

Obsessive–compulsive disorder: an integrative genetic and neurobiological perspective

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Abstract | Obsessive–compulsive disorder (OCD) is characterized by repetitive thoughts and behaviours that are experienced as unwanted. Family and twin studies have demonstrated that OCD is a multifactorial familial condition that involves both polygenic and environmental risk factors. Neuroimaging studies have implicated the cortico–striato–thalamo–cortical circuit in the pathophysiology of the disorder, which is supported by the observation of specific neuropsychological impairments in patients with OCD, mainly in executive functions. Genetic studies indicate that genes affecting the serotonergic, dopaminergic and glutamatergic systems, and the interaction between them, play a crucial part in the functioning of this circuit. Environmental factors such as adverse perinatal events, psychological trauma and neurological trauma may modify the expression of risk genes and, hence, trigger the manifestation of obsessive–compulsive behaviours.

Obsessive–compulsive disorder (OCD)¹ is a relatively common, frequently debilitating neuropsychiatric disorder that affects approximately 2% of the population in the United States². It is characterized by repetitive thoughts (obsessions) and repetitive behaviours (compulsions) that are experienced as unwanted (FIG. 1). OCD is a clinically heterogeneous disorder with a wide range of symptomatic expression. The age at onset ranges from very early childhood into adulthood. Indeed, 30–50% of individuals with OCD have onset in childhood³, often before 10 years of age. It is possible that childhood-onset OCD is a distinct neurodevelopmental form of the disorder^{4,5}.

Empirically validated treatments include serotonergic antidepressants (selective serotonin-reuptake inhibitors (SSRIs)) and cognitive behavioural therapy that involves exposure and response prevention. The effect size is modest for drug treatment⁶ and somewhat higher for cognitive behavioural therapy⁷, and there are additive effects for combined treatment. The ‘serotonergic hypothesis’ (REF. 8), which proposes that OCD is primarily a disorder of the serotonin system and which is based on the observed benefit of serotonergic antidepressants on OCD severity, has received mixed scientific support. However, there is evidence suggesting a role for dopaminergic mechanisms in the manifestation of OCD. For example, results from human and animal studies

using pharmacological manipulations, as well as from functional imaging and positron emission tomography (PET), all provide evidence that dopamine is important for the manifestation of OCD⁹. Furthermore, as discussed in later sections, there is growing evidence that glutamate and GABA also have a role in the expression of OCD. Clearly, further research is needed to more fully understand the aetiology, pathogenesis and pathophysiology of OCD in its various forms. This Review summarizes recent findings regarding the heterogeneity, inheritance and neural basis of OCD and proposes a model for possible neuroepigenetic mechanisms for the disorder.

Phenotypic heterogeneity

Obsessions and compulsions encompass the entire range of human thought and behaviour, and are unique to the affected individual. Contamination concerns and consequent washing rituals are well known examples of obsessions and compulsions, respectively, but the clinical expression of obsessions and compulsions is broad. For example, a person may develop contamination fears or disgust (a powerful affect that drives many OCD behaviours) in response to an abhorrent event, place or personal experience that has little to do with germs or dirt. So-called transformation obsessions occur when a person develops a fear of acquiring a certain

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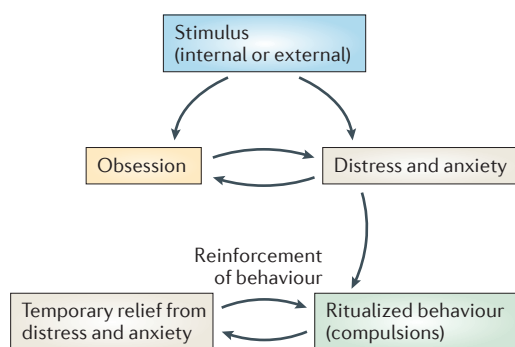


Figure 1 | The theoretical basis of obsessive-compulsive behaviour. An individual with obsessive-compulsive disorder experiences exaggerated concerns about danger, hygiene or harm that result in persistent conscious attention to the perceived threat or threats; in other words, they result in obsessions. In response to the distress and/or anxiety associated with these obsessions, the person acts (that is, performs a behaviour) to neutralize the distress and/or anxiety, which provides temporary relief from the anxiety associated with the obsession. However, this relief leads to reinforcement of the behaviours, leading to repetitive, compulsive behaviour when obsessions recur.

unwanted trait (for example, unpopularity or antisocial behaviour) from another person, leading to avoidance behaviours and contamination concerns. Obsession-only OCD also occurs, for example, in individuals who have a fear of causing harm to self or others, in which case there may be avoidance behaviour but no rituals. Mental compulsions, such as internal reviewing of interpersonal interactions to determine whether something offensive or humiliating has transpired, may also be invisible to the clinician, and in many cases they can only be exposed by careful symptom elicitation.

Several studies have been undertaken to investigate and better characterize the clinical heterogeneity of OCD. Most of them have used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)¹⁰ to assess the presence of OCD. The Y-BOCS is a ten-item anchored ordinal scale (0–4) that rates the clinical severity of the disorder by scoring the time occupied by obsessions and compulsions, the degree to which they interfere with daily life, the subjective distress they cause, the individual's internal resistance to the obsessions and compulsions, and the degree of control an individual has over his or her obsessions and compulsions. The Y-BOCS also includes a symptom checklist of over 70 symptoms of obsessions and compulsions — which are categorized by the various types of symptoms that can occur — such as hoarding, washing, checking and fear of contamination. Equally important in the Y-BOCS are quantitative measures of avoidance, insight, indecisiveness, 'pathological' responsibility, doubt and obsessional 'slowness'. The Y-BOCS is a clinician-administered instrument that is most informative when given to both subjects and their close or intimate relatives.

Exposure and response prevention

The first-line behavioural therapeutic technique for the treatment of obsessive-compulsive disorder, anxiety disorders and phobias. This technique involves exposing the patient to stimuli that the patient perceives as threatening, anxiety-provoking or dangerous. This gradual exposure accompanies the prevention of responses that the patient usually undertakes in order to avoid or decrease anxiety. This technique is theoretically anchored in the Pavlovian extinction of conditioned fear.

Probands

People who serve as the starting point of a genetic study.

To assess whether a limited number of symptom clusters could be identified within the diverse symptoms of OCD, an early study¹¹ used a factor analytic approach to analyse data from the Y-BOCS symptom checklists¹⁰ from 107 adults with OCD. Three principal components of symptoms emerged from this analysis, which the authors labelled 'symmetry-hoarding', 'contamination-cleaning' and 'pure obsessions'. Twenty subsequent factor analytic studies were also based on Y-BOCS checklist data^{12–31}. Although there was some variability in results among the studies — some reported three factors, others reported four or five — there was remarkable similarity in terms of the symptoms that loaded onto the various factors. Indeed, most of these studies found that the following four factors best reflected the symptom dimensions in OCD: symmetry obsessions and compulsions; contamination and cleaning; aggressive, sexual and religious obsessions; and hoarding obsessions and compulsions. A meta-analysis³² of all 21 studies published between 1994 and 2008, with a total sample size of 5,124 patients, reported that the heterogeneity of symptoms was best explained by a structure with four similar factors (BOX 1): the first factor included symmetry obsessions and repeating, ordering and counting compulsions; the second included symptoms of aggressive, sexual, religious and somatic obsessions and checking compulsions; the third included contamination obsessions and cleaning compulsions; and the fourth factor included hoarding obsessions and compulsions. Notably, this meta-analysis included 18 studies of adults and 3 of children. An analysis of only the studies of adults yielded the same factor structure as that of the larger meta-analysis³², whereas in a separate meta-analysis of the three studies of children, 'checking compulsions' loaded on the first factor and 'somatic obsessions' on the third factor. The findings from all of the factor analyses, as well as findings from treatment^{33,34} and imaging³⁵ studies, have resulted in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*³⁶ categorization of hoarding as a distinct but OCD-related disorder.

