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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.

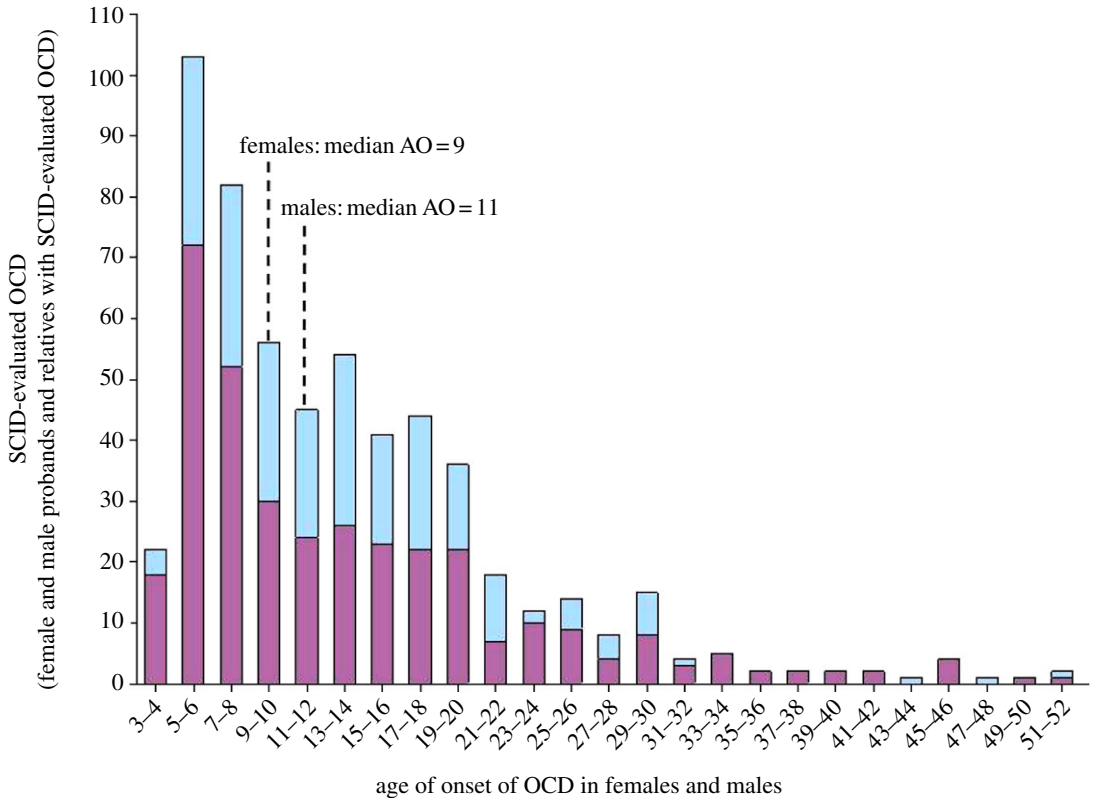

Figure 1. OCD age of onset (AO) of consecutive admissions of OCD probands and relatives of probands with OCD diagnosis based on SCID-evaluated DSM-IV/IV-TR criteria from the NIMH Intramural Research Program (Laboratory of Clinical Science) (females, $n = 349$; males, $n = 227$; total $n = 576$) [5,6].

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 §6*a*). 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_AL_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

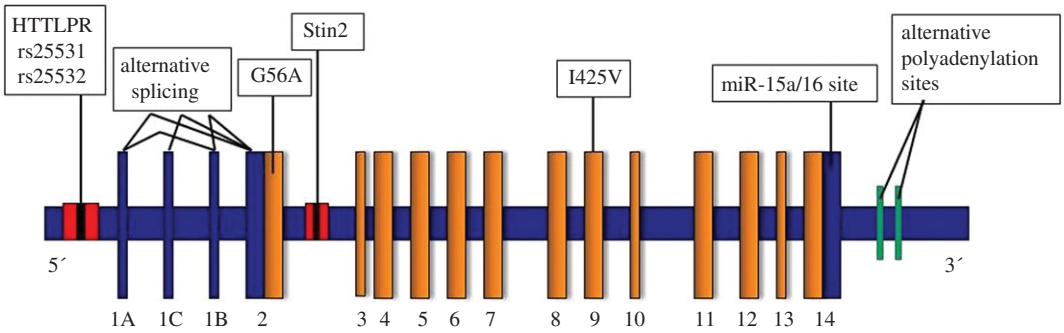

Figure 2. Human *SERT* gene organization, with multiple functional variants.

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-haploytpe 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–thalamocortical (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 neurocircuitry 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 postsynaptic 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 re-sequenced 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-$HT_{1B/D}$, 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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References

1. Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, Rössler W. 2004 Obsessive–compulsive severity spectrum in the community: prevalence, comorbidity, and course. *Eur. Arch. Psychiat. Clin. Neurosci.* **254**, 156–164. (doi:10.1007/s00406-004-0459-4)
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. 2005 Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiat.* **62**, 593–602. (doi:10.1001/archpsyc.62.6.593)
3. Saxena S, Rauch SL. 2000 Functional neuroimaging and the neuroanatomy of obsessive–compulsive disorder. *Psychiat. Clin. North Am.* **23**, 563–586. (doi:10.1016/S0193-953X(05)70181-7)
4. Mataix-Cols D, van den Heuvel OA. 2006 Common and distinct neural correlates of obsessive–compulsive and related disorders. *Psychiat. Clin. North Am.* **29**, 391–410. (doi:10.1016/j.psc.2006.02.006)
5. LaSalle VH, Cromer KR, Nelson KN, Kazuba D, Justement L, Murphy DL. 2004 Diagnostic interview assessed neuropsychiatric disorder comorbidity in 334 individuals with obsessive–compulsive disorder. *Depress. Anxiety* **19**, 163–173. (doi:10.1002/da.20009)
6. Murphy DL, Timpano KR, Wheaton MG, Greenberg BD, Miguel EC. 2010 Obsessive–compulsive disorder and its related disorders: a reappraisal of obsessive–compulsive spectrum concepts. *Dialogues Clin. Neurosci.* **12**, 131–148.
