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Review article

Is obsessive–compulsive disorder an anxiety disorder?

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Abstract

Obsessive–compulsive disorder (OCD) is classified as an anxiety disorder in the DSM-IV-TR [American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, Fourth ed., rev. Washington, DC: Author]; however, the notion of a spectrum of obsessive–compulsive (OC) related disorders that is comprised of such disparate disorders as OCD, body dysmorphic disorder, certain eating disorders, pathological gambling, and autism, is gaining acceptance. The fact that these disorders share obsessive–compulsive features and evidence similarities in patient characteristics, course, comorbidity, neurobiology, and treatment response raises the question of whether OCD is best conceptualized as an anxiety or an OC spectrum disorder. This article reviews evidence from comorbidity and family studies, as well as biological evidence related to neurocircuitry, neurotransmitter function, and pharmacologic treatment response that bear on this question. The implications of removing OCD from the anxiety disorders category and moving it to an OC spectrum disorders category, as is being proposed for the DSM-V, is discussed.

Keywords: Anxiety disorder; Nosology; Obsessive–compulsive disorder (OCD); Obsessive–compulsive spectrum

Contents

Abbreviations: CRH, corticotrophin releasing hormone; DSM, Diagnostic and Statistical Manual of Mental Disorders; GABA, gamma aminobutyric acid; GAD, generalized anxiety disorder; HPA, hypothalamic–pituitary–adrenal; MDD, major depressive disorder; OC, obsessive–compulsive; OCD, obsessive–compulsive disorder; OCPD, obsessive–compulsive personality disorder; PAG, periaqueductal gray; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; SRI, serotonin reuptake inhibitor; TS, Tourette's syndrome.

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1. Introduction

Obsessive–compulsive disorder (OCD) is currently classified as an anxiety disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000). Indeed, throughout most of the twentieth century, OCD has been viewed as an anxiety disorder or neurosis (Tynes et al., 1990). However, the notion of a spectrum of obsessive–compulsive (OC) related disorders that is comprised of such disparate disorders as OCD, body dysmorphic disorder, certain eating disorders, pathological gambling, and autism, is gaining acceptance. The fact that these disorders share obsessive–compulsive features and evidence similarities in patient characteristics, course, comorbidity, neurobiology, and treatment response raises the question of whether OCD is best conceptualized as an anxiety disorder or as part of an OC spectrum of disorders. In this article, we evaluate evidence from comorbidity and family studies, as well as biological evidence related to neurocircuitry, neurotransmitter function, and pharmacologic treatment response that bear on this issue. Because other articles in this issue cover the OC spectrum in detail, we will focus primarily on similarities and differences between OCD and other anxiety disorders and will be less concerned with research related to the OC spectrum (the reader is also referred to Hollander et al., 2005a, for an in-depth discussion of the OC spectrum). We conclude with a discussion of the implications of removing OCD from the anxiety disorders category and moving it to an OC spectrum disorders category, as is being proposed for the DSM-V.

2. The current nosology of obsessive–compulsive disorder

OCD is a debilitating disorder marked by two distinct phenomena: recurrent, disturbing, intrusive thoughts (obsessions) and overt repetitive behaviors or mental acts (compulsions) that are performed to reduce distress caused by obsessions. The most common obsessions concern thoughts about contamination, pathological doubt, and order/symmetry (Eisen and Rasmussen, 2002). Other obsessions include sexual obsessions as well as concerns about aggressive or horrific impulses (e.g., hurting a loved one or shouting obscenities in inappropriate places). In addition to their intrusive and disturbing quality, obsessions have traditionally been conceptualized as ego-dystonic (i.e., alien to the self, and outside of one's control); however, this feature has recently been challenged by reports of individuals with OCD who believe their obsessions are reasonable, resulting in the addition of the specifier–"with poor insight"–to the DSM-IV (Foa and Kozak, 1995).

Individuals with OCD typically engage in repetitive, compulsive behaviors or mental acts. These compulsions often take on a driven quality because of their role in reducing the distress associated with obsessions. The most common compulsions include checking, washing, counting, need to ask or confess, symmetry and precision (e.g., ordering), and hoarding (Eisen and Rasmussen, 2002). By definition, obsessions and compulsions in OCD must cause marked distress, be time consuming, and seriously interfere with daily functioning. Because of the powerful role obsessions and compulsions can play in a person's life, individuals with OCD often avoid those things or situations that trigger their obsessive and/or compulsive behaviors; thus, avoidance behavior is also a central feature of OCD.

OCD is currently categorized as an anxiety disorder in the DSM-IV-TR along with such other anxiety disorders as panic disorder (with or without agoraphobia), agoraphobia, specific phobia, social phobia (social anxiety disorder), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD) (American Psychiatric Association, 2000). The primary symptom characterizing these disorders is anxiety, which can manifest itself as panic, phobic avoidance, intrusive experiences, excessive worry and/or difficulty controlling worry (American Psychiatric Association, 2000). The primary basis for categorizing OCD as an anxiety disorder is the central role anxiety plays in OCD (Tynes et al., 1990). Obsessions lead to a sense of mounting anxiety and engaging in compulsive behaviors or mental acts reduces anxiety. Moreover, similar to other anxiety disorders, as noted earlier, avoidance plays an important role in OCD (Tynes et al., 1990). The problem with this rationale, however, is that it is symptom focused: OCD is conceptualized as an anxiety disorder because of the prominence of anxiety; however, anxiety is a relatively non-specific symptom that is associated with a number of other psychiatric disorders (e.g., depression, bipolar disorder, and schizophrenia). Thus, although conceptualizing OCD as an anxiety disorder may be useful from a diagnostic perspective, ultimately it does little to further the understanding of OCD and to address questions related to the etiology and treatment of this disorder.

3. The obsessive–compulsive spectrum disorders

In the past two decades the notion of an OC spectrum of related disorders has gained popularity (Hollander, 1993; Hollander et al., 2005a; Jenike, 1990; McElroy et al., 1994; Stein, 2002). The OC spectrum was proposed in response to observations that a number of disparate disorders, for example, body dysmorphic disorder, hypochondriasis, some eating disorders, and some impulse control disorders, share obses-

sive–compulsive features—that is, they are marked by obsessive thinking and/or compulsive behavior. Although the content of the obsessions can differ from those found in OCD, as McElroy et al. (1994) point out, often they are remarkably similar (e.g., symmetry, illness fears, and need for reassurance). Similarities in patient characteristics, course, comorbidity, neurobiology, and treatment response provide further support for the notion that these disorders may have a special relationship and thus should be conceptualized as a spectrum of related disorders.

As theory and research progress, consensus is emerging about the specific disorders comprising the OC spectrum. Our group has sub-divided the OC spectrum disorders into three distinct clusters: 1) body image/body sensitization/body weight concern disorders; 2) impulse control disorders; and 3) neurological disorders with repetitive behaviors (Hollander et al., 2005a). The first cluster is characterized by preoccupations with the body and includes hypochondriasis, body dysmorphic disorder, anorexia nervosa, binge eating disorder, and depersonalization disorder. As McElroy et al. (1994) note, these disorders have a number of structural similarities with OCD. They are marked by intense preoccupations that are often experienced as intrusive and anxiety-provoking, as well as engagement in repetitive behaviors, which are performed to reduce the distress caused by the obsessions (e.g., repeated visits to the doctor, requests for reassurance, mirror-checking, repeated cosmetic surgeries, etc.). Moreover, the content of the preoccupations is similar to those observed in OCD (e.g., health issues or symmetry preoccupations). Other similarities include overvalued ideas and ritualistic behaviors.

The second cluster is characterized by impulsivity—especially with respect to aggressive behaviors or behaviors that have negative consequences. Like those with OCD, individuals with impulse control disorders often experience increased arousal and tension in relation to their impulsive behaviors, but different from those with OCD, engaging in the impulsive behavior is typically associated with pleasure, albeit short-lived (McElroy et al., 1994). This cluster includes pathological gambling, sexual disorders (i.e., obsessions, compulsions, and paraphilias), and trichotillomania (i.e., recurrent hair-pulling). In addition, three new disorders, which have been proposed for inclusion in the DSM-V and are currently being validated, are included in this category: compulsive shopping disorder, internet usage disorder, and pathological excoriation (i.e., excessive skin-picking). Although the behaviors associated with these disorders are characterized as impulsive, there is a compulsive element to them because they function to reduce anxiety (Hollander and Wong, 1995). Moreover, obsessions are prominent in many of the impulse control disorders. For example, pathological gamblers often have obsessive thoughts about gambling, and have been found to exhibit higher levels of obsessionality compared to healthy controls (Blaszczynski, 1999).

The third cluster consists of neurologically based disorders with repetitive behaviors and includes Tourette's syndrome (TS), autism, and Sydenham's chorea. Different from the other two clusters, this cluster is characterized by repetitive motor behaviors, and obsessions are less common. Moreover, there is evidence for underlying neurological dysfunction in this cluster. Specifically, these disorders have been found to be associated with functional disturbances in the basal ganglia, and it is theorized that this may lead to the repetitive, stereotyped behaviors that mark these disorders (Dale, 2003; Peterson et al., 2003; Sears et al., 1999). The obsessions and compulsions that characterize these disorders also differ from those found in OCD. For example, TS is distinguished by mental play, echophenomena, touching, and self-injurious behavior (Cath et al., 2001). Likewise, autism is distinguished by repetitive ordering, hoarding, telling/asking, and touching, whereas self-injurious behavior and aggressive, contamination, sexual, religious, symmetry, and somatic concerns are less common as are checking, cleaning, and counting compulsions (McDougle et al., 1995).