In summary, OCD is a multidimensional disorder that consists of four or five symptom clusters. These findings may be helpful in elucidating the pathophysiology and aetiology underlying this complex condition, as different clusters of symptoms may have distinct neural circuitry³⁵ and distinct genetic or aetiological origins^{26,37}.

Heritability

Family studies. Since 1930, it has been consistently reported that OCD is transmitted within families (that is, it is familial)³⁸. Indeed, out of 18 studies^{39–57} involving families of adult probands with OCD, only 2 concluded that OCD was not familial^{44,47}, and all 7 studies^{58–64} involving relatives of children or adolescents with OCD reported that OCD is familial (for a complete review of all family studies, see REF. 38). Risk of OCD is significantly higher for relatives of patients with childhood-onset OCD, and clinicians should be looking for the possible emergence of obsessive-compulsive symptoms in family members who have not yet passed through a period of peak risk (7–12-year-olds).

Box 1 | Factor structure of obsessive–compulsive symptoms for adults and children

Factor analysis has been used to identify symptom dimensions (or subtypes) of obsessive–compulsive disorder (OCD). A factor analysis³² on data from 21 studies of children and adults with OCD revealed that a structure with four factors (or dimensions) best explained the heterogeneity of symptoms (see the table); this solution accounted for 79.0% of the variance. The first factor comprised symmetry obsessions and repeating, ordering and counting compulsions, and accounted for 26.7% of the variance. The second factor involved ‘taboo thoughts’ and included symptoms of aggressive, religious, sexual and somatic obsessions and checking compulsions; it accounted for 21.0% of the variance. The third factor included contamination obsessions and cleaning compulsions and accounted for 15.9% of the variance. The fourth factor included hoarding obsessions and compulsions and accounted for 15.4% of the variance. The structure obtained was slightly different when data from children were considered. In children, somatic obsessions were included in the contamination factor and checking compulsions were included in the symmetry factor. Data in table from REF. 32.

Factor (% variance)	Obsession	Compulsion
Symmetry (26.7)	Symmetry	<ul style="list-style-type: none"> • Counting • Ordering • Repeating
Taboo thoughts (21.0)	<ul style="list-style-type: none"> • Aggressive • Religious • Sexual • Somatic 	Checking
Contamination (15.9)	Contamination	Cleaning
Hoarding (15.4)	Hoarding	Hoarding

A selection of family studies is presented in TABLE 1. All of the studies included in TABLE 1 used similar methodology. First, all subjects underwent a structured clinical interview to assess the presence of obsessive–compulsive symptoms, and this assessment included the Y-BOCS; second, family history information was collected from individuals close to the person being described about the presence of obsessive–compulsive symptoms and whether they resulted in impaired functioning in that relative (this was done for both first-degree relatives of patients with OCD and relatives of control subjects); and third, medical records were obtained for all first-degree relatives of patients with OCD and control subjects when available. Thus, these studies used both interview data and family history data to assess the presence of OCD symptoms in family members of patients with OCD, with the exception of one study⁵⁵. The goal of this study⁵⁵ was to determine whether diagnosing relatives on the basis of only interview data differed from diagnosing them with data from a combination of interview and family history data. Findings from this study suggested that when data from both interviews and family history were included in the diagnostic process, the proportion of relatives of patients with OCD who were diagnosed with OCD was similar to that found in the other studies that used this methodology. By contrast, when the assessment was based only on interview data, evidence for familiarity (that is, increased rate of illness) was seen only when an expanded phenotype was used that included subclinical OCD cases (that is, cases in which individuals reported that they had significant obsessive and/or compulsive symptoms but information about severity was not available) (TABLE 1). This is an important finding because many individuals with OCD are secretive about their symptoms and may deny having them or show limited insight around their behaviours, thus making it difficult to determine whether they meet the criteria for OCD. Furthermore, affected relatives, albeit with milder forms, may not have sought treatment, in which case no medical records would be available to validate any diagnosis. This could result in an underestimate of the true rate of illness in relatives.

What is evident from most of the studies carried out in families of children with OCD is that the rate of OCD among these relatives is significantly higher than the rates in families of adults with OCD (TABLE 1). Thus, childhood-onset OCD may be different — and possibly have a different aetiology — from adult-onset OCD⁵. Childhood onset usually refers to onset before the age of 12 years (that is, before the start of puberty), although there is some disagreement with regard to the specific age at onset⁵. Individuals with childhood-onset OCD are predominantly male and are often also diagnosed with tic disorders, attention deficit hyperactivity disorder and/or oppositional defiant disorder, as well as with other developmental disorders of learning and enuresis. Nevertheless, they have a better outcome than individuals with adult-onset OCD⁶⁵. This different pattern of familial risk for childhood-onset OCD versus adult-onset OCD has also been observed in studies of other psychiatric disorders — for example, in schizophrenia and bipolar illness^{66,67}. This suggests that there may be genetic and/or epigenetic factors that affect the age at which disease symptoms manifest in an individual and that these factors are also present in (or transmitted to) the relatives of individuals with an early onset of disease.

As noted above, the studies of childhood-onset OCD demonstrate that there is a significantly increased rate of OCD among first-degree relatives of these individuals compared with relatives of adults with OCD. The odds ratios obtained from studies of childhood-onset OCD range from 12 to 30, whereas the odds ratios calculated from studies of adults are approximately 5 (REFS 51,52,56). One study also observed an increased rate of Tourette syndrome and/or chronic tics among first-degree relatives of people with childhood-onset OCD compared with relatives of people with adult-onset OCD⁶². These findings are consistent with studies that found an increased rate of OCD in families of Tourette syndrome probands⁶⁸, suggesting that the two disorders may have common neurobiological mechanisms.

Enuresis

Involuntary control of urination, such as bed-wetting.

Odds ratios

Measures of effect size, defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. In the context of a genetic-association study, this might be the odds of obsessive–compulsive disorder occurring in one genotype group against the odds of it occurring in another genotype group.

Table 1 | Frequency of OCD among relatives of adults and children with and without OCD

Studies	Relatives of cases		Relatives of controls	
	Frequency of OCD	Frequency of subclinical OCD	Frequency of OCD	Frequency of subclinical OCD
Adult family studies				
Pauls <i>et al.</i> ⁵¹	0.103	0.079	0.019	0.020
Nestadt <i>et al.</i> ⁵²	0.117	0.046	0.027	0.030
Fyer <i>et al.</i> ⁵⁴	0.062	0.084	0.000	0.000
Lipsitz <i>et al.</i> ⁵⁵	0.026	0.057	0.013	0.013
Grabe <i>et al.</i> ⁵⁶	0.064	0.055	0.012	0.030
Black <i>et al.</i> ⁵⁷	0.101	0.006	0.033	0.005
Child family studies				
Reddy <i>et al.</i> ⁶¹	0.050	ND	0.000	ND
Hanna <i>et al.</i> ⁶³	0.225	ND	0.026	ND
do Rosario-Campos <i>et al.</i> ⁶²	0.227	0.065	0.009	0.015

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It has been suggested⁵¹ that there may be at least four different types of OCD, three of which are familial forms of the disorder. These familial forms include an early-onset type of OCD that is comorbid with tics (expressed as Tourette syndrome and/or chronic tics), an early-onset type of OCD without tics, and a later-onset form of OCD without tics. The non-familial type (that is, sporadic OCD) also does not seem to be associated with tics.

Twin studies. Familiarity does not necessarily mean that a condition is genetic; it simply indicates that a condition is 'transmitted' within families. This familiarity could be due to genetic factors but could also be due to a shared environment. Twin studies can provide evidence of the extent to which a condition is influenced by genetic factors and by environmental factors⁶⁹. A meta-analysis⁷⁰ that included 37 samples with a total of 24,161 twin pairs from 14 published studies examined the heritability of obsessive-compulsive behaviours. Findings from this meta-analysis support the hypothesis that genetic factors are important in the manifestation of obsessive-compulsive behaviours. Specifically, additive genetic variance accounted for approximately 40% of the phenotypic variance of obsessive-compulsive behaviours that was observed in this sample of twins, and non-shared environmental factors accounted for 51%. Notably, shared environmental factors (for example, factors in the family environment) did not contribute to the variance of obsessive-compulsive behaviours that was observed in the twin pairs. A key result from these studies is that genetic factors are important for the manifestation of obsessive-compulsive behaviours and that non-genetic, non-shared environmental factors also have a considerable influence on the manifestation of OCD, presumably through epigenetic mechanisms.

