the name of this category should be changed to reflect this proposed change. Depression and Anxiety 27:495–506, 2010. © 2010 Wiley-Liss, Inc.

> Key words: obsessive-compulsive disorder; anxiety disorder; obsessive-compulsive spectrum disorder; classification; nosology

# INTRODUCTION

Ls obsessive-compulsive disorder (OCD) an anxiety disorder? In DSM-III, DSM-III-R, and DSM-IV, a

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<sup>9</sup>Department of Psychiatry, Butler Hospital and Alpert Medical School of Brown University, Providence, Rhode Island number of disorders, including OCD, were categorized as anxiety disorders, reflecting a sharing of the core symptom of anxiety. In ICD-10, the "neurotic, stressrelated, and somatoform disorders" were classified together; this grouping of disorders includes seven subcategories: phobic anxiety disorders, other anxiety disorders (e.g., panic disorder (PD)), OCD, reaction to

The authors disclose the following financial relationships within the past 3 years: Contract grant sponsors: Astrazeneca; Eli-Lilly; GlaxoSmithKline; Jazz Pharmaceuticals; Johnson & Johnson; Lundbeck; Orion; Pfizer; Pharmacia; Roche; Servier; Solvay; Sumitomo; Takeda; Tikvah; Wyeth.

This Article is being co-published by *Depression and Anxiety* and the American Psychiatric Association.

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Received for publication 8 November 2009; Revised 4 March 2010; Accepted 7 March 2010

DOI 10.1002/da.20699

Published online in Wiley InterScience (www.interscience.wiley. com).

severe stress and adjustment disorders, dissociative disorders, somatoform disorders, and other neurotic disorders (e.g., depersonalization-derealization syndrome). Since the publication of these classification systems, there have been further advances in understanding anxiety disorders (other than OCD), OCD, and putative obsessive-compulsive (OC)-spectrum disorders. Here we review the relevant literature in order to address the question of whether OCD should be classified within the anxiety disorders, and bearing in mind the possibility that certain disorders may be characterized as OC-spectrum disorders. We consider the literature in terms of a range of external validators, and we also consider clinical utility.

This article was commissioned by the DSM-V Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group. It represents the work of the authors for consideration by the work group. *Recommendations provided in this article should be considered preliminary at this time; they do not necessarily reflect the final recommendations or decisions that will be made for DSM-V, as the DSM-V development process is still ongoing.* It is possible that this article's recommendations will be revised as additional data and input from experts and the field are obtained.

# STATEMENT OF THE ISSUES

During the preparation of DSM-V, attention has been paid to the question of how best to categorize different diagnostic entities. In DSM-IV there are 16 chapters of disorders, whereas ICD-10 uses 10 categories, consistent with a decimal classification. Ideally, the classification system should optimize diagnostic validity, reflecting the relatedness among disorders (for example, advances in our understanding of the underlying psychobiology of particular disorders) and maximize clinical utility (contributing, for example, to the appropriate assessment and treatment of these conditions). One of the DSM-V Research Planning Conferences focused on the OC-spectrum disorders,<sup>[1,2]</sup> reflecting growing acceptance that this construct is a valuable one, scientific advances in understanding overlapping phenomenology and psychobiology across a number of disorders, and the possibility that such a grouping of disorders may contribute to improved evaluation of and intervention for these conditions. This immediately raises the related question, however, of whether OCD itself should be classified with the anxiety disorders. This review focuses largely on the relationship of OCD to anxiety disorders; a separate article reviews the OC-spectrum disorders and their relationship to other disorders, including OCD and selected other anxiety disorders (Phillips et al., this issue).

# SIGNIFICANCE OF THE ISSUES

Changing the categorization of a particular disorder does not affect caseness (i.e., which individuals receive a particular diagnosis). Nevertheless, categorization may well influence conceptualizations of disorders, and ultimately potentially the way in which they are assessed and treated. For this reason, the question of where OCD should be located in the diagnostic system has received attention and generated debate.<sup>[3-5]</sup> Some of this debate reflects different judgments about the relevant data on diagnostic validation; here we review data on a series of validators. However, some of this debate also reflects different judgments about clinical utility; thus, we also consider arguments for and against the inclusion of OCD as an anxiety disorder from this perspective. The issue of where to categorize OCD ultimately gains its significance from the possibility it creates for maximizing the validity and utility of the diagnostic system.

# **SEARCH METHOD**

A literature search was conduced using the electronic databases Pubmed and PsychLit, with no time limit. Reference sections of published articles were also examined. Search terms included "anxiety disorder," "OCD," "OC-spectrum disorder," "OC-related disorder." The Annotated Listings of Changes in each DSM, the DSM-IV Sourcebooks, and the DSM-IV Options Book were consulted, as were the proceedings and/or monographs of the preparatory conference series for DSM-V, particularly the *Obsessive-Compulsive Spectrum Disorder* conference.<sup>[1]</sup>

# RESULTS

#### VALIDATORS

There has been significant discussion in the literature of which diagnostic validators are the most important and useful;<sup>[6]</sup> those considered here were developed during the DSM-V process and are representative of recent thinking.<sup>[7]</sup> We use these validators to examine the relatedness of OCD to other anxiety disorders in order to address whether these disorders should be classified together in the same section of DSM-V.

Symptom similarity/diagnostic stability. Anxiety disorders are characterized by psychological (fear, anxiety) and somatic (e.g., panic attacks) manifestations of anxiety. From a phenomenological perspective, they may be differentiated according to the predominant fear or anxiety, although there is considerable overlap between disorders. In OCD, the focused repertoire of obsessions, their intrusiveness and ego-dystonic nature, and the associated stereotyped compulsive rituals help differentiate obsessions from the ruminations of generalized anxiety disorder (GAD) and symptoms of other anxiety disorders. Intrusive thoughts and worries can also be differentiated in nonclinical populations, although there may again be some overlapping features.<sup>[8]</sup> OC-spectrum disorders share with OCD both prominent obsessions and compulsive rituals (e.g., body dysmorphic disorder (BDD)) or repetitive motoric behaviors that may resemble compulsions (e.g., trichotillomania, tic disorders) (see Philips et al., this issue).

Clinical experience suggests that anxiety symptoms in OCD and OC-spectrum disorders are somewhat variable and heterogenous.<sup>[9]</sup> For this reason, anxiety is not usually recognized as a key indicator of OCD severity. Similarly, different anxiety symptoms may predominate at different stages of the disorder. Obsessions are usually accompanied by anxiety, even to the extent of panic (see Leckman et al., this issue). With time, however, phobic fear and avoidance of cues that trigger obsessions or compulsions may supervene. In some patients, including those with prominent avoidance or symmetry-related obsessions and compulsions, anxiety appears less prominent.