7. Nestadt G *et al*. 2008 Obsessive–compulsive disorder: subclassification based on co-morbidity. *Psychol. Med.* **39**, 1–11. (doi:10.1017/S0033291708004753)
8. Nestadt G, Samuels J, Riddle MA, Liang KY, Bienvenu OJ, Hoehn-Saric R, Grados M, Cullen B. 2001 The relationship between obsessive–compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD family study. *Psychol. Med.* **31**, 481–487. (doi:10.1017/S0033291701003579)
9. Miguel EC *et al*. 2008 The Brazilian research consortium on obsessive–compulsive spectrum disorders: recruitment, assessment instruments, methods for the development of multicenter collaborative studies and preliminary results. *Rev. Bras. Psiquiatr.* **30**, 185–196. (doi:10.1590/S1516-44462008000300003)
10. Hasler G *et al*. 2007 Familiality of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD collaborative genetics study. *Biol. Psychiat.* **61**, 617–625. (doi:10.1016/j.biopsych.2006.05.040)
11. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. 2010 The epidemiology of obsessive–compulsive disorder in the national comorbidity survey replication. *Mol. Psychiat.* **15**, 53–63. (doi:10.1038/mp.2008.94)
12. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS. 1994 Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the national comorbidity survey. *Arch. Gen. Psychiat.* **51**, 8–19. (doi:10.1001/archpsyc.1994.03950010008002)
13. Timpano KR, Rubenstein LM, Murphy DL. 2012 Phenomenological features and clinical impact of affective disorders in OCD: a focus on the bipolar disorder and OCD connection. *Depress. Anxiety* **29**, 226–233. (doi:10.1002/da.20908)
14. Nestadt G, Bienvenu OJ, Cai G, Samuels J, Eaton WW. 1998 Incidence of obsessive–compulsive disorder in adults. *J. Nerv. Ment. Dis.* **186**, 401–406. (doi:10.1097/00005053-199807000-00003)
15. Nestadt G, Samuels JF, Romanoski AJ, Folstein MF, McHugh PR. 1994 Obsessions and compulsions in the community. *Acta Psychiat. Scand.* **89**, 219–224. (doi:10.1111/j.1600-0447.1994.tb01504.x)
16. De Luca V, Gershenzon V, Burroughs E, Javaid N, Richter MA. 2011 Age at onset in Canadian OCD patients: mixture analysis and systematic comparison with other studies. *J. Affect. Disord.* **133**, 300–304. (doi:10.1016/j.jad.2011.03.041)
17. Delorme R, Golmard JL, Chabane N, Millet B, Krebs MO, Mouren-Simeoni MC, Leboyer M. 2005 Admixture analysis of age at onset in obsessive–compulsive disorder. *Psychol. Med.* **35**, 237–243. (doi:10.1017/S0033291704003253)
18. Hantouche EG, Demonfaucon C. 2008 Resistant obsessive–compulsive disorder (ROC): clinical picture, predictive factors and influence of affective temperaments. *Encephale* **34**, 611–617. (doi:10.1016/j.encep.2007.12.008)
19. Hanna GL, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, Leventhal BL, Cook EH. 2002 Genome-wide linkage analysis of families with obsessive–compulsive disorder ascertained through pediatric probands. *Am. J. Med. Genet.* **114**, 541–552. (doi:10.1002/ajmg.10519)
20. Willour VL *et al*. 2004 Replication study supports evidence for linkage to 9p24 in obsessive–compulsive disorder. *Am. J. Hum. Genet.* **75**, 508–513. (doi:10.1086/423899)
21. Hanna GL *et al*. 2007 Evidence for a susceptibility locus on chromosome 10p15 in early-onset obsessive–compulsive disorder. *Biol. Psychiat.* **62**, 856–862. (doi:10.1016/j.biopsych.2007.01.008)
22. Shugart YY *et al*. 2006 Genomewide linkage scan for obsessive–compulsive disorder: evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. *Mol. Psychiat.* **11**, 763–770. (doi:10.1038/sj.mp.4001847)
23. Samuels JF *et al*. 2006 The OCD collaborative genetics study: methods and sample description. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **141B**, 201–207. (doi:10.1002/ajmg.b.30224)
24. Wang Y *et al*. 2009 Gender differences in genetic linkage and association on 11p15 in obsessive–compulsive disorder families. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **150B**, 33–40. (doi:10.1002/ajmg.b.30760)
25. Samuels J *et al*. 2007 Significant linkage to compulsive hoarding on chromosome 14 in families with obsessive–compulsive disorder: results from the OCD collaborative genetics study. *Am. J. Psychiat.* **164**, 493–499. (doi:10.1176/appi.ajp.164.3.493)

26. Psychiatric GWAS Consortium Steering Committee. 2009 A framework for interpreting genome-wide association studies of psychiatric disorders. *Mol. Psychiat.* **14**, 10–17. (doi:10.1038/mp.2008.126)
27. Sklar P *et al*. 2008 Whole-genome association study of bipolar disorder. *Mol. Psychiat.* **13**, 558–569. (doi:10.1038/sj.mp.4002151)
28. Stewart SE *et al*. In press. Genome-wide association study of obsessive–compulsive disorder. *Mol. Psychiat*. (doi:10.1038/mp.2012.85)
29. Welch JM *et al*. 2007 Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature* **448**, 894–900. (doi:10.1038/nature06104)
30. Hettema JM, Neale MC, Kendler KS. 2001 A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am. J. Psychiat.* **158**, 1568–1578. (doi:10.1176/appi.ajp.158.10.1568)
31. Nestadt G, Samuels J, Riddle M, Bienvenu III OJ, Liang KY, LaBuda M, Walkup J, Grados M, Hoehn-Saric R. 2005 A family study of obsessive–compulsive disorder. *Arch. Gen. Psychiat.* **57**, 358–363. (doi:10.1001/archpsyc.57.4.358)
32. Pauls DL, Alsobrook II JP, Goodman W, Rasmussen S, Leckman JF. 1995 A family study of obsessive–compulsive disorder. *Am. J. Psychiat.* **152**, 76–84.
33. Nestadt G *et al*. 2000 Complex segregation analysis provides compelling evidence for a major gene underlying obsessive–compulsive disorder and for heterogeneity by sex. *Am. J. Hum. Genet.* **67**, 1611–1616. (doi:10.1086/316898)
34. Hanna GL, Himle JA, Curtis GC, Gillespie BW. 2005 A family study of obsessive–compulsive disorder with pediatric probands. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **134**, 13–19. (doi:10.1002/ajmg.b.30138)
35. Cavallini MC, Pasquale L, Bellodi L, Smeraldi E. 1999 Complex segregation analysis for obsessive compulsive disorder and related disorders. *Am. J. Med. Genet.* **88**, 38–43. (doi:10.1002/(SICI)1096-8628(19990205)88:1<38::AID-AJMG7>3.0.CO;2-#)
36. Alsobrook JP, Leckman JF, Goodman WK, Rasmussen SA, Pauls DL. 1999 Segregation analysis of obsessive–compulsive disorder using symptom-based factor scores. *Am. J. Med. Genet.* **88**, 669–675. (doi:10.1002/(SICI)1096-8628(19991215)88:6<669::AID-AJMG17>3.0.CO;2-N)
37. Eapen V, Pauls DL, Robertson MM. 2006 The role of clinical phenotypes in understanding the genetics of obsessive–compulsive disorder. *J. Psychosom. Res.* **61**, 359–364. (doi:10.1016/j.jpsychores.2006.07.021)
38. Cryan EM, Butcher GJ, Webb MG. 1992 Obsessive–compulsive disorder and paraphilia in a monozygotic twin pair. *Br. J. Psychiat.* **161**, 694–698. (doi:10.1192/bjp.161.5.694)
39. Marks IM, Crowe M, Drewe E, Young J, Dewhurst WG. 1969 Obsessive compulsive neurosis in identical twins. *Br. J. Psychiat.* **115**, 991–998. (doi:10.1192/bjp.115.526.991)
40. McGuffin P, Mawson D. 1980 Obsessive–compulsive neurosis: two identical twin pairs. *Br. J. Psychiat.* **137**, 285–287. (doi:10.1192/bjp.137.3.285)
41. Woodruff R, Pitts Jr FN, 1964 Monozygotic twins with obsessional illness. *Am. J. Psychiat.* **120**, 1075–1080.
42. Carey G, Gottesman II. 1981 Twin and family studies of anxiety, phobic, and obsessive disorders. In *Anxiety: new research and changing concepts* (eds DF Klein, JG Rabkin), pp. 117–136. New York, NY: Raven Press.
43. Inouye E. 1965 Similar and dissimilar manifestations of obsessive–compulsive neuroses in monozygotic twins. *Am. J. Psychiat.* **121**, 1171–1175.
44. Jonnal AH, Gardner CO, Prescott CA, Kendler KS. 2000 Obsessive and compulsive symptoms in a general population sample of female twins. *Am. J. Med. Genet.* **96**, 791–796. (doi:10.1002/1096-8628(20001204)96:6<791::AID-AJMG19>3.0.CO;2-C)
45. van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. 2005 Twin studies on obsessive–compulsive disorder: a review. *Twin Res. Hum. Genet.* **8**, 450–458.
