Review

Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive–compulsive disorder as an example of overlapping clinical and genetic heterogeneity

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Individuals with obsessive–compulsive disorder (OCD) have also been shown to have comorbid lifetime diagnoses of major depressive disorder (MDD; rates greater than 70%), bipolar disorder (rates greater than 10%) and other anxiety disorders (e.g. panic disorder, post-traumatic stress disorder (PTSD)). In addition, overlap exists in some common genetic variants (e.g. the serotonin transporter gene (*SLC6A4*), the brain-derived neurotrophic factor (BDNF) gene), and rare variants in genes/chromosomal abnormalities (e.g. the 22q11 microdeletion syndrome) found across the affective/anxiety disorder spectrums. OCD has been proposed as a possible independent entity for DSM-5, but by others thought best retained as an anxiety disorder subtype (its current designation in DSM-IV), and yet by others considered best in the affective disorder spectrum. This review focuses on OCD, a well-studied but still puzzling heterogeneous disorder, regarding alterations in serotonergic, dopaminergic and glutamatergic neurotransmission in addition to other systems involved, and how related genes may be involved in the comorbidity of anxiety and affective disorders. OCD resembles disorders such as depression, in which gene × gene interactions, gene × environment interactions and stress elements coalesce to yield OC symptoms and, in some individuals, full-blown OCD with multiple comorbid disorders.

1. Introduction

The official classification schemes for affective, anxiety and related disorders have been marked by controversy with respect to identifying the most precise diagnostic designations. The persistent classification debate is currently highlighted in the deliberations for the upcoming DSM-5 (*Diagnostic and statistical manual of mental disorders*, fifth edition, to be released in 2013) and the recently issued ICD-10 (International classification of diseases, tenth revision). Prominent and discrete clinical features have formed the primary basis for subdividing affective and anxiety disorders, and these criteria provide valuable guides for prognosis and treatment. Some potential aetiological contributions also seem distinct for these groups of disorders and have been identified through brain imaging findings, investigations of endophenotypes and genetic studies. In contrast to these examples of distinctiveness, many studies have also underscored points of similarity and overlap between the affective and anxiety disorders. Of particular interest are the extremely high rates of comorbidity among these disorders, in addition to similar patterns of comorbidity with other classes of syndromes (e.g. substance use disorders).

The overlap between the various mood and anxiety disorders, along with disorder-specific heterogeneity, may represent one roadblock for the advancement of aetiological investigations, and this is particularly challenging for genetic studies. Increasingly, scientists are focusing on points within any given disorder that could be used to identify more homogeneous subgroups. Although this represents a laudable endeavour, greater attention in the future should be given to points of overlap *between* disorders, as this may represent another approach to identify more accurate phenotypes. This review will focus its discussion on obsessive–compulsive disorder (OCD), highlighting both clinical and genetic heterogeneity. We will discuss how this dual heterogeneity impacts the study of genes and chromosomal regions probably involved in the development of OCD. Although cross-disorder aetiological overlap has not been studied extensively, we hope that our discussion will fuel further investigations.

Specifically, we will first consider the general clinical phenomenon of OCD, highlighting points of phenotypic heterogeneity. In addition, we will discuss the genetic heterogeneity inherent in this disorder. Next, we will explore past attempts at identifying more homogeneous sub-phenotypes within OCD and OCD-related spectrum disorders. Special attention will be given to secondary phenotypes or subgroups that have recently been identified through genetic investigations. We will subsequently consider the recently nominated chromosomal regions and specific genes identified as relevant to OCD. In addition, animal models of OCD-like behaviours are discussed in terms of discovery of possible genes involved in OCD in humans. Furthermore, we describe specific problems in past research and outline recommendations for future investigations. Finally, we will discuss advances in the study of OCD genetics, including recent findings regarding both common and rare gene variants that have considered the overlap between anxiety and affective disorders, a previously neglected area.

2. Obsessive–compulsive disorder: a brief overview of phenomenological features

OCD is a debilitating, severe neuropsychiatric disorder, with an estimated lifetime prevalence of 2.5 per cent in the USA. In populations worldwide, epidemiological-based surveys have established its prevalence as 2–3%, a rate similar to that of bipolar disorder (1.6%) and over twofold more than that of schizophrenia, panic disorder or autism (approx. 1%) [1,2].

The overarching characteristic features of OCD are persistent, intrusive, senseless thoughts (obsessions) and repetitive, intentional behaviours (compulsions). Patients with this disorder generally recognize that their thoughts and behaviours are excessive and unreasonable, and they struggle to resist them, endorsing high self-ratings of anxiety and mood difficulties. Affective disorders are the most common comorbid disorder group with OCD, and they often represent the initial reason why individuals with OCD seek treatment. The difficulties, impairments and stresses experienced by individuals with OCD and their family members are considerable [3,4], and contribute to our understanding of OCD as a major public health concern.

High rates of comorbidity with other psychiatric disorders have been established as a hallmark feature of OCD [5–11] (table 1). Compared with the rates of neuropsychiatric disorders in the general US population, individuals with OCD have comorbidity rates that are two- to eightfold higher [12]. Specific comorbidity patterns have been increasingly investigated. For example, a recent investigation by our group [13] highlighted the potential overlap between the affective disorders and OCD. We found that comorbid affective disorders were present in greater than 80 per cent of individuals diagnosed with OCD ($n = 605$); 70 per cent of the samples were diagnosed with comorbid major depressive disorder (MDD) and approximately 10 per cent of the sample met criteria for bipolar disorder [6].

The period of greatest risk for OCD onset is generally from adolescence to early adulthood [14,15]; however, symptoms with associated social and behavioural impairments can occur as young as age three or in later adulthood. Our data indicate that the majority of patients experience significant symptoms before age 21, with only minor gender differences (figure 1). Of note, these data and those of others indicate a unimodal, non-normal distribution of age of OCD-related impairment [16], unlike some prior suggestions that age of OCD onset might have a bimodal pattern, with separate peaks in childhood and in adulthood [17].

With respect to stability across the lifespan, most patients with OCD experience a chronic course with waxing and waning symptoms. A smaller number endorses a more pronounced episodic course, representative of a somewhat cyclic disorder with marked exacerbations and remissions [18]. There are hints that this cyclic course might be related to a somewhat surprisingly high comorbidity with bipolar disorder [5,13].

OCD symptoms are usually only partially responsive to pharmacological treatments. Whereas behavioural-based treatments have been established as highly efficacious, patients do not always have access to treatment providers. It has been estimated that approximately 40 per cent of individuals with OCD do not receive sufficient services, leading to a lifelong struggle with persistent symptoms that substantially impair functioning.

3. Genetic heterogeneity in studies of obsessive–compulsive disorder

Ongoing genetics research is being conducted to determine chromosomal regions and specific genes that might be relevant to OCD. This section summarizes findings based on the studies using linkage approaches, genome-wide association studies (GWAS) and family and twin study approaches.