Furthermore, the results of this meta-analysis were independent of symptom severity or sex of the patients, suggesting that genetic and/or environmental factors that are relevant to the expression of OCD do not

influence the severity of the illness. Notably, in these twin studies, the contribution of a non-shared environment increased with age, suggesting that environmental factors may have a greater role in the later-onset expression of obsessive-compulsive symptoms. Finally, results of this meta-analysis⁷⁰ implied a role for gene-environment interactions in the aetiology of obsessive-compulsive symptoms. Thus, it seems that specific non-shared environmental events that interact with risk genes may be crucial for the development of OCD.

In summary, it is clear that genetic factors play a part in the manifestation of obsessions and compulsions, whether they are clinically significant or not. However, it might be argued that this is not proof that genetic factors contribute to the manifestation of the disorder. One study⁷¹ investigated the relationship between commonly observed, non-pathological repetitive behaviours in childhood (for example, bedtime rituals) and a childhood obsessive-compulsive symptom syndrome. These investigators also examined the extent to which this relationship might be genetically mediated. They screened a community sample of 4,662 6-year-old twin pairs and interviewed 854 pairs to determine the presence of OCD and of repetitive routines that commonly occur in children. Using standard genetic methods⁶⁹, they reported a significant correlation (due to genetic factors) between the frequency of apparently normal childhood rituals and the later appearance of clinical OCD. Thus, commonly observed rituals in childhood may be a risk factor for the later development of OCD. What remains to be determined is which additional factors are necessary for the clinical expression of the disorder. The findings from the twin studies imply that non-shared environmental factors may trigger the disorder. Alternatively, it is possible that there are additional genes or non-shared factors that specifically increase the severity of expression of the symptoms, which then results in manifestation of the full syndrome.

Genetic linkage studies. Given the evidence that OCD is familial and at least in part genetic, several genetic linkage studies were undertaken to locate the chromosomal regions that harbour risk genes for OCD. It should be noted, however, that linkage studies are not optimal for finding genes that have only a small to moderate effect (which is often the case in complex multifactorial disorders); linkage studies are most useful when there are a small number of genes (one or two), each with a large effect, that increase the risk of a disorder. In the case of OCD, a complex disorder, a linkage study might identify a rare gene of larger effect in one family, and this gene could perhaps provide a clue as to the genetic pathways that might be involved in the disorder — a scenario similar to that in a study of Tourette syndrome⁷². Thus, several linkage studies were undertaken in the hope of identifying such ‘large-effect’ genes.

The largest study⁷³ included 966 individuals from 219 families. The data indicated possible risk loci on chromosomes 1q, 3q, 6q, 7p and 15q. The strongest evidence was obtained for markers on chromosome 3q27–28 when a broad definition of OCD (that is, including both definite and subclinical cases) was used. However, these results did not reach accepted levels of statistical significance, suggesting that there were no genes of large effect in these families. Additional analyses conducted by the same group of investigators⁷⁴ examined whether compulsive hoarding might show linkage to genomic markers. When families that included two or more relatives showing hoarding were considered, there was strong suggestive but statistically non-significant evidence for linkage on chromosome 14. Notably, there was no evidence of linkage for markers on chromosome 3q, suggesting that hoarding may have a different genetic aetiology from other forms of OCD. This is consistent with a previous study⁷⁵ and has contributed to the inclusion in DSM-5 (REF. 36) of hoarding as a diagnosis that is separate from OCD.

The first reported genome-wide linkage study of OCD involved 66 individuals from 7 families, which were identified through childhood OCD probands⁷⁶. Semi-structured psychiatric interviews were used to assess the presence of OCD symptoms, through which 32 relatives were identified as meeting DSM-IV criteria for a diagnosis of OCD. A genome scan with 349 microsatellite markers revealed suggestive (statistically non-significant) evidence for linkage on chromosome 9p. A subsequent⁷⁷ attempt to replicate this finding in 50 pedigrees of individuals with OCD also yielded modest evidence for linkage in the same region. The closest gene to the linkage peaks in both studies was *SLC1A1* (also known as *EAAT3*), which encodes a glutamate transporter⁷⁷.

A second genome-wide linkage study⁷⁸ analysed data from 26 multigenerational families. Relatives of patients with OCD were assessed on the basis of data from semi-structured psychiatric interviews and all other available sources of information. This second study⁷⁸ showed suggestive linkage for a region on chromosome 10p15. However, when the data from both studies from these investigators were combined, evidence for linkage to this region decreased, although it was still modestly positive⁷⁸.

A recent genome-wide study⁷⁹ of three families — from a genetically isolated population in the Central Valley of Costa Rica — in which two or more individuals had childhood-onset OCD analysed data from a panel of ~6,000 single-nucleotide polymorphisms (SNPs) using both parametric and non-parametric methods. This revealed four genomic areas for which there was suggestive evidence for linkage: 1p21, 15q14, 16q24 and 17p12. The region on chromosome 15q14 provided the strongest evidence for linkage. Notably, this region was also identified in the largest linkage study completed to date⁷³.

A fifth genome-wide study⁸⁰ included 33 Caucasian families (a total of 245 individuals with genotype data) from the United States in which at least 2 individuals had childhood-onset OCD. Families were genotyped with a panel of SNPs, and parametric and non-parametric linkage analyses were conducted, followed by fine-mapping analyses in genomic regions for which there was initial suggestive evidence for linkage. This yielded five chromosomal regions with suggestive evidence for linkage: 1p36, 2p14, 5q13, 6p25 and 10p13. The strongest result was at 1p36.33–p36.32. None of these findings overlaps with the linkage results summarized above.

All of these findings should be interpreted with caution. First, none of the findings reached accepted levels of statistical significance. Second, with the exception of one study⁷³, the sample sizes were small. Third, as mentioned above, genetic linkage studies are not the optimal design for identifying risk alleles for complex (that is, non-Mendelian) traits such as those in OCD. Thus, despite the fact that one study⁷³ included 219 families with almost 1,000 individuals, and another⁸⁰ included 33 multigenerational families, it is unlikely that these studies could have yielded significant evidence for linkage, given that OCD is probably a multigenic disorder with a large number of risk loci of small to moderate effect⁸¹. Nevertheless, at least two genomic regions (on chromosomes 9 and 15) were identified in different studies^{73,76,77,79}, and candidate gene studies have provided evidence that the gene on chromosome 9 (*SLC1A1*) is associated with at least some cases of OCD^{82–90}. Although linkage studies are not optimal for finding genes of small to moderate effect, it is possible that once genes have been identified through association studies, linkage strategies together with whole genome-sequencing studies in large families will be helpful in determining the functions of those genes.

Candidate gene studies. More than 100 candidate gene studies of OCD have been published. Most of these focused on genetic variants within pathways for serotonin, dopamine and glutamate or on genes involved in immune and white matter pathways. These studies were designed on the basis of the current understanding of the neurocircuitry and neurotransmitters involved in OCD^{91–93}. A recent study⁹⁴ reported the results of two meta-analyses of the 230 polymorphisms that have been described in 113 studies that provided sufficient information to be included in a meta-analysis. The first

Genetic linkage studies

Studies that explore the possibility that a risk gene for a particular disorder is located near a gene or DNA marker localized to a specific chromosomal region and is thus inherited together with that locus during meiosis. These studies are based on the observation that genes that are close to each other on the same chromosome are less likely to be separated during chromosomal crossover and are therefore said to be genetically linked.

Single-nucleotide polymorphisms

(SNPs). DNA sequence variations that occur when a single nucleotide at a specific site in the genome differs between paired chromosomes.