It is not known with certainty to what extent the anxiety associated with OCD arises in response (i.e., is secondary) to obsessions and compulsions, or generates the repetitive thoughts and behaviors.<sup>[9]</sup> Support for the latter view may be derived from the observation that OC symptoms in humans,<sup>[10]</sup> and habitual behaviors in animals,<sup>[11]</sup> tend to worsen under stress. Intrusive cognitions may occur in a number of different anxiety disorders, but individuals with OCD may find intrusive mental processes particularly discomforting.<sup>[12]</sup>

Although anxiety symptoms commonly occur in OCD, it does not necessarily follow that OCD is an anxiety disorder. After all, anxiety is integral across a range of disorders, including affective, developmental, and psychotic disorders. Behavioral models of OCD indicate that compulsions represent just one form of anxiety-driven avoidance behavior that takes various forms across the anxiety disorders including OCD, such as overt and covert avoidance of objects or situations, reliance on safety signals, compulsive rituals, and reassurance seeking. Developmental and evolutionary theories of OČD emphasize, however, the highly conserved nature of compulsions.<sup>[13]</sup> In addition to compulsions, other key symptoms such as characteristic obsessional themes (sex, religion, violence), sometimes delusional qualities, magical thinking, and prominent motor behaviors have historically been considered important descriptors that distinguish OCD from anxiety disorders. Tic-related OCD is discussed in more detail elsewhere in this issue (Leckman et al., this issue).

In summary, obsessions and compulsions may be accompanied by anxiety symptoms that appear similar to those in anxiety disorders, although anxiety may be less stable and reliably present in OCD. Although compulsions may have some similarities to the avoidance behaviors associated with other anxiety disorders, the highly stereotyped, driven, repetitive, and nonfunctional quality of compulsive behaviors differentiates OCD from normal acts and from the types of avoidance that occur in other anxiety disorders. At the same time, analysis of symptom similarity and related data (e.g., sociodemographic correlates) in each of the anxiety disorders shows that these vary not only between the anxiety disorders and OCD, but also within each anxiety disorder.<sup>[9]</sup>

**Course of illness.** Anxiety disorders, including OCD, often have a chronic course.<sup>[14]</sup> At the same time, each of the anxiety disorders has a somewhat distinct course, with variation, for example, in age of onset, and in periodicity of symptoms. Specific phobias, as well as OCD and certain OC-spectrum disorders, can have a particularly early age of onset. Elsewhere in this issue early onset OCD is discussed in more detail (Leckman et al., this issue). Behavioral inhibition can also be seen early but syndromal social anxiety disorder tends to begin later.<sup>[15]</sup> In contrast, panic and GAD tend to have a later onset. It is also notable that a sizeable percentage of early onset OCD cases possibly remits over time, <sup>[16]</sup> which may not be true of other anxiety disorders. In summary, there are some overlaps, but also important distinctions, in the course of various anxiety disorders and OCD.

**Comorbidity.** Each anxiety disorder has somewhat different comorbidity patterns. OCD comorbidity studies have recently been reviewed elsewhere; the most common Axis I disorder in both anxiety disorders and OCD is major depressive disorder.<sup>[17]</sup> In both cases, the depression is more likely to onset after rather than before the anxiety disorder or OCD. The most common anxiety disorder.<sup>[17]</sup> Conversely, OCD is social anxiety disorder.<sup>[17]</sup> Conversely, OCD is commonly comorbid in anxiety disorders, although there are variations in such comorbidity across these disorders.<sup>[18]</sup> Indeed, Nestadt et al. have undertaken latent structure analyses which have suggested different classes of OCD based on comorbid relationships with anxiety/affective spectrum disorders.<sup>[19,20]</sup>

Richter et al. compared the prevalence of OCspectrum disorders in patients with OCD, PD, and social anxiety disorder; OCD patients were more likely to have OC-spectrum disorders than patients with panic or social anxiety.<sup>[21]</sup> Lochner et al. have similar findings, although PD patients were more likely to have hypochondriasis, and BDD patients were more likely to have social anxiety disorder (unpublished data). Conversely, OCD is a common Axis I disorder in a number of OC-spectrum disorders (e.g., Tourette's disorder, BDD) (Phillips et al., under review, this issue). In summary, comorbidity studies provide some evidence of overlap of anxiety disorders, OCD, and OCspectrum disorders, although there are also differences in the extent of such overlap for each of the relevant conditions.

Meta-structure analyses have found that internalizing and externalizing disorders tend to group together.<sup>[22]</sup> However, those few studies that have included OCD have yielded inconsistent findings,<sup>[23,24]</sup> and none have focused on OC-spectrum disorders. A recent metastructure analysis by Wittchen et al., which included OCD, has raised further questions by showing little consistency in structure when different age groups or different diagnoses were included in the models.<sup>[25]</sup>

Neuronal circuitry. Contemporary neurocircuitry models of anxiety disorders have principally relied upon results from animal research as well as brain imaging data from humans. Based in part on an extensive literature pertaining to fear conditioning and extinction, neurocircuitry models of anxiety disorders have focused on amygdalo-cortical interactions.<sup>[26,27]</sup> The amygdala is known to play a central role in threat assessment and the fear response, whereas specific cortical regions are known to modulate amygdala function in this regard. In particular, ventromedial prefrontal cortex (vmPFC) is purported to suppress amygdala response as it mediates the recall of extinction information, whereas the hippocampus is also able to modulate amygdala responses by providing information regarding safe versus dangerous contexts.<sup>[28-30]</sup> Thus, amygdalo-centric models of anxiety disorders propose some combination of exaggerated amygdala responses and/or deficient top-down modulation of the amygdala due to insufficient function of vmPFC and/or hippocampus.<sup>[27]</sup> Support for such a model has been well established in studies of posttraumatic stress disorder (PTSD), where evidence for all three elements has been replicated: exaggerated amygdala responses and deficient function (and smaller volumes) of vmPFC and hippocampus.<sup>[31]</sup> Amygdala hyper-responsivity is a candidate common attribute of anxiety disorders; when subjects are exposed to disorder-specific cues (e.g., the objects of their principal fear/concern), evidence of exaggerated amygdala responses has been found in PTSD, specific phobias, social phobia, PD, GAD, and OCD.<sup>[32]</sup> However, amygdala hyper-responsivity is not specific to the anxiety disorders, as it has also been reported in BDD<sup>[33]</sup> and major depression.<sup>[34]</sup> Despite findings of vmPFC and hippocampal deficiency in PTSD, comparable findings are not broadly convergent across the other anxiety disorders. Rather, hyper-responsivity within the insula, which is known to mediate interoception, as a possible mechanism underlying anxiety sensitivity may be common across some anxiety disorders,<sup>[35–37]</sup> including OCD.<sup>[38–40]</sup> Insular hyperresponsivity remains, however, to be fully tested as a candidate common attribute across all anxiety disorders. Moreoever, as with amygdala hyper-responsivity, there is evidence that insular findings are not limited to anxiety disorders.