(a) Linkage approaches

The first genome-wide linkage scan for well-diagnosed, early onset OCD identified one candidate region on chromosome 9p24, although this region met criteria only 'suggestive' of significance (log of the odds score (LOD) = 1.97) [19]. In an attempt to replicate this finding, a second study of 50 OCD families focused on microsatellite markers spanning this 9p24 candidate region and, in support of the original report, a non-parametric linkage (NPL) analysis identified a linkage signal at marker D9S1813 with an NPL value of 2.52 ($p = 0.006$) [20]. This peak lies within 0.5 cM (less than 350 kb) of the original 9p24 linkage peak at D9S288 [19,20]. In addition, pedigree-based association analyses implicated the 9p24 candidate region by identifying two additional

Table 1. Comorbidity with OCD in six clinical and one epidemiological investigation of adult OCD compared with the prevalence of these disorders in the general US population.[a] Dash denotes not reported.

population	OCD (n = 334) [5]	OCD (n = 206) [7]	OCD (n = 80) [8]	OCD (n = 630) [9]	OCD (n = 418) [10]	OCD (n = 2073) [11]	general population (n = 8098) [12]
affective disorders							
major depressive disorder	66	38	54	70	67	41	17
dysthymia	24	—	8	11	14	13	13
bipolar I/II disorder	13	7	1	10	7	23	2
anxiety disorders							
social phobia	23	—	36	37	43	44	13
panic disorder	23	19	21	6	21	20	4
generalized anxiety disorder	18	43	13	35	46	8	5
agoraphobia	18	—	17	6	16	8	5
specific phobia	12	—	31	—	39	43	11
post-traumatic stress disorder	8	—	—	16	10	19	—
substance use disorders							
alcohol abuse/dependence	23	—	15	8	16	39	23
substance abuse/dependence	14	—	8	2	9	22	12
OCD-spectrum disorders							
trichotillomania	10	—	—	36	9	—	—
Tourette syndrome	4	—	—	7	—	—	—
eating disorders							
bulimia nervosa	10	—	—	3	5	—	—
anorexia nervosa	9	—	—	3	6	—	—
other disorders							
body dysmorphic disorder	6	—	—	12	12	—	—
autism spectrum disorder	3	—	—	—	—	—	—

[a]Percentage of total N of individuals reported with OCD or in the general population.
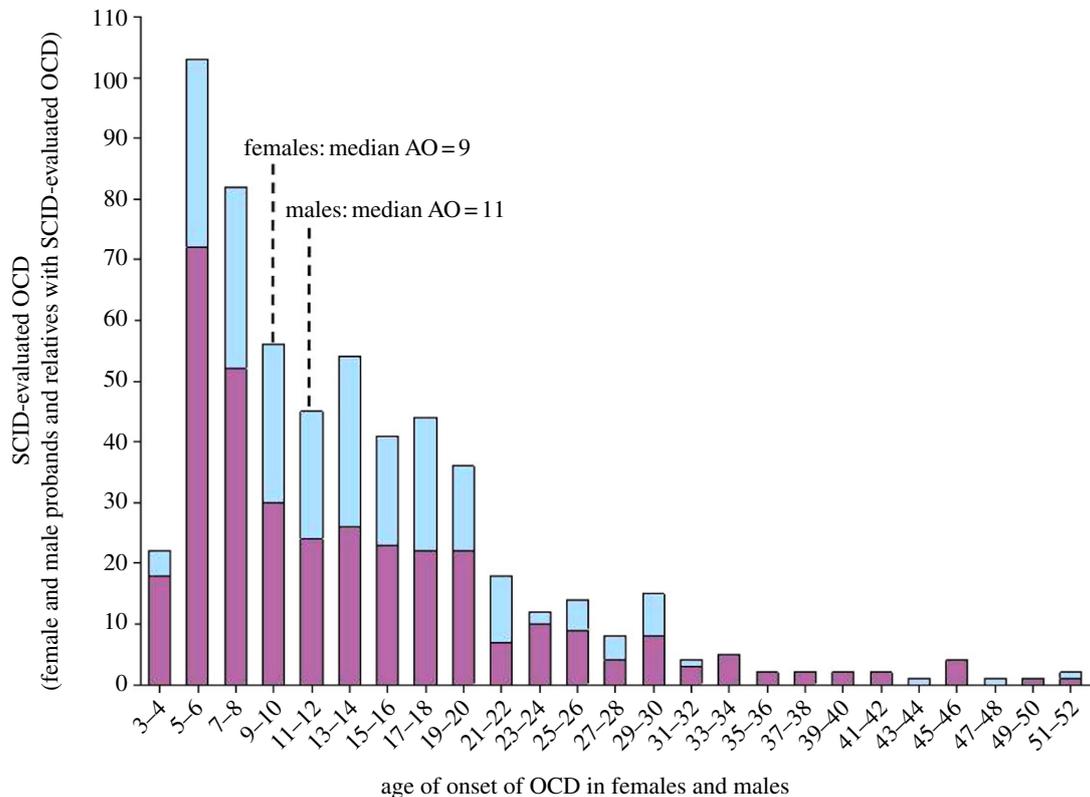
Figure 1. OCD age of onset (AO) of consecutive admissions of OCD probands and relatives of probands with OCD diagnosis based on SCID-evaluated DSM-IV/IV-TR criteria from the NIMH Intramural Research Program (Laboratory of Clinical Science) (females, $n = 349$; males, $n = 227$; total $n = 576$) [5,6].

markers with trend-level evidence for association [20]. In a third investigation, a genome-wide linkage scan was performed; although only 'suggestive' linkage was supported, linkage was identified on chromosome 10p15 with a maximum NPL LOD score of 2.43 [21]. Family-based association studies of the 10p15 region identified nominal association with three single nucleotide polymorphisms (SNPs), but none survived correction for multiple testing.

In the fourth and thus far largest genome-wide linkage study, OCD probands, their OCD-affected sib-pairs and some extended family members were genotyped and evaluated using an NPL method ($n = 1008$) [22]. Evidence for susceptibility loci was found on chromosomes 1q, 3q, 6q, 7p and 15q. None of these linkage peaks exceeded values needed for more than 'suggestive' linkage with OCD. Of major concern was the lack of peak in chromosome 9, in contrast to the positive findings at 9p24 in the two previous studies described earlier [19,20,22]. This lack of concordance between findings using a linkage approach may exemplify the relatively substantial genetic heterogeneity at play in OCD.

Of note is that OCD comorbidity with affective, anxiety or other disorders does not seem to have been taken into account in these linkage studies. However, the largest linkage studies did specifically exclude individuals with Tourette syndrome (TS) co-diagnosis [22,23].

(i) Age of obsessive–compulsive disorder onset and gender as genetically related subgroups

Several investigations have considered early age of onset (less than 18) as a potentially more homogeneous subgroup within OCD. When Shugart et al. [22] re-classified their sample based on age of onset, they found stronger, but still just 'suggestive' linkage for the early age of onset group at 1q23–24 (LOD =

3.21; $p = 0.0001$). A second, smaller shift in the LOD score peaks was observed on chromosome 3. These findings were confirmed when this sample was divided further into those families with two or more individuals with earlier OCD age of onset. This same group of researchers further considered the subgroup of gender within the sample. When the linkage scan was divided based on the proband's gender (78 male probands' families; 141 female probands' families), an increase in an original small linkage signal at 11p15 was observed [24]. After genotyping additional microsatellite markers, the gender-stratified analysis revealed an LOD score of 3.02 ($p = 0.0001$) for the male group [24]. These results suggest that additional findings were obtained by considering both age of onset and gender as subgroups within the larger phenomenon of OCD.