4. Is OCD an anxiety disorder? Comorbidity studies

One way to demonstrate a relationship between two disorders is to show that patients with disorder A are more

Table 1
Recent studies of percentage rates (and odds ratios) of lifetime and current mood and anxiety disorder comorbidity in patients with a primary diagnosis of OCD

	Lifetime				Current	
	LaSalle et al. (2004) (n=334)	Fireman et al. (2001) (n=1078)	Brown et al. (2001) (n=77)	Nestadt et al. (2001) (n=80)	Denys et al. (2004a) (n=420)	Brown et al. (2001) (n=77)
Major depressive disorder	65.9	56	61 (1.24)	54.1	20.7 (10)	22 (1.14)
Dysthmia	24.0		12 (1.04)	8.0	2.8 (1.8)	10 (1.26)
Social phobia	23.4	1	27 (1.36)	36.0	3.6 (.96)	26 (1.21)
Panic disorder	23.1	14	1 (.61)	20.8	1.4 (1.7)	1 (.86)
Agoraphobia (with or without PD)	17.7	2	10 (.85)	16.7	2.6 (1.7)	8 (.88)
Generalized anxiety disorder	18.3	14	12 (.96)	13.0	.95 (1.2)	12 (.93)
Specific phobia	12.0		13 (.80)	30.7	.95 (.17)	12 (.91)
Posttraumatic stress disorder	8.4	3	1 (.22)		1.6	0 (–)

likely to have disorder B and, conversely, that patients with disorder B are more likely to have disorder A; however, when evaluating comorbidity patterns it is important to consider whether the comorbid disorder is a long-term complication of the primary disorder.

4.1. OCD and anxiety disorders

In the past decade, a number of studies have investigated comorbidity patterns of mood and anxiety disorders in OCD (for review see LaSalle et al., 2004). Table 1 summarizes some of the most recent investigations involving relatively large samples. Across these studies, major depressive disorder (MDD) was the most common additional diagnosis with prevalence rates ranging from 20.7% to 22% and from 54% to 66% for additional current and lifetime diagnoses, respectively. With the exception of Fireman et al. (2001), social phobia was the most common anxiety disorder diagnosis, ranging from 3.6% to 26% and from 23 to 36% for additional current and lifetime diagnoses, respectively. The prevalence rate for the other anxiety disorders ranged from 0% to 12% (for current diagnosis) and from 1% to 23% (lifetime diagnosis).

Comparisons of anxiety disorder prevalence rates in OCD probands compared to prevalence rates found in the general population have yielded mixed results. Nestadt et al. (2001) found that all of the anxiety disorders they investigated occurred more frequently in OCD probands compared to matched control probands (the difference for specific phobia was marginal), and that there was a 10-fold difference for panic disorder, agoraphobia, and GAD; MDD (recurrent and brief) was also more prevalent in case than in control probands. Similarly, LaSalle et al. (2004) found that individuals with OCD had a four- to five-fold increase in the prevalence of affective disorders, a three and one half- to four-fold increase in the prevalence of panic disorder, agoraphobia, and GAD, and a two-fold increase in the prevalence of social phobia compared to estimates based on norms from the general population. By contrast, although Denys et al. (2004a) found that MDD was 10 times more prevalent in OCD compared to the general population, these researchers did not find increased prevalence rates for anxiety disorders in OCD (although as the authors note, this may have been due to methodological differences and sample characteristics). Likewise, Brown et al. (2001) found that individuals with OCD only had a significantly increased risk for developing lifetime MDD, but did not have an increased risk of developing any other current or lifetime affective or anxiety disorder.

In summary, across studies, MDD was the most common comorbid axis I disorder for individuals with OCD. All but one study found that social phobia was the most common anxiety disorder diagnosis in OCD patients. The important question, however, is whether individuals with OCD have an increased risk of developing an additional diagnoses compared to what is found in the general population. Studies consistently support the notion that individuals with OCD have an increased risk for developing MDD. Importantly, however, as Denys et al. (2004a) note, studies investigating the onset of comorbid disorders have typically found that OCD precedes rather than follows depression; this finding suggests that depression is likely the result of OCD, and does not have an etiological relationship with OCD. By contrast, the results are mixed for whether individuals with OCD have an increased risk for developing an additional anxiety disorder.

4.2. OCD and OC spectrum disorders

Table 2 summarizes recent investigations of the current and lifetime prevalence rates of OC spectrum disorder diagnoses in patients with primary OCD. Hypochondriasis, body dysmorphic disorder, trichotillomania, and compulsive buying had the highest lifetime prevalence rates. Eating disorders also had fairly high lifetime prevalence rates in some investigations. With respect to making comparisons to prevalence rates found

Table 2
Recent studies of percentage rates (and odds ratios) of lifetime and current OC spectrum disorder comorbidity in patients with a primary diagnosis of OCD

	Lifetime			Current	
	LaSalle et al. (2004) (n=334)	du Toit et al. (2001) (n=85)	Jaisoorya et al. (2003) (n=231)	Denys et al. (2004a) (n=420)	du Toit et al. (2001) (n=85)
Hypochondriasis		8.2	13.0	2.8	7.1
Body dysmorphic disorder	6.3	12.9	3.0		12.9
Anorexia nervosa	9.3	5.9	0.4		2.4
Bulimia nervosa	9.6	4.7	0.0		3.5
Binge eating disorder	0.9	0.0			0.0
Any eating disorder			0.4	2.4 (8)	
Trichotillomania	9.6	12.9	3.0		7.1
Pathological gambling		1.2	0.0		0.0
Sexual compulsions		7.1	0.4		4.7
Compulsive buying		12.9	0.4		10.6
Any impulse control				3.0	
Tourette's syndrome	3.9	2.4	3.0	2.1	2.4
Tic disorder NOS			16.0	1.5	
Asperger's syndrome	2.7				

in the general population, as du Toit et al. (2001) note, it is difficult to make comparisons for many OC spectrum disorders because prevalence rates for these disorders in the general population are unavailable. In du Toit et al.'s (2001) study, OCD patients tended to have higher prevalence rates for anorexia and bulimia nervosa, hypochondriasis, TS, trichotillomania, and compulsive buying. Denys et al. (2004a) found that eating disorders were eight times more prevalent in individuals with OCD compared to the general population. Also of note is LaSalle et al.'s (2004) finding that individuals with OCD had a lifetime prevalence rate of 2.7% for Asperger's syndrome. Although definite data on the prevalence of Asperger's syndrome is lacking, this rate is well above current estimates, which are approximated to be 2.5/10,000 (Fombonne, 2003).

It should be noted that until recently most research investigating the prevalence rate of OC spectrum disorders in OCD has focused on specific spectrum disorders and some of these studies have found higher prevalence rates than those reported in the studies just described. Moreover, studies investigating OCD in individuals with primary OC spectrum disorder diagnoses have also found higher prevalence rates. For example, in a large sample of patients with body dysmorphic disorder, Gunstad and Phillips (2003) found a lifetime OCD prevalence rate of 30%. Higher comorbidity rates between OCD and some eating disorders have also been found. One clinical investigation found that 37% of patients with anorexia met lifetime diagnostic criteria for OCD (compared to only 3% of those with bulimia nervosa) (Thornton and Russell, 1997).

In summary, comorbidity studies suggest a possible relationship between OCD and at least some of the putative OC spectrum disorders (i.e., somatoform disorders, some impulse control disorders, TS, and possibly Asperger's syndrome). Some studies however have yielded divergent findings. Jaisoorya et al. (2003) did not find evidence of increased prevalence rates for eating and impulse control disorders in patients with primary OCD; however, these disorders were rare among healthy control participants and, as the authors note, cross-cultural variation in the prevalence rate of these disorders may have been a factor. The heterogeneous nature of OCD may also contribute to inconsistent findings. Specifically, it may be that some OCD subtypes have distinct comorbidity patterns. For example, the prevalence rate of TS was fairly low in the investigations described here, however, a longitudinal study investigating 101 children with TS, found that 50% of patients had comorbid OCD, and an additional 8% subsequently developed OCD during the observation period of the study (Park et al., 1993). Indeed, as Grados et al. (2003) and others have suggested, childhood OCD (which tends to be of the tic-related subtype) and TS may share a common genetic vulnerability. This may also apply to pathological gambling. The studies described here did not find evidence for an increased prevalence rate of pathological gambling in OCD, and other investigations have been conflicting in this regard (see Hollander et al., 2005a). Hollander et al. (2005a) speculate that a specific OCD sub-type with comorbid attention deficit hyperactivity disorder may be at increased risk for comorbid impulse control disorders like pathological gambling compared to other OCD sub-types.

Although comorbidity studies are informative, the conclusions that can be drawn from them are limited—especially with respect to the classification of OCD. Perhaps one of the most important issues concerns comparisons with appropriate control groups. To make a compelling case for the classification of OCD as an OC spectrum disorder, it would be necessary to show not just that OCD is highly comorbid with OC spectrum disorders, but that the relationship between OCD and OC spectrum disorders differs from the relationship between other anxiety disorders and OC spectrum disorders. If there is a shared etiology between OCD and OC spectrum disorders, then OC spectrum disorders should be more prevalent in OCD than in other anxiety disorders. Richter et al. (2003) addressed this question in a study investigating the lifetime prevalence of OC spectrum disorders in three groups of patients characterized by a primary diagnosis of OCD, panic disorder, or social phobia. Results revealed that compared to the panic disorder and social phobia groups, the OCD group had a greater number of individuals (37%) suffering from any (clinical or subclinical) lifetime spectrum disorder, and individuals in the OCD group were affected by a greater number of spectrum conditions. Although there were no group differences in the proportion of individuals in each group having a history of one spectrum condition, the OCD group had a greater number of individuals suffering from multiple lifetime spectrum conditions (15% for OCD compared to 2% and 1% for panic disorder and social phobia, respectively).

5. Is OCD an anxiety disorder? Family studies

In addition to showing evidence of high comorbidity rates, a unique relationship between OCD and one or more other disorders would be supported by evidence showing increased prevalence of the disorder(s) in relatives of patients with OCD.