46. Hemmings SM, Stein DJ. 2006 The current status of association studies in obsessive–compulsive disorder. *Psychiat. Clin. North Am.* **29**, 411–444. (doi:10.1016/j.psc.2006.02.011)
47. Torres GE, Caron MG. 2003 Center stage for the serotonin transporter: a gain-of-function polymorphism in persons with obsessive–compulsive disorder. *Mol. Pharmacol.* **64**, 196–198. (doi:10.1124/mol.64.2.196)
48. Murphy DL, Lerner A, Rudnick G, Lesch KP. 2004 Serotonin transporter: gene, genetic disorders, and pharmacogenetics. *Mol. Interv.* **4**, 109–123. (doi:10.1124/mi.4.2.8)
49. Altemus M, Murphy DL, Greenberg B, Lesch KP. 1996 Intact coding region of the serotonin transporter gene in obsessive–compulsive disorder. *Am. J. Med. Genet.* **67**, 409–411. (doi:10.1002/(SICI)1096-8628(19960726)67:4<409::AID-AJMG16>3.0.CO;2-N)
50. Bengel D, Greenberg BD, Cora-Locatelli G, Altemus M, Heils A, Li Q, Murphy DL. 1994 Association of the serotonin transporter promoter regulatory region polymorphism and obsessive–compulsive disorder. *Mol. Psychiat.* **4**, 463–466. (doi:10.1038/sj.mp.4000550)
51. McDougle CJ, Epperson CN, Price LH, Gelernter J. 1998 Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive–compulsive disorder. *Mol. Psychiat.* **3**, 270–273. (doi:10.1038/sj.mp.4000391)
52. McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. 1994 Haloperidol addition in fluvoxamine-refractory obsessive–compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. *Arch. Gen. Psychiat.* **51**, 302–308. (doi:10.1001/archpsyc.1994.03950040046006)
53. Insel TR, Mueller EA, Alterman I, Linnoila M, Murphy DL. 1985 Obsessive–compulsive disorder and serotonin: is there a connection? *Biol. Psychiat.* **20**, 1174–1188. (doi:10.1016/0006-3223(85)90176-3)
54. Hollander E, DeCaria C, Gully R, Nitescu A, Suckow RF, Gorman JM, Klein DF, Liebowitz MR. 1991 Effects of chronic fluoxetine treatment on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine in obsessive–compulsive disorder. *Psychiat. Res.* **36**, 1–17. (doi:10.1016/0165-1781(91)90113-4)
55. Zohar J, Insel TR. 1987 Drug treatment of obsessive–compulsive disorder. *J. Affect. Disord.* **13**, 193–202. (doi:10.1016/0165-0327(87)90023-1)
56. Pigott TA, Hill JL, Grady TA, L'Heureux F, Bernstein S, Rubenstein CS, Murphy DL. 1993 A comparison of the behavioral effects of oral versus intravenous mCPP administration in OCD patients and the effect of metergoline prior to i.v. mCPP. *Biol. Psychiat.* **33**, 3–14. (doi:10.1016/0006-3223(93)90272-F)
57. Lesch K-P *et al*. 1996 Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527–1531. (doi:10.1126/science.274.5292.1527)
58. Bloch MH, Landeros-Weisenberger A, Sen S, Dombrowski P, Kelmendi B, Coric V, Pittenger C, Leckman JF. 2008 Association of the serotonin transporter polymorphism and obsessive–compulsive disorder: systematic review. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **147**, 850–858. (doi:10.1002/ajmg.b.30699)
59. Dickel DE *et al*. 2007 Association studies of serotonin system candidate genes in early-onset obsessive–compulsive disorder. *Biol. Psychiat.* **61**, 322–329. (doi:10.1016/j.biopsych.2006.09.030)
60. Hu XZ *et al*. 2006 Serotonin transporter promoter gain-of-function genotypes are linked to obsessive–compulsive disorder. *Am. J. Hum. Genet.* **78**, 815–826. (doi:10.1086/503850)
61. Wendland JR, DeGuzman TB, McMahon F, Rudnick G, Detera-Wadleigh SD, Murphy DL. 2008 SERT Ileu425Val in autism, Asperger syndrome and obsessive–compulsive disorder. *Psychiat. Genet.* **18**, 31–39. (doi:10.1097/YPG.0b013e3282f08a06)
62. Wendland JR, Kruse MR, Cromer KC, Murphy DL. 2007 A large case–control study of common functional SLC6A4 and BDNF variants in obsessive–compulsive disorder. *Neuropsychopharmacology* **33**, 1476. (doi:10.1038/sj.npp.1301515)
63. Wendland JR, Moya PR, Kruse MR, Ren-Patterson RF, Jensen CL, Timpano KR, Murphy DL. 2008 A novel, putative gain-of-function haplotype at SLC6A4 associates with obsessive-compulsive disorder. *Hum. Mol. Genet.* **17**, 717–723. (doi:10.1093/hmg/ddm343)
64. Murphy DL, Moya PR. 2011 Human serotonin transporter gene (SLC6A4) variants: their contributions to understanding pharmacogenomic and other functional G × G and G × E differences in health and disease. *Curr. Opin. Pharmacol.* **11**, 3–10. (doi:10.1016/j.coph.2011.02.008)
65. Pezawas L *et al*. 2008 Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Mol. Psychiat.* **13**, 709–716. (doi:10.1038/mp.2008.32)

66. Uher R, McGuffin P. 2009 The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression. *Mol. Psychiat.* **15**, 18–22. (doi:10.1038/mp.2009.123)
67. Caspi A *et al*. 2003 Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**, 386–389. (doi:10.1126/science.1083968)
68. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. 2010 Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am. J. Psychiat.* **167**, 509–527. (doi:10.1176/appi.ajp.2010.09101452)
69. Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, Rudnick G, Murphy DL. 2003 Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. *Mol. Psychiat.* **8**, 933–936. (doi:10.1038/sj.mp.4001365)
70. Delorme R *et al*. 2005 Support for the association between the rare functional variant I425V of the serotonin transporter gene and susceptibility to obsessive compulsive disorder. *Mol. Psychiat.* **10**, 1059–1061. (doi:10.1038/sj.mp.4001728)
71. Kilic F, Murphy DL, Rudnick G. 2003 A human serotonin transporter mutation causes constitutive activation of transport activity. *Mol. Pharmacol.* **64**, 440–446. (doi:10.1124/mol.64.2.440)
72. Holmes A. 2008 Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. *Neurosci. Biobehav. Rev.* **32**, 1293–1314. (doi:10.1016/j.neubiorev.2008.03.006)
73. Greenberg BD, Tolliver TJ, Huang SJ, Li Q, Bengel D, Murphy DL. 1999 Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. *Am. J. Med. Genet.* **88**, 83–87. (doi:10.1002/(SICI)1096-8628(19990205)88:1<83::AID-AJMG15>3.0.CO;2-0)
74. Lothe A, Boni C, Costes N, Gorwood P, Bouvard S, Le Bars D, Lavenne F, Ryvlin P. 2009 Association between triallelic polymorphism of the serotonin transporter and [18F]MPPF binding potential at 5-HT1A receptors in healthy subjects. *NeuroImage* **47**, 482–492. (doi:10.1016/j.neuroimage.2009.04.067)
75. Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger D. 2005 A susceptibility gene for affective disorders and the response of the human amygdala. *Arch. Gen. Psychiat.* **62**, 146–152. (doi:10.1001/archpsyc.62.2.146)
76. Murphy DL, Uhl GR, Holmes A, Ren-Patterson R, Hall FS, Sora I, Detera-Wadleigh S, Lesch K-P. 2003 Experimental gene interaction studies with SERT mutant mice as models for human polygenic and epistatic traits and disorders. *Genes Brain Behav.* **2**, 350–364. (doi:10.1046/j.1601-1848.2003.00049.x)
77. Murphy DL, Lesch KP. 2008 Targeting the murine serotonin transporter: insights into human neurobiology. *Nat. Rev. Neurosci.* **9**, 85–96. (doi:10.1038/nrn2284)
78. Fox MA, Jensen CL, French HT, Stein AR, Huang SJ, Tolliver TJ, Murphy DL. 2008 Neurochemical, behavioral, and physiological effects of pharmacologically enhanced serotonin levels in serotonin transporter (SERT)-deficient mice. *Psychopharmacology* **201**, 203–218. (doi:10.1007/s00213-008-1268-7)
79. Jennings KA *et al*. 2006 Increased expression of the 5-HT transporter confers a low-anxiety phenotype linked to decreased 5-HT transmission. *J. Neurosci.* **26**, 8955–8964. (doi:10.1523/JNEUROSCI.5356-05.2006)
80. Murphy DL, Fox MA, Timpano KR, Moya PR, Ren-Patterson R, Andrews AM, Holmes A, Lesch K-P, Wendland JR. 2008 How the serotonin story is being rewritten by new gene-based discoveries principally related to SLC6A4, the serotonin transporter gene, which functions to influence all cellular serotonin systems. *Neuropharmacology* **55**, 932–960. (doi:10.1016/j.neuropharm.2008.08.034)
81. Homberg JR *et al*. 2007 Characterization of the serotonin transporter knockout rat: a selective change in the functioning of the serotonergic system. *Neuroscience* **146**, 1662–1676. (doi:10.1016/j.neuroscience.2007.03.030)
82. Homberg JR, van den Bos R, den Heijer E, Suer R, Cuppen E. 2008 Serotonin transporter dosage modulates long-term decision-making in rat and human. *Neuropharmacology* **55**, 80–84. (doi:10.1016/j.neuropharm.2008.04.016)
83. Homberg JR, Contet C. 2009 Deciphering the interaction of the corticotropin-releasing factor and serotonin brain systems in anxiety-related disorders. *J. Neurosci.* **29**, 13743–13745. (doi:10.1523/JNEUROSCI.4362-09.2009)
84. Shugart YY *et al*. 2009 A family-based association study of the glutamate transporter gene SLC1A1 in obsessive–compulsive disorder in 378 families. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **150B**, 886–892. (doi:10.1002/ajmg.b.30914)
85. Dickel DE *et al*. 2006 Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive–compulsive disorder. *Arch. Gen. Psychiat.* **63**, 778–785. (doi:10.1001/archpsyc.63.7.778)
86. Wang Y *et al*. 2010 A screen of SLC1A1 for OCD-related alleles. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **153**, 675–679.