Contemporary neurocircuitry models of OCD have focused on fronto-striatal circuitry, consistent with the role this circuitry is known to play in mediating ritualized behaviors, negative cognitions, error detection, and implicit learning.<sup>[41–44]</sup> Convergent findings across numerous studies have implicated orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum (especially caudate nucleus) in OCD; the regions are hyperactive at rest, and the regional activity is accentuated during symptom provocation and attenuated following successful treatment.<sup>[45–47]</sup> This full profile of baseline hyperactivity and hyper-response within lateral OFC, ACC, and caudate is not found in imaging studies of other anxiety disorders, distinguishing OCD from them. Furthermore, OCD may be distinguished from other anxiety disorders in that when exposed to nonspecific threat-related stimuli (i.e., unrelated to their anxiety symptoms), OCD appears to be uniquely characterized by hyporesponsivity of the amygdala.<sup>[48]</sup>

There are fewer imaging studies of putative OCspectrum disorders such as Tourette's disorder, BDD, and trichotillomania<sup>[17]</sup> (see Phillips et al., under review, this issue). In general, however, the data that do exist suggest that these conditions may have a closer relationship to OCD than to other anxiety disorders, insofar as they appear to share involvement of frontal–striatal circuitry.<sup>[49–52]</sup> Nonetheless, there is also evidence implicating the insular cortex in Tourette's disorder.<sup>[53,54]</sup> Here it is important to acknowledge that the profile of regional brain involvement in OCD is heterogeneous, reflecting heterogeneity of OCD subtyping such as by symptom dimensions.<sup>[38,55–57]</sup>

It is essential to emphasize the limitations of the imaging database, including the relative lack of studies using similar paradigms across different psychiatric disorders, inability to control fully for the heterogeneity of each of the relevant disorders, and the small number of studies of certain OC-spectrum disorders. Given current information, at best the human data provide heuristic neurocircuitry models of anxiety disorders, OCD, and purported OC-spectrum disorders. As yet, there are no pathognomonic findings and no imaging profiles of sufficient specificity and sensitivity to enable diagnosis.

In summary, based on animal data, limited human imaging findings, and heuristic models, anxiety disorders, OCD, and BDD appear to share the attribute of amygdala hyper-response to disorder-specific stimuli, and to some extent also insular hyperactivation. These findings may not be specific to anxiety disorders, however, as they may also extend to other conditions such as major depression. OCD appears to be distinct from other anxiety disorders with respect to frontostriatal hyperactivity and hyper-responsivity as well as attenuated amygdala response to disorder-independent threat stimuli. This may be indicative of OCD as a disorder of implicit processing deficits, and negative intrusive cognitions, rather than anxiety per se. Although the profile of OCD may be distinct from other anxiety disorders in important ways, there is heterogeneity of the profiles across subtypes of OCD. Furthermore, although they share some similarities with respect to cortico-striatal involvement, there is not yet compelling evidence that OCD and purported OC-spectrum disorders are more alike with respect to neurocircuitry than are OCD and the other anxiety disorders.

Familiality, genetic risk factors, environmental risk factors. The anxiety disorders, including OCD, demonstrate significant familial aggregation, with genetic factors playing a key role.<sup>[58]</sup> A critical question is whether other anxiety disorders share a genetic etiology with OCD. This would be definitively demonstrated if a known genetic variant had a demonstrable causal link to both OCD and other anxiety disorders. In the absence of a definitive causal genetic variant, probabilistic evidence of a genetic relationship between anxiety disorders and OCD may be obtained from family or twin studies. The four extant family studies with the potential to determine familial relationships between OCD and anxiety disorders have shown somewhat variable results. In the first such study, Black et al. found that anxiety disorders (as a group), and GAD in particular, were more common in relatives of OCD-affected probands than in relatives of control probands.<sup>[59]</sup> In the largest prior study, Nestadt et al.<sup>[60]</sup> found that GAD, PD, agoraphobia (Ag), social phobia, and separation anxiety disorder (SAD) were more common in relatives of OCD probands than in relatives of controls. When adjusting for relative OCD diagnosis and proband diagnosis of the same anxiety disorder, GAD and Ag remained more common in case than control relatives. The results suggested that GAD and Ag share a familial etiology with OCD not explicable in terms of transmission of OCD itself or independent transmission of these other anxiety disorders.<sup>[60]</sup> In contrast, Carter et al.<sup>[61]</sup> did not find that anxiety disorders were more common in relatives of OCD-affected probands than in relatives of controls. In that study, anxiety disorders were only more common among these relatives in the presence of OCD; the authors noted that the discrepant results may partially be attributable to lower statistical power than in the study of Nestadt et al.<sup>[61]</sup> In the last such study, Fyer et al.<sup>[62]</sup> found trends toward higher prevalences of GAD, PD, and SAD in relatives of OCD-affected probands than in relatives of control probands (the authors did not report on Ag). However, when OCDaffected probands with the disorders under study were removed from the analysis, only GAD demonstrated that trend. As in the study by Carter et al., the authors noted the potential of a type II error due to relatively lower statistical power than the study of Nestadt et al.<sup>[62]</sup> Bolton et al.<sup>[63]</sup> found in a twin study that there were strong familial aggregations between sub-threshold OCD and tics, and between sub-threshold OCD and other anxiety disorders, although it was not possible to differentiate genetic from shared environmental effects. Tambs et al., using twin data, found that the anxiety disorders, including OCD, all shared genetic and environmental risk factors.<sup>[64]</sup>

Also of interest is whether OCD "runs in the families" of patients with other anxiety disorders; results to date are mixed. Early controlled family studies of PD, Ag, and GAD that used Research Diagnostic Criteria or hierarchical DSM-III diagnoses did not suggest substantial or elevated prevalences of OCD in first-degree relatives.<sup>[65–67]</sup> In a more recent large PD family study using DSM-III-R criteria, OCD was too uncommon to allow detection of familial aggregation.<sup>[68]</sup> However, in a study of children at varying risk for PD, the prevalence of OCD was statistically significantly elevated in children of parents with PD or GAD.<sup>[69]</sup> It would be useful for future family studies of anxiety disorders other than OCD to explore more systematically the relationship of such conditions with OCD and disorders that are widely considered to be members of the OC spectrum.