(ii) Hoarding as a sub-phenotype

Samuels et al. [25] considered hoarding symptoms as an additional factor to increase the homogeneity of the sample. When this linkage sample was stratified based on the presence of two or more relatives with OCD and hoarding symptoms (74 hoarding families; 145 non-hoarding families), a 'suggestive' linkage with OCD-hoarding was found at 14q31–32 (LOD = 2.99; $p = 0.0001$) [25]. No peak had been observed in this 14q31–32 region in the original analysis of the overall OCD sample [22], nor was one observed in the non-hoarding family group in this follow-up study [25]. One group of positional candidate genes in this 14q31–32 region includes three serotonin receptor genes, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E}, although only 5-HT_{3C} is known to be expressed in brain [25].

(b) Genome-wide association study approaches

As with other genetically complex medical disorders, methodological approaches in psychiatric genetics are considering newly available technology. GWA studies have made more comprehensive SNP-based assessments possible [26,27]. The first GWAS on OCD was recently published [28], comprised of approximately 1500 cases and more than 5000 controls, plus 400 complete trios after data cleaning. In the case–control sample, the two most significant p-values ($p = 2.49 \times 10^{-6}$ and $p = 3.44 \times 10^{-6}$) were SNPs located within the *DLGAP1* gene, which is expressed in the neuronal postsynaptic density complex. Interestingly, another member of the same gene family, *DLGAP3*, has been implicated in OCD based on findings from a mouse model [29] (see §6a). In the trio analysis, a SNP near *BTBD3* was observed to have genome-wide significance threshold ($p = 3.84 \times 10^{-8}$), but did not survive when a meta-analysis was conducted combining trios and case–controls [28].

(c) Family and twin studies

Risk for OCD and OC symptoms in first-degree relatives of OCD probands is higher when compared with first-degree relatives of psychiatrically healthy controls, with an increase in the range of four- to eightfold [30–32]. Segregation analyses of OCD families based on either OCD diagnosis or OC symptoms found results most consistent with a complex genetic model, including a possible major single locus, most often in combination with multiple other minor contributing loci, suggestive of a mixed model of inheritance [31,33–37]. In a still-limited number of studies, monozygotic twins have been reported as strongly concordant for OC symptoms [38–41]. Although reports contrasting the rates of the disorder in monozygotic versus dizygotic twins with OCD are few in number, in the Maudsley twin register, the concordance rates in monozygotic and dizygotic twin pairs were 87 per cent and 47 per cent, respectively, giving a heritability estimate of 80 per cent [42], and a Japanese study found concordance for OC symptoms in 80 per cent of monozygotic twins compared with 50 per cent of dizygotic twin pairs [43]. No adoption or separation studies comparing the rates of OCD in twins raised together or apart have been reported. The most recent reviews of OCD or OC symptoms in twins found intermediate estimates of heritability that were statistically significant in paediatric onset probands; however, in OCD probands with an adult age of onset, clear-cut conclusions were not evident [44,45].

4. Further genetic heterogeneity: potential candidate genes for obsessive–compulsive disorder

Numerous gene products seem highly relevant to neurotransmitter systems and developmental sequences important in OCD, but relatively few have been investigated [46]. Those that have been studied include molecules in serotonin, glutamate and dopamine neurotransmitter systems, in addition to neurotrophic and neurodevelopmental genes and their products. Additional candidates include genes indirectly related to OCD via comorbid anxiety, mood and motor disorders, or based on evidence from animal models of OCD-related behaviours (see §6).

(a) SLC6A4

SLC6A4, the gene coding for the serotonin transporter (SERT), was initially considered a prime candidate for investigation in OCD, as the only well-validated drug treatment for OCD is the use of serotonin reuptake inhibitors (SRIs such as clomipramine and selective SRIs (SSRIs) such as fluoxetine). Thus, while depressive disorders seem to be equally well treated with tricyclic and monoamine oxidase (MAO)-inhibiting antidepressants, these other antidepressants have not proved beneficial in treating OCD, suggesting a possible role for SERT [47–53]. Further evidence suggesting possible involvement of the serotonin system came from studies demonstrating that some serotonin receptor agonists (e.g. meta-chlorophenypeperazine (mCPP)) can exacerbate OCD symptoms [48,53–56].

SLC6A4 was among the very first genes found to be associated with OCD, as a series of studies found associations between OCD and an insertion/deletion variant in the promoter region of this gene. Specifically, OCD was linked with the greater-expressing long (L) allele at the serotonin transporter-linked polymorphic region (5HTTLPR), and this finding was subsequently replicated in several case–control and family-based studies [50,52,57]. Although a series of non-replications were later reported, several reviews and a recent meta-analysis indicated that the L allele was significantly associated with therapeutic responses in certain OCD subgroups, including childhood onset OCD and Caucasian OCD populations, as well as therapeutic responses in some anxiety/affective disorder subgroups [58,59].

Further interest in *SLC6A4* arose when other variants in the promoter region were discovered and found to differentially affect the expression of *SLC6A4*. A shorter, lesser-expressing L_G variant was found to convert the L allele into the equivalent of the lesser-expressing short (S) allele [60]. Thus, in previous studies, L_A (higher-expressing) and the L_G alleles were erroneously combined into one L group, introducing a functional classification error (from 1 to 24%, depending upon ethnicity) with important consequences for the association of the L allele with OCD [60–62].

In a study by Hu *et al.* [60], associations between OCD diagnosis and the L_A allele and $L_A L_A$ genotype were found in a family-based study of 175 trios, and also in a replicate case–control study of 169 OCD probands and 253 controls. A recent study from our group reported another new variant in the 5HTTLPR region, rs25532 (figure 2), which also affects reporter gene expression by 15–80% depending on the combinations of variants and the cells chosen to evaluate expression [62]. Association of a novel haplotype that included this variant together with the triallelic 5HTTLPR plus rs16965628 (located in intron 1) with OCD was found in a large sample of OCD probands and controls. Of note, the haplotype associated with OCD contains the higher-expressing allele at each locus [63]. Thus, from the very earliest studies, which genotyped only the 5HTTLPR, to the more recent studies that investigated rs25531 and rs25532 alone or together and with other newly discovered variants, all support the concept that increased SERT function contributes to OCD [61–64]. This is interesting in light of the fact that decreased SERT function (specifically the 5HTTLPR SS genotype) has been associated
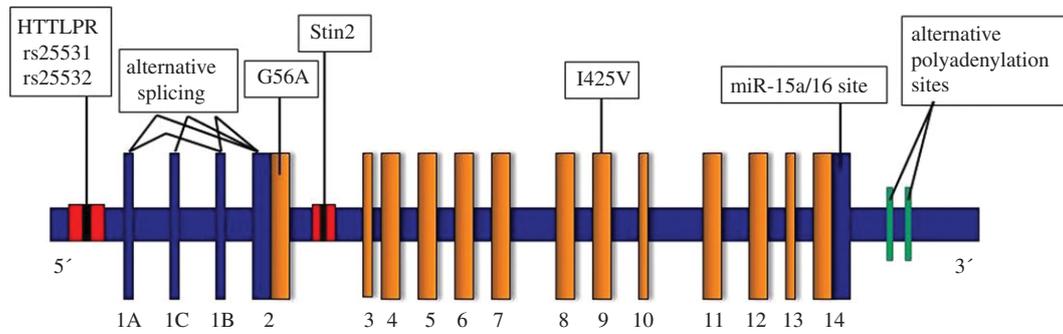
Figure 2. Human *SERT* gene organization, with multiple functional variants.