Candidate gene studies

Studies that assess whether specific ‘candidate’ genes are involved in the variation observed for a particular trait based on prior knowledge, such as the function of the gene and polymorphisms in the gene that are known to alter its function.

meta-analysis examined 20 polymorphisms that had been studied in at least five separate data sets. The second set of analyses included the 210 polymorphisms that had been examined in less than five studies. Results of the first analysis suggested that OCD is associated with polymorphisms in two serotonin-system-related genes, *5-HTTLPR* (also known as *SLC6A4*) and *HTR2A* (5-hydroxytryptamine (serotonin) receptor 2A)⁹⁴. In addition, variants in two genes (*COMT* (catechol-O-methyltransferase) and *MAOA* (monoamine oxidase A)) were shown to be associated with OCD only in males⁹⁴. Furthermore, there were non-significant trends for associations with polymorphisms in two dopamine-system-related genes (*DAT1* (also known as *SLC6A3*) and *DRD3* (dopamine receptor D3)) and one in a glutamate-system-related gene (*SLC1A1*)⁹⁴. One possible reason that the dopamine- and glutamate-related genes did not reach statistical significance in either of these meta-analyses is that the number of studies that were included was considerably smaller than the number of studies that were included in the evaluation of serotonin-system-related genes. In the second set of analyses, mean odds ratios were calculated for polymorphisms. Significant associations ($P < 0.01$) were observed for polymorphisms in trophic factors, GABA, glutamate, serotonin, bradykinin, acetylcholine, glycine, ubiquitin, immunological factors and myelination. But as the author points out, these findings need to be interpreted with caution as a number of them were based on a single study. Nevertheless, these results suggest that additional study is potentially fruitful.

Genome-wide association studies. Two genome-wide association studies (GWASs) of OCD have been reported^{95,96}. The first GWAS — by the International OCD Foundation Genetics Collaborative — involved 1,465 cases, 5,557 ancestry-matched controls and 400 trios (consisting of affected probands and their parents or an affected proband, one parent and one sibling) and analysed 469,410 autosomal and 9,657 X chromosomal SNPs. In the case-control analysis, two SNPs located in *DLGAP1* (discs large-associated protein 1) — a member of the neuronal postsynaptic density complex — showed the strongest associations with OCD ($P = 2.49 \times 10^{-6}$ and $P = 3.44 \times 10^{-6}$, respectively). In the trio analysis, a SNP near *BTBD3* (BTB (POZ) domain-containing 3) exceeded the genome-wide significance threshold ($P = 3.84 \times 10^{-8}$). However, in the meta-analyses that included the trios, the results did not reach genome-wide significance ($P = 3.62 \times 10^{-5}$).

In the meta-analyses of all of the data (trios and case-control samples), the SNP rs297941 near *FAIM2* (FAS apoptotic inhibitory molecule 2) on chromosome 12 showed the strongest association with OCD ($P = 4.99 \times 10^{-7}$). This gene is highly expressed in the CNS, and its protein has a role in FAS-mediated cell death⁹⁷ and is associated with neuroprotection following transient brain ischaemia⁹⁸. Furthermore, in rats, *Faim2* is expressed at the postsynaptic membrane in a subset of synapses and in dendrites, and colocalizes with the glutamate receptor subunit GluR2 (REF. 97).

As stated earlier, genome-wide significant results were observed in the trio sample for *BTBD3*, which is a part of a large family of transcription factors. *BTBD3* is important for the regulation of transcription, ion channel assembly and gating, and post-translational modification and degradation of proteins⁹⁹. It is expressed in the brain, and its highest level of expression occurs in childhood and adolescence, the time when the first obsessive-compulsive symptoms are experienced in most individuals with OCD. The SNP associated with *BTBD3* also seems to be associated with the gene encoding *ISM1* (isthmin 1), which is also located on chromosome 20 and is marginally associated ($P = 0.0036$) with OCD. *ISM1* expression is correlated with expression of *ADCY8* (adenylyl cyclase 8)^{95,100}, a gene on chromosome 8 with an allele that is strongly associated with OCD and has been shown to be associated with fear memory^{95,98}. In addition, *ISM1* expression is associated with the expression of the glutamate-system-related genes *GRIK1* (glutamate receptor ionotropic, kainate 1), *GRIK4*, *DLGAP3* (also known as *SAPAP3*), *SHANK3* (SH3 and multiple ankyrin repeat domains 3) and *ADARB2* (adenosine deaminase, RNA-specific, B2)⁹⁵.

The second GWAS⁹⁶ — by the OCD Collaborative Genetics Association Study (OC GAS) — examined 1,065 families that included 1,406 patients with OCD. In addition, a case-control subsample was included to increase power, resulting in a total sample of 5,061 individuals. A marker on chromosome 9, near the gene encoding *PTPRD* protein, was the most strongly associated marker observed ($P = 4.13 \times 10^{-7}$). *PTPRD* is a member of the tyrosine phosphatase family that regulates cell growth and differentiation as well as other processes within the cell¹⁰¹. Furthermore, presynaptic *PTPRD* promotes the differentiation of glutamatergic synapses^{102–105} and interacts with *SLIT* and *NTRK*-like protein 3 (*SLITRK3*) (a postsynaptic adhesion molecule) to selectively regulate GABAergic synapse development¹⁰⁶. Of note, genes encoding other *SLIT* and *NTRK*-like family members (specifically, *SLITRK1* and *SLITRK5*) have been reported to be associated with OCD-like behaviours in mice¹⁰⁷ and with Tourette syndrome⁷². In addition, mice deficient in *Ptprd* show impairment in learning and memory tasks¹⁰⁸, and memory deficits have been reported for OCD¹⁰⁹.

Although the OC GAS group did not identify any SNPs associated with OCD at the genome-wide significance level⁹⁶, they conducted follow-up analyses to compare their findings with results obtained in the first GWAS of OCD⁹⁵. Both studies found 15 genes, which were in the top hits of each study, with 12 of the 15 showing association with the same marker allele in the same direction. Additional analyses to examine the interaction between *DLGAP1* and *GRIK2* (both of which showed evidence for association in the OC GAS study and the original GWAS study^{95,96}) revealed a trend of association for a set of genes. These included *NEUROD6* (a gene involved in the development and maintenance of the mammalian nervous system), *SV2A* (a gene that has a role in the control of regulated secretion in neural

Genome-wide association studies

(GWASs). Studies in which many common genetic variants are examined to determine whether they are associated with a trait. These studies typically focus on associations between single-nucleotide polymorphism and commonly occurring disorders.

Genome-wide significance

A statistical threshold ($P = 5 \times 10^{-8}$) based on the testing of one million single-nucleotide polymorphisms in a genome-wide association study and on the use of a Bonferroni correction for multiple testing (that is, 0.05/1,000,000).

and endocrine cells), *GRIA4* (a glutamate receptor that functions as a ligand-gated ion channel in the CNS), *SLC1A2* (the principal transporter that clears glutamate from the extracellular space at synapses in the CNS) and *PTPRD*.

In summary, the results of family, twin and association studies support the hypothesis that OCD is familial and that genetic factors have a role in the manifestation of OCD. Twin studies suggest that the genetic component of OCD is predominantly polygenic, and the results of the two GWASs are consistent with that finding⁸¹. Accordingly, the results of the GWASs and meta-analyses of candidate gene studies also suggest that several genes may contribute to the increased risk of OCD and that the genes in the glutamatergic, serotonergic and dopaminergic systems (among others) play an important part in the expression of OCD. Indeed, it has been suggested that OCD is probably due to a dysregulation of genes that function in a brain network rather than single genes that simply cumulatively add risk¹⁰. However, it is clear from both twin studies and from analyses of the GWAS data⁸¹ that non-genetic factors are also crucial for the manifestation of OCD. If it is the case that several genes of mild to moderate effect act together to increase vulnerability to OCD and that environmental factors also contribute to the manifestation of OCD, then it is clear that the GWASs cited above were underpowered to achieve acceptable statistical significance and, as has been demonstrated in studies of other neuropsychiatric disorders, much larger sample sizes are required to identify risk genes for OCD¹¹¹. Nevertheless, the data from these initial studies can be included in future association studies, and it is expected that risk genes for OCD will eventually be identified.