A secondary data analysis commissioned by our DSM-V Workgroup explored familial relationships among OCD, anxiety disorders, and certain putative OC-spectrum disorders; this is the largest OCD family study to date (382 OCD-affected probands and 974 of their first-degree relatives). Preliminary results suggest similar results to the study of Nestadt et al.[60] Specifically, SAD, PD, Ag, social phobia, and GAD were significantly more common in OCD probands than in control probands and also in first-degree relatives of OCD probands than in first-degree relatives of control probands. Results were similar when controlling for potential demographic confounders or proband diagnosis of the same disorder. As in the study by Nestadt et al.<sup>[60]</sup> Ag and GAD were more common in case relatives even when also controlling for OCD in the relatives (Bienvenu et al., unpublished data). Furthermore, the following putative OC-spectrum disorders were significantly more common in OCD probands than in control probands and also in first-degree relatives of OCD probands than in firstdegree relatives of control probands: trichotillomania, BDD, tic disorder, hypochondriasis, OC personality disorder, and skin picking disorder. Taken together, these results suggest that, using comorbidity and familiality data, there is evidence supporting both grouping OCD with anxiety disorders and grouping some OC-spectrum disorders with OCD.

Less direct evidence regarding the familial relationship between anxiety disorders and OCD is provided by studies that have investigated anxiety-related personality measures in relatives of OCD-affected probands and controls.<sup>[70,71]</sup> Samuels et al.<sup>[70]</sup> found higher neuroticism, and Ettelt et al.<sup>[71]</sup> found higher "harm avoidance," in the relatives of OCD-affected probands compared to relatives of controls.

A number of different gene variants have been studied in various anxiety disorders and in OCD. Certain gene variants (e.g., brain-derived neurotrophic factor, catechol-*O*-methyl transferase) may play a role in mediating a range of different anxiety disorders, including OCD.<sup>[72,73]</sup> Similarly, certain gene–environment interactions may be relevant across different affective and anxiety disorders.<sup>[74]</sup> At the same time, there may be some differentiators (e.g., genes involved in mediating hypothalamic–pituitary–adrenal axis function have to date been associated only with certain anxiety disorders).<sup>[75]</sup> Although there have been relatively few whole genome scans in anxiety disorders including OCD, preliminary data would again suggest that there are differences across these conditions.<sup>[76,77]</sup> Although some of the putative OC-spectrum disorders have not been well characterized genetically, it is notable that rare gene variants may result in increased vulnerability specifically to Tourette's and other putative OC-spectrum disorders within extended families.<sup>[78]</sup>

Environmental risk factors have been the subject of only a limited number of studies in anxiety disorders and in OCD. By definition, trauma plays a key role in posttraumatic disorder. However, there is also evidence of an association between early adversity and several other affective and anxiety disorders, as well as of an association between trauma and OCD and certain OC-spectrum disorders.<sup>[79,80]</sup> At the same time, not all data are consistent.<sup>[81]</sup> Although psychological trauma seems too blunt a construct to serve as a validator of distinctions between the different anxiety and OC-spectrum disorders, future work on gene-environment interactions may prove useful in contributing to our understanding of how particular stressors lead to different outcomes in different individuals.<sup>[74]</sup> Work on infectious precipitants of OCD is at an early stage (see Leckman et al., this issue), but may ultimately also be useful in validating similarities and/or distinctions between anxiety and putative OC-spectrum disorders.

In summary, there is evidence from family studies linking OCD to anxiety disorders, particularly GAD, and linking OCD to OC-spectrum disorders. Importantly, patterns of association between anxiety disorders and OCD or OC-spectrum disorders may differ for different anxiety disorders. However, the strength of this evidence remains somewhat limited, requiring additional study. The data from studies of particular genes, specific environments, and their interactions on the relationship between anxiety disorders and OCD, and between OC-spectrum disorders and OCD, remain limited. Conclusions must necessarily be tentative in the absence of studies that systematically compare findings across different anxiety and OCspectrum disorders in the same populations, and in view of the complexity of the underlying genetics.

**Other biomarkers.** There are relatively few biomarkers of either anxiety disorders or OCD. Decreased heart rate variability has been associated with anxiety and depressive disorders, but there is less or no data on this in OCD or OC-spectrum disorders.<sup>[82,83]</sup> Neurotransmitter, neuropeptide, and neuroendocrine function has recently been reviewed in anxiety disorders, OCD, and OC-spectrum disorders.<sup>[17]</sup> Although there is some evidence of overlap across these conditions, there also appear to be important distinctions. Nevertheless, important methodological limitations of this literature must be noted. For example, measurement of peripheral neurotransmitters may not be a valid reflection of central neurotransmitter activity. Much further work is needed in order to identify and contrast the "molecular signatures" of anxiety disorders, OCD, and OC-spectrum disorders.

Temperamental antecedents/personality correlates. Behavioral inhibition appears to be a key antecedent of anxiety disorders, particularly social anxiety disorder.<sup>[15]</sup> There is less or no investigation of behavioral inhibition in OCD or OC-spectrum disorders, but one study showed that reports of childhood levels of behavioral inhibition significantly predicted levels of OCD symptoms in adulthood.<sup>[84]</sup> Perfectionism has been associated with OCD<sup>[85,86]</sup> and BDD,<sup>[87]</sup> but it remains unclear if it is a vulnerability factor, or secondary to symptoms of these disorders. Perfectionism may also be seen in other anxiety disorders and depression, although it is possible that different dimensions of perfectionism are involved in different disorders.<sup>[88]</sup> Similarly, although neuroticism has been associated with anxiety disorders including OCD.<sup>[89]</sup> it has also been associated with a range of other psychiatric disorders.<sup>[90]</sup> There may be some differences in personality disorder comorbidity between anxiety disorder and OCD, although again further systemic research is needed across these conditions as well as the OC disorders.<sup>[17,91]</sup>

**Cognitive-emotional processing.** There are a range of overlapping and distinct disturbances in cognitive-emotional processing in OCD and other anxiety disorders.<sup>[83]</sup> For example, anxiety disorders are characterized by various specific biases in attention to threat and in startle response.<sup>[83,92,93]</sup> In contrast, OCD may be particularly strongly characterized by thought-action fusion, or the belief that thinking about an unacceptable event makes that event more probable, leading to an inflated sense of responsibility, although not all data are consistent.<sup>[94]</sup>

Table 1 summarizes the profile of cognitive deficits across individual anxiety disorders. It can be seen that although OCD shares at least some of these abnormalities, it can be distinguished by a different and characteristic profile of additional executive dysfunction involving impaired inhibitory processes such as attentional setshifting, which is thought to reflect cognitive inflexibility, and impaired inhibition of prepotent motor responses representing motor impulsivity which have been found to extend to unaffected family members.<sup>[95]</sup> These cognitive deficits have been linked to structural abnormalities in orbitofrontal and striatal gray matter, anatomically associated white matter tracts, and dysfunctional activation of the OFC, and are considered to represent neurocognitive endophenotypes-or vulnerability markers—for OCD.<sup>[96]</sup> In contrast to OCD, executive impairments have been inconsistently found in non-OCD anxiety disorders. For example, studies by Ooster-laan et al.<sup>[97]</sup> and Cassada and Roache<sup>[98]</sup> failed to find evidence of response inhibition deficits in young people with anxiety and adults with PTSD, respectively. Castaneda et al.<sup>[99]</sup> reviewed the neurocognitive literature for young adults with a range of anxiety disorders and concluded that the profile of cognitive dysfunction