with gene × environment (G × E) interactions of stress reactivity associated with depression [65–68].

Interest in *SLC6A4* was also stimulated by observation of a rare coding region functional variant, SERT I425V, originally found to be associated with OCD in a complex, comorbid phenotype [69]. This finding was subsequently replicated in larger studies [61,70]. Functional studies found that the rare 425V variant led to dysregulation of SERT protein expressed in cell systems, in contrast to the predominant 425I allele. The 425V variant was associated with an enhanced basal SERT function that could not be further stimulated by a nitric oxide precursor, unlike the common 425I allele [71]. Thus, both this regulatory abnormality and a nearly twofold greater basal SERT expression in cultured cells were found as consequences of the I425V mutation [71]. Follow-up evaluation of the studies of I425V in OCD cases and controls, as well as in autism cases, led to the conclusion that this mutation was most consistently associated with OCD, and that this association was highly statistically significant and highly associated with a more than sixfold increased risk for OCD occurrence (OR = 6.54, $p = 0.004$), with I425V found in 1.5 per cent of a total sample of 530 individuals with OCD and 0.23 per cent of control populations totalling 1300 individuals [61,70]. *SLC6A4* I425V has now been designated 'OCD-1' in online mutations in man (OMIM) in Pubmed, in recognition of its high penetrance and replicated associations with OCD.

Of related interest, alterations in *SLC6A4* and SERT are associated with other neuropsychiatric disorders, as well as diverse medical disorders, in humans [48,64]. Changes related to different *SLC6A4* genotypes include alterations in amygdala and thalamo-cortico-basal ganglial functions, and may represent an endophenotype for a broad class of related disorders. These changes were discovered in brain imaging studies of healthy and clinical human populations, as well as in studies of human and mouse anxiety-like, depression-like and stress hormone responses, changes in serotonin receptor density and function, in addition to G × E interactions [57,65,66,72–76]. Further, genetically engineered mouse and rat models of SERT deficiency and over-expression [72,77–83] led to numerous biochemical, pharmacological and anatomical alterations and features related to disease.

(b) *SLC1A1*

SLC1A1 encodes the only neuronal glutamate transporter (EAAC1, EAAT3) and is an attractive OCD candidate gene for multiple reasons. Glutamate is the major excitatory neurotransmitter, which contributes to brain development and plays a central role in circuits consistently implicated in OCD, including direct driving influences on serotonergic dorsal raphe neurons related to anxiety and tic behaviours [84–86]. *SLC1A1* is located approximately 350 kb centromeric to the linkage peak on 9p24, which is the region identified in the first genome-wide linkage study of OCD and supported by a second study focused on this region [19,20]. Although no signal in this region was detected in two subsequent genome-wide linkage studies [21,22] nor in a recently published GWAS [28], a series of direct, positive studies have examined *SLC1A1* as well as additional glutamate system candidate genes in OCD.

There are five major studies of *SLC1A1* in OCD, all of which reported significant association of SNPs in this gene with OCD. Four of these investigations were family-based studies, primarily using trio samples [84,85,87,88], and these studies were supported by a fifth large case–control study [89]. Additional recent results from an in-depth study of *SLC1A1* revealed one rare, non-synonymous variant (T164A) in one OCD family [86]. This variant has been shown to have a functional impact on transporter activity (reducing V_{max} and K_m) [90]. In a functional approach to evaluating the possible importance of *SLC1A1* in OCD, we evaluated whether *SLC1A1* SNPs exhibited effects on functional gene expression, using three measures: (i) mRNA expression in lymphoblast cell lines, followed by (ii) expression analysis of *SLC1A1* in prefrontal cortex from 90 subjects and (iii) a more restricted evaluation of the positive results from these first two analyses using reporter gene expression assays [89]. The strongest evidence implicating *SLC1A1* in OCD in this study came from a haplotype that was almost twice as frequent in OCD patients as in controls (OR = 1.89, $p < 0.001$). Two of the three SNPs in this haplotype were expression quantitative trait loci. Consideration of OCD sub-phenotypes revealed that one of the SNPs in the 5′ regulatory region was significantly associated with hoarding symptoms ($p = 0.005$) [89].

Biological and neurodevelopmental studies support the glutamatergic system as being involved in the neurocircuitry of OCD, including studies using brain imaging and direct magnetic resonance spectroscopy-based evaluations of brain glutamate concentrations in OCD and in OCD treatment studies [91–93]. In addition, several glutamatergic drugs have been recently assessed in the treatment of OCD (for a review, see Wu *et al.* [94]). For example, riluzole, an antiglutamatergic agent, has been evaluated in several smaller treatment trials of OCD patients, with positive results in all reports [95–97]. However, replicated, placebo-controlled trials of riluzole in OCD patients have not yet been reported. In addition, the *N*-methyl-D-aspartic acid (NMDA) antagonist memantine has been shown to be effective an as add-on treatment for OCD

in case studies [98–100], in open-label studies [101,102] and in a case–control study [103]. Interestingly, rapid (1 day) antidepressant responses have been observed following treatment with ketamine, another glutamatergic agent, in MDD patients, which may be relevant to OCD based on high comorbidity with MDD [104]. In fact, a recent case study showed effectiveness of ketamine in treatment-resistant OCD [105]. However, in a recent small open-label trial, although ketamine had a small acute effect, it did not have a sustained or potent effect in decreasing OCD symptoms [106].

(c) Additional candidate genes

In addition to SLC1A1, the glutamatergic gene GRIN2B, which encodes for a subunit of the NMDA receptor, has been associated with OCD and OC symptoms, but as yet has not been studied as extensively [91,107,108] (for a review, see Hu et al. [94]). Further, strong data suggest that the neurotrophin gene brain-derived neurotrophic factor (BDNF) might be associated with OCD [109] or with a hoarding sub-phenotype [110]. The seminal investigation conducted by Hall et al. [109] found that multiple SNPs and haplotypes in the BDNF gene were associated with OCD diagnosis. The findings from this study have been supported by several other evaluations of BDNF in OCD [62] as well as in rodent models of stress-related and anxiety-like behaviours [111].