The neural basis of OCD

Since the late 1980s, a rapid growth in the number of imaging studies of individuals with OCD and improvements in imaging technology and methods have led to considerable advancement in our understanding of the neural substrates of OCD pathophysiology. Functional imaging research in OCD has shown a high degree of concordance across studies that is among the most robust in the psychiatric literature¹¹². As discussed below, neurobiological (mainly neuroimaging), neuropsychological and treatment studies have implicated frontal-subcortical circuits in the pathophysiology of OCD. Indeed, a cortico–striato–thalamo–cortical (CSTC) model of OCD (also termed the frontostriatal model or corticostriatal model)¹¹³ has been the prevailing model regarding the neural and pathophysiological underpinnings of OCD, although some modifications of the model have recently been proposed¹¹⁴.

The typical conceptualization of frontostriatal circuitry entails a direct and indirect pathway (FIG. 2). In healthy individuals, the excitatory, direct pathway is modulated by the indirect pathway’s inhibitory function (FIG. 2). Based on convergent findings from animal and human research, the prevailing model postulates that a lower threshold for activation of this system results in excessive activity in the direct pathway over the indirect pathway¹¹³, leading to hyperactivation of the orbitofrontal–subcortical pathway. As a result, exaggerated concerns about danger, hygiene or harm — mediated by the orbitofrontal cortex (OFC) — may result in persistent conscious attention to the perceived threat (that is, obsessions) and, subsequently, to compulsions aimed at neutralizing the perceived threat. The temporary relief that results from performing compulsions leads to reinforcement and repetitive (or ritualistic) behaviour when obsessions recur¹¹³ (FIG. 1).

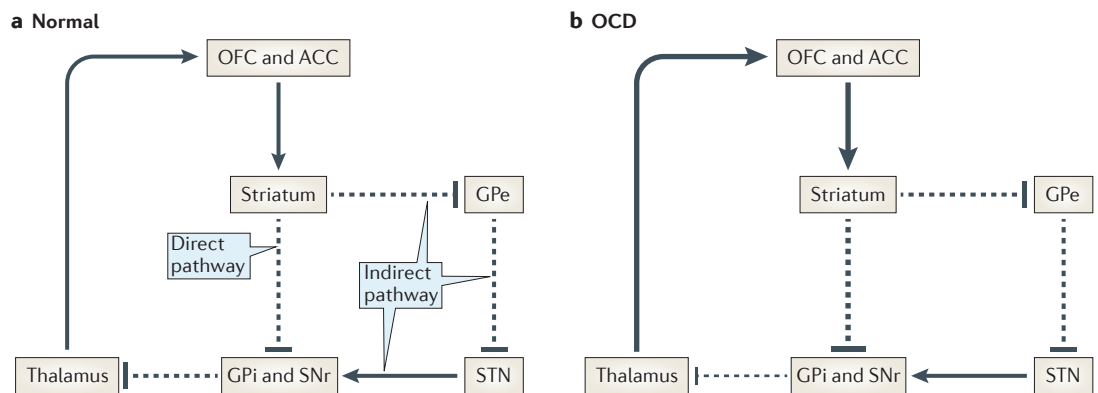


Figure 2 | The cortico–striato–thalamo–cortical circuitry. Solid arrows depict glutamate (excitatory) pathways and dashed lines depict GABAergic (inhibitory) pathways. **a** | In the normally functioning cortico–striato–thalamo–cortical circuit, glutamatergic signals from the frontal cortex (specifically, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)) lead to excitation in the striatum. Through the so-called direct pathway, striatal activation increases inhibitory GABA signals to the globus pallidus interna (GPi) and the substantia nigra (SNr). This decreases the inhibitory GABA output from the GPi and SNr to the thalamus, resulting in excitatory glutamatergic output from the thalamus to the frontal cortex. This direct pathway is a positive-feedback loop. In an indirect, external loop, the striatum inhibits the globus pallidus externa (GPe), which decreases its inhibition of the subthalamic nucleus (STN). The STN is then free to excite the GPi and SNr and thereby inhibit the thalamus. **b** | In patients with obsessive–compulsive disorder (OCD), an imbalance between the direct and indirect pathways results in excess tone in the former over the latter.

Imaging studies. Results from structural imaging investigations, functional connectivity studies and functional imaging studies examining specific regions of interest have provided support for the model described above. The most consistent findings in functional imaging studies of OCD pertain to abnormally increased activation of the lateral and medial OFC, which has been observed in both paediatric and adult individuals with OCD^{115,116}. The caudate nucleus has also been implicated in the pathophysiology of OCD, with most studies reporting hyperactivity in the head of the caudate nuclei bilaterally in both adult^{115,117,118} and paediatric¹¹⁹ patients. The anterior cingulate cortex (ACC)⁹⁵, which is thought to have a central role in evaluating high-conflict situations and error monitoring, has also been implicated in the pathophysiology of OCD¹¹³, as individuals with OCD consistently show hyperactivation in this area in both resting-state and symptom-provocation studies^{120–123}. Notably, ablative neurosurgical procedures that can reduce OCD symptoms in patients with otherwise refractory illness target some of these same regions (for example, cingulotomy)¹²⁴ and circuits¹²⁵. However, it should be noted that excessive striatal or prefrontal activity in itself is neither sufficient to drive excess CSTC activity nor OCD-specific. Findings in these regions of interest in patients with OCD are thought to reflect an OCD-specific pathophysiology associated with a particular imbalance between the direct and indirect pathways. Thus, although ablative surgery targets specific regions, the ultimate goal of the surgery is to interrupt this circuitry imbalance in OCD, which is perpetuated by the intrinsic properties of a positive-feedback loop.

Individuals with OCD also show functional abnormalities in other brain areas, including the dorsolateral prefrontal cortex and parietal lobes^{123,126}, both of which are thought to subservise planning and working memory¹¹⁵. Further support for the CSTC model of OCD has been provided by functional connectivity studies that show aberrant functional connectivity between prefrontal and striatal regions^{116,127} in patients with OCD.

In line with the clinical observations — discussed above — suggesting that there may be several dimensional subtypes of OCD, some functional imaging studies that primarily used a symptom provocation design have found distinct neural correlates of specific OCD symptom dimensions: namely, those that are associated with washing, checking and hoarding symptoms^{55,128,129}. In addition, preliminary structural imaging studies suggest that partially distinct neuronal systems may mediate different symptom dimensions in OCD^{130,131}. However, it is premature to make cogent inferences regarding these findings, particularly owing to the paucity of studies, the small sample sizes used in studies and the complex issue of overlap and concurrence of symptom dimensions presented by patients with OCD³⁷.

Imaging approaches that examine specific neurochemical signals in regions of interest may yield findings that support structural and functional MRI findings and the CSTC model. Proton magnetic resonance spectroscopy (¹H-MRS) quantifies resonance peaks that are unique to molecules of interest, including

N-acetylaspartate (NAA), *N*-acetylaspartylglutamate (NAAG), creatine, phosphocreatine (PCr), total choline-containing compounds (tCho), glutamate, glutamine and GABA. A recent study¹³² critically reviewed 28 investigations that used ¹H-MRS to compare subjects with OCD and healthy controls or to assess treatment effects in subjects with OCD. Not surprisingly, the studies focused on the ACC, the striatum, the thalamus and the OFC. As the study reports¹³², there is little agreement between these investigations, probably because of several factors, including: the small number of subjects (mean = 13) per study; the use of heterogeneous samples that include comorbid conditions and varying severity, symptom subtype, age at onset, illness duration and treatment condition; and the varied and often suboptimal spectroscopic methods used, such as low magnetic field (<3 Tesla), single-voxel assay and relative measures of signals using ratios with PCr or tCho rather than absolute signal intensity. Thus, it is extremely difficult to evaluate the reported findings. For example, a few studies reported decreased NAA resonance peaks (a measure of neuronal integrity) in the ACC (five studies) and the striatum (four studies) in subjects with OCD, but the majority of studies found no difference in NAA resonance peaks between individuals with OCD and controls. Furthermore, two out of eight studies reported decreased glutamate peaks in the ACC and one (out of three) found increased Glx peaks (that is, combined glutamate and glutamine peaks) in the OFC of patients with OCD¹³². Initially, Rosenberg *et al.*¹³³ reported an increased Glx peak in the head of the left caudate nucleus in patients with OCD that decreased in parallel with symptom reduction induced by paroxetine. However, other studies failed to replicate this finding, and four longitudinal studies failed to show any changes in the Glx peak after treatment¹³². The lack of consensus should not be interpreted as absence of chemical biomarkers in OCD. For example, changes in Glx may be limited to a subset of subjects with polymorphisms in glutamate genes. Further studies that combine functional imaging, genetics, more homogeneous cohorts and advanced spectroscopic techniques such as high field strength, better spectral resolution (for example, to separate glutamate and glutamine peaks) and multiple-voxel assays are likely to yield important findings in the future.