87. Stewart SE *et al*. 2007 Association of the SLC1A1 glutamate transporter gene and obsessive–compulsive disorder. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **144B**, 1027–1033. (doi:10.1002/ajmg.b.30533)
88. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. 2006 Glutamate transporter gene SLC1A1 associated with obsessive–compulsive disorder. *Arch. Gen. Psychiat.* **63**, 769–776. (doi:10.1001/archpsyc.63.7.769)
89. Wendland JR, Moya PR, Timpano KR, Anavitarte AP, Kruse MR, Wheaton MG, Ren-Patterson RF, Murphy DL. 2009 A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive–compulsive disorder. *Arch. Gen. Psychiat.* **66**, 408–416. (doi:10.1001/archgenpsychiatry.2009.6)
90. Veenstra-Vanderweele J *et al*. 2012 Functional studies and rare variant screening of SLC1A1/EAAC1 in males with obsessive–compulsive disorder. *Psychiat. Genet.* **22**, 256–260. (doi:10.1097/YPG.0b013e328353fb63)
91. Arnold PD *et al*. 2009 Glutamate receptor gene (GRIN2B) associated with reduced anterior cingulate glutamatergic concentration in pediatric obsessive–compulsive disorder. *Psychiat. Res.* **172**, 136–139. (doi:10.1016/j.pscychresns.2009.02.005)
92. Rosenberg DR, Hanna GL. 2000 Genetic and imaging strategies in obsessive–compulsive disorder: potential implications for treatment development. *Biol. Psychiat.* **48**, 1210–1222. (doi:10.1016/S0006-3223(00)01073-8)
93. Moore GJ, MacMaster FP, Stewart C, Rosenberg DR. 1998 Case study: caudate glutamatergic changes with paroxetine therapy for pediatric obsessive–compulsive disorder. *J. Am. Acad. Child Adolesc. Psychiat.* **37**, 663–667. (doi:10.1097/00004583-199806000-00017)
94. Wu K, Hanna GL, Rosenberg DR, Arnold PD. 2012 The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder. *Pharmacol. Biochem. Behav.* **100**, 726–735. (doi:10.1016/j.pbb.2011.10.007)
95. Coric V *et al*. 2005 Riluzole augmentation in treatment-resistant obsessive–compulsive disorder: an open-label trial. *Biol. Psychiat.* **58**, 424–428. (doi:10.1016/j.biopsych.2005.04.043)
96. Grant P, Lougee L, Hirschtritt M, Swedo SE. 2007 An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive–compulsive disorder. *J. Child Adolesc. Psychopharmacol.* **17**, 761–767. (doi:10.1089/cap.2007.0021)
97. Schwenkreis P, Liepert J, Witscher K, Fischer W, Weiller C, Malin JP, Tegenthoff M. 2000 Riluzole suppresses motor cortex facilitation in correlation to its plasma level. A study using transcranial magnetic stimulation. *Exp. Brain Res.* **135**, 293–299. (doi:10.1007/s002210000532)
98. Hezel DM, Beattie K, Stewart SE. 2009 Memantine as an augmenting agent for severe pediatric OCD. *Am. J. Psychiat.* **166**, 237. (doi:10.1176/appi.ajp.2008.08091427)
99. Poyurovsky M, Weizman R, Weizman A, Koran L. 2005 Memantine for treatment-resistant OCD. *Am. J. Psychiat.* **162**, 2191–2192. (doi:10.1176/appi.ajp.162.11.2191-a)
100. Pasquini M, Biondi M. 2006 Memantine augmentation for refractory obsessive–compulsive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiat.* **30**, 1173–1175. (doi:10.1016/j.pnpbp.2006.04.013)
101. Feusner JD, Kerwin L, Saxena S, Bystritsky A. 2009 Differential efficacy of memantine for obsessive–compulsive disorder versus generalized anxiety disorder: an open-label trial. *Psychopharmacol. Bull.* **42**, 81–93.
102. Aboujaoude E, Barry JJ, Gamel N. 2009 Memantine augmentation in treatment-resistant obsessive–compulsive disorder: an open-label trial. *J. Clin. Psychopharmacol.* **29**, 51–55. (doi:10.1097/JCP.0b013e318192e9a4)

103. Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L, Jenike MA. 2010 A single-blinded case–control study of memantine in severe obsessive–compulsive disorder. *J. Clin. Psychopharmacol.* **30**, 34–39. (doi:10.1097/JCP.0b013e3181c856de)
104. Machado-Vieira R, Salvadore G, Ibrahim LA, Diaz-Granados N, Zarate Jr CA. 2009 Targeting glutamatergic signaling for the development of novel therapeutics for mood disorders. *Curr. Pharm. Des.* **15**, 1595–1611. (doi:10.2174/138161209788168010)
105. Rodriguez CI, Kegeles LS, Flood P, Simpson HB. 2011 Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive–compulsive disorder. *J. Clin. Psychiat.* **72**, 567–569. (doi:10.4088/JCP.10l06653)
106. Bloch MH *et al*. 2012 Effects of ketamine in treatment-refractory obsessive–compulsive disorder. *Biol. Psychiat.* **72**, 964–970. (doi:10.1016/j.biopsych.2012.05.028)
107. Alonso P *et al*. 2012 Association between the NMDA glutamate receptor GRIN2B gene and obsessive–compulsive disorder. *J. Psychiat. Neurosci.* **37**, 273–281. (doi:10.1503/jpn.110109)
108. Arnold PD, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA. 2004 Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive–compulsive disorder: a preliminary study. *Psychopharmacology* **174**, 530–538. (doi:10.1007/s00213-004-1847-1)
109. Hall D, Dhilla A, Charalambous A, Gogos JA, Karayiorgou M. 2003 Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive–compulsive disorder. *Am. J. Hum. Genet.* **73**, 370–376. (doi:10.1086/377003)
110. Timpano KR, Schmidt NB, Wheaton MG, Wendland JR, Murphy DL. 2011 Consideration of the BDNF gene in relation to two phenotypes: hoarding and obesity. *J. Abnorm. Psychol.* **120**, 700–707. (doi:10.1037/a0024159)
111. Ren-Patterson RF, Cochran LW, Holmes A, Sherrill S, Huang SJ, Tolliver T, Lesch K-P, Lu B, Murphy DL. 2005 Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. *J. Neurosci. Res.* **79**, 756–771. (doi:10.1002/jnr.20410)
112. Nicolini H *et al*. 1996 DRD2, DRD3 and 5HT2A receptor genes polymorphisms in obsessive–compulsive disorder. *Mol. Psychiat.* **1**, 461–465.
113. Hemmings SM, Kinnear CJ, Niehaus DJ, Moolman-Smook JC, Lochner C, Knowles JA, Corfield VA, Stein DJ. 2003 Investigating the role of dopaminergic and serotonergic candidate genes in obsessive–compulsive disorder. *Eur. Neuropsychopharmacol.* **13**, 93–98. (doi:10.1016/S0924-977X(02)00129-3)
114. Cruz C, Camarena B, King N, Paez F, Sidenberg D, de la Fuente JR, Nicolini H. 1997 Increased prevalence of the seven-repeat variant of the dopamine D4 receptor gene in patients with obsessive–compulsive disorder with tics. *Neurosci. Lett.* **231**, 1–4. (doi:10.1016/S0304-3940(97)00523-5)
115. Millet B *et al*. 2003 Association between the dopamine receptor D4 (DRD4) gene and obsessive–compulsive disorder. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **116**, 55–59. (doi:10.1002/ajmg.b.10034)
116. Billett EA *et al*. 1998 Investigation of dopamine system genes in obsessive–compulsive disorder. *Psychiat. Genet.* **8**, 163–169. (doi:10.1097/00041444-199800830-00005)
117. Catalano M, Sciuto G, Di Bella D, Novelli E, Nobile M, Bellodi L. 1994 Lack of association between obsessive–compulsive disorder and the dopamine D3 receptor gene: some preliminary considerations. *Am. J. Med. Genet.* **54**, 253–255. (doi:10.1002/ajmg.1320540312)
118. Walitza S *et al*. 2008 Transmission disequilibrium studies in early onset of obsessive–compulsive disorder for polymorphisms in genes of the dopaminergic system. *J. Neural. Transm.* **115**, 1071–1078. (doi:10.1007/s00702-008-0051-6)
119. Karayiorgou M, Sobin C, Blundell ML, Galke BL, Malinova L, Goldberg P, Ott J, Gogos JA. 1999 Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive–compulsive disorder. *Biol. Psychiat.* **45**, 1178–1189. (doi:10.1016/S0006-3223(98)00319-9)
120. Camarena B, Rinetti G, Cruz C, Gomez A, de la Fuente JR, Nicolini H. 2001 Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive–compulsive disorder. *Am. J. Med. Genet.* **105**, 279–282. (doi:10.1002/ajmg.1323)
121. Pulver AE *et al*. 1994 Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. *J. Nerv. Ment. Dis.* **182**, 476–478. (doi:10.1097/00005053-199408000-00010)
122. Bienvenu OJ *et al*. 2008 Sapap3 and pathological grooming in humans: results from the OCD collaborative genetics study. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **150**, 710–720. (doi:10.1002/ajmg.b.30897)
123. Gothelf D *et al*. 2004 Obsessive–compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **126**, 99–105. (doi:10.1002/ajmg.b.20124)
124. Feinstein C, Eliez S, Blasey C, Reiss AL. 2002 Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biol. Psychiat.* **51**, 312–318. (doi:10.1016/S0006-3223(01)01231-8)
125. Papolos DF, Faedda GL, Veit S, Goldberg R, Morrow B, Kucherlapati R, Shprintzen RJ. 1996 Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am. J. Psychiat.* **153**, 1541–1547.