5.1. OCD and anxiety disorders

Nestadt et al. (2001) reported results from the Johns Hopkins OCD Family Study, a blind, controlled investigation of the familial relationship between OCD and anxiety and affective disorders. There were 80 case and 73 control probands and 343 case and 300 control relatives. As previously noted, case probands had higher rates of all anxiety and affective disorders compared to control probands. Case relatives also had higher rates of GAD, panic disorder, agoraphobia, separation anxiety disorder, and recurrent MDD compared to control relatives. Importantly, panic disorder, separation anxiety disorder, and recurrent MDD occurred more frequently if the relative was diagnosed with OCD, whereas GAD and agoraphobia occurred more frequently in case relatives independent of OCD. The authors suggest that a possible familial relationship may exist between OCD and GAD and agoraphobia, whereas other anxiety disorders that co-occur with OCD likely result as a consequence of OCD. The findings from this study are consistent with an earlier

investigation by Black et al. (1995), which suggested a possible shared etiology between OCD and GAD.

Carter et al. (2004) also report findings from a large, blind, controlled family study investigating OCD and anxiety and affective disorders. Overall, the prevalence rate of OCD was elevated in case relatives compared to control relatives. In contrast to Nestadt et al. (2001), there were no differences between case and control relatives in the prevalence rates of other anxiety disorders or of MDD. Importantly, rates of panic disorder, GAD, and MDD were elevated only if the case relative had clinical or subclinical OCD, suggesting that these disorders may result as a consequence of OCD. In contrast to Nestadt et al. (2001) and Black et al. (1995), these findings question the notion of a shared etiology between OCD and GAD.

5.2. OCD and OC spectrum disorders

There is some evidence suggesting that OCD may have a familial–and possibly genetic–relationship with some OC spectrum disorders. Drawing upon data collected from the Johns Hopkins OCD Family Study, Bienvenu et al. (2000) investigated the relationship between OCD and hypochondriasis, body dysmorphic disorder, anorexia and bulimia nervosa, pathological grooming conditions (i.e., trichotillomania, pathological excoriation, and nail biting), and impulse control disorders (i.e., kleptomania, pathological gambling, and pyromania). Case probands had elevated prevalence rates of body dysmorphic disorder, hypochondriasis, anorexia and bulimia nervosa, and grooming disorders. With respect to first-degree relatives, elevated prevalence rates were found for hypochondriasis, body dysmorphic disorder, and all grooming disorders compared to relatives of control probands. Notably, these conditions occurred more frequently regardless of whether or not the OCD proband had the same disorder, lending support to a possible spectrum relationship between these disorders and OCD. Eating and impulse control disorders were not more prevalent in case than in control relatives.

Although the results from Bienvenu et al. (2000) are consistent with an earlier study conducted by Black et al. (1994), which found no evidence for increased lifetime prevalence of eating disorders (anorexia and bulimia nervosa combined) or pathological gambling in first-degree relatives of OCD probands, other studies have found evidence for a familial link between some eating disorders and OCD or obsessive–compulsive personality disorder (OCPD). Bellodi et al. (2001) found an increased morbidity risk for OC spectrum disorders (i.e., OCD and tic disorders) in first-degree relatives of eating disorder probands, suggesting a common etiology among these disorders. Moreover, the risk for developing these OC spectrum disorders was independent of whether the eating disordered proband had received a diagnosis of the disorder. By contrast, Lilenfeld et al. (1998) did not find evidence for a common etiological relationship between eating disorders and OCD (i.e., OCD was transmitted independently from eating disorders in relatives), but did find evidence of increased risk of OCPD in relatives of anorexic probands, suggesting a possible shared familial transmission of these two disorders.

There is also evidence that neurologically based OC spectrum disorders may have a familial relationship with OCD. The lifetime prevalence of TS and tic disorders (e.g., transient tic disorder, and chronic motor and vocal tics) has been found to be greater in relatives of OCD patients compared to relatives of controls (Grados et al., 2001). Hollander et al. (2003a) found that parents of autistic children who scored high on the repetitive behaviors domain were more likely to have OCD or obsessive–compulsive spectrum traits than parents of autistic children who scored lower on this domain. Moreover, a study of multiplex autism families found that the strongest evidence for concordance of linked loci on chromosome 1 occurred in a subset of families most severely affected with obsessive–compulsive behaviors (Buxbaum et al., 2004). Other evidence for a genetic relationship between OCD and some OC spectrum disorders comes from animal studies. Greer and Capecchi (2002) found that mutations on the hoxb8 gene in mice were associated with excessive grooming and hair removal—behaviors that are characteristic of trichotillomania. Furthermore, these researchers suggest that the fact that the hoxb8 gene is expressed in regions of the central nervous system known as the OCD circuit point to the possibility that trichotillomania and OCD have common neurobiological substrates.

To summarize, studies suggest that most anxiety disorders and affective disorders do not have a familial relationship with OCD. The relationship between GAD and OCD, however, is less clear: two studies found evidence supporting a familial relationship, whereas one study did not. With respect to a familial relationship between OCD and OC spectrum disorders, research suggests a shared etiology between OCD and hypochondriasis, body dysmorphic disorder, and grooming disorders. There is also evidence for a familial relationship between OCD and such neurologically based OC spectrum disorders as TS, other tic disorders, and autism (especially in cases involving a high degree of repetitive behaviors). Evidence for a familial relationship between OCD and eating disorders is mixed. As discussed, focusing on specific OCD sub-types may clarify some of the conflicting findings from family studies.

Along these lines, Nestadt et al. (2003) employed latent class analysis to identify OCD related subgroups based on comorbidity. Analyses revealed a four-class structure. The first three classes consisted of (1) minimal disorder, (2) predominant GAD and recurrent major depressive disorder, and (3) highly comorbid; these classes were theorized to reflect a common pathology, differing only in degree of severity. By contrast, the forth class, which consisted of panic disorder or agoraphobia, tic disorders, and separation anxiety disorder was thought to be qualitatively distinct. Based on the findings from this investigation, the authors propose two distinct OCD subtypes with different etiologies.

6. Is OCD an anxiety disorder? Neurocircuitry

6.1. The neurocircuitry of OCD

Drawing upon functional neuroimaging data and earlier theorizing, Saxena and Rauch (2000) put forward a model for

the pathophysiology of OCD that points to dysfunction in orbitofrontal–subcortical circuitry. This circuitry is thought to be comprised of a direct and an indirect pathway, both of which originate in the frontal cortex and project to the striatum. From the striatum, however, the direct pathway projects to the globus pallidus interna/substantia nigra, pars reticulate (GPi/SHr) complex–the primary output location of the basal ganglia–and back to the cortex. This pathway is thought to facilitate complex motor programs by activating the thalamic system. By comparison, the indirect pathway projects to the globus pallidus externa, the subthalamic nucleus, globus pallidus-substantia nigra pars reticula, thalamus, and back to the cortex. This pathway is thought to suppress complex motor programs by inhibiting activation of the thalamus. It is theorized that these pathways balance each other out in healthy individuals, but that there is a bias in favor of the direct pathway in OCD patients, leading to increased activity in the orbitofrontal cortex, ventromedial caudate, and medial dorsal thalamus, resulting in characteristic obsessions and compulsions (Saxena and Rauch, 2000).

In general, research supports involvement of the corticostriatal–thalamocortical neural circuit in OCD. Functional imaging studies have implicated the orbitofrontal cortex, caudate nucleus, thalamus, and anterior cingulate gyrus in OCD (Saxena et al., 1998; also see Saxena and Rauch, 2000; Saxena et al., 2001; Whiteside et al., 2004, for reviews). However, some inconsistencies have been noted. Recently, Whiteside et al. (2004) conducted a meta-analysis investigating 13 functional neuroimaging (positron emission tomography and single-photon emission computerized tomography) studies in OCD and found consistent differences between OCD patients and healthy controls in the orbital gyrus and head of the caudate nucleus. By contrast, no consistent differences were found across studies for the orbitofrontal cortex, caudate nucleus, or other regions previously investigated (i.e., frontal cortex, parietal, left temporal, right temporal, anterior cingulate, or thalamus). Although these findings only partially support the model outlined by Saxena and Rauch (2000), as the authors note, this meta-analysis was limited by the small number of studies included and by the methodology used in those studies, which may have made it difficult to identify regions of interest for comparison.

In addition to frontal–striatal circuitry, some research has found limbic system activation in OCD. Following symptom provocation, Breiter et al. (1996) found that individuals with OCD exhibited significant amygdala activation in addition to activation in the medial orbitofrontal, lateral frontal, anterior temporal, anterior cingulate insular cortex, and caudate. Although activation of the limbic system is consistent with the anxiety and fear that individuals with OCD often experience, as the authors acknowledge, the paralimbic and limbic findings in this study were more prominent then those found in other investigations.

6.2. The neurocircuitry of anxiety disorders

Whereas dysfunction in the frontal–striatal circuitry is implicated in the pathophysiology of OCD, a "fear neurocircuitry" centering on the amygdala has been postulated in the pathophysiology of many anxiety disorders (Charney, 2003; Kent and Rauch, 2003). Specifically, amygdala is thought to be involved in coordinating autonomic and behavioral responses to fear because of its role in assessing the emotional significance of stimuli and its involvement in the development of memories related to emotion. Multiple prefrontal cortical structures are thought to play a role in modulating anxiety by providing feedback to the amygdala. As Kent and Rauch (2003) explain, the medial prefrontal cortex is thought to play a role in attenuating fear responses and in extinguishing responses to fear-conditioned stimuli (e.g., by alerting the amygdala when the threat of danger has passed or when the importance of a feared stimulus has changed). Finally, the hippocampus is also thought to be involved in some anxiety disorders because of its role in contextual fear conditioning.

PTSD is thought to reflect a fear-conditioned response involving emotional learning circuitry associated with the amygdala and the failure of such prefrontal structures as the anterior cingulate and prefrontal cortex to extinguish fear-conditioned responses (Charney, 2003). The hippocampus is also implicated in PTSD because of its role in contextual fear conditioning. A number of investigations have found evidence of amygdala hyper-responsivity as well as diminished activity in the medial prefrontal structures in PTSD (Kent and Rauch, 2003). For example, Shin et al. (2005) showed fearful (versus happy) faces to individuals with PTSD and found evidence of exaggerated amygdala response and deficient medial prefrontal cortex responses, illustrating the functional relationship between the amygdala and the medial prefrontal cortex in PTSD. With respect to the hippocampus, numerous studies have found evidence of decreased hippocampal volume in PTSD patients compared to healthy controls (Bremner et al., 1997; Gurvits et al., 1996; Wignall et al., 2004; Winter and Irle, 2004).