TABLE 1. Cognitive deficits across anxiety disorders<sup>[106]</sup>

Cognitive domain	GAD	PD	SAD	Simple phobia	PTSD	OCD
Working memory	+++	_	++	_	+++	++
Attentional bias (emotional stroop and dot probe)	+ + +	+ + +	+ + +	+++	+++	+
Increased baseline startle	++	+ + +	+ + +	?	+++	+++
Cognitive flexibility (e.g., WCST, ID/ED)	_	_	$+^{a}$	-	_	+++
Response inhibition (e.g., go/nogo, SSRT)	-	_	_	-	-	+++
Disgust sensitivity	-	-	-	++	-	+

+ = limited effect, ++ = moderate effect, +++ = strong effect, - = evidence of no effect, ? = no evidence. WCST, Wisconsin card sort test; SSRT, stop signal reaction time test; ID/ED, intradimensional-extradimensional set-shifting task.

<sup>a</sup>When tested under stress.

depended on anxiety disorder subtype, with OCD standing apart from the other disorders by virtue of stronger evidence of impaired executive functioning and visual memory. However, they commented that the conflicting findings derived from the otherwise small number of published studies in anxiety disorders other than OCD were inadequate evidence upon which to draw firm conclusions.

Direct comparisons between task performance in OCD and other anxiety disorders has been performed for some cognitive domains. The results have generally shown greater impairment in the OCD group. For example, controlled studies have shown that patients with OCD showed greater executive impairment than those with PD on tasks probing cognitive flexibility (attentional setshifting), planning and strategy, and spatial recognition memory.<sup>[100–102]</sup> A further study by Airaksinen et al.<sup>[103]</sup> showed that OCD and PD patients were impaired compared to healthy controls on trail-making, verbal fluency, and episodic memory tasks, whereas patients with social anxiety disorder and GAD were not. A study by Van den Heuvel et al.<sup>[102]</sup> added to the neurocognitive findings by showing differences between OCD and PD in functional neuroimaging during an emotional attentional bias task; patients with OCD did not display a general attentional bias relative to controls. In contrast, generalized emotional interference effects were found in PD involving ventral and widespread dorsal brain regions, thought to reflect increased unconscious emotional stimulus processing and cognitive elaboration.

Nevertheless, there may also be other areas of overlap between OCD and anxiety disorders; for example, altered responsiveness to disgust stimuli has been suggested to play a role in both specific phobia and OCD.<sup>[104,105]</sup> Similarities and differences in cognitive-emotional processing among OC-spectrum disorders, OCD, and other anxiety disorders are somewhat variable and are discussed in a separate review in this issue (Phillips et al., this issue). Limitations in this literature should be noted; many cognitive-emotional processing paradigms have not been directly compared across anxiety disorders and OCD or OC-spectrum disorders.<sup>[106]</sup>

In summary, anxiety disorders appear to be characterized by faulty nonconscious emotional processing that appears to have some overlap with that in OCD. However, OCD appears to be characterized by distinct neurocognitive deficits related to fronto-striatal neurocircuitry that have not so far been reliably identified in other anxiety disorders. In OCD, the neurocognitive evidence seems to indicate the primacy of compulsive behaviors as symptoms of basal ganglia dysregulation.

Treatment response. Several national and international guidelines suggest that the first-line pharmacotherapy of anxiety disorders and of OCD are the serotonin reuptake inhibitors (SRIs).<sup>[107-109]</sup> Antidepressants with broader effects (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors) are effective in a number of anxiety disorders, but not all (e.g., there is inconsistent evidence for tricyclic antidepressants in social anxiety disorder<sup>[110]</sup>). Similarly, the benzodiazepines are effective in a number of different anxiety disorders but not in all (e.g., specific phobia, PTSD). In contrast, results for nonserotonergic agents in OCD are notably poor.<sup>[111,112]</sup> Randomized controlled trials of tricyclic antidepressants and anxiolytic drugs such as benzodiazepines and buspirone do not show efficacy in treating OCD. Other pharmacological characteristics that differentiate OCD from anxiety disorders include its positive dose-response relationship to SRI treatment, with the highest licensed doses producing the best clinical effects, lower placebo response rates, and a slower time to treatment response that develops over weeks and months.<sup>[111]</sup> Treatment response of some OC-spectrum disorders (e.g., BDD) but not others (e.g., tic disorders) appears somewhat similar to that of OCD (see Phillips et al., this issue). Neurosurgical interventions for OCD are based on and have contributed to a fronto-striatal model of this disorder, and further emphasize its distinctiveness.  $^{\left[ 44\right] }$ 

Psychotherapy for anxiety disorders often includes a component of behavioral exposure. Similarly, in OCD, exposure is a key approach, although effective behavioral treatment also includes response prevention, which is not a core component of treatments for other anxiety disorders.<sup>[113]</sup> In anxiety disorders and OCD, cognitive restructuring is thought to be useful,<sup>[113]</sup> although its added value over exposure and response prevention remains to be substantiated for OCD.<sup>[114]</sup> Similar approaches appear useful in BDD (Phillips et al., this

issue). Behavioral techniques such as habit reversal appear particularly effective in Tourette's syndrome and trichotillomania.<sup>[115,116]</sup>

In summary, although there is strong evidence for differentiating the anxiety disorders from OCD on the basis of effective interventions, findings also suggest some degree of overlap in treatment response across these conditions.

#### CLINICAL UTILITY

Various arguments have been put forth to support the clinical utility of keeping OCD in the anxiety disorders category or removing it and putting it in a separate category of OC-spectrum disorders.<sup>[3,4]</sup> For example, one argument for differentiating OCD and OC-spectrum disorders from anxiety disorders that is particularly important from the perspective of clinical utility is that the former may require specific treatments (i.e., SRIs and response prevention/habit reversal), whereas anxiety disorders may respond to a broader range of interventions. At the same time, there are some similarities in treatment approaches across anxiety disorders, OCD, and certain OC-spectrum disorders. In addition, screening for OCD is often emphasized particularly by clinicians interested in anxiety disorders, whereas screening for OC-spectrum disorders is often emphasized particularly by clinicians interested in OCD. In the context of a discussion of clinical utility, it is relevant to note the phenomenological links between hypochondriasis (or health anxiety disorder) and PD, and between BDD and social anxiety disorder.

In summary, from the perspective of clinical utility, there are advantages for keeping OCD in, and adding OC-spectrum disorders to, the category of anxiety disorders. As discussed above, there are many important areas of overlap across these conditions, suggesting that similar conceptual approaches, assessment methods, and treatment interventions are useful. However, there may also be advantages to removing OCD and OC-spectrum disorders from anxiety disorders, as these conditions requires a somewhat distinctive conceptual, assessment and interventional approach.