126. Saunders-Pullman R *et al*. 2002 Myoclonus dystonia: possible association with obsessive–compulsive disorder and alcohol dependence. *Neurology* **58**, 242–245. (doi:10.1212/WNL.58.2.242)
127. Doheny D *et al*. 2002 Clinical findings of a myoclonus-dystonia family with two distinct mutations. *Neurology* **59**, 1244–1246. (doi:10.1212/WNL.59.8.1244)
128. Marechal L *et al*. 2003 Severe myoclonus-dystonia syndrome associated with a novel epsilon-sarcoglycan gene truncating mutation. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **119**, 114–117. (doi:10.1002/ajmg.b.10062)
129. Zimprich A *et al*. 2001 Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat. Genet.* **29**, 66–69. (doi:10.1038/ng709)
130. Verkerk AJ, Mathews CA, Joosse M, Eussen BH, Heutink P, Oostra BA. 2003 CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics* **82**, 1–9. (doi:10.1016/S0888-7543(03)00097-1)
131. Boghosian-Sell L, Comings DE, Overhauser J. 1996 Tourette syndrome in a pedigree with a 7;18 translocation: identification of a YAC spanning the translocation breakpoint at 18q22.3. *Am. J. Hum. Genet.* **59**, 999–1005.
132. Petek E, Windpassinger C, Vincent JB, Cheung J, Boright AP, Scherer SW, Kroisel PM, Wagner K. 2001 Disruption of a novel gene (IMMP2L) by a breakpoint in 7q31 associated with Tourette syndrome. *Am. J. Hum. Genet.* **68**, 848–858. (doi:10.1086/319523)
133. Diaz-Anzaldua A, Joober R, Riviere JB, Dion Y, Lesperance P, Chouinard S, Richer F, Rouleau GA, 2004 Association between 7q31 markers and Tourette syndrome. *Am. J. Med. Genet. A* **127**, 17–20. (doi:10.1002/ajmg.a.20631)
134. Grimes DA, Han F, Lang AE, St George-Hyssop P, Racacho L, Bulman DE. 2002 A novel locus for inherited myoclonus-dystonia on 18p11. *Neurology* **59**, 1183–1186. (doi:10.1212/WNL.59.8.1183)
135. de Carvalho Aguiar P, Fazzari M, Jankovic J, Ozelius LJ. 2004 Examination of the SGCE gene in Tourette syndrome patients with obsessive–compulsive disorder. *Mov. Disord.* **19**, 1237–1238. (doi:10.1002/mds.20156)
136. Heiman G, Ottman R, Saunders-Pullman R, Ozelius L, Risch N, Bressman S. 2006 Obsessive–compulsive disorder is not a clinical manifestation of the DYT1 dystonia gene. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **144**, 361–364. (doi:10.1002/ajmg.b.30431)
137. Bihari K, Hill JL, Murphy DL. 1992 Obsessive–compulsive characteristics in patients with idiopathic spasmodic torticollis. *Psychiat. Res.* **42**, 267–272. (doi:10.1016/0165-1781(92)90118-M)
138. Bihari K, Pigott TA, Hill JL, Murphy DL. 1992 Blepharospasm and obsessive–compulsive disorder. *J. Nerv. Ment. Dis.* **180**, 130–132. (doi:10.1097/00005053-199202000-00011)
139. Voon V, Butler T, Ekanayake V, Gallea C, Ameli R, Hallet M. 2010 Psychiatric symptoms associated with focal hand dystonia. *Mov. Disord.* **25**, 2249–2252. (doi:10.1002/mds.23250)

140. Cavallaro R, Galardi G, Cavallini MC, Henin M, Amodio S, Bellodi L, Comi G. 2002 Obsessive compulsive disorder among idiopathic focal dystonia patients: an epidemiological and family study. *Biol. Psychiat.* **52**, 356–361. (doi:10.1016/S0006-3223(02)01332-X)
141. Chan P, Gonzalez-Maeso J, Ruf F, Bishop DF, Hof PR, Sealfon SC. 2005 Epsilon-sarcoglycan immunoreactivity and mRNA expression in mouse brain. *J. Comp. Neurol.* **482**, 50–73. (doi:10.1002/cne.20377)
142. Rauch SL, Whalen PJ, Curran T, Shin LM, Coffey BJ, Savage CR, McInerney SC, Baer L, Jenike MA. 2001 Probing striato-thalamic function in obsessive–compulsive disorder and Tourette syndrome using neuroimaging methods. *Adv. Neurol.* **85**, 207–224.
143. Lerner A *et al*. 2009 Involvement of insula and cingulate cortices in control and suppression of natural urges. *Cereb. Cortex* **19**, 218–223. (doi:10.1093/cercor/bhn074)
144. McLean-Tooke A, Spickett GP, Gennery AR. 2007 Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. *Scand. J. Immunol.* **66**, 1–7. (doi:10.1111/j.1365-3083.2007.01949.x)
145. Antshel KM, Kates WR, Roizen N, Fremont W, Shprintzen RJ. 2005 22q11.2 deletion syndrome: genetics, neuroanatomy and cognitive/behavioral features keywords. *Neuropsychol. Dev. Cogn. C Child Neuropsychol.* **11**, 5–19. (doi:10.1080/09297040590911185)
146. Eichstedt JA, Arnold SL. 2001 Childhood-onset obsessive–compulsive disorder: a tic-related subtype of OCD? *Clin. Psychol. Rev.* **21**, 137–157. (doi:10.1016/S0272-7358(99)00044-6)
147. Fisher SE *et al*. 2002 A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *Am. J. Hum. Genet.* **70**, 1183–1196. (doi:10.1086/340112)
148. Azzam A, Mathews CA. 2003 Meta-analysis of the association between the catecholamine-*O*-methyl-transferase gene and obsessive–compulsive disorder. *Am. J. Med. Genet. B Neuropsychiat. Genet.* **123**, 64–69. (doi:10.1002/ajmg.b.20013)
149. Michaelovsky E *et al*. 2008 Association between a common haplotype in the COMT gene region and psychiatric disorders in individuals with 22q11.2DS. *Int. J. Neuropsychopharmacol.* **11**, 351–363. (doi:10.1017/S1461145707008085)
150. Pooley EC, Fineberg N, Harrison PJ. 2007 The met(158) allele of catechol-O-methyltransferase (COMT) is associated with obsessive–compulsive disorder in men: case–control study and meta-analysis. *Mol. Psychiat.* **12**, 556–561. (doi:10.1038/sj.mp.4001951)
151. Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF. 2005 Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. *Nat. Neurosci.* **8**, 594–596. (doi:10.1038/nn1438)
152. Cryan JF, Slattery DA. 2007 Animal models of mood disorders: recent developments. *Curr. Opin. Psychiat.* **20**, 1–7. (doi:10.1097/YCO.0b013e3280117733)
153. Cryan JF, Holmes A. 2005 The ascent of mouse: advances in modelling human depression and anxiety. *Nat. Rev. Drug Discov.* **4**, 775–790. (doi:10.1038/nrd1825)
154. Post AM, Weyers P, Holzer P, Painsipp E, Pauli P, Wultsch T, Reif A, Lesch K-P. 2011 Gene-environment interaction influences anxiety-like behavior in ethologically based mouse models. *Behav. Brain Res.* **218**, 99–105. (doi:10.1016/j.bbr.2010.11.031)
155. Savignac HM, Hyland NP, Dinan TG, Cryan JF. 2011 The effects of repeated social interaction stress on behavioural and physiological parameters in a stress-sensitive mouse strain. *Behav. Brain Res.* **216**, 576–584. (doi:10.1016/j.bbr.2010.08.049)
156. Muller JM, Morelli E, Ansorge M, Gingrich JA. 2011 Serotonin transporter deficient mice are vulnerable to escape deficits following inescapable shocks. *Genes Brain Behav.* **10**, 166–175. (doi:10.1111/j.1601-183X.2010.00652.x)