Panic disorder is associated with sudden episodes of panic that often strike without warning. Again, amygdala hypersensitivity and a failure of cortical circuitry to effectively govern the amygdala are implicated in panic disorder. In addition, similar to PTSD, hippocampal structures also appear to play a role in panic disorder. Imaging studies investigating individuals with panic disorder at rest have found abnormalities in cerebral blood flow and glucose metabolism in the hippocampus and parahippocampal gyrus (Reiman et al., 1984; Nordahl et al., 1990; Bisaga et al., 1998; De Cristofaro et al., 1993). Symptom provocation studies have found increases in cerebral blood flow in the anterior insula, the anteromedial cerebellum and midbrain (Reiman et al., 1989). Provocation studies have also found evidence of abnormal global cerebral blood flow in panic disorder (Stewart et al., 1988; Ponto et al., 2002). Some research suggests that the periaqueductal gray (PAG) may be involved in panic disorder because of the important role the PAG plays in fear-potentiated startle, a paradigm that has been used to model the neurobiological processes involved in panic disorder. Stimulating the dorsal PAG has been found to elicit fear behaviors and autonomic arousal (Jenck et al., 1995), whereas lesions to this area have been found to thwart fear-potentiated startle (Fendt et al., 1996). Finally, although the

amygdala is thought to be involved in panic disorder; to date, only a few studies support amygdala involvement in this disorder. Massana et al. (2003) found that patients with panic disorder had smaller left- and right-sided amygdalar volumes compared to healthy controls.

Currently, there is little research supporting a specific pathophysiological model for simple phobias. However, one study suggests an area of overlap between phobic responses and those found in OCD. A study investigating animal phobias found increased blood flow to areas associated with other anxiety states (e.g., lateral orbital/anterior insular cortex, the pregenual anterior cingulate and the anteromedial cerebellum) following the initial presentation of a feared stimulus; however, upon habituation, whereas the magnitude of the response diminished in the insula and medial cerebellum, it increased in the left posterior orbitofrontal cortex (Drevets et al., 1995). Interestingly, increased blood flow in this region has also been found in OCD patients in response to phobic stimuli (Rauch et al., 1994). Recently, Straube et al. (2004) found increased activation in the prefrontal cortex, insula, and posterior cingulate cortex in phobic subjects in response to phobic words, suggesting a possible neural network for processing threatening stimuli.

More research has focused on social phobia than on simple phobia. It is believed that social phobia also involves the fear network—that is, the amygdala, hippocampal region, and prefrontal cortex (Tillfors, 2004). Compared to healthy controls, individuals with social anxiety disorder have been found to evidence increased amygdala responsivity following presentation of facial stimuli (Birbaumer et al., 1998). In a symptom provocation paradigm (i.e., public speaking), individuals with social anxiety disorder had significantly greater regional cerebral blood flow in the right amygdala and periamygdaloid cortex, but decreased regional cerebral blood flow in the orbitofrontal and insular cortices and temporal pole compared to healthy controls (Tillfors et al., 2001). As Kent and Rauch (2003) note, while this pattern is similar to the fear neurocircuitry model in which subcortical activity is increased and frontal cortical activity is decreased, social anxiety disorder may reflect increased sensitivity in a specialized system (i.e., threat assessment in the context of social cues).

To date, there have been only a handful of neuroimaging studies investigating GAD, and the neurocircuitry associated with this disorder is yet to be defined. Wu et al. (1991) found increased metabolism in parts of the occipital, temporal, and frontal lobes, and decreased activity in the basal ganglia, which were reversed following treatment with benzodiazepine therapy. Of note was the fact that, in contrast to some other anxiety disorders, no asymmetry was found in the hippocampus. Recently, Mathew et al. (2004) found evidence of asymmetric increases in the *N*-acetylaspartate/creatine ratio in the prefrontal cortex in GAD patients, suggesting a possible marker of neuronal viability. Finally, Hoehn-Saric et al. (2004) investigated the effects of citalopram on worry and brain activation in GAD patients and found that worry statements (compared to neutral statements) elicited greater brain activation in the prefrontal and thalamo-striatal regions prior to treatment. These regions are associated with evaluating and responding to threatening information, and have been implicated in OCD. This study had a small sample size and no control group, so limited conclusions can be drawn.

In summary, overall, research suggests that the pathophysiology of OCD differs from that of other anxiety disorders. OCD is thought to involve dysfunction in the frontal–striatal circuitry, whereas pathophysiological models of anxiety disorders point to the amygdala and associated fear neurocircuitry. Research findings indicate abnormalities in the orbitofrontal cortex, caudate nuclei, and the thalamus in OCD. By contrast, the amygdala, the hippocampus (in some instances), and such governing prefrontal cortical structures as the medial prefrontal cortex are implicated in anxiety disorders. There is also evidence that the dorsal PAG may be involved in some anxiety disorders, in particular, panic disorder. Nevertheless, there are areas of overlap. For example, some research supports involvement of the amygdala in OCD, and some anxiety disorders have been found to involve regions associated with OCD (e.g., increased activation in the left posterior orbitofrontal cortex in simple phobia and in the prefrontal and thalamo-striatal regions in GAD).

6.3. The neurocircuitry of OC spectrum disorders

Although relatively few neuroimaging studies have been conducted on OC spectrum disorders, some parallels have been found with OCD, in particular, alterations of the basal ganglia. Below is a brief review of the findings from these studies (the reader is referred to Hollander et al., 2005a, for an in-depth discussion of the neurocircuitry of the OC spectrum disorders). Peterson et al. (2003) found evidence of decreased caudate volume in both children and adults with TS, and decreased putamen and globus pallidus volume in adults with TS. Basal ganglia dysfunction has also been implicated in autism. Research has found evidence of enlarged caudate volume in autistic patients; moreover, ritualistic behavior (but not social or communication) was correlated with caudate volume (Sears et al., 1999). Hollander et al. (2005d) also found evidence of increased right caudate volume in autistic subjects, and found a positive correlation between the severity of repetitive behaviors and right caudate and putamen volumes. Other OC spectrum disorders have also been associated with basal ganglia abnormalities. Rauch et al. (2003) found evidence of a leftward shift in the caudate nucleus asymmetry as well as increased total white matter volume in body dysmorphic disorder patients compared to a control group. Basal ganglia abnormalities have also been implicated in some eating disorders. One study found that girls with anorexia nervosa had antiputamen antibody levels greater than two standard deviations above the mean (Harel et al., 2001).

7. Is OCD an anxiety disorder? Neurotransmitter function and pharmacologic treatment response

A number of neurotransmitter systems have been implicated in anxiety disorders, in particular monoaminergic transmitters

(i.e., norepinephrine, serotonin, and dopamine), amino acid transmitters (i.e., gamma aminobutyric acid (GABA) and glutamate), and peptidergic neurotransmitters (i.e., corticotrophin releasing hormone (CRH), neuropeptide Y, and substance P) (Charney, 2003). Evidence for the role of specific neurotransmitters is supported by neurochemical, pharmacologic, and neuroimaging clinical investigations and by animal models.

7.1. OCD

The primary neurotransmitters thought to be involved in OCD are serotonin and dopamine (Goodman et al., 1990a; Harvey et al., 2002). Most of the evidence supporting the role of serotonin in OCD comes from treatment studies pointing to the antiobsessional effects of selective serotonin reuptake inhibitors (SSRIs). Indeed, SSRIs are the first line in the pharmacological treatment of OCD (Kaplan and Hollander, 2003). Studies investigating serotonin receptor function also provide evidence for the role of this neurotransmitter in OCD. Zohar et al. (1987) found that OCD patients experienced an increase in obsessive–compulsive symptoms following administration of meta-chlorophenylpiperazine (mCPP), a serotonin 5-HT2c and 5-HT1d agonist. Similarly, Hollander et al. (1992) found that OCD patients experienced a worsening of symptoms following mCPP administration, and Stein et al. (1999) found that administration of sumatriptan, also a 5-HT1d agonist, showed a worsening of symptoms. More recently, Adams et al. (2005) found evidence of increased 5-HT2A receptor binding in the caudate nuclei of untreated OCD patients. These researchers speculate that the upregulation of 5-HT2A receptors may occur to compensate for deficient serotonin in the feedback loop between the thalamus, orbitofrontal cortex, caudate nuclei, and globus pallidus.

Dopamine is also thought to play a role in OCD. In their recent review, Denys et al. (2004b) cite evidence from clinical treatment and neuroimaging studies supporting the role of dopamine in OCD. For example, although anti-psychotics alone have not been found to be effective in treating OCD–and indeed have even been found to induce OCD symptoms in psychotic disorders–research suggests that anti-psychotics used in combination with SSRIs can be helpful. For example, McDougle et al. (1994) found that tic-related OCD patients who did not respond to SSRIs benefited from dopaminergic augmentation. Neuroimaging studies also support the involvement of dopamine in OCD. van der Wee et al. (2004) found evidence of enhanced dopamine transporter density in the left caudate and left putamen in OCD patients compared to a control group. Dopamine is also implicated in studies using putative animal models. Szechtman et al. (1998) and Tizabi et al. (2002) found evidence for the development of compulsive checking behaviors in rats following treatment with the dopamine D2/D3 receptor agonist quinpirole.