#### EXPERT OPINION

An international survey of authors of OCD publications posed the question of whether OCD should be moved out of the anxiety disorders section of DSM.<sup>[117]</sup> Approximately 60% of the 187 respondents supported moving OCD out of the anxiety disorders section, whereas 40% disagreed. There was a significant difference in opinion between psychiatrists (75% supported a move) and other professionals (40–45% supported a move). The most frequent reason for supporting a move out of the anxiety disorders section was that obsessions and compulsions, rather than anxiety, are the fundamental features of the disorder. The main reasons for disagreeing with such a move were that OCD and other anxiety disorders respond to similar treatments and tend to co-occur.

#### **OPTIONS**

Several options are available for DSM-V. First, OCD could remain as one of the anxiety disorders. A problem with this option is that it ignores much of the research evidence indicating differences between OCD and other anxiety disorders across a number of validators, including psychobiology and treatment. And if OCD, but not OC-spectrum disorders, were included in the section of anxiety disorders, this would not reflect the growing set of data that OCD should be classified along with a number of other OC-spectrum disorders. In general, then, the data do not seem to strongly support this option.

Second, DSM-V could remove OCD from the anxiety disorders and have a separate category, either of OCD alone or of OCD and OC-spectrum disorders. This approach reflects the growing research base indicating similarities among these disorders across different domains. However, a problem with this option is that it ignores those data which do point to an important link between OCD and the other anxiety disorders. An additional problem with this approach is that it ignores the links between various OC-spectrum disorders and the anxiety disorders (for example, the links between BDD and social anxiety disorder, and between hypochondriasis and PD).

Third, the category of anxiety disorders could be changed to include both anxiety and OC-spectrum disorders-e.g., "Anxiety and OC-Spectrum Disorders," or possibly "Anxiety, Posttraumatic and OC-Spectrum Disorders." (The classification of PTSD is the subject of a separate review.) This is a compromise position; it allows an emphasis on the established links between these disorders while also emphasizing some of the important distinctions between them. As such, it has both strengths (it incorporates a range of views) and weaknesses (in particular, the link between anxiety disorders and certain OC-spectrum disorders is not well established). However, the majority of the authors of this review feel that the option of a broader category that includes both anxiety and OC-spectrum disorders is the most satisfactory at the current time. This approach has some similarities to that taken in the ICD-10.

#### CONCLUSION

In conclusion, our preliminary recommendation is that DSM-V change the section on anxiety disorders to include OC spectrum disorders (also see Phillips et al., this issue). The proposed name of this section is "Anxiety and Obsessive Compulsive-Spectrum Disorders." Although we realize that this option has important limitations, we believe that it best reflects available evidence and that it will contribute to increasing the diagnostic validity and clinical utility of the classification system.

Acknowledgments. We wish to thank Dr. Michelle Craske for her comments on a draft of this manuscript. We also wish to thank experts in obsessive–compulsive disorder and anxiety disorders who responded to a survey about the nosology of these conditions. Dr. Stein has received research grants and/or consultancy honoraria from Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth.

# REFERENCES

- http://www.psych.org/MainMenu/Research/DSMIV/DSMV/ DSMRevisionActivities/ConferenceSummaries/ObsessiveCom pulsiveSpectrumDisordersConference.aspx. 2009.
- 2. Hollander E, Kim S, Zohar J. OCDs in the forthcoming DSM-V. CNS Spectrums 2007;12:320–323.
- 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.
- Storch EA, Abramowitz J, Goodman WK. Where does obsessive-compulsive disorder belong in DSM-V? Depress Anxiety 2008;25:336–347.
- Stein DJ. Is disorder x in category or spectrum y? General considerations and application to the relationship between obsessive-compulsive disorder and anxiety disorders. Depress Anxiety 2008;25:330–335.
- Kendler KS. Towards a scientific nosology: strengths and limitations. Arch Gen Psychiatry 1990;47:969–973.
- Hyman SE. Can neuroscience be integrated into the DSM-V? Nat Rev Neurosci 2007;8:725–732.
- Langlois F, Freeston MH, Ladouceur R. Differences and similarities between obsessive intrusive thoughts and worry in a non-clinical population: study 1. Behav Res Ther 2000;38: 157–173.
- Nutt D, Malizia A. Anxiety and OCD—the chicken or the egg? J Psychopharmacol 2006;20:729–731.
- Parkinson L, Rachman S. Are intrusive thoughts subject to habituation. Behav Res Ther 1980;18:409–418.
- Dias-Ferreira E, Sousa JC, Melo I, et al. Chronic stress causes frontostriatal reorganization and affects decision-making. Science 2009;325:621–625.
- 12. Ladouceur R, Freeston MH, Rheaume J, et al. Strategies used with intrusive thoughts: a comparison of OCD patients with anxious and community controls. J Abnorm Psychol 2000;109: 179–187.
- Leckman JF, Mayes LC. Understanding developmental psychopathology: how useful are evolutionary accounts. J Am Acad Child Adolesc Psychiatry 1998;37:1011–1021.
- Kessler RC, Angermeyer M, Anthony JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007;6:168–176.
- Rosenbaum JF, Biederman J, Faraone SV, et al. Behavioral inhibition in childhood: a risk factor for anxiety disorders. Biol Psychiatry 1997;42:145S.
- Stewart SE, Geller DA, Jenike M, et al. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and

qualitative review of the literature. Acta Psychiatr Scand 2004; 110:4–13.