157. Neumann ID, Wegener G, Homberg JR, Cohen H, Slattery DA, Zohar J, Olivier JDA, Mathé AA. 2010 Animal models of depression and anxiety: What do they tell us about human condition? *Prog. Neuropsychopharmacol. Biol. Psychiat.* **35**, 1357–1375. (doi:10.1016/j.pnpbp.2010.11.028)
158. Cryan JF *et al*. 2004 Norepinephrine-deficient mice lack responses to antidepressant drugs, including selective serotonin reuptake inhibitors. *Proc. Natl Acad. Sci. USA* **101**, 8186–8191. (doi:10.1073/pnas.0401080101)
159. Lesch KP. 2011 When the serotonin transporter gene meets adversity: the contribution of animal models to understanding epigenetic mechanisms in affective disorders and resilience. *Curr. Top. Behav. Neurosci.* **7**, 251–280. (doi:10.1007/7854_2010_109)
160. Hoyle D *et al*. 2011 Shared changes in gene expression in frontal cortex of four genetically modified mouse models of depression. *Eur. Neuropsychopharmacol.* **21**, 3–10. (doi:10.1016/j.euroneuro.2010.09.011)
161. Ting JT, Feng G. 2011 Neurobiology of obsessive–compulsive disorder: insights into neural circuitry dysfunction through mouse genetics. *Curr. Opin. Neurobiol.* **21**, 842–848. (doi:10.1016/j.conb.2011.04.010)
162. Tordera RM, Garcia-Garcia AL, Elizalde N, Segura V, Aso E, Venzala E, Ramãrez MJ, Del Rio J. 2011 Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. *Eur. Neuropsychopharmacol.* **21**, 23–32. (doi:10.1016/j.euroneuro.2010.06.016)
163. Joel D, Zohar O, Afek M, Hermesh H, Lerner L, Kuperman R, Grossisseroff R, Weizman A, Inzelberg R. 2005 Impaired procedural learning in obsessive–compulsive disorder and Parkinson's disease, but not in major depressive disorder. *Behav. Brain Res.* **157**, 253–263. (doi:10.1016/j.bbr.2004.07.006)
164. Dodman NH, Karlsson EK, Moon-Fanelli A, Galdzicka M, Perloski M, Shuster L, Lindblad-Toh K, Ginns EI. 2009 A canine chromosome 7 locus confers compulsive disorder susceptibility. *Mol. Psychiat.* **15**, 8–10. (doi:10.1038/mp.2009.111)
165. Thomas A, Burant A, Bui N, Graham D, Yuva-Paylor LA, Paylor R. 2009 Marble burying reflects a repetitive and perseverative behavior more than novelty-induced anxiety. *Psychopharmacology* **204**, 361–373. (doi:10.1007/s00213-009-1466-y)
166. Albelda N, Joel D. 2011 Animal models of obsessive–compulsive disorder: exploring pharmacology and neural substrates. *Neurosci. Biobehav. Rev.* **36**, 47–63. (doi:10.1016/j.neubiorev.2011.04.006)
167. Wang L, Simpson HB, Dulawa SC. 2009 Assessing the validity of current mouse genetic models of obsessive–compulsive disorder. *Behav. Pharmacol.* **20**, 119–133. (doi:10.1097/FBP.0b013e32832a80ad)
168. Joel D. 2006 Current animal models of obsessive compulsive disorder: a critical review. *Prog. Neuropsychopharmacol. Biol. Psychiat.* **30**, 374–388. (doi:10.1016/j.pnpbp.2005.11.006)
169. Korff S, Harvey BH. 2006 Animal models of obsessive–compulsive disorder: rationale to understanding psychobiology and pharmacology. *Psychiat. Clin. North Am.* **29**, 371–390. (doi:10.1016/j.psc.2006.02.007)
170. Holden C, Travis J. 2010 Profile: Nicholas Dodman. Can dogs behaving badly suggest a new way to treat OCD? *Science* **329**, 386–387. (doi:10.1126/science.329.5990.386)
171. Shmelkov SV *et al*. 2010 Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive–compulsive-like behaviors in mice. *Nat. Med.* **16**, 598–602. (doi:10.1038/nm.2125)
172. Chen SK, Tvrdik P, Peden E, Cho S, Wu S, Spangrude G, Capecchi MR. 2010 Hematopoietic origin of pathological grooming in Hoxb8 mutant mice. *Cell* **141**, 775–785. (doi:10.1016/j.cell.2010.03.055)
173. Shanahan NA, Holick Pierz KA, Masten VL, Waeber C, Ansorge M, Gingrich JA, Geyer MA, Hen R, Dulawa SC. 2009 Chronic reductions in serotonin transporter function prevent 5-HT1B-induced behavioral effects in mice. *Biol. Psychiat.* **65**, 401–408. (doi:10.1016/j.biopsych.2008.09.026)
174. Shanahan NA, Velez LP, Masten VL, Dulawa SC. 2011 Essential role for orbitofrontal serotonin 1B receptors in obsessive–compulsive disorder-like behavior and serotonin reuptake inhibitor response in mice. *Biol. Psychiat.* **70**, 1039–1048. (doi:10.1016/j.biopsych.2011.07.032)
175. Mundo E, Richter MA, Zai G, Sam F, McBride J, Macciardi F, Kennedy JL. 2002 5HT1Dbeta receptor gene implicated in the pathogenesis of obsessive–compulsive disorder: further evidence from a family-based association study. *Mol. Psychiat.* **7**, 805–809. (doi:10.1038/sj.mp.4001059)
176. Mundo E, Richter MA, Sam F, Macciardi F, Kennedy JL. 2000 Is the 5-HT(1Dbeta) receptor gene implicated in the pathogenesis of obsessive–compulsive disorder? *Am. J. Psychiat.* **157**, 1160–1161. (doi:10.1176/appi.ajp.157.7.1160)

177. Zuchner S *et al*. 2009 Multiple rare SAPAP3 missense variants in trichotillomania and OCD. *Mol. Psychiat.* **14**, 6–9. (doi:10.1038/mp.2008.83)
178. O'Sullivan RL, Keuthen NJ, Christenson GA, Mansueto CS, Stein DJ, Swedo SE. 1997 Trichotillomania: behavioral symptom or clinical syndrome? *Am. J. Psychiat.* **154**, 1442–1449.
179. Stein MB, Schork NJ, Gelernter J. 2008 Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology* **33**, 312–319. (doi:10.1038/sj.npp.1301422)
180. Rauch SL, Wright CI, Savage CR, Martis B, McMullin KG, Wedig MM, Gold AL, Keuthen NJ. 2007 Brain activation during implicit sequence learning in individuals with trichotillomania. *Psychiat. Res.* **154**, 233–240. (doi:10.1016/j.pscychresns.2006.09.002)
181. Swedo SE, Rapoport JL, Leonard HL, Schapiro MB, Rapoport SI, Grady CL. 1991 Regional cerebral glucose metabolism of women with trichotillomania. *Arch. Gen. Psychiat.* **48**, 828–833. (doi:10.1001/archpsyc.1991.01810330052008)
182. Chou-Green JM, Holscher TD, Dallman MF, Akana SF. 2003 Compulsive behavior in the 5-HT2C receptor knockout mouse. *Physiol. Behav.* **78**, 641–649. (doi:10.1016/S0031-9384(03)00047-7)
183. Palvimaki EP, Majasuo H, Syvalahti E, Hietala J. 2005 Serotonin 5-HT2C receptor-mediated phosphoinositide hydrolysis in rat choroid plexus after fluoxetine and citalopram treatments. *Pharmacol. Res.* **51**, 419–425. (doi:10.1016/j.phrs.2004.11.005)
184. Tecott LH, Abdallah L. 2003 Mouse genetic approaches to feeding regulation: serotonin 5-HT2C receptor mutant mice. *CNS Spectrums* **8**, 584–588.
185. Campbell KM *et al*. 1999 OCD-Like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1+ neurons. *J. Neurosci.* **19**, 5044–5053.