Finally, a number of indirect findings point to the possible role of some neuropeptides in OCD. As McDougle et al. (1999) summarize: animals studies have found a marked increase in grooming behaviors following the central administration of oxytocin; women with OCD often report OCD onset or a worsening of OCD symptoms following pregnancy (a period during which central oxytocin levels are know to increase); evidence of increased CSF oxytocin levels have been found in an adult OCD subgroup (non-tic-related) compared to adults with tic-related OCD; and, finally, the oxytocin system has extensive interactions with the 5-HT and dopamine systems, which are known to be disrupted in OCD. That said, the specific role that oxytocin plays in OCD is unclear. In addition to oxytocin, McDougle et al. (1999) postulate that adrenocorticotropic hormone and corticotrophin releasing factor may be involved in the pathological cleaning behavior evidenced by some OCD patients, given the evidence for the link between these neuropeptides and grooming behavior in animals.

7.2. Anxiety disorders

The hypothalamic–pituitary–adrenal (HPA) axis and serotonergic system have primarily been implicated in PTSD. One study found that PTSD patients showed greater cortisol suppression following the administration of low doses of dexamethasone than did healthy control subjects, suggesting enhanced negative feedback sensitivity of the HPA axis in PTSD (Yehuda et al., 1993). However, over the years, studies investigating HPA axis in PTSD have produced a number of different findings (see Rasmusson et al., 2003, for a review and discussion), thus the precise nature of the abnormalities have yet to be specified. Dysregulation of the catecholamine neurotransmitter system has also been suggested in relation to PTSD (Yehuda et al., 1998). PTSD is responsive to a range of medications including tricyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, SSRIs, and some anticonvulsants (Ballenger, 1999; Albucher and Liberzon, 2002).

A number of neurotransmitters have been implicated in panic disorder, including serotonin, norepinephrine, GABA, and glutamate (Westenberg and Liebowitz, 2004; Uys et al., 2003). Charney et al. (1984) found evidence of increased sensitivity to administration of α_2-adrenoreceptor antagonists in panic disorder patients. Research has found that serotonin receptor agonists may cause increased anxiety, and increased cortisol and prolactin levels in panic disorder patients compared to healthy controls (Targum and Marshall, 1989). Moreover, evidence of reduced 5-HT1A receptor binding has been reported in panic disorder patients (Neumeister et al., 2004). Maron et al. (2004) also found evidence of decreased 5-HTT binding in the midbrain, temporal lobes, and thalamus in panic disorder patients. GABA has also been implicated in panic disorder: benzodiazepine agonists, which increase GABA, have been found to reduce panic, whereas antagonists have led to increased subjective anxiety ratings and actual panic attacks in panic disorder patients but not in healthy controls (Nutt et al., 1990). (Although some subsequent studies failed to replicate this finding, as Lydiard (2003) points out, this failure to replicate may have been due to methodological differences). Goddard et al. (2004) found evidence of reduced GABA neuronal response following acute benzodiazepine administration in panic disorder patients, and suggested the possibility of a

trait-like abnormality in neuronal function. Neuropeptide cholecystokinin receptor agonists have also been found to induce panic in panic disorder patients (Bradwejn et al., 1991), whereas it has been suggested that antagonists may reduce this effect (Bradwejn et al., 1994). Finally, fear-potentiated startle has been found to be sensitive to such glutamate agonists as *N*-methyl-D-asparate (Anthony and Nevins, 1993). Tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, and some benzodiazepines have been found to be effective in treating panic disorder (Sheehan, 1999; Ballenger, 1999).

Dopamine and serotonin have been implicated in the pathophysiology of (generalized) social anxiety disorder (Stein et al., 2002; Westenberg and Liebowitz, 2004). Pallanti et al. (1999) reported evidence for the development of social anxiety disorder in schizophrenic patients following treatment with the neuroleptic clozapine, a dopamine antagonist. Other evidence for the role of dopamine comes from the high rate of social anxiety in patients with Parkinson's disease (which is associated with low levels of dopamine in the striatum) compared to the general population (Richard et al., 1996). As Westenberg and Liebowitz (2004) note in their review, altered dopamine transporter density in the basal ganglia has also been found in patients with social anxiety disorder (although the precise mechanism is unclear), supporting the involvement of dopamine in social anxiety disorder. Serotonin has also been implicated in this disorder: SSRIs have been found to decrease social submissiveness in non-human primates (Raleigh et al., 1985), and healthy controls have been reported to evidence increased sociability following long-term SSRI treatment (Knutson et al., 1998). Hollander et al. (1998) also reported that partial serotonin receptor agonists may induce increased cortical response in patients with social anxiety disorder compare to controls. Benzodiazepines, buspirone, and SSRIs have all been found to be effective in treating social anxiety disorder (Ballenger, 1999).

Altered functions of the GABAergic and serotonergic systems have been implicated in GAD (Jetty et al., 2001; Uys et al., 2003). Specifically, GABA receptor dysfunction may predispose people to the development of GAD and/or other anxiety disorders; support for this comes from the finding that benzodiazepines are effective in treating GAD (Ballenger, 1999), and from studies that have found reduced peripheral lymphocyte benzodiazepine receptors in GAD patients (Ferrarese et al., 1990; Rocca et al., 1998). In their review, Jetty et al. (2001) cite several clinical studies supporting the role of serotonin in GAD; however, as these authors note, it is unclear whether the dysfunction is related to hyper- or hypoactivity. Treatment studies further support the role of GABA and serotonin in GAD. GAD responds to a number of pharmacological agents including benzodiazepines, buspirone, and both tricyclic and SSRI antidepressants (Ballenger, 1999).

7.3. OC spectrum disorders

Similar to OCD, serotonin and/or dopamine appears to play a role in a number of OC spectrum disorders; below we highlight some of these findings (again, for a more comprehensive discussion, see Hollander et al., 2005a). Research by Chugani (2002) suggests that a serotonin deficiency may disrupt connections in the sensory cortices that take place during normal development leading to autism, and Hollander et al. (2000a) found evidence pointing to serotonin receptor dysfunction in autism. Serotonin is also implicated in eating disorders. Ramacciotti et al. (2003) found evidence of decreased 5-HT activity in eating disordered patients compared to controls, and Hu et al. (2003) found a link between excessive dieting and heightened 5-HT2c receptor sensitivity. Moreover, the strength of this association was found to be a function of the Ser23cys polymorphism, suggesting that individuals with that allele may have a predisposition to develop and be at risk for increased severity of anorexia nervosa (Hu et al., 2003).

Abnormal serotonin, dopamine, and noradrenergic neurotransmission are implicated in pathological gambling (Goudriaan et al., 2004). Deficiencies in 5-HT are suggested by studies that have found decreased platelet monoamine oxidase B activity in pathological gamblers (DeCaria et al., 1996; Blanco et al., 1996). Stojanov et al. (2003) found evidence of disrupted sensory motor gating on measures of pre-pulse inhibition, suggesting possible increased endogenous dopamine activity. Bergh et al. (1997) found evidence of decreased dopamine and increased 3,4-dihydroxyphenylacetic acid and homovanilic acid in pathological gamblers compared to controls. In contrast, Meyer et al. (2004) found that problem-gamblers had higher dopamine levels during a casino gambling game compared to non-problem gamblers. Other studies suggest that dopamine may be involved in the development of problem gambling behavior. A recent study investigating patients with unipolar depression found reduced sensitivity to reward in a gambling game following acute phenylalanine and tyrosine depletion (a dietary intervention that selectively lowers dopamine synthesis) (Roiser et al., 2005). Moreover, three cases have been reported in which Parkinson's patients (with no prior history of gambling) developed pathological gambling in response to dopamine replacement therapy or dopamine agonist treatment (Avanzi et al., 2004; Seedat et al., 2000). Researchers are beginning to examine dopamine dysfunction in other OC spectrum disorders. A recent PET study found increased putamen dopamine release in TS patients compared to controls following intravenous injections of amphetamine, which enhances dopamine release and blocks dopamine reuptake (Singer et al., 2002).

Oxytocin may be another area of overlap between OCD and some OC spectrum disorders. As noted, oxytocin may play a role in the compulsive and repetitive behaviors associated with OCD (McDougle et al., 1999). Insel et al. (1999) theorized that the neuropeptides oxytocin and vasopressin may contribute to the repetitive behaviors and social deficits found in autism. Supporting this idea, Hollander et al. (2003b) found a significant reduction in repetitive behaviors in individuals with autism spectrum disorders following oxytocin infusion. Although the oxytocin theory is intriguing, further research is needed to confirm and elucidate the role of this complex neuropeptide in OCD as well as in other such OC spectrum disorders as autism.

Treatment studies also support the role of serotonin and dopamine in some OC spectrum disorders. Placebo-controlled and open-label studies have found SRIs to be effective in the treatment of both adults and children with autism (McDougle et al., 1996; Hollander et al., 2000a,b). Preliminary evidence from pilot open label and double-blind, placebo controlled studies suggests that SRIs are effective in treating pathological gambling (Zimmerman et al., 2002; Hollander et al., 2000b; Kim et al., 2002); however, SRIs may not be the best course if there is comorbidity with ADHD and/or mood instability, in which case sustained-release lithium carbonate may be more effective (Hollander et al., 2005c). A number of open label and placebo-controlled studies have investigated SRIs in the treatment of compulsive shopping; however, to date, results have been mixed (see Hollander et al., 2005a, for a review). Patients with body dysmorphic disorder appear to respond well to SRIs (Hollander et al., 1999) and preliminary evidence from an open label study suggests that patients with hypochondriasis may also respond to SRI treatment (Fallon et al., 1993). Studies investigating SRIs in the treatment of anorexia nervosa have been mixed. In a double-blind, placebo-controlled study, Kaye et al. (2001) found evidence of increased weight gain in anorexic patients following treatment with fluoxetine. Other studies, however, have not found weight gain following SRI treatment but have found evidence that SRIs can alleviate other symptoms including depression and impulsiveness (Fassino et al., 2002; Santonastaso et al., 2001). A number of studies have found positive effects for several different SRIs in the treatment of binge eating disorder (see Hollander et al., 2005a, for a review). Finally, as noted, atypical antipsychotics that block postsynaptic dopamine transmission can be an effective augmentation strategy to SRIs in treating OCD (McDougle et al., 2000). A similar strategy has been found to be effective with some OC spectrum disorders, in particular, trichotillomania and TS (Stein et al., 1997; Scahill et al., 2003).