Finally, animal studies using the recently developed technique of optogenetics provide further support for the CSTC model of OCD. This technique combines genetics and optics, which enables manipulation of specific cells in living organisms by using light to activate specific neurons, and is a promising development for our understanding of the neuroscience of OCD¹³⁴. In one study¹³⁵, repeated, precise optogenetic excitation of a neuronal tract connecting the OFC and the striatum resulted in repetitive behaviour (that is, excessive grooming) in mice. In a second study¹³⁶, repetitive behaviours in a genetic mouse model of OCD (based on deletion of the synaptic scaffolding gene *Dlgap3*) could be suppressed by optogenetic excitation of the lateral OFC and its terminals in the striatum. Despite the methodological and ethical considerations involved in applying optogenetics

Cingulotomy

A form of a neurosurgical procedure, usually performed in psychiatric patients, that involves surgical severing of the anterior cingulum.

Optogenetics

A novel technique that combines genetics and optics to enable manipulation of specific cells in living organisms, utilizing light to activate genetically sensitized neurons.

Endophenotype

(Also known as an intermediate phenotype). A quantifiable construct that mediates low-level genetic variability and high-level phenotypic expression.

Go–no-go task

A task of response inhibition in which stimuli (for example, coloured squares) are continuously presented and the individual is asked to respond as fast as possible to all coloured squares (that is, go stimuli) except for one type of no-go stimulus (for example, a red square). Responding to a no-go stimulus is considered to be a commission error — a strong indicator for response inhibition impairments.

Stroop task

A task in which participants are presented with colour names printed in different font colour. In one trial block, the colour name and font colour are incongruent. The difference in performance or reaction time between congruent and incongruent blocks is defined as the Stroop effect.

Stop signal task

A response-inhibition task in which participants are asked to respond as fast as possible to a certain feature of a specific stimulus. On some trials, the go stimulus is followed by a signal indicating that the response should be withheld.

Iowa gambling task

A decision-making task in which the goal is to earn as much money as possible. Participants are faced with four decks of cards. Each card may earn or lose the participant a monetary reward. The decks vary in the percentage of non-rewarding cards. Healthy controls will tend to quickly focus on a 'good' deck, whereas patients with orbitofrontal dysfunction will tend to persevere on 'bad' decks.

Monetary incentive delayed task

A reward task in which participants are required to respond within a time window and be potentially rewarded depending on their response time.

in humans, this technique may offer new avenues for advancing our understanding of compulsive behaviours as well as potential novel interventions.

Treatment studies. Cognitive behavioural therapy (which includes an exposure component and a response-prevention component), SSRIs or a combination of the two are the most effective first-line treatments for OCD, as suggested by expert clinical guidelines^{137,138}. Numerous studies have shown reductions in metabolic activity in the OFC, caudate and ventrolateral prefrontal cortex post-treatment relative to pre-treatment in trials assessing the effects of cognitive behavioural therapy and pharmacotherapy in patients with OCD^{122,139–144}, which provides support for the CSTC model.

Similarly, neuromodulation therapies that target the circuitry implicated in OCD have yielded early encouraging results that are broadly consistent with prevailing models of OCD pathophysiology. For example, deep brain stimulation (DBS) is a neurosurgical procedure in which implanted electrodes are continuously directing electrical current to a specific brain region. The most commonly targeted DBS brain regions in OCD are the anterior limb of the internal capsule, the nucleus accumbens and ventral striatum, and the subthalamic nucleus, all of which have been implicated in OCD pathophysiology. A recent review of this approach in OCD¹⁴⁵ concluded that DBS may be a promising treatment for refractory OCD. Indeed, half of all patients who received DBS responded to the treatment. Furthermore, the partial NMDA receptor agonist D-cycloserine has been shown to modulate fear extinction after exposure and response-prevention therapy in subjects with OCD as well as other anxiety disorders, including social anxiety disorder, thereby enhancing new learning that can rationalize obsessions and reduce rituals¹⁴⁶.

Neuropsychological studies. The growing interest in neurobiological findings and functional imaging research has led to an interest in neuropsychological investigations of OCD. The CSTC model of OCD suggests that aberrant frontostriatal activity could be associated with impaired functioning in cognitive domains that are mediated by this system. However, results from neuropsychological studies in adult and paediatric patients with OCD are less consistent than the functional imaging findings discussed above^{119,147,148}.

The OFC is thought to monitor alterations in reinforcement contingencies, so that learned behaviour can change as a function of the motivational value of stimuli. Inhibition of previously learned behavioural responses (for example, compulsions to relieve anxiety) must occur to permit new behaviour (for example, not performing compulsions). The ability to constrain previously learned behaviour suggests a prominent inhibitory role of the OFC¹¹⁵ in successful cognitive behavioural therapy. Thus, the CSTC model of OCD predicts that affected individuals should exhibit impaired performance and slowness on executive function tasks that assess response inhibition, reward-based decision making, task switching and planning.

Deficient response inhibition has been proposed as a neuropsychological endophenotype of OCD¹¹². However, the evidence for such impairment in individuals with OCD is variable. The most common tasks used to assess response inhibition are the go–no-go task, the Stroop task and the stop signal task. Some investigations reported that patients with OCD made more commission errors on go–no-go tasks^{149,150}, whereas others did not find such a difference^{151,152}. Similarly, deficient performance on the Stroop task (mainly a larger Stroop interference effect) in people with OCD has been reported by some^{153,154} but not other¹⁴⁹ studies. Finally, some studies reported impaired performance on the stop signal task in patients with OCD^{150,155}. Notably, a recent meta-analysis of stop signal task results reported an overall effect size of 0.49, representing underperformance on response inhibition tests among adult patients with OCD compared with control adults¹⁴⁶.

Decision-making tasks such as the Iowa gambling task or the monetary incentive delayed task have been used to study the ability of patients with OCD to modify responses as a function of reward or feedback (an ability that is thought to be associated with both the OFC and ACC). These studies revealed that patients with OCD exhibit an impaired ability to adjust their behaviour on the basis of monetary gains and losses for 'correct' responses. Other studies reported unimpaired performance on the monetary incentive delayed task in patients with OCD but did observe aberrant ventral-striatal activity during the task^{156,157}. Furthermore, several studies reported that individuals with OCD show a significantly higher percentage of perseverative errors on the Wisconsin card sorting test (WCST), which suggests that they have an impaired ability to modify responses on the basis of feedback^{158,159}. Furthermore, errors on the WCST positively correlated with left frontal cortex and left caudate activation in patients with OCD¹⁶⁰.

In accordance with the predictions of the CSTC model of OCD, set-shifting impairments have also been observed in individuals with OCD, for example, in the CANTAB object alternation test¹⁶¹ and the set-shifting task^{162–165}. Furthermore, studies have noted set-shifting impairments in individuals with OCD on the WCST¹⁶⁶ and the trail-making test part B^{153,167}, in which performance negatively correlated with metabolic rates in the putamen¹⁶⁸.