- Bartz JA, Hollander E. Is obsessive-compulsive disorder an anxiety disorder? Prog Neuro-Psychopharmacol Biol Psychiatry 2006;30:338–352.
- Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 2010;15:53–63.
- Nestadt G, Addington A, Samuels J, et al. The identification of OCD-related subgroups based on comorbidity. Biol Psychiatry 2003;53:914–920.
- Nestadt G, Di CZ, Riddle MA, et al. Obsessive-compulsive disorder: subclassification based on co-morbidity. Psychol Med 2009;39:1491–1501.
- Richter MA, Summerfeldt LJ, Antony MM, et al. Obsessivecompulsive spectrum conditions in obsessive-compulsive disorder and other anxiety disorders. Depress Anxiety 2003;18: 118–127.
- 22. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999;56:921–926.
- Slade TIM, DAVI Watson. The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. Psychol Med 2006;36:1593–1600.
- 24. Cox BJ, Clara IP, Hills AL, et al. Obsessive-compulsive disorder and the underlying structure of anxiety disorders in a nationally representative sample: confirmatory factor analytic findings from the German Health Survey. J Anxiety Disord 2010;24:30–33.
- 25. Wittchen HU, Beesdo-Baum K, Gloster AT, Höfler M, Klotsche J, Lieb R, Beauducel A, Bühner M, Kessler RC. The structure of mental disorders re-examined: is it developmentally stable and robust against additions? Int J Methods Psychiatr Res 2009;18:189–203.
- Shin LM, Liberzon I. The Neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 2010;35:169–191.
- 27. Rauch SL, Drevets WC. Neuroimaging and neuroanatomy of stress-induced and fear circuitry disorders. In: Andrews G, Charney DS, Sirovatka PJ, Regier DA, editors. Stress-Induced and Fear Circuitry Disorders: Refining the Research Agenda for DSM-V. Arlington, VA: American Psychiatric Association
- Phelps EA, Delgado MR, Nearing KI, et al. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 2004; 43:897–905.
- Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J Neurosci 2006;26:9503–9511.
- Milad MR, Wright CI, Orr SP, et al. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007;62:446–454.
- Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol Psychiatry 2006; 60:76–382.
- 32. Simon D, Kaufmann C, Müsch K, Kischkel E, Kathmann N. Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. Psychophysiology 2010; in press.
- Feusner JD, Townsend J, Bystritsky A, et al. Visual information processing of faces in body dysmorphic disorder. Arch Gen Psychiatry 2007;64:1417–1426.
- 34. Sheline YI, Barch DM, Donnelly JM, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 2001;50:651–658.

- 35. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 2007; 164:1476–1488.
- Paulus MP, Stein MB. An insular view of anxiety. Biol Psychiatry 2006;60:383–387.
- Warwick JM, Carey P, van der Linden G, et al. A comparison of the effects of citalopram and moclobemide on resting brain perfusion in social anxiety disorder. Metab Brain Dis 2006; 21:241–245.
- van den Heuvel OA, Remijnse PL, Mataix-Cols D, et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain 2009; 132:853–868.
- Shapira NA, Liu Y, He AG, et al. Brain activation by disgustinducing pictures in obsessive-compulsive disorder. Biol Psychiatry 2003;54:751–756.
- Stein DJ, Arya M, Pietrini P, et al. Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission tomography study. Metab Brain Dis 2006;21:267–277.
- Fitzgerald KD, Welsh RC, Gehring WJ, et al. Error-related hyperactivity of the anterior cingulate cortex in obsessivecompulsive disorder. Biol Psychiatry 2005;57:287–294.
- 42. Rauch SL, Wedig MM, Wright CI, et al. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. Biol Psychiatry 2007;61:330–336.
- Rauch SL. Baxter Jr LR. Neuroimaging in obsessivecompulsive disorder and related disorders. In: Jenicke MA, Baer L, Minichiello WE, editors. Obsessive-Compulsive Disorders: Practical Management. 3rd ed. St. Louis, MI: Mosby; 1998.
- Greenberg BD, Suzanne SLR, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology 2010;35:317–336.
- 45. Menzies L, Chamberlain SR, Laird AR, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 2008;32:525–549.
- 46. Rotge JY, Guehl D, Dilharreguy B, et al. Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. J Psychiatry Neurosci 2008;33:405–412.
- Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. Psychiatry Res Neuroimaging 2004;132:69–79.
- Cannistraro PA, Wright CI, Wedig MM, et al. Amygdala responses to human faces in obsessive-compulsive disorder. Biol Psychiatry 2004;56:916–920.
- Feusner JD, Moody T, Hembacher E, et al. Abnormalities of visual processing and fronto-striatal systems in body dysmorphic disorder. Arch Gen Psychiatry 2010;67:197–205.
- Frey KA, Albin RL. Neuroimaging of Tourette syndrome. J Child Neurol 2006;21:672–677.
- 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 Neuroimaging 2003;122:13–19.
- 52. Stein DJ. Psychobiology of anxiety disorders and obsessivecompulsive spectrum disorders. CNS Spectrums 2008;13: 23–28.
- Bohlhalter S, Goldfine A, Matteson S, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain 2006;129:2029–2037.

- Hampson M, Tokoglu F, King RA, et al. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. Biol Psychiatry 2009;65:594–599.
- Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. Am J Psychiatry 2004;161:1038–1048.
- Rauch SL, Shin LM, Whalen PJ, Pitman RK. Neuroimaging and the neuroanatomy of posttraumatic stress disorder. CNS Spectrums 1998;3:31–41.
- Mataix-Cols D, Wooderson S, Lawrence N, et al. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry 2004;61:564–576.
- Hettema JM, Neale MC, Kendler KS. A review and metaanalysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001;158:1568–1578.
- Black DW, Noyes R, Goldstein RB, et al. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49: 362–368.
- 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.
- 61. Carter AS, Pollock RA, Suvak MK, et al. Anxiety and major depression comorbidity in a family study of obsessive-compulsive disorder. Depress Anxiety 2004;20:165–174.
- Fyer AJ, Lipsitz JD, Mannuzza S, et al. A direct interview family study of obsessive-compulsive disorder. I. Psychol Med 2005;35:1611–1621.
- Bolton D, Rijsdijk F, O'Connor TG, et al. Obsessivecompulsive disorder, tics and anxiety in 6-year-old twins. Psychol Med 2007;37:39–48.
- Tambs K, Czajkowsky N, Roysamb 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.
- Noyes R, Crowe RR, Harris EL, et al. Relationship between panic disorder and agoraphobia—a family study. Arch Gen Psychiatry 1986;43:227–232.
- Noyes R, Clarkson C, Crowe RR, et al. A family study of generalized anxiety disorder. Am J Psychiatry 1987;144: 1019–1024.
- Mendlewicz J, Papadimitriou G, Wilmotte J. Family study of panic disorder—comparison with generalized anxiety disorder, major depression and normal subjects. Psychiatr Genet 1993;3: 73–78.
- Goldstein RB, Weissman MM, Adams PB, et al. Psychiatricdisorders in relatives of probands with panic disorder and/or major depression. Arch Gen Psychiatry 1994;51: 383–394.
- Biederman J, Petty C, Faraone SV, et al. Effects of parental anxiety disorders in children at high risk for panic disorder: a controlled study. J Affect Disord 2006;94:191–197.
- Samuels J, Nestadt G, Bienvenu OJ, et al. Personality disorders and normal personality dimensions in obsessive-compulsive disorder. Br J Psychiatry 2000;177:457–462.
- Ettelt S, Grabe HJ, Ruhrmann S, et al. Harm avoidance in subjects with obsessive-compulsive disorder and their families. J Affect Disord 2008;107:265–269.
- Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nat Neurosci 2007;10: 1089–1093.
- 73. Hemmings SMJ, Kinnear CJ, Van Der Merwe L, et al. Investigating the role of the brain-derived neurotrophic factor

(BDNF) val66met variant in obsessive-compulsive disorder (OCD). World J Biol Psychiatry 2008;9:126–134.