In summary, OCD is associated with dysregulation of the dopaminergic and serotonergic systems. With the exception of social anxiety disorder, there is little evidence of dopamine dysregulation in other anxiety disorders. Rather, other anxiety disorders–in particular, panic disorder and GAD–are characterized by GABA dysregulation. Moreover, all of the anxiety disorders except OCD respond to benzodiazepines, which are GABA agonists. With respect to serotonin, dysregulation of the serotonergic system and a preferential response to SSRIs was characteristic of both OCD and the other anxiety disorders. Along similar lines, although not a primary focus of this article, OCD and most other anxiety disorders respond to cognitive behavioral therapy and such techniques as exposure and response prevention and cognitive restructuring (Ballenger, 1999). This commonality in treatment could be taken as support for the notion that OCD and the other anxiety disorders involve many of the same psychological mechanisms and comprise a single continuum (cf. Ballenger, 1999). However, although most anxiety disorders respond to SSRIs, they also respond to other pharmacological agents, whereas SSRIs are needed at a minimum for the treatment of OCD and some OC spectrum disorders. Moreover, several studies have found that pharmacological agents that are effective in treating other anxiety disorders (e.g., norepinephrine reuptake inhibitors) are ineffective in treating OCD (Goodman et al., 1990b; Thoren et al., 1980). We believe that a shared treatment response in and of itself does not establish a unique relationship between OCD and the other anxiety disorders, and, indeed, that the selective efficacy of SSRIs in OCD argues against such a relationship.

8. Commentary

In an effort to clarify the relationship between OCD and other anxiety disorders, including PTSD, panic disorder, specific and social phobia, and GAD, this article reviewed comorbidity and family studies as well as studies investigating neurocircuitry, neurotransmitter function, and treatment response. Studies investigating comorbidity patterns between OCD and other anxiety disorders are mixed: some suggest increased prevalence rates for current and lifetime anxiety disorders in OCD, whereas others do not. Comorbidity studies alone, however, do not make a strong case for establishing an etiological relationship between two or more disorders. With respect to family studies, there is little evidence to suggest that first-degree relatives of individuals with OCD have an increased prevalence rate for other anxiety disorders (when transmitted independently from OCD). One exception to this finding is GAD, and possibly agoraphobia, but again studies are mixed and future research will be needed to resolve this question. Research focusing on OCD subtypes may be especially important in clarifying the nature of these relationships. With respect to GAD, it is interesting to note that the appropriateness of classifying GAD as an anxiety disorder has also been questioned, and some have suggested that GAD be included with the depressive disorders in the DSM-V because of similarities in pathophysiology and because GAD regularly leads to depression when left untreated.

From the perspective of neurocircuitry, neurotransmitter function, and treatment response, OCD is distinguished from other anxiety disorders. OCD is associated with frontal–striatal abnormalities and dysregulation of the serotonergic and dopaminergic systems and a selective response to SSRIs. By contrast, anxiety disorders are associated with the amygdala, hippocampus, and some pre-frontal cortical structures, and although serotonin plays a role in the other anxiety disorders, dopamine was only implicated in social anxiety disorder.

We believe OCD would be better conceptualized as an OC spectrum disorder. From a phenomenological perspective, there are more similarities between OCD and other OC spectrum disorders than between OCD and other anxiety disorders. Evidence from comorbidity studies and family studies is also accumulating to support a possible etiological relationship between OCD and at least some OC spectrum disorders. Research findings suggest frontal–striatal abnormalities in some OC spectrum disorders, in particular involving the basal ganglia, and there is some evidence for the involvement of dopamine in at least some OC spectrum disorders; these findings are preliminary, however, and more research in this area is needed.

9. Implications of changing OCD classification in the DSM-V

It is currently being proposed that OCD be removed from the anxiety disorders category in the DSM-V and clustered with other putative OC spectrum disorders. Removing OCD from the anxiety disorders category will likely highlight the distinct features of OCD and, hopefully, raise awareness about OCD, increasing the likelihood of detection and appropriate treatment. It is believed that many OCD cases go undetected because patients are embarrassed about their symptoms and, consequently, are reluctant to report them, or because patients only report vague symptoms of anxiety. As a result, the onus is on clinicians to probe for OCD. Unfortunately, clinicians are often led astray by complaints of anxiety, and do not scrutinize for OCD. Although there is overlap in the treatment of anxiety disorders and OCD, OCD patients do not respond to many common anxiety disorder treatments (e.g., benzodiazepines). Thus, if OCD goes undetected, it may likely go untreated even if anxiety symptoms are being addressed. Distinguishing OCD from other anxiety disorders may thus encourage vigilance in systematically screening for OCD when patients present with anxiety symptoms. In addition to improving diagnosis and treatment of OCD, other putative OC spectrum disorders will likely benefit from this change in classification. By understanding what drives the repetitive thoughts and behaviors in OCD, this knowledge can be applied to understanding and treating other OC spectrum disorders. More generally, linking psychiatric disorders to biological factors rather than shared symptomatology, and basing decisions about classification on these factors, stresses the notion that these are medical conditions.

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References

Adams KH, Hansen ES, Pinborg LH, Hasselbalch SG, Svarer C, Holm S, et al. Patients with obsessive–compulsive disorder have increased 5-HT2A receptor binding in the caudate nuclei. Int J Neuropsychopharmacol 2005;8:1–11.

Albucher RC, Liberzon I. Psychopharmacological treatment in PTSD: a critical review. J Psychiatr Res 2002;36:355–67.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth ed., rev. Washington, DC: Author; 2000.

Anthony EW, Nevins ME. Anxiolytic-like effects of *N*-methyl-D-aspartate-associated glycine receptor ligands in the rat potentiated startle test. Eur J Pharmacol 1993;250:317–24.

Avanzi M, Uber E, Bonfa F. Pathological gambling in two patients on dopamine replacement therapy for Parkinson's disease. Neurol Sci 2004; 25:98–101.

Ballenger JC. Current treatments of the anxiety disorders in adults. Biol Psychiatry 1999;46:1579–94.

Bellodi L, Cavallini MC, Bertelli S, Chiapparino D, Riboldi C, Smeraldi E. Morbidity risk for obsessive–compulsive spectrum disorders in first-degree relatives of patients with eating disorders. Am J Psychiatry 2001; 158:563–9.

Bergh C, Eklund T, Sodersten P, Nordin C. Altered dopamine function in pathological gambling. Psychol Med 1997;27:473–5.

Bienvenu OJ, Samuels JF, Riddle MA, Hoehn-Saric R, Liang KY, Cullen BA, et al. The relationship of obsessive–compulsive disorder to possible spectrum disorders: results from a family study. Biol Psychiatry 2000; 48:287–93.

Birbaumer N, Grodd W, Diedrich O, Klose U, Erb M, Lotze M, et al. fMRI reveals amygdala activation to human faces in social phobics. NeuroReport 1998;9:1223–6.

Bisaga A, Katz JL, Antonini A, Wright CE, Margouleff C, Gorman JM, et al. Cerebral glucose metabolism in women with panic disorder. Am J Psychiatry 1998;155:1178–83.

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;35:145–8.

Black DW, Goldstein RB, Noyes R, Blum N. Psychiatric disorders in relatives of probands with obsessive–compulsive disorder and co-morbid major depression or generalized anxiety. Psychiatr Genet 1995;5:37–41.

Blanco C, Orensanz-Munoz L, Blanco-Jerez C, Saiz-Ruiz J. Pathological gambling and platelet MAO activity: a psychobiological study. Am J Psychiatry 1996;153:119–21.

Blaszczynski A. Pathological gambling and obsessive–compulsive spectrum disorders. Psychol Rep 1999;84:107–13.

Bradwejn J, Koszycki D, Shriqui C. Enhanced sensitivity to cholecystokinin tetrapeptide in panic disorder Clinical and behavioral findings. Arch Gen Psychiatry 1991;48:603–10.

Bradwejn J, Koszycki D, Couetoux du Tertre A, van Megen H, den Boer J, Westenberg H. The panicogenic effects of cholecystokinin-tetrapeptide are antagonized by L-365,260, a central cholecystokinin receptor antagonist, in patients with panic disorder. Arch Gen Psychiatry 1994;51:486–93.

Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN, et al. Functional magnetic resonance imaging of symptom provocation in obsessive–compulsive disorder. Arch Gen Psychiatry 1996;53:595–606.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry 1997;41:23–32.

Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol 2001;110:585–99.

Buxbaum JD, Silverman J, Keddache M, Smith CJ, Hollander E, Ramoz N, et al. Linkage analysis for autism in a subset of families with obsessive–compulsive behaviors: evidence for an autism susceptibility gene on chromosome 1 and further support for susceptibility genes on chromosome 6 and 19. Mol Psychiatry 2004;9:144–50.

Carter AS, Pollock RA, Suvak MK, Pauls DL. Anxiety and major depression comorbidity in a family study of obsessive–compulsive disorder. Depress Anxiety 2004;20:165–74.

Cath DC, Spinhoven P, Hoogduin CA, Landman AD, van Woerkom TC, van de Wetering BJ, et al. Repetitive behaviors in Tourette's syndrome and OCD with and without tics: what are the differences? Psychiatry Res 2001; 101:171–85.

Charney DS. Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Scand 2003;417:38–50 [Suppl.].

Charney DS, Heninger GR, Breier A. Noradrenergic function in panic anxiety Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 1984;41:751–63.

Chugani DC. Role of altered brain serotonin mechanisms in autism. Mol Psychiatry 2002;7(Suppl. 2);S16–7.

Dale RC. Autoimmunity and the basal ganglia: new insights into old diseases. QJM 2003;96:183–91.