Dopamine system abnormalities provide a strong hypothetical basis for OCD development, especially owing to their contributions to modifying glutamate system functions that seem to be involved in OCD. Reciprocal SERT influence on dopamine-rich nigral and striatal brain regions and functions have also been observed [112]. However, compelling direct evidence for dopamine gene contributions is lacking in the studies of OCD populations. Dopamine DRD2, DRD3 and DRD4 receptor genes, the dopamine transporter (DAT) gene (SLC6A3), as well as several genes in the catabolic pathways for dopamine and other catecholamines, have yielded results that have been partially replicated (especially for DRD4), although conflicting gender-related differences were found [112–118]. Likewise, the monoamine oxidase isoform A (MAOA) gene, which is involved in both catecholamine and serotonin metabolism, was found to be associated with OCD in two studies, although gender results were again in conflict [119,120].

5. The other heterogeneity conundrum: chromosomal anomalies and additional gene involvement in obsessive–compulsive disorder

Uncommon chromosomal anomalies have come under increasing scrutiny in OCD and OCD-related disorders, particularly TS. Among the approximately 14 such additional rare gene or chromosome abnormalities, most have been reported in rare pedigrees [15,109,111,119–130]. The two findings with the greatest frequencies were OCD associated with the myoclonus dystonia syndrome (MDS) [126–129] and OCD associated with the 22q11 microdeletion syndrome (which overlaps with the velocardiofacial syndrome) [121,123–125]. The former is of special interest because its 7q21–q31 locus is near the chromosomal anomalies

described in other cases associated with OCD and TS at 7q31 and 7q35–q36 [130–132]. Additionally, a family-based association study using markers in the 7q31 region demonstrated biased transmission of 7q31 marker alleles in individuals with comorbid TS, OCD and attention deficit hyperactivity disorder (ADHD) [133].

(a) Myoclonus dystonia syndrome

In one study of three extended MDS families, individuals with OCD meeting direct interview-based DSM-IV criteria were identified in 25 per cent (4/16) of symptomatic MDS carriers with the 7q21 haplotype, but in only 9 per cent (1/11) of non-symptomatic haplotype carriers, and in 0 per cent (0/28) of the non-haplotype carriers [126]. OCD comorbidity with generalized anxiety disorder (GAD) and MDD was also statistically significant in these three families (but neither GAD nor MDD with MDS alone) [126]. In another study of three extended families with MDS, OCD was diagnosed in three members of one of the families, all three of whom were symptomatic MDS carriers. By contrast, OCD was not present in any of the other 10 members of this family nor in 14 members of the other two families from whom psychiatric profiles were obtained [127]. Individuals in this family with MDS and OCD had a 7q21 deletion mutation shown to truncate the DYT11 locus (ε-sarcoglycan; SGCE; a transmembrane component of the dystrophin–glycoprotein complex, which links the cytoskeleton to the extracellular matrix). However, the importance of an association with OCD was more difficult to ascertain in this family, because there was co-occurrence of a DRD2 missense mutation (located in chromosome 11q23).

In a third family study, three of six individuals with MDS and OCD (together with diagnoses of depression) had MDS attributed to a truncating mutation within the SGCE locus [128,129]. MDS has also been found to be linked to two other loci besides DYT11 at 7q21, a 16.9 cm region between DISS1132 and D183843 on 18p11 [134], and the previously mentioned region on 11q23, where two independent mutations were found in DRD2 [127]. Most recently, a direct examination of the SGCE gene in 32 TS patients with OCD detected no abnormalities in this gene in comparison with 60 Centre d'Etude du Polymorphisme Humain control subjects [135]. Furthermore, OCD was not increased in mutation carriers of the DYT1 gene at 9q34 (torsin A; TOR1A) among probands with dystonia or their family members [136].

Some prior evidence of a dystonia–OCD connection has been suggested on the basis of an elevated frequency of OCD symptoms measured by the Maudsley OCD questionnaire and the Yale–Brown obsessive compulsive scale (YBOCS) in individuals with two dystonic syndromes: spasmodic torticollis and blepharospasm [137,138]. In addition, OCD was found to be associated with focal hand dystonia [139]. Further, a 14–20% incidence of OCD has been found in two studies of over 100 patients with focal dystonias (relative to the approx. 2.5% OCD prevalence in the general population) [139,140]. SGCE immunoreactivity and its RNA expression has been shown to be high in dopaminergic and serotonergic neuron areas of the mouse brain, compatible with suggestions of decreased activity of the same cortical–striatal–thalamo-cortical (CSTC) circuit in TS and OCD [141]. All of these disorders, including dystonias, OCD and TS, appear to share alterations in the CSTC pathways, although some differences in pathway involvement require further elucidation via

ongoing brain imaging, electrophysiological post-mortem brain studies and transgenic mouse studies [140,142,143].

(b) Chromosome 22q deletion syndrome

The 22q11.2 contiguous microdeletion syndrome occurs in approximately 0.3 per cent of live births, generally in sporadic cases (de novo), although a minority of cases (approx. 10%) may follow an autosomal dominant inheritance pattern. The size of the deletion is 1.5–3 mb, involving approximately 25 genes. Initially recognized because of facial and cardiac malformations associated with learning disabilities, other abnormalities have been subsequently noted, including endocrine changes, immunodeficiency and autoimmune abnormalities [144]. More extensive evaluations of children and adults with this deletion uncovered diverse psychopathology, ranging from ADHD, pervasive developmental disorder and anxiety disorders—including OCD—to schizophrenia and bipolar disorder [145].

In one evaluation of children with the 22q deletion syndrome, OC behaviours were reported to be associated with this chromosomal anomaly, although none of the children in this study received a full diagnosis of OCD [146]. Nonetheless, groups of adult and mixed-age clinic subjects meeting full diagnostic criteria for OCD have been noted in four studies of individuals with 22q11 deletions, although all but one of these reports were focused primarily on schizophrenia or affective disorders rather than on OCD [121,123,125,147]. Psychiatric evaluation of one cohort of 14 22q deletion syndrome patients over age 15 revealed four with schizophrenia or schizoaffective disorder, two of whom also met OCD diagnostic criteria [121]. A study of a similar cohort of patients with 22q deletion syndrome who were psychiatrically evaluated found that most of the patients shared common mood, anxiety and OC symptoms, but that the majority received bipolar, schizoaffective and ADHD diagnoses (64%); 8 per cent met OCD criteria [125]. In the only comprehensive study that used the YBOCS of OCD severity together with psychiatric interviews in evaluating a 22q deletion syndrome clinic sample, 33 per cent of 43 patients met full DSM-IV criteria for OCD diagnosis [123]. In this study, the most common comorbid diagnoses in those with OCD were ADHD, simple phobia and social phobia. Only one of the six cases of familial 22q deletion syndrome received an OCD diagnosis. The highly varied forms of psychopathology found in 22q deletion syndrome probands, and the large range of 8–33% OCD occurrence in these four studies, clearly requires further evaluation. This will be of interest, as the catechol-O-methyltransferase (COMT), a cathecolamine-degrading enzyme, locus lies within the 22q deletion, and several studies found that the V158M COMT variant was associated with OCD and other disorders [119,148–150]. One interesting future direction might be to consider changes in the forebrain metabolism of dopamine, which has been shown to be altered in individuals with the functional COMT V158M variant [151], but which has not yet been specifically evaluated in individuals with 22q deletion syndrome.