Perhaps the most compelling findings in OCD neuropsychological research pertain to non-verbal memory, which in most investigations was assessed using the Rey–Osterrieth complex figure test (RCFT)¹⁶⁹. One study demonstrated that executive function-related impairments in organizational strategies associated with encoding visual–spatial information mediated the poor performance on the RCFT in patients with OCD¹⁷⁰, a result that has since been replicated¹⁷¹. Following cognitive retraining aimed at improving organizational strategies, patients with OCD demonstrated performance improvements in the RCFT that were significantly larger than those of the control group¹⁷².

Consistent with findings suggesting that different OCD symptom dimensions are associated with distinct neural substrates, several studies suggest that they are also associated with different neuropsychological

Wisconsin card sorting test

A test in which participants are presented with stimulus cards that differ in the number, form and colour of shapes they show. Participants are required to match each card to one of four target cards according to a dimensional rule that is not explicitly articulated. Participants may understand the rule only by either a 'correct' or 'wrong' feedback from the experimenter, who changes the sorting rules throughout the task. The participant is required to discover the rules in order to succeed in this task.

Object alternation test

A test in which participants are presented with two objects, and a target stimulus that may be located under one of the objects. The examiner covers the objects and changes the location of the target stimulus. This task assesses working memory and set shifting.

Set-shifting task

In set-shifting tasks, participants are required to alternate between two judgements within a set of stimuli, as fast as and as accurately as possible.

Trail-making test

In the first part of this test, which assesses psychomotor functioning and processing speed, participants are asked to connect the dots between numbered circles as fast as possible. In the second part, which assesses set shifting, participants are asked to connect the dots according to an ascending order of a series of letters and numbers.

Tower of London test

A task that assesses planning. It consists of three coloured discs placed on pegs. Participants are required to arrange the discs according to specific models using the fewest possible moves. The number of excess moves is an indicator for deficient planning ability.

Wechsler memory scale logical memory

A subtest of the Wechsler memory scale test battery in which participants are asked to remember a short, detailed story.

profiles. Results from this limited body of research suggest that the symmetry–ordering dimension of OCD is associated with deficient performance on tasks of executive function, specifically tasks of response inhibition, set shifting and verbal fluency^{173,174}, but also on tasks of non-verbal memory^{167,175}. Some studies that compared patients with OCD who have primary washing compulsions with patients with OCD who have checking compulsions revealed that the latter dimension is associated with worse performance on executive function and non-verbal memory tasks^{176,177}. Finally, although preliminary evidence from some studies^{176,177} supports the notion that the hoarding compulsion has different neural substrates from washing and checking compulsions, the inconclusive results emerging from a limited number of studies do not yet permit a conclusion regarding an association between distinct neuropsychological deficits and hoarding¹⁷⁸.

In summary, results from neuropsychological studies are heterogeneous¹⁴⁷ but generally support the notion that patients with OCD show underperformance in tests of executive functioning. Findings that neuropsychological test performance improves after successful treatment and that frontostriatal activity during performance of executive function tasks is altered in patients with OCD further support this notion. However, few studies have reported an association between symptom severity and neuropsychological impairments in patients with OCD^{149,179–181}. These contrasting results reflect an ongoing debate regarding the 'state' or 'trait' nature of neuropsychological impairments in OCD^{148,151}.

Endophenotype research

Endophenotypes¹⁸² are state-independent markers that do not include any symptoms that are necessary for the diagnosis of a particular condition; that is, they are present regardless of whether an individual shows clinical symptoms of the disorder. These markers (which can be neurocognitive, neurobiological and imaging measures) are presumed to be intermediate expressions of genetic vulnerability factors. This means that a true endophenotype of a disorder should be present among family members of affected individuals¹⁸². The ultimate aim of research into endophenotypes in psychiatric disorders is to enable early detection of individuals at risk of developing these conditions. Furthermore, identifying endophenotypes will promote our understanding of disorder-specific aetiological factors that may lead to the development of novel and more effective treatments. A few studies have used imaging techniques to examine patients with OCD and their relatives, and the results support the notion that the neurobiological abnormalities that may underlie OCD are also present in relatives of patients with OCD. Specifically, one study reported reduced lateral OFC activation, reduced lateral prefrontal cortex activation and decreased parietal responsiveness in both patients with OCD and their unaffected first-degree relatives during performance on a reversal-learning task¹¹⁵. In a recent study, patients with OCD and unaffected relatives showed increased activity (relative to

controls) in the left pre-supplementary motor region during successful inhibition in a response-inhibition task¹⁸³. Furthermore, an electroencephalography study noted increased error-related brain potentials in both patients with OCD and their unaffected relatives, compared with controls¹⁸⁴.

Studies examining neuropsychological functioning have also found some deficits in both patients with OCD and unaffected relatives, predominantly in executive functioning, decision making and memory. Specifically, compared with control subjects, patients with OCD and their unaffected relatives performed equally worse on planning tasks (Tower of London test and Tower of Hanoi task)^{158,185}, decision-making tasks (Iowa gambling task)¹⁵⁸, set-shifting tasks^{186,187}, response-inhibition tasks (the Stroop test and the stop signal task)^{186,187}, and delayed verbal and non-verbal memory tests (Wechsler memory scale logical memory, Wechsler memory scale visual memory and the Rey auditory verbal learning test subtests)^{185,187}.

In summary, although more research is needed, preliminary evidence suggests that there are changes in brain activity and executive functioning deficiencies in both patients with OCD and their non-affected relatives. This supports the notion that genetic findings of familial risk of OCD can be used in translational studies to investigate the effects of specific genetic variants on neural activity in frontostriatal circuits and OCD-like behaviours.

Integrating genetic and neurobiological findings

Historical and prevailing models of OCD pathophysiology have focused on corticostriatal circuitry and three principal candidate neurotransmitter systems: serotonin⁸, dopamine⁸ and glutamate¹⁸⁸. Furthermore, models of OCD pathogenesis include potential risk-conferring contributions from both genes and environmental factors¹⁸⁹. Below, we propose a model of OCD that seeks to integrate circuitry, neurochemistry and genetic as well as epigenetic elements (FIG. 3).

OCD is familial and the results from a meta-analysis of twin studies demonstrate that part of this familiality is due to several gene variants that have additive effects on disease risk. Thus, it is unlikely that there are genes of large effect that contribute substantially to the expression of this condition. The findings from GWASs are consistent with this as well, as they have not identified any loci that achieved genome-wide significance and the loci that were associated with OCD seemed to have moderate to small effects. Of note, however, is that several of these loci are in regions that harbour genes related to the glutamatergic and GABAergic systems.

This is an important observation considering the following: the neural circuitry of OCD seems to involve the CSTC circuit. In the normally functioning CSTC circuit, glutamatergic signals from the frontal cortex lead to excitation in the striatum, increasing inhibitory GABA signals to the globus pallidus interna (GPi) and the substantia nigra (SNr) (FIG. 2). This, in turn, reduces inhibitory output to the thalamus and increases glutamatergic output from the thalamus to the prefrontal cortex in an excitatory loop. Downregulation of

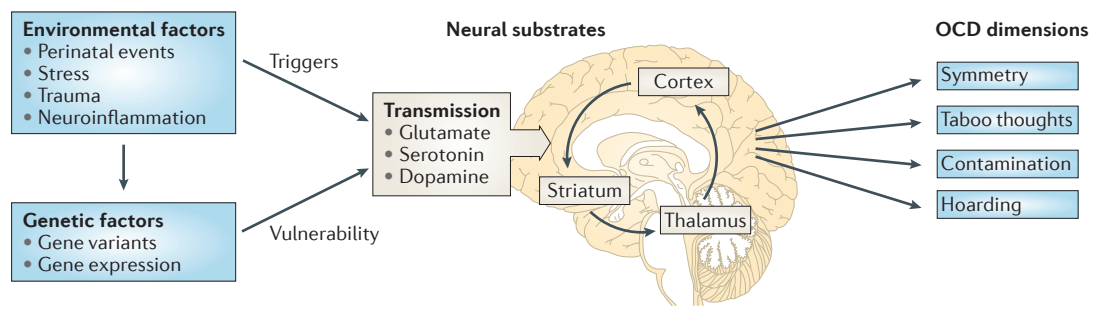


Figure 3 | An integrative model of genetics, environment and neurobiology for the expression of OCD. Individuals with obsessive-compulsive disorder (OCD) may be genetically vulnerable to the impact of environmental factors that may trigger modification of the expression of glutamate-, serotonin- and dopamine-system-related genes through epigenetic mechanisms. In turn, neuroanatomical expression of these modifications results in an OCD-specific imbalance between the direct and indirect loops of the cortico-striato-thalamo-cortical (CSTC) circuit. Aberrant activation along the CSTC loop is associated with phenotypic presentation of OCD phenomenology. Although OCD is clinically heterogeneous, it is generally and universally characterized by obsessive concerns about threats or danger and subsequent engagement in rituals to neutralize the threats and/or distress that accompany obsessions. This negative reinforcement cycle, when left untreated, perpetuates OCD psychopathology.

serotonergic transmission is associated with treatment response in patients with OCD¹⁹⁰, a decrease in serotonin metabolites in the cerebrospinal fluid and reduced activity in the CSTC circuit.