DeCaria CM, Hollander E, Grossman R, Wong CM, Mosovich SA, Cherkasky S. Diagnosis, neurobiology, and treatment of pathological gambling. J Clin Psychiatry 1996;57(Suppl. 8);S80–3 [discussion 83–84].

De Cristofaro MT, Sessarego A, Pupi A, Biondi F, Faravelli C. Brain perfusion abnormalities in drug-naive, lactate-sensitive panic patients: a SPECT study. Biol Psychiatry 1993;33:505–12.

Denys D, Tenney N, van Megen HJ, de Geus F, Westenberg HG. Axis I and II comorbidity in a large sample of patients with obsessive–compulsive disorder. J Affect Disord 2004a;80:155–62.

Denys D, Zohar J, Westenberg HG. The role of dopamine in obsessive–compulsive disorder: preclinical and clinical evidence. J Clin Psychiatry 2004b;65(Suppl. 14);S11–7.

Drevets WC, Burton H, Videen TO, Snyder AZ, Simpson Jr JR, Raichle ME. Blood flow changes in human somatosensory cortex during anticipated stimulation. Nature 1995;373:249–52.

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.

Eisen JL, Rasmussen SA. Phenomenology of obsessive–compulsive disorder. In: Stein DJ, Hollander E, editors. Textbook of anxiety disorders. Washington, DC: American Psychiatric Publishing; 2002. p. 173–89.

Fallon BA, Liebowitz MR, Salman E, Schneier FR, Jusino C, Hollander E, et al. Fluoxetine for hypochondriacal patients without major depression. J Clin Psychopharmacol 1993;13:438–41.

Fassino S, Leombruni P, Daga G, Brustolin A, Migliaretti G, Cavallo F, et al. Efficacy of citalopram in anorexia nervosa: a pilot study. Eur Neuropsychopharmacol 2002;12:453–9.

Fendt M, Koch M, Schnitzler HU. Lesions of the central gray block conditioned fear as measured with the potentiated startle paradigm. Behav Brain Res 1996;74:127–34.

Ferrarese C, Appollonio I, Frigo M, Perego M, Piolti R, Trabucchi M, et al. Decreased density of benzodiazepine receptors in lymphocytes of anxious patients: reversal after chronic diazepam treatment. Acta Psychiatr Scand 1990;82:169–73.

Fireman B, Koran LM, Leventhal JL, Jacobson A. The prevalence of clinically recognized obsessive–compulsive disorder in a large health maintenance organization. Am J Psychiatry 2001;158:1904–10.

Foa EB, Kozak MJ. DSM-IV field trial: obsessive–compulsive disorder. Am J Psychiatry 1995;152:90–6.

Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 2003;33:365–82.

Goddard AW, Mason GF, Appel M, Rothman DL, Gueorguieva R, Behar KL, et al. Impaired GABA neuronal response to acute benzodiazepine administration in panic disorder. Am J Psychiatry 2004;161:2186–93.

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 1990a;51:S36–43 [Suppl., discussion, 55–58].

Goodman WK, Price LH, Delgado PL, Palumbo J, Krystal JH, Nagy LM, et al. Specificity of serotonin reuptake inhibitors in the treatment of obsessive–compulsive disorder Comparison of fluvoxamine and desipramine. Arch Gen Psychiatry 1990b;47:577–85.

Goudriaan AE, Oosterlaan J, de Beurs E, Van den Brink W. Pathological gambling: a comprehensive review of biobehavioral findings. Neurosci Biobehav Rev 2004;28:123–41.

Grados MA, Riddle MA, Samuels JF, Liang KY, Hoehn-Saric R, Bienvenu OJ, et al. The familial phenotype of obsessive–compulsive disorder in relation to tic disorders: the Hopkins OCD family study. Biol Psychiatry 2001;50:559–65.

Grados MA, Walkup J, Walford S. Genetics of obsessive–compulsive disorders: new findings and challenges. Brain Dev 2003;25(Suppl. 1);S55–S61.

Greer JM, Capecchi MR. Hoxb8 is required for normal grooming behavior in mice. Neuron 2002;33:23–34.

Gunstad J, Phillips KA. Axis I comorbidity in body dysmorphic disorder. Compr Psychiatry 2003;44:270–6.

Gurvits TV, Gilbertson MW, Lasko NB, Orr SP, Pitman RK. Neurological status of combat veterans and adult survivors of sexual abuse PTSD. Ann NY Acad Sci 1996;821:468–71.

Harel Z, Hallett J, Riggs S, Vaz R, Kiessling L. Antibodies against human putamen in adolescents with anorexia nervosa. Int J Eat Disord 2001;29:463–9.

Harvey BH, Brink CB, Seedat S, Stein DJ. Defining the neuromolecular action of myo-inositol: application to obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:21–32.

Hoehn-Saric R, Schlund MW, Wong SH. Effects of citalopram on worry and brain activation in patients with generalized anxiety disorder. Psychiatry Res 2004;131:11–21.

Hollander E. Obsessive–compulsive related disorders. Washington, DC: American Psychiatric Press; 1993.

Hollander E, Wong CM. Obsessive–compulsive spectrum disorders. J Clin Psychiatry 1995;56(Suppl. 4);3–6.

Hollander E, DeCaria CM, Nitescu A, Gully R, Suckow RF, Cooper TB, et al. Serotonergic function in obsessive–compulsive disorder Behavioral and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. Arch Gen Psychiatry 1992;49:21–8.

Hollander E, Kwon J, Weiller F, Cohen L, Stein DJ, DeCaria C, et al. Serotonergic function in social phobia: comparison to normal control and obsessive–compulsive disorder subjects. Psychiatry Res 1998;79:213–217.

Hollander E, Allen A, Kwon J, Aronowitz B, Schmeidler J, Wong C, 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;56:1033–9.

Hollander E, Kaplan A, Cartwright C, Reichman D. Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report. J Child Neurol 2000a;15:132–5.

Hollander E, DeCaria CM, Finkell JN, Begaz T, Wong CM, Cartwright C. A randomized double-blind fluvoxamine/placebo crossover trial in pathologic gambling. Biol Psychiatry 2000b;47:813–7.

Hollander E, King A, Delaney K, Smith CJ, Silverman JM. Obsessive–compulsive behaviors in parents of multiplex autism families. Psychiatry Res 2003a;117:11–6.

Hollander E, Novotny S, Hanratty M, Yaffe R, DeCaria CM, Aronowitz BR, et al. Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. Neuropsychopharmacology 2003b;28:193–8.

Hollander E, Friedberg JP, Wasserman S, Yeh C-C, Iyengar R. The case for the OCD spectrum. In: Abramowitz JS, Houts AC, editors. Handbook of controversial issues in obsessive–compulsive disorder. Kluwer Academic Press; 2005a.

Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology 2005b;30:582–9.

Hollander E, Pallanti S, Allen A, Sood E, Baldini Rossi N. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am J Psychiatry 2005c;162:137–45.

Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol Psychiatry 2005d;58:226–32.

Hu X, Giotakis O, Li T, Karwautz A, Treasure J, Collier DA. Association of the 5-HT2c gene with susceptibility and minimum body mass index in anorexia nervosa. NeuroReport 2003;14:781–3.

Insel TR, O'Brien DJ, Leckman JF. Oxytocin, vasopressin, and autism: is there a connection? Biol Psychiatry 1999;45:145–57.

Jaisoorya TS, Reddy YC, Srinath S. The relationship of obsessive–compulsive disorder to putative spectrum disorders: results from an Indian study. Compr Psychiatry 2003;44:317–23.

Jenck F, Moreau JL, Martin JR. Dorsal periaqueductal gray-induced aversion as a simulation of panic anxiety: elements of face and predictive validity. Psychiatry Res 1995;57:181–91.

Jenike MA. Illnesses related to obsessive–compulsive disorder. In: Jenike MA, Baer LB, Minichiello WE, editors. Obsessive compulsive disorders: theory and management, Second ed. Year Book Medical; 1990. p. 39–60.

Jetty PV, Charney DS, Goddard AW. Neurobiology of generalized anxiety disorder. Psychiatr Clin North Am 2001;24:75–97.

Kaplan A, Hollander E. A review of pharmacologic treatments for obsessive–compulsive disorder. Psychiatr Serv 2003;54:1111–8.

Kaye WH, Nagata T, Weltzin TE, Hsu LK, Sokol MS, McConaha C, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. Biol Psychiatry 2001;49: 644–652.

Kent JM, Rauch SL. Neurocircuitry of anxiety disorders. Curr Psychiatry Rep 2003;5:266–73.

Kim SW, Grant JE, Adson DE, Shin YC, Zaninelli R. A double-blind placebo-controlled study of the efficacy and safety of paroxetine in the treatment of pathological gambling. J Clin Psychiatry 2002;63:501–7.

Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC, et al. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry 1998;155:373–9.

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; 19:163–73.

Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, et al. A controlled family study of anorexia nervosa and bulimia nervosa: psychiatric disorders in first-degree relatives and effects of proband comorbidity. Arch Gen Psychiatry 1998;55:603–10.

Lydiard RB. The role of GABA in anxiety disorders. J Clin Psychiatry 2003;64(Suppl. 3);21–7.

Maron E, Kuikka JT, Shlik J, Vasar V, Vanninen E, Tiihonen J. Reduced brain serotonin transporter binding in patients with panic disorder. Psychiatry Res 2004;132:173–81.

Massana G, Serra-Grabulosa JM, Salgado-Pineda P, Gasto C, Junque C, Massana J, et al. Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging. NeuroImage 2003;19:80–90.

Mathew SJ, Mao X, Coplan JD, Smith EL, Sackeim HA, Gorman JM, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton magnetic resonance spectroscopic imaging study. Am J Psychiatry 2004;161:1119–21.

McDougle CJ, Goodman WK, Price LH. Dopamine antagonists in tic-related and psychotic spectrum obsessive compulsive disorder. J Clin Psychiatry 1994;55:S24–31 [Suppl.].