186. Nordstrom EJ, Burton FH. 2002 A transgenic model of comorbid Tourette's syndrome and obsessive–compulsive disorder circuitry. *Mol. Psychiat.* **7**, 617–625, 524. (doi:10.1038/sj.mp.4001144)
187. Cryan JF, Kelliher P, Kelly JP, Leonard BE. 1999 Comparative effects of serotonergic agonists with varying efficacy at the 5-HT(1A) receptor on core body temperature: modification by the selective 5-HT(1A) receptor antagonist WAY 100635. *J. Psychopharmacol.* **13**, 278–283. (doi:10.1177/026988119901300310)
188. Berridge KC, Aldridge JW, Houchard KR, Zhuang X. 2005 Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. *BMC Biol.* **3**, 4. (doi:10.1186/1741-7007-3-4)
189. McGrath MJ, Campbell KM, Parks CR, Burton FH. 2000 Glutamatergic drugs exacerbate symptomatic behavior in a transgenic model of comorbid Tourette's syndrome and obsessive–compulsive disorder. *Brain Res.* **877**, 23–30. (doi:10.1016/S0006-8993(00)02646-9)
190. Zhuang X, Oosting RS, Jones SR, Gainetdinov RR, Miller GW, Caron MG, Hen R. 2001 Hyperactivity and impaired response habituation in hyperdopaminergic mice. *Proc. Natl Acad. Sci. USA* **98**, 1982–1987. (doi:10.1073/pnas.98.4.1982)
191. Fox MA, Panessiti MG, Hall FS, Uhl GR, Murphy DL. In press. An evaluation of the serotonin system and perseverative, compulsive, stereotypical, and hyperactive behaviors in dopamine transporter (DAT) knockout mice. *Psychopharmacology*.
192. Fullana MA, Mataix-Cols D, Caspi A, Harrington H, Grisham JR, Moffitt TE, Poulton R. 2009 Obsessions and compulsions in the community: prevalence, interference, help-seeking, developmental stability, and co-occurring psychiatric conditions. *Am. J. Psychiat.* **166**, 329–336. (doi:10.1176/appi.ajp.2008.08071006)
193. Hanna GL, Fingerlin TE, Himle JA, Boehnke M. 2005 Complex segregation analysis of obsessive–compulsive disorder in families with pediatric probands. *Hum. Hered.* **60**, 1–9. (doi:10.1159/000087135)
194. Hanna GL, Fischer DJ, Chadha KR, Himle JA, Van Etten M. 2005 Familial and sporadic subtypes of early-onset obsessive–compulsive disorder. *Biol. Psychiat.* **57**, 895–900. (doi:10.1016/j.biopsych.2004.12.022)
195. Hemmings SM, Kinnear CJ, Lochner C, Niehaus DJ, Knowles JA, Moolman-Smook JC, Corfield VA, Stein DJ. 2004 Early- versus late-onset obsessive–compulsive disorder: investigating genetic and clinical correlates. *Psychiat. Res.* **128**, 175–182. (doi:10.1016/j.psychres.2004.05.007)
196. Ackerman DL, Greenland S, Bystritsky A. 1996 Use of receiver-operator characteristic (ROC) curve analysis to evaluate predictors of response to clomipramine therapy. *Psychopharmacol. Bull.* **32**, 157–165.
197. Ackerman DL, Greenland S, Bystritsky A, Morgenstern H, Katz RJ. 1994 Predictors of treatment response in obsessive–compulsive disorder: multivariate analyses from a multicenter trial of clomipramine. *J. Clin. Psychopharmacol.* **14**, 247–254.
198. Fontenelle LF, Marques C, Versiani M. 2002 The effect of gender on the clinical features and therapeutic response in obsessive–compulsive disorder. *Rev. Bras. Psiquiatr.* **24**, 7–11. (doi:10.1590/S1516-44462002000100005)
199. Geller DA, Biederman J, Griffin S, Jones J, Lefkowitz TR. 1996 Comorbidity of juvenile obsessive–compulsive disorder with disruptive behavior disorders. *J. Am. Acad. Child Adolesc. Psychiat.* **35**, 1637–1646. (doi:10.1097/00004583-199612000-00016)
200. Geller DA, Biederman J, Jones J, Shapiro S, Schwartz S, Park KS. 1998 Obsessive–compulsive disorder in children and adolescents: a review. *Harv. Rev. Psychiat.* **5**, 260–273. (doi:10.3109/10673229809000309)
201. Rosario-Campos MC *et al*. 2001 Adults with early-onset obsessive–compulsive disorder. *Am. J. Psychiat.* **158**, 1899–1903. (doi:10.1176/appi.ajp.158.11.1899)
202. Zohar AH, Ratzoni G, Pauls DL, Apter A, Bleich A, Kron S, Rappaport M, Weizman A, Cohen DJ. 1992 An epidemiological study of obsessive–compulsive disorder and related disorders in Israeli adolescents. *J. Am. Acad. Child Adolesc. Psychiat.* **31**, 1057–1061. (doi:10.1097/00004583-199211000-00010)
203. Schooler C, Revell AJ, Timpano KR, Wheaton M, Murphy DL. 2008 Predicting genetic loading from symptom patterns in obsessive-compulsive disorder: a latent variable analysis. *Depress. Anxiety* **25**, 680–688. (doi:10.1002/da.20444)
204. Mataix-Cols D, Rosario-Campos MC, Leckman JF. 2005 A multidimensional model of obsessive–compulsive disorder. *Am. J. Psychiat.* **162**, 228–238. (doi:10.1176/appi.ajp.162.2.228)
205. Abramowitz JS, Franklin ME, Schwartz SA, Furr JM. 2003 Symptom presentation and outcome of cognitive-behavioral therapy for obsessive–compulsive disorder. *J. Consult. Clin. Psychol.* **71**, 1049–1057. (doi:10.1037/0022-006X.71.6.1049)
206. Black DW, Monahan P, Gable J, Blum N, Clancy G, Baker P. 1998 Hoarding and treatment response in 38 nondepressed subjects with obsessive–compulsive disorder. *J. Clin. Psychiat.* **59**, 420–425. (doi:10.4088/JCP.v59n0804)
207. Winsberg ME, Cassic KS, Koran LM. 1999 Hoarding in obsessive–compulsive disorder: a report of 20 cases. *J. Clin. Psychiat.* **60**, 591–597. (doi:10.4088/JCP.v60n0905)
208. Samuels JF, Bienvenu OJ, Grados MA, Cullen B, Riddle MA, Liang KY, Eaton WW, Nestadt G. 2008 Prevalence and correlates of hoarding behavior in a community-based sample. *Behav. Res. Ther.* **46**, 836–844. (doi:10.1016/j.brat.2008.04.004)
209. Samuels JF *et al*. 2008 Sex-specific clinical correlates of hoarding in obsessive–compulsive disorder. *Behav. Res. Ther.* **46**, 1040–1046. (doi:10.1016/j.brat.2008.06.005)
210. Wheaton M, Timpano KR, Lasalle-Ricci VH, Murphy D. 2008 Characterizing the hoarding phenotype in individuals with OCD: associations with comorbidity, severity and gender. *J. Anxiety Disord.* **22**, 243–252. (doi:10.1016/j.janxdis.2007.01.015)
211. Grisham JR, Brown TA, Liverant GI, Campbell-Sills L. 2005 The distinctiveness of compulsive hoarding from obsessive–compulsive disorder. *J. Anxiety Disord.* **19**, 767–779. (doi:10.1016/j.janxdis.2004.09.003)
212. Wu KD, Watson D. 2005 Hoarding and its relation to obsessive–compulsive disorder. *Behav. Res. Ther.* **43**, 897–921. (doi:10.1016/j.brat.2004.06.013)
213. Frost RO, Steketee G, Williams LF, Warren R. 2000 Mood, personality disorder symptoms and disability in obsessive compulsive hoarders: a comparison with clinical and nonclinical controls. *Behav. Res. Ther.* **38**, 1071–1081. (doi:10.1016/S0005-7967(99)00137-0)
214. Samuels J, Bienvenu III OJ, Riddle MA, Cullen BA, Grados MA, Liang KY, Hoehn-Saric R, Nestadt G. 2002 Hoarding in obsessive compulsive disorder: results from a case–control study. *Behav. Res. Ther.* **40**, 517–528. (doi:10.1016/S0005-7967(01)00026-2)

215. Samuels JF *et al*. 2007 Hoarding in obsessive–compulsive disorder: results from the OCD collaborative genetics study. *Behav. Res. Ther.* **45**, 673–686. (doi:10.1016/j.brat.2006.05.008)
216. Abramowitz JS, Wheaton MG, Storch EA. 2008 The status of hoarding as a symptom of obsessive–compulsive disorder. *Behav. Res. Ther.* **46**, 1026–1033. (doi:10.1016/j.brat.2008.05.006)
217. Pertusa A, Fullana MA, Singh S, Alonso P, Menchon JM, Mataix-Cols D. 2008 Compulsive hoarding: OCD symptom, distinct clinical syndrome, or both? *Am. J. Psychiat.* **165**, 1289–1298. (doi:10.1176/appi.ajp.2008.07111730)