It is still early in the development of these investigations. It is noteworthy that there appear to be no studies reported as of yet in OCD proband groups of the rare candidate genes SGCE or GCH1 themselves, or of candidate genes in the chromosomal regions noted earlier. However, even for

22q11 and 17q variants, insufficient data exist for OCD, other disorders such as dystonias, autism spectrum disorders and anorexia, in addition to other anxiety and affective disorders to draw firm conclusions at this time.

6. Animal models of obsessive–compulsive disorder-like behaviours: contributions to identification of genes involved in obsessive–compulsive disorder and comorbid disorders

Recent investigations and reviews describing animal models have noted the complexity of anxiety-like and depression-related behaviours, in addition to effects of combined stress and other environmental stimuli [77,152–157]. In addition, G × E approaches have used non-human primate polymorphisms and gene-targeted rodents to evaluate, for example, serotonin-related genes such as Slc6a4 and the effects of SRI treatment on anxiety- and depressive-like behaviours [77,154,158,159]. Gene-targeted and other mouse models have also been used to dissect specific brain regions and neuro-circuitry patterns involved in anxiety-like, depression-like and OCD-related behaviours [160–162].

In rodents, dogs and non-human primates, OCD-like features include perseverative behaviours, compulsive grooming, food restriction-induced compulsive wheel running or drinking, and behaviours such as marble burying [29,163–165] (for reviews, see [161,166–170]). However, despite 'face validity' and in some instances apparent validity based on biological neurocircuitry involvement or similar drug responses in OCD in humans, few models have implicated specific genes. The most informative models have used knockout or transgenic mouse models of Sapap3, 5-HT$_{2C}$, D1CT and DAT described below, in addition to Slitrk5 [171], and Hoxb8 [172]. In addition, pharmacological assessments in mouse models suggest a possible role for 5-HT$_{1B}$ receptors in OCD [173,174], with some evidence for a role for 5-HT$_{1B}$ (5-HT$_{1D\beta}$) in OCD from human studies as well [175,176]. Further, trichotillomania (TTM) is currently considered an OCD-spectrum disorder characterized by self-induced and recurrent loss of hair [177], and spontaneous barbering has been evaluated in mice of different background strains, and is suggested to be an animal model of TTM [167].

(a) Sapap3

Sapap3 (also known as Dlgap3) is a gene encoding a post-synaptic density component of important scaffolding machinery in glutamatergic synapses. In mice lacking Sapap3, excessive facial self-grooming was the primary phenotype [29]. Rescue of this prominent over-grooming phenotype was essentially 100 per cent by replacement expression of Sapap3 in the striatum (using a lentiviral vector), as well as by chronic treatment with the SSRI fluoxetine, an antidepressant and anti-OCD agent [29].

Based on this animal model, a follow-up study resequenced the SAPAP3 gene (located on chromosome 1p35) in several patient populations across two primary sites (Duke University and the NIMH Intramural Research Program), comparing healthy controls with individuals with OCD, OCD plus TTM and those with TTM alone [177]. The major finding was a trend towards an increase in rare

SAPAP3 variants, some identified as gene structure damaging, in the TTM and the OCD plus TTM groups (2.1%; 7/330) compared with controls (0.56%; 2/356; $p = 0.08$). A second family study of *SAPAP3* in OCD focused specifically on the presence of the so-called 'grooming disorders', as defined by the occurrence of pathological nail biting, pathological skin picking and/or TTM. Thirty two per cent of OCD participants and their family members from 383 families met the defined criteria for this constellation of grooming disorders, and 65 per cent of these grooming disorder participants met lifetime diagnostic criteria for OCD [122]. Neither OCD diagnosis itself nor the overall group of grooming disorders taken together was significantly associated with any of six SNPs or three haplotypes in *SAPAP3*. However, within the grooming disorder subgroup, a nominal association between at least one grooming disorder with four of the six SNPs genotyped ($p < 0.05$), and at least one grooming disorder with all of the three haplotypes ($p < 0.05$), was observed [122]. These results were not corrected for multiple testing and thus should be considered preliminary. It is of interest, however, that some brain imaging studies of TTM probands have found striatal abnormalities such as those observed in OCD [178,179], although there has also been only a partial replication of these studies [180,181]. Interestingly, the recent GWAS in OCD showed that the two most significant *p*-values were within *DLGAP1*, another member of the same gene family of proteins expressed at the postsynaptic density complex (see §2*b*) [28].

(b) 5-HT$_{2C}$

Although the serotonergic system has been considered a likely basis for OCD susceptibility, the only serotonergic component implicated thus far in genetic animal model studies is the 5HT$_{2C}$ receptor. 5-HT$_{2C}$ knockout mice chew more non-edible clay and chew circular plastic screens in a more regular ('neat') pattern compared with wild-type control mice. These mice also exhibit more head-dipping behaviour, suggested to be a compulsive behaviour, compared with controls [182]. As mentioned earlier, in humans, the partially selective 5-HT$_{2C}$ receptor agonist mCPP preferentially elicits or exacerbates OCD symptoms, as well as anxiety responses, in OCD patients relative to controls, with more consistent results after intravenous than after oral mCPP administration [54–56]. Of note, fluoxetine and particularly its major metabolite norfluoxetine has direct antagonist actions on 5-HT$_{2C}$ receptors, in addition to their primary effects on serotonin reuptake [183]. Problems with this 5-HT$_{2C}$ receptor model for OCD aetiology include the multiple other abnormalities found in 5-HT$_{2C}$ knockout mice, as well as their generalized hyperphagia that leads to obesity [184]. In addition, head-dipping behaviours are also considered exploratory and anxiety-related phenotypes; head-dipping behaviour is diminished by treatment with benzodiazepines, which are not an effective treatment for OCD and thus further confound this model [182].

(c) D1CT

D1CT mice are transgenic mice bearing the cholera toxin gene controlled by the dopamine D1 receptor promoter, which drives expression in cortical and limbic areas. D1CT mice displayed complex tics and abnormal perseverative behaviours, repeated hair and skin biting and pulling, non-aggressive biting of cage-mates and themselves during grooming, along with increased anxiety-like behaviours [185–189]. As such, D1CT mice have been suggested to comprise a model for TS, TTM and OCD. Although no SRI treatment studies appear to have been reported within this interesting model, neuroleptics, as well as the α-2 adrenergic antagonist clonidine—effective in human tic-related disorders—suppressed tics in these mice [186].

(d) DAT

Deletion of the DAT gene in mice results in chronic overactivity of the entire dopaminergic system. In addition to consistently reported hyperactivity in DAT knockout mice [190], these mice display an increase in grooming time (specifically related to longer grooming bouts, not an increase in the number of bouts) together with a grooming sequence that is stereotyped and predictable, which has been suggested to reflect OCD- or TS-like phenomena [188]. Marble burying, considered a repetitive and perseverative OCD-like behaviour [165], is also altered in these mice, although interpretation of these results is complicated by their marked hyperactivity [191].