- 74. Stein MB, Schork NJ, Gelernter J. Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. Neuropsychopharmacology 2008;33: 312–319.
- Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 Polymorphisms and Childhood Abuse With Risk of Posttraumatic Stress Disorder Symptoms in Adults. JAMA 2008;299: 1291–1305.
- Fyer AJ, Hamilton SP, Durner M, et al. A third-pass genome scan in panic disorder: evidence for multiple susceptibility loci. Biol Psychiatry 2006;60.
- 77. 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.
- Abelson JF, Kwan KY, O'Roak BJ, et al. Sequence variants in SLITRK1 are associated with Tourette's syndrome. Science 2005;310:317–320.
- Lochner C, du Toit PL, Zungu-Dirwayi N, et al. Childhood trauma in obsessive-compulsive disorder, trichotillomania, and controls. Depress Anxiety 2002;15:66–68.
- Didie ER, Tortolani CC, Pope CG, et al. Childhood abuse and neglect in body dysmorphic disorder. Child Abuse Negl 2006; 30:1105–1115.
- Grabe HJ, Ruhrmann S, Spitzer C, et al. Obsessive-compulsive disorder and posttraumatic stress disorder. Psychopathology 2008;41:129–134.
- Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. Am Heart J 2000;140:577–583.
- Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE, What is an anxiety disorder? Depress Anxiety 2009;26:1066–1068.
- Coles ME, Schofield CA, Pietrefesa AS. Behavioral inhibition and obsessive-compulsive disorder. J Anxiety Disord 2006;20: 1118–1132.
- Chik HM, Whittal ML, O'Neill ML. Perfectionism and treatment outcome in obsessive-compulsive disorder. Cogn Ther Res 2008;32:676–688.
- Lee JC, Prado HS, Diniz JB, et al. Perfectionism and sensory phenomena: phenotypic components of obsessive-compulsive disorder. Compr Psychiatry 2009;50:431–436.
- Buhlmann U, Etcoff NL, Wilhelm S. Facial attractiveness ratings and perfectionism in body dysmorphic disorder and obsessive-compulsive disorder. J Anxiety Disord 2008;22: 540–547.
- Sassaroli S, Lauro LJR, Ruggiero GM, et al. Perfectionism in depression, obsessive-compulsive disorder and eating disorders. Behav Res Ther 2008;46:757–765.
- Hur YM. Genetic and environmental covariations among obsessive-compulsive symptoms, neuroticism, and extraversion in South Korean adolescent and young adult twins. Twin Res Hum Genet 2009;12:142–149.
- Lahey BB. Public health significance of neuroticism. Am Psychol 2009;64:241–256.
- Baer L, Jenike MA. Personality-disorders in obsessive-compulsive disorder. Psychiatr Clin North Am 1992;15:803–812.
- Roy AK, Vasa RA, Bruck M, et al. Attention bias toward threat in pediatric anxiety disorders. J Am Acad Child Adolesc Psychiatry 2008;47:1189–1196.
- 93. Reeb-Sutherland BC, Helfinstein SM, Degnan KA, et al. Startle response in behaviorally inhibited adolescents with a lifetime

occurrence of anxiety disorders. J Am Acad Child Adolesc Psychiatry 2009;48:610-617.

- 94. Shafran R, Rachman S. Thought-action fusion: a review. J Behav Ther Exp Psychiatry 2004;35:87–107.
- Chamberlain SR, Fineberg NA, Blackwell AD, et al. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. Am J Psychiatry 2006;163: 1282–1284.
- Menzies L, Achard S, Chamberlain SR, et al. Neurocognitive endophenotypes of obsessive-compulsive disorder. Brain 2007; 130:3223–3236.
- Oosterlaan J, Logan GD, Sergeant JA. Response inhibition in AD/HD, CD, comorbid AD/HD+CD, anxious, and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry 1998;39:411–425.
- Casada JH, Roache JD. Dissociation of physiology and behavior in PTSD. Int J Psychophysiol 2006;62:243–248.
- Castaneda AE, Tuuio-Henriksson A, Marttunen M, et al. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord 2008; 106:1–27.
- Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological deficits in obsessive-compulsive disorder: a comparison with unipolar depression, panic disorder, and normal controls. Arch Gen Psychiatry 1998;55:415–423.
- 101. Boldrini M, Del Pace L, Placidi GPA, et al. Selective cognitive deficits in obsessive-compulsive disorder compared to panic disorder with agoraphobia. Acta Psychiatr Scand 2005;111: 150–158.
- 102. van den Heuvel OA, Veltman DJ, Groenewegen HJ, et al. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Arch Gen Psychiatry 2005;62:922–933.
- Airaksinen E, Larsson M, Forsell Y. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. J Psychiatr Res 2005; 39:207–214.
- Thorpe SJ, Salkovskis PM. Studies on the role of disgust in the acquisition and maintenance of specific phobias. Behav Res Ther 1998;36:877–893.
- 105. Stein DJ, Liu Y, Shapira NA, et al. The psychobiology of obsessive-compulsive disorder: how important is the role of disgust? Curr Psychiatry Rep 2001;3:281–287.
- 106. Craig K, Chamberlain S. The neuropsychology of anxiety disorders. In: Stein DJ, Hollander E, Rothbaum BO, editors. Textbook of Anxiety Disorders. 2nd ed. Washington, DC: American Psychiatric Publishing; 2010.
- 107. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005;19:567–596.
- 108. 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. World J Biol Psychiatry 2008;9:248–312.
- Stein DJ, Ipser JC, Baldwin DS, et al. Treatment of obsessivecompulsive disorder. CNS Spectrums 2007;12:28–35.
- Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder. Cochrane Database Syst Rev 2004; CD001206.
- Fineberg NA, Gale TM. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int J Neuropsychopharmacol 2005;8:107–129.

#### Stein et al.

- 112. Stein DJ, Denys D, Gloster AT, et al. Obsessive-compulsive disorder: diagnostic and Treatment Issues. Psychiatr Clin North Am 2009;32:665–666.
- 113. Geffken GR, Storch EA, Gelfand KM, et al. Cognitivebehavioral therapy for obsessive-compulsive disorder: review of treatment techniques. J Psychosoc Nurs Ment Health Serv 2004;42:44–51.
- 114. Arch JJ, Craske MG. First-line treatment: a critical appraisal of cognitive behavioral therapy developments and alternatives. Psychiatr Clin North Am 2009;32:525–552.
- 115. Himle MB, Woods DW, Piacentini JC, et al. Brief review of habit reversal training for Tourette syndrome. J Child Neurol 2006;21:719–725.
- 116. Bloch MH, Landeros-Weisenberger A, Dombrowski P, et al. Systematic review: pharmacological and behavioral treatment for trichotillomania. Biol Psychiatry 2007;62: 839–846.
- 117. 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.