218. Zhang H, Leckman JF, Pauls DL, Tsai CP, Kidd KK, Campos MR. 2002 Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette syndrome. *Am. J. Hum. Genet.* **70**, 896–904. (doi:10.1086/339520)
219. Leckman JF, Bloch MH. 2008 A developmental and evolutionary perspective on obsessive–compulsive disorder: whence and whither compulsive hoarding? *Am. J. Psychiat.* **165**, 1229–1233. (doi:10.1176/appi.ajp.2008.08060891)
220. Mataix-Cols D, Frost RO, Pertusa A, Clark LA, Saxena S, Leckman JF, Stein DJ, Matsunaga H, Wilhelm S. 2010 Hoarding disorder: a new diagnosis for DSM-V. *Depress. Anxiety* **27**, 556–572. (doi:10.1002/da.20693)
221. Graybiel AM. 2008 Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.* **31**, 359–387. (doi:10.1146/annurev.neuro.29.051605.112851)
222. Cavallini MC, Di Bella D, Siliprandi F, Malchiodi F, Bellodi L. 2002 Exploratory factor analysis of obsessive–compulsive patients and association with 5-HTTLPR polymorphism. *Am. J. Med. Genet.* **114**, 347–353. (doi:10.1002/ajmg.1700)
223. Miguel EC, Leckman JF, Rauch S, do Rosario-Campos MC, Hounie AG, Mercadante MT, Chacon P, Pauls DL. 2005 Obsessive–compulsive disorder phenotypes: implications for genetic studies. *Mol. Psychiat.* **10**, 258–275. (doi:10.1038/sj.mp.4001617)
224. Atmaca M, Yildirim BH, Ozdemir BH, Aydin BA, Tezcan AE, Ozler AS. 2006 Volumetric MRI assessment of brain regions in patients with refractory obsessive–compulsive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiat.* **30**, 1051–1057. (doi:10.1016/j.pnpbp.2006.03.033)
225. Soriano-Mas C, Pujol J, Alonso P, Cardoner N, Menchon JM, Harrison BJ, Deus J, Vallejo J, Gaser C. 2007 Identifying patients with obsessive–compulsive disorder using whole-brain anatomy. *NeuroImage* **35**, 1028–1037. (doi:10.1016/j.neuroimage.2007.01.011)
226. Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, del Campo N, Sahakian BJ, Robbins TW, Bullmore E. 2007 Neurocognitive endophenotypes of obsessive–compulsive disorder. *Brain* **130**, 3223–3236. (doi:10.1093/brain/awm205)
227. Chamberlain SR *et al*. 2008 Orbitofrontal dysfunction in patients with obsessive–compulsive disorder and their unaffected relatives. *Science* **321**, 421–422. (doi:10.1126/science.1154433)
228. Greenberg BD, Rauch SL, Haber SN. 2010 Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology* **35**, 317–336. (doi:10.1038/npp.2009.128)
229. Murphy DL, Pigott TA. 1990 A comparative examination of a role for serotonin in obsessive compulsive disorder, panic disorder, and anxiety. *J. Clin. Psychiat.* **51**(Suppl. 53–58); discussion 9–60.
230. Saxena S, Brody AL, Maidment KM, Dunkin JJ, Colgan M, Alborzian S, Phelps ME, Baxter LR. 1999 Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive–compulsive disorder. *Neuropsychopharmacology* **21**, 683–693. (doi:10.1016/S0893-133X(99)00082-2)
231. Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter Jr LR. 2003 Differential brain metabolic predictors of response to paroxetine in obsessive–compulsive disorder versus major depression. *Am. J. Psychiat.* **160**, 522–532. (doi:10.1176/appi.ajp.160.3.522)
232. Sattler R, Rothstein JD. 2007 Targeting an old mechanism in a new disease-protection of glutamatergic dysfunction in depression. *Biol. Psychiat.* **61**, 137–138. (doi:10.1016/j.biopsych.2006.11.011)
233. Delgado PL, Goodman WK, Price LH, Heninger GR, Charney DS. 1990 Fluvoxamine/pimozide treatment of concurrent Tourette's and obsessive–compulsive disorder. *Br. J. Psychiat.* **157**, 762–765. (doi:10.1192/bjp.157.5.762)
234. Maina G, Pessina E, Albert U, Bogetto F. 2008 8-Week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive–compulsive disorder. *Eur. Neuropsychopharmacol.* **18**, 364–372. (doi:10.1016/j.euroneuro.2008.01.001)
235. Grisham JR, Anderson TM, Sachdev PS. 2008 Genetic and environmental influences on obsessive–compulsive disorder. *Eur. Arch. Psychiat. Clin. Neurosci.* **258**, 107–116. (doi:10.1007/s00406-007-0789-0)
236. Cromer KR, Schmidt NB, Murphy DL. 2007 Do traumatic events influence the clinical expression of compulsive hoarding? *Behav. Res. Ther.* **45**, 2581–2592. (doi:10.1016/j.brat.2007.06.005)
237. Cromer KR, Schmidt NB, Murphy DL. 2007 An investigation of traumatic life events and obsessive–compulsive disorder. *Behav. Res. Ther.* **45**, 1683–1691. (doi:10.1016/j.brat.2006.08.018)
238. Binder EB *et al*. 2008 Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *J. Am. Med. Assoc.* **299**, 1291–1305. (doi:10.1001/jama.299.11.1291)
239. Grabe HJ, Lange M, Wolff B, Volzke H, Lucht M, Freyberger HJ, John U, Cascorbi I. 2005 Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol. Psychiat.* **10**, 220–224. (doi:10.1038/sj.mp.4001555)
240. Koenen KC. 2007 Genetics of posttraumatic stress disorder: review and recommendations for future studies. *J. Trauma Stress* **20**, 737–750. (doi:10.1002/jts.20205)
241. Sasson Y, Dekel S, Nacasch N, Chopra M, Zinger Y, Amital D, Zohar J. 2005 Posttraumatic obsessive–compulsive disorder: a case series. *Psychiat. Res.* **135**, 145–152. (doi:10.1016/j.psychres.2004.05.026)
242. Lipinski JJ. 1994 Do 'flashbacks' represent obsessional imagery? *Compr. Psychiat.* **35**, 245–247. (doi:10.1016/0010-440X(94)90014-0)
243. Gershuny BS, Baer L, Radomsky AS, Wilson KA, Jenike MA. 2003 Connections among symptoms of obsessive–compulsive disorder and posttraumatic stress disorder: a case series. *Behav. Res. Ther.* **41**, 1029–1041. (doi:10.1016/S0005-7967(02)00178-X)
244. Gershuny BS, Baer L, Parker H, Gentes EL, Infield AL, Jenike MA. 2008 Trauma and posttraumatic stress disorder in treatment-resistant obsessive–compulsive disorder. *Depress. Anxiety* **25**, 69–71. (doi:10.1002/da.20284)
245. Grabe HJ *et al*. 2008 Obsessive–compulsive disorder and posttraumatic stress disorder. *Psychopathology* **41**, 129–134. (doi:10.1159/000112029)
246. Berthier ML, Kulisevsky J, Gironell A, Lopez OL. 2001 Obsessive–compulsive disorder and traumatic brain injury: behavioral, cognitive, and neuroimaging findings. *Neuropsychiat. Neuropsychol. Behav. Neurol.* **14**, 23–31.
247. Coetzer R, Stein DJ, Du Toit PL. 2001 Executive function in traumatic brain injury and obsessive–compulsive disorder: an overlap? *Psychiat. Clin. Neurosci.* **55**, 83–87. (doi:10.1046/j.1440-1819.2001.00792.x)
248. Grados MA. 2003 Obsessive–compulsive disorder after traumatic brain injury. *Int. Rev. Psychiat.* **15**, 350–358. (doi:10.1080/09540260310001606737)
249. Silver JM, Kramer R, Greenwald S, Weissman M. 2001 The association between head injuries and psychiatric disorders: findings from the New Haven NIMH epidemiologic catchment area study. *Brain Inj.* **15**, 935–945. (doi:10.1080/02699050110065295)
250. McKeon J, Roa B, Mann A. 1984 Life events and personality traits in obsessive–compulsive neurosis. *Br. J. Psychiat.* **144**, 185–189. (doi:10.1192/bjp.144.2.185)
251. Kant R, Smith-Seemiller L, Duffy JD. 1996 Obsessive–compulsive disorder after closed head injury: review of literature and report of four cases. *Brain Inj.* **10**, 55–63. (doi:10.1080/026990596124728)