7. Problems facing genetic investigations of obsessive–compulsive disorder: discussion and future directions

The literature reviewed earlier highlights both advances and limitations in past research. Heterogeneity is one of the hallmark features of OCD, however, it also represents one of the greatest rate-limiting steps in conducting further genetic investigations. In addition, there has been a lack of attention paid to additional variables—particularly environmental factors—that may also play a role in the aetiology of OCD and related disorders, either as unique predictors or in conjunction with other factors. In §7*a* will discuss in further detail such problems facing future genetic studies, and will also outline suggestions for moving forward.

(a) Problem 1: the heterogeneity of obsessive–compulsive disorder: approaches to identifying more homogenous subgroups and sub-phenotypes

(i) Consideration of symptom stability and age of onset

For the large part, OCD is characterized by a chronic and relapsing course. It has also been established that without the assistance of either cognitive behavioural therapy or efficacious pharmacological interventions, full remissions are rare. For example, a birth cohort, longitudinal study in Australia evaluated individuals at age 11, 26 and 32 and found that obsessions and compulsions were fairly stable across time. Temporal stability was also noted for specific symptom dimensions, such as fear of harming others and checking [192]. Results also revealed that even sub-clinical obsessions and compulsions are associated with substantial impairment and occur in conjunction with other psychiatric disorders [192].

As discussed in §3, age of OCD onset (usually defined as onset before age 18) has been identified as one factor by which to reduce heterogeneity, and there is ample research suggesting that younger age of onset may represent a

discrete, aetiological-based OCD subgroup. Younger age of OCD onset has been associated with a greater proportion of first-degree relatives with OCD [34,70,193–195], particularly for female probands [31]. In addition to the increased familial risk, early onset OCD has been distinguished from later onset OCD by the nature and severity of the OCD symptoms, the pattern of comorbidity, the course of illness and treatment responses, and also by the regional cerebral blood flow pattern in frontal–subcortical circuits that are most frequently implicated in OCD [146,196–202]. Given these considerations, relying on this more homogeneous OCD subsample may provide more power for genetic and related investigations, as illustrated in a recent linkage study [22].

(ii) Comorbidity and symptom-based obsessive–compulsive disorder sub-phenotypes

In addition to age of onset, there are several clinical features that may be useful for grouping OCD into more homogeneous familial phenotypes for aetiological investigations, such as G × E studies. The most striking clinical feature to consider is comorbidity, and within the broad category of comorbidity, the high frequency of affective disorders is notable [6]. Comorbid chronic tic disorders, anxiety disorders (particularly panic disorder) and OC personality disorder all emerge as additional potential comorbidities that could be associated with more homogeneous sub-phenotypes. In a latent class analysis of comorbid psychiatric conditions, two OCD subgroups were identified: a dimensional anxiety plus depression class, and a panic plus tic class [7]. In a follow-up investigation, a novel latent variable mixture model analysis that considered age of onset, symptom severity and comorbidity simultaneously was conducted. Two statistically significant separate OCD subpopulations emerged; particularly noteworthy was the first group, which had a significantly higher proportion of OCD-affected relatives (i.e. familial OCD), earlier age of OCD onset, more severe OCD symptoms, greater psychiatric comorbidity and greater impairment [203].

In addition to considerations of comorbidity, research has also attempted to identify more homogenous subgroups based on symptom type. In factor analytic approaches to the evaluation of possible OCD symptom patterns in adults, four major symptom factors have most often been found using the YBOCS checklist: an aggressive/sexual/religious obsessional factor; a contamination/washing factor; a symmetry/ordering factor; and a hoarding factor (for a review, see Mataix-Cols *et al.* [204]). An example of a cluster-based analysis of OCD symptoms, instead of a factor-based analysis, also resulted in a four-factor grouping [6]. Several investigations have found that these factors are associated with different clinical features, including age of onset, brain imaging findings and treatment response [3,204–207]. There is some indication that these symptom dimensions may have differential genetic and/or transmission patterns. For example, one study based on OCD-affected sib-pairs found relatively stronger heritability for two of the four factors—the hoarding factor and a somatic, sexual, aggressive factor [10]. The finding that these symptom factors appear to be transmitted within families is consistent with a symptom-specific genetic hypothesis.

(iii) Consideration of a hoarding sub-phenotype

It has increasingly been observed that there are key differences between individuals with primary hoarding symptoms and those with non-hoarding OCD on a constellation of features, including clinical and biological factors, as well as associations with gender and heritability estimates [5,10,208–213]. Genetic evidence, as reviewed earlier, in addition to a series of clinical investigations, is beginning to provide support for hoarding as a discrete phenomenon [25,89,214–219]. Although more extensive research will need to be conducted to discern the relationship between OCD and hoarding, current hypotheses suggest that hoarding might represent a separate disorder, although some hoarding symptoms may also be characterized as an OCD-form of hoarding [217,220]. Regardless of the final decisions to be made by the DSM-5 task force regarding the diagnostic future of hoarding, considering these symptoms separately from the other symptom dimensions of OCD might aid in efforts to reduce heterogeneity.

(iv) Pathophysiology of obsessive–compulsive disorder

Hypotheses of OCD pathophysiology focus most strongly on cortico-striato-pallido-thalamic (CSPT) circuit or CSTC abnormalities. The neurocircuitry of OCD is among the most well-developed pathophysiological models. There is a considerable body of neuroimaging research, and to a lesser extent cognitive neuroscience research, focusing on this aetiological hypothesis for OCD [3,221]. Although a primary process underlying core OCD symptoms has not yet been definitively identified, functional imaging studies have established that brain metabolism or perfusion in CSPT circuits is altered in OCD patients [3,36,204,222–228].

Neuropharmacological-based hypotheses of OCD pathophysiology have been greatly influenced by strong evidence that serotonergic systems modulate OCD symptomatology [53,229–231]. SERT and several serotonin receptor subtypes including $5\text{-HT}_{1B/D}$, 5-HT_{2A} and 5-HT_{2C} (as well as tryptophan hydroxylase, the enzyme that most strongly regulates serotonin synthesis) have been implicated in OCD. These proteins and receptors are all in the ventral striatum and brain stem where they could influence the function of the CSTC circuits. Other neurotransmitter systems, especially the glutamate system, are present within the CSTC circuit and individually (or via their interactions with serotonin) may play a role in susceptibility, course, or response to OCD treatment and anxiety/affective disorders. Glutamate system agents such as riluzole and memantine, and perhaps some β-lactam antibiotics with glutamate transporter-affecting properties, such as ceftriaxone, show some promise as OCD treatments, perhaps via suppressing motor cortex facilitation responses [94–103,232]. Dopaminergic mechanisms have also been implicated by controlled studies demonstrating that dopamine system neuroleptics (and similar agents such as risperidone) may be beneficial when added to ongoing SRI treatment [52,233,234]. Other CSTC neurotransmitter systems and modulators are candidates for involvement in OCD on the basis of their anatomical localization or functional roles in CSPT circuits; these include GABA, BDNF, substance P, bradykinin and its receptor BDKRB2, and cholinergic and endogenous opioid systems.