Furthermore, results from several studies suggest that dopamine is important in frontostriatal circuits⁹. For example, dopamine is hypothesized to contribute to the adaptation of behaviour and cognitive flexibility, and patients with OCD have demonstrated deficits in cognitive flexibility¹⁶³. Cognitive flexibility, including reversal learning, task switching and attentional set shifting, is subserved by the prefrontal cortex. The prefrontal cortex, striatum and thalamus have reciprocal projections, which suggests that striatal regions and segregated frontostriatal circuits also contribute to the regulation of cognitive flexibility. Depletion of dopamine but not serotonin in the caudate nucleus impairs performance during reversal learning, whereas dopamine depletion in the OFC leads to impaired extinction. Findings of altered dopamine signalling in OCD have been replicated several times¹⁹¹⁻¹⁹³. Furthermore, it has been shown that dopamine antagonists can augment the therapeutic effect of SSRIs in patients with OCD¹⁹⁴. By contrast, treatment with an SSRI caused increased binding to striatal dopamine D2 receptors in medication-naïve patients with OCD, indicating a functional association between serotonin and dopamine¹⁹². In summary, dopaminergic modulation of frontostriatal circuits seems to play a part in OCD, and this possibly involves a change in the balance between OFC serotonin levels and dorsal striatal dopamine levels¹⁹⁵. As noted earlier, variants of a number of genes in the glutamatergic system are moderately associated with OCD in GWASs. In addition, findings from two meta-analyses (reported in REF. 94) suggested that two serotonin-system-related genes, two dopamine-system-related genes and two genes involved in catecholamine modulation (only in males) are associated with OCD expression, with relatively modest effects. Thus, it is plausible that all three systems interact to affect the functioning of the CSTC circuit.

Animal studies have provided supporting evidence that serotonin and dopamine systems are related to the expression of OCD-like behaviours, primarily in terms of excessive self-grooming and anxiety^{189,196}. However, only a few animal models of OCD have identified specific genes that might be involved, even though some of the models seem to have some apparent validity based on drug response⁸ and neurocircuitry¹⁹⁷. Knockout or transgenic animals have been the most informative models, and studies using such animals have provided some evidence that glutamatergic alterations are related to the expression of OCD-like behaviours¹⁹⁷.

Indeed, *Dlgap3*-knockout mice show excessive grooming behaviours and have defects in glutamatergic transmission at corticostriatal synapses, and these behavioural and synaptic defects were ameliorated by restoration of *Dlgap3* expression in the striatum¹⁹⁸. Another study showed that mice lacking *Slitrk5* have excessive anxiety and self-grooming behaviours¹⁰⁷. *SLITRK5* regulates neurite outgrowth and neuronal survival, and mice deficient in *SLITRK5* have substantial changes in striatal ionotropic glutamate receptor expression and disruption of corticostriatal glutamatergic transmission¹⁰⁷. Treatment with the SSRI fluoxetine normalized the behavioural abnormalities in both *DLGAP3*-deficient mice and *SLITRK5*-deficient mice^{107,198}, suggesting a relationship between serotonin levels and glutamatergic functioning. Finally, mice lacking the glutamate transporter *SLC1A1* have increased susceptibility to the effects of oxidative stress and show disproportionate aggression and self-grooming behaviours¹⁹⁹. This is interesting given the strong expression and perisynaptic localization of this glutamate transporter in the CSTC circuitry²⁰⁰. *SLC1A1* interacts with the NMDA receptor (which is expressed in the CSTC circuit). *SLC1A1* loss of function in humans causes dicarboxylic aminoaciduria, a rare disease of renal dysfunction. Interestingly, one patient with this condition reported lifelong OCD behaviours²⁰⁰. Although this could be a chance occurrence, it is worthwhile to assess whether other individuals who have this rare disease also have OCD-like behaviours.

Rey auditory verbal learning test

A verbal memory test in which participants are asked to memorize a list of words read aloud by the examiner.

Overall, the evidence for the involvement of serotonin, dopamine and glutamate suggests that gene variants in each of these systems might increase the risk of OCD, although it is unlikely that each individual variant would by itself be sufficiently strong to cause the full expression of the disorder. This is consistent with findings from twin studies that suggest that small-to-moderate additive genetic effects are the main source of risk in OCD. In addition, recent optogenetic studies have demonstrated that stimulation of corticostriatal glutamatergic neurons results in compulsive-like grooming behaviour in mice¹³⁵. The compulsive-like behaviour was expressed after approximately 2 weeks of repeated stimulation, which the investigators interpreted to mean that “repeated stimulation led to chronic circuit changes that ultimately resulted in sustained, stimulation-independent OCD-like behaviour” (REF. 135).

A proposed neuroepigenetic model of OCD. How do all of these findings translate into a model of OCD? On the basis of data from twin studies, the heritability of OCD is estimated to be approximately 40% and the remaining variation seems to be due to environmental events. Examples of environmental triggers for OCD include adverse perinatal events²⁰¹, psychosocial stressors²⁰², and trauma and inflammatory processes²⁰³. It is possible that these events modify the expression of genes related to the serotonin system, the dopamine system, catecholamine modulation and glutamate pathways (which are well documented to interact^{204,205}) through epigenetic mechanisms²⁰⁶. This could then result in changes in glutamatergic activity in the CSTC circuit and thereby result in the

manifestation of OCD. In support of this hypothesis is the finding that among the top hits in the first GWAS was a significant enrichment of methylation quantitative trait loci⁹⁵ (methylation being one of the mechanisms responsible for epigenetic changes in the nucleus).

More work is needed to elucidate the aetiology and pathology of OCD. This work should include genetics studies that are designed to replicate and extend current findings as well as epigenetic studies that are focused on interactions between identified risk genes and the environment. Furthermore, once genes that increase the risk of OCD have been located, they should be incorporated into imaging and treatment studies to elucidate their function in the brain. This research should also incorporate the fact that OCD is a multidimensional condition that consists of four or five symptom clusters — each cluster representing specific components of behaviour that might be influenced by specific genes, changes in specific neural pathways and responses to specific environmental events. In other words, the different symptom dimensions of OCD may each have their own aetiology and pathophysiology. The replication of genetics studies should include genome-wide sequencing experiments and studies seeking to identify rare copy number variants that might have a larger effect on the manifestation of OCD, much like studies that have identified genes for schizophrenia²⁰⁷. Finally, a better understanding of the underlying neurocircuitry and pathophysiology, including the role of glutamatergic, serotonergic and dopaminergic pathways, as well as fear extinction mechanisms, is needed to develop more specific and targeted treatment.

Copy number variants

Copy number variants correspond to regions of the genome that have been deleted or duplicated on certain chromosomes. The deletions and/or duplications can result in gene expression changes that can elucidate specific aetiological pathways.

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Competing interests statement

The authors declare [competing interests](#): see Web version for details.