McDougle CJ, Kresch LE, Goodman WK, Naylor ST, Volkmar FR, Cohen DJ, et al. A case-controlled study of repetitive thoughts and behavior in adults with autistic disorder and obsessive–compulsive disorder. Am J Psychiatry 1995;152:772–7.

McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996;53:1001–8.

McDougle CJ, Barr LC, Goodman WK, Price LH. Possible role of neuropeptides in obsessive compulsive disorder. Psychoneuroendocrinology 1999;24:1–24.

McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive–compulsive disorder. Arch Gen Psychiatry 2000;57:794–801.

McElroy SL, Phillips KA, Keck PE. Obsessive compulsive spectrum disorder. J Clin Psychiatry 1994;55(Suppl. 10);33–51.

Meyer G, Schwertfeger J, Exton MS, Janssen OE, Knapp W, Stadler MA, et al. Neuroendocrine response to casino gambling in problem gamblers. Psychoneuroendocrinology 2004;29:1272–80.

Nestadt G, Samuels J, Riddle MA, Liang KY, Bienvenu OJ, Hoehn-Saric R, et al. The relationship between obsessive–compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med 2001;31:481–7.

Nestadt G, Addington A, Samuels J, Liang KY, Bienvenu OJ, Riddle M, et al. The identification of OCD-related subgroups based on comorbidity. Biol Psychiatry 2003;53:914–20.

Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, et al. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci 2004;24:589–91.

Nordahl TE, Semple WE, Gross M, Mellman TA, Stein MB, Goyer P, et al. Cerebral glucose metabolic differences in patients with panic disorder. Neuropsychopharmacology 1990;3:261–72.

Nutt DJ, Glue P, Lawson C, Wilson S. Flumazenil provocation of panic attacks Evidence for altered benzodiazepine receptor sensitivity in panic disorder. Arch Gen Psychiatry 1990;47:917–25.

Pallanti S, Quercioli L, Rossi A, Pazzagli A. The emergence of social phobia during clozapine treatment and its response to fluoxetine augmentation. J Clin Psychiatry 1999;60:819–23.

Park S, Como PG, Cui L, Kurlan R. The early course of the Tourette's syndrome clinical spectrum. Neurology 1993;43:1712–5.

Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, et al. Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. Arch Gen Psychiatry 2003;60:415–24.

Ponto LL, Kathol RG, Kettelkamp R, Watkins GL, Richmond JC, Clark J, et al. Global cerebral blood flow after CO_2 inhalation in normal subjects and patients with panic disorder determined with [15O]water and PET. J Anxiety Disord 2002;16:247–58.

Raleigh MJ, Brammer GL, McGuire MT, Yuwiler A. Dominant social status facilitates the behavioral effects of serotonergic agonists. Brain Res 1985;348:274–82.

Ramacciotti CE, Coli E, Paoli R, Marazziti D, Dell'Osso L. Serotonergic activity measured by platelet [3H]paroxetine binding in patients with eating disorders. Psychiatry Res 2003;118:33–8.

Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, et al. Regional cerebral blood flow measured during symptom provocation in obsessive–compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry 1994;51:62–70.

Rauch SL, Phillips KA, Segal E, Makris N, Shin LM, Whalen PJ, et al. A preliminary morphometric magnetic resonance imaging study of regional brain volumes in body dysmorphic disorder. Psychiatry Res 2003;122: 13–19.

Reiman EM, Raichle ME, Butler FK, Herscovitch P, Robins E. A focal brain abnormality in panic disorder, a severe form of anxiety. Nature 1984; 310:683–5.

Reiman EM, Raichle ME, Robins E, Mintun MA, Fusselman MJ, Fox PT, et al. Neuroanatomical correlates of a lactate-induced anxiety attack. Arch Gen Psychiatry 1989;46:493–500.

Richard IH, Schiffer RB, Kurlan R. Anxiety and Parkinson's disease. J Neuropsychiatry Clin Neurosci 1996;8:383–92.

Richter MA, Summerfeldt LJ, Antony MM, Swinson RP. Obsessive–compulsive spectrum conditions in obsessive–compulsive disorder and other anxiety disorders. Depress Anxiety 2003;18:118–27.

Rocca P, Beoni AM, Eva C, Ferrero P, Zanalda E, Ravizza L. Peripheral benzodiazepine receptor messenger RNA is decreased in lymphocytes of generalized anxiety disorder patients. Biol Psychiatry 1998; 43:767–73.

Roiser JP, McLean A, Ogilvie AD, Blackwell AD, Bamber DJ, Goodyer I, et al. The subjective and cognitive effects of acute phenylalanine and tyrosine depletion in patients recovered from depression. Neuropsychopharmacology 2005;30:775–85.

Santonastaso P, Friederici S, Favaro A. Sertraline in the treatment of restricting anorexia nervosa: an open controlled trial. J Child Adolesc Psychopharmacol 2001;11:143–50.

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

Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal–subcortical circuitry in obsessive–compulsive disorder. Brit J Psychiatry 1998;35:26–37.

Saxena S, Bota RG, Brody AL. Brain–behavior relationships in obsessive–compulsive disorder. Semin Clin Neuropsychiatry 2001;6:82–101.

Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology 2003; 60:1130–5.

Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:613–24.

Seedat S, Kesler S, Niehaus DJ, Stein DJ. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depress Anxiety 2000;11:185–6.

Sheehan DV. Current concepts in the treatment of panic disorder. J Clin Psychiatry 1999;60(Suppl. 18);16–21.

Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 2005;62:273–81.

Singer HS, Szymanski S, Giuliano J, Yokoi F, Dogan AS, Brasic JR, et al. Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. Am J Psychiatry 2002;159:1329–36.

Stein DJ. Neurobiology of the obsessive–compulsive spectrum disorders. Biol Psychiatry 2002;47:296–304.

Stein DJ, Bouwer C, Maud CM. Use of the selective serotonin reuptake inhibitor citalopram in treatment of trichotillomania. Eur Arch Psychiatry Clin Neurosci 1997;247:234–6.

Stein DJ, Van Heerden B, Wessels CJ, Van Kradenburg J, Warwick J, Wasserman HJ. Single photon emission computed tomography of the brain with Tc-99m HMPAO during sumatriptan challenge in obsessive–compulsive disorder: investigating the functional role of the serotonin autoreceptor. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:1079–99.

Stein DJ, Westenberg HG, Liebowitz MR. Social anxiety disorder and generalized anxiety disorder: serotonergic and dopaminergic neurocircuitry. J Clin Psychiatry 2002;63(Suppl. 6);12–9.

Stewart RS, Devous Sr MD, Rush AJ, Lane L, Bonte FJ. Cerebral blood flow changes during sodium-lactate-induced panic attacks. Am J Psychiatry 1988;145:442–9.

Stojanov W, Karayanidis F, Johnston P, Bailey A, Carr V, Schall U. Disrupted sensory gating in pathological gambling. Biol Psychiatry 2003;54:474–84.

Straube T, Mentzel HJ, Glauer M, Miltner WH. Brain activation to phobia-related words in phobic subjects. Neurosci Lett 2004;372:204–8.

Szechtman H, Sulis W, Eilam D. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive–compulsive disorder (OCD). Behav Neurosci 1998;112:1475–85.

Targum SD, Marshall LE. Fenfluramine provocation of anxiety in patients with panic disorder. Psychiatry Res 1989;28:295–306.

Thoren P, Asberg M, Bertilsson L, Mellstrom B, Sjoqvist F, Traskman L. Clomipramine treatment of obsessive–compulsive disorder II Biochemical aspects. Arch Gen Psychiatry 1980;37:1289–94.

Thornton C, Russell J. Obsessive compulsive comorbidity in the dieting disorders. Int J Eat Disord 1997;21:83–7.

Tillfors M. Why do some individuals develop social phobia? A review with emphasis on the neurobiological influences. Nord J Psychiatry 2004; 58:267–76.

Tillfors M, Furmark T, Marteinsdottir I, Fischer H, Pissiota A, Langstrom B, et al. Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. Am J Psychiatry 2001;158:1220–6.

Tizabi Y, Louis VA, Taylor CT, Waxman D, Culver KE, Szechtman H. Effect of nicotine on quinpirole-induced checking behavior in rats: implications for obsessive–compulsive disorder. Biol Psychiatry 2002;51:164–71.

Tynes LL, White K, Steketee GS. Toward a new nosology of obsessive compulsive disorder. Compr Psychiatry 1990;31:465–80.

Uys JD, Stein DJ, Daniels WM, Harvey BH. Animal models of anxiety disorders. Curr Psychiatry Rep 2003;5:274–81.

van der Wee NJ, Stevens H, Hardeman JA, Mandl RC, Denys DA, van Megen HJ, et al. Enhanced dopamine transporter density in psychotropic-naive patients with obsessive–compulsive disorder shown by [123I]{beta}-CIT SPECT. Am J Psychiatry 2004;161:2201–6.

Westenberg HG, Liebowitz MR. Overview of panic and social anxiety disorders. J Clin Psychiatry 2004;65(Suppl. 14);22–6.

Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive–compulsive disorder. Psychiatry Res 2004; 132:69–79.

Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, et al. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. Biol Psychiatry 2004;56:832–6.

Winter H, Irle E. Hippocampal volume in adult burn patients with and without posttraumatic stress disorder. Am J Psychiatry 2004;161:2194–200.

Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. Biol Psychiatry 1991;29:1181–99.

Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW. Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 1993;150:83–6.

Yehuda R, Siever LJ, Teicher MH, Levengood RA, Gerber DK, Schmeidler J, et al. Plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol concentrations and severity of depression in combat posttraumatic stress disorder and major depressive disorder. Biol Psychiatry 1998;44:56–63.

Zimmerman M, Breen RB, Posternak MA. An open-label study of citalopram in the treatment of pathological gambling. J Clin Psychiatry 2002;63:44–8.

Zohar J, Mueller EA, Insel TR, Zohar-Kadouch RC, Murphy DL. Serotonergic responsivity in obsessive–compulsive disorder Comparison of patients and healthy controls. Arch Gen Psychiatry 1987;44:946–51.