(b) Problem 2: integration of environmental contributions to obsessive–compulsive disorder and other anxiety and affective disorders

There exists some evidence that diverse, non-familial, non-genetic factors contribute to OCD onset, OCD severity and

other features of OCD [6,235,236]. Study design differences and small subject numbers, as well as the paucity of studies examining interactions between any of these factors with specific gene variants for potential G × E consequences, reflect the need for more extensive, in-depth studies.

(i) Traumatic life events

One of the primary environmental factors considered within the OCD literature is traumatic or stressful life events. In one of the largest studies to date, 52 per cent of 365 individuals with a lifetime OCD diagnosis endorsed one or more lifetime traumatic life events (TLEs) [237]. The subgroup of participants with a lifetime TLE history was found to have significantly higher YBOCS OCD severity scores. This association remained significant after controlling for multiple other factors, including age of onset, age, depressive symptoms and other comorbidities. The important question of whether TLE occurrence preceded OCD onset could not be evaluated owing to the retrospective nature of the study [237].

Relevant to the association between TLEs and OCD is the consideration of the relationship between OCD and post-traumatic stress disorder (PTSD). A number of investigations have examined the rates of comorbidity between these two disorders, along with differential time of onset [66,179,238–240]. A case report series of 13 military veterans reported that the onset of OCD appeared clearly related to preceding specific traumatic events [241]. The authors carefully considered the presenting symptoms and were able to demonstrate that the OCD symptoms were clearly OCD-like and not traumatic event flashbacks common to PTSD, as described by others [242]. Another investigation provided some empirical support to the conclusions outlined in the case report series. Specifically, in a treatment-resistant OCD subgroup, it was found that the majority of patients had comorbid PTSD, and that the PTSD preceded the onset of OCD [243]. A subsequent study found that 82 per cent of 104 OCD patients reported a history of trauma, and that 50 per cent of those reporting trauma met criteria for PTSD [244], a percentage similar to that reported previously [237]. However, the literature is also marked with conflicting findings. A recent study using extremely stringent criteria for 'severe traumatization' found a non-significant difference between OCD patients (6.2%) and controls (8.3%) for the number of TLEs experienced [245]. This investigation also identified that the lifetime prevalence of PTSD diagnosis was not different between probands with OCD and controls [245]. Methodological differences across these studies are major issues that require resolution in future studies of TLEs in the development of OCD.

(ii) Onset of obsessive–compulsive disorder after acute traumatic brain injury and in association with other types of neuropathology

A considerable number of case reports have described the apparently acute onset of new OCD in previously healthy individuals who suffered a documented brain injury, usually after accidents (for reviews, see [246–248]). Besides OCD, other psychiatric disorders that follow brain injuries have been documented in epidemiological studies [249]. In one of these studies, which retrospectively evaluated 5034 individuals among whom 361 (8.5% weighted average) reported a history of brain trauma with loss of consciousness or confusion, lifetime prevalence for many disorders including

OCD, MDD plus PTSD and other anxiety disorders was significantly increased compared with those without head injuries. Of note, rates of schizophrenia and bipolar disorder were not increased in this sample of individuals with brain trauma [249].

Adding to the traumatic brain injury literature, additional case studies report onset of OCD up to several months following traumatic brain injury [246,250,251]. One of three studies documented a typical array of OCD symptoms using YBOCS ratings [245]. Compared with matched controls, the patients with post-brain injury OCD symptoms had poorer performance on an array of cognitive measures, including executive functions. Also, the patients with the most severe traumatic brain imaging abnormalities had more frequent abnormal MRI exams involving the fronto-temporal cortex and caudate nucleus [246]. Some of these reports emphasized negative prior personal or familial OCD symptoms or diagnoses.

8. Comments and conclusions

Until recently, with the exception of sporadic candidate gene studies, three small linkage studies and the recently published GWAS, OCD has been relatively neglected as a disorder of interest to geneticists compared with affective disorders, some anxiety disorders and schizophrenia. This is surprising given OCD's status as a chronic disorder that is widely recognized as a major public health burden. As mentioned in §1, the incidence of OCD in the US and world populations is similar to that of bipolar disorder and higher than that of schizophrenia. Despite this, bipolar disorder and schizophrenia have been the objects of more than 20 genome-wide linkage analyses, recent GWA studies, and several twin-, family- and gene-associated neurobiological studies.

Considering the current OCD literature, it is encouraging to note several avenues for future investigations. The 9p24 chromosomal region was highlighted in the first genome-wide scan [19] and was further supported by a study using more dense markers targeted exclusively at this 9p24 region [20]. Importantly, this region includes *SLC1A1*, thus far the most-replicated candidate gene in OCD, with positive findings in five studies. Several of the *SLC1A1* SNPs associated with OCD show substantial evidence of functional consequences in HapMap gene expression data, human brain expression data, and in studies of gene expression [89]. Future work is required to confirm whether a single major functional *SLC1A1* gene variant or localized related gene variants contribute to OCD. Other types of functional studies, such as those in transgenic mouse models, might point towards mechanisms whereby animals with alterations in this neuronal glutamate transporter gene might contribute to understanding such abnormalities in OCD patients.

One of the more striking features of the current status of genetic contributions to OCD, such as those of other anxiety and affective disorders, are the ongoing approaches to consider the genotypic and phenotypic heterogeneity of OCD. Evaluation of phenotypic considerations, such as a focus on age of onset, gender, compulsive hoarding, and additional subgroups and sub-phenotypes, have shown influences of these variables on genome-wide linkage analyses [22,24,25]. These have primarily been the consequence of large-scale quantitative phenotypical variable assessment built into the

second genome-wide study of OCD and other studies from this collaborative group [10,23,25,208,209,214,215], and also the recent GWAS by another consortium [28].

For future investigations, it may additionally be advantageous to expand the consideration of phenotypes from *within* disorder to *across* disorders. Our discussion of comorbidity highlights how OCD is highly related to other affective and anxiety disorders. By focusing on phenotypes that these disorders have in common, we may be able to further hone genetic and other aetiological investigations.

As discussed earlier, the impressive array of major neurotransmitter system genes contributing to dopaminergic, serotonergic, glutamatergic, neurotrophic and neuropeptide neurodevelopmental systems presents opportunities for the development of several interesting hypotheses for future investigation. Importantly, these hypotheses may converge towards the discovery of a complex 'cloud' of genes that form part of the biological basis for OCD and related disorders. Additional partial gene-based contributions may emerge through comorbidity with other anxiety and affective disorders. In addition, these gene-based vulnerabilities may interact with environmental factors, such as stress or trauma. This complex interplay between a range of biological and environmental factors may lead to symptom development, and the subsequent clinical manifestations of specific affective and anxiety disorders, such as OCD.

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