Obsessive-compulsive disorder

Jonathan S Abramowitz, Steven Taylor, Dean McKay

Obsessive-compulsive disorder is a severe and disabling clinical condition that usually arises in late adolescence or early adulthood and, if left untreated, has a chronic course. Whether this disorder should be classified as an anxiety disorder or in a group of putative obsessive-compulsive-related disorders is still a matter of debate. Biological models of obsessive-compulsive disorder propose anomalies in the serotonin pathway and dysfunctional circuits in the orbito-striatal area and dorsolateral prefrontal cortex. Support for these models is mixed and they do not account for the symptomatic heterogeneity of the disorder. The cognitive-behavioural model of obsessive-compulsive disorder, which has some empirical support but does not fully explain the disorder, emphasises the importance of dysfunctional beliefs in individuals affected. Both biological and cognitive models have led to empirical treatments for the disorder—ie, serotonin-reuptake inhibitors and various forms of cognitive-behavioural therapy. New developments in the treatment of obsessive-compulsive disorder involve medications that work in conjuction with cognitive-behavioural therapy, the most promising of which is D-cycloserine.

Lancet 2009; 374: 491–99

University of North Carolina, Chapel Hill, NC, USA (Prof J S Abramowitz PhD); **University of British Columbia, Vancouver, BC, Canada** (Prof S Taylor PhD); **and Fordham University, NY, USA** (D McKay PhD)

Correspondence: Dr Jonathan S Abramowitz, Department of Psychology, University of North Carolina, Chapel Hill, NC 27599, USA
jabramowitz@unc.edu

Introduction

Obsessive-compulsive disorder is characterised by the occurrence of either obsessions, compulsive rituals or, most commonly, both.[1] Obsessions have four essential features: they are recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and cause great anxiety; they are not simply excessive worries about real life issues; the affected individual attempts to ignore, suppress, or neutralise them with some other thought or action; and the affected individual recognises that these thoughts are a product of his or her mind.[1] Examples of obsessions include unwanted thoughts or images of harming loved ones, persistent doubts that one has not locked doors or switched off electrical appliances, intrusive thoughts of being contaminated, and morally or sexually repugnant thoughts (eg, intrusive thoughts of behaving in a way that violates one's morals or runs counter to one's sexual preferences).

Compulsions are repetitive behaviours (eg, repetitive hand washing, ordering, or checking) or mental acts (eg, repetitive praying, counting, or thinking good thoughts to undo or replace bad thoughts) that the affected individual feels compelled to do in response to an obsession, or according to rigid rules (eg, checking that a light switch is turned off by switching it on and off exactly ten times). Compulsions are aimed at preventing or reducing distress, or preventing some dreaded event.[1] However, they are excessive or not realistically connected to what they are intended to prevent.

Obsessive-compulsive disorder is a symptomatically heterogeneous condition, in which various different kinds of obsessions and compulsions exist. However, research indicates that certain obsessions and compulsions tend to co-occur to form five main dimensions:[2]

- obsessions about being responsible for causing or failing to prevent harm; checking compulsions and reassurance-seeking;
- symmetry obsessions, and ordering and counting rituals;
- contamination obsessions, and washing and cleaning rituals;
- repugnant obsessions concerning sex, violence, and religion;
- hoarding, which are obsessions about acquiring and retaining objects, and associated collecting compulsions.

Recent findings have supported these five dimensions across ages from childhood through adulthood.[3,4] Although hoarding has traditionally been regarded as a form of obsessive-compulsive disorder, the differences between hoarding and the other obsessive-compulsive symptom dimensions are compelling enough that some researchers now think that hoarding is a separate disorder.[5]

No laboratory tests exist for obsessive-compulsive disorder, and the diagnosis is made by clinical interview. To diagnose the disorder according to the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) criteria,[1] the affected individual must suffer from either obsessions or compulsions that cause great distress, are time-consuming (more than 1 h per day), or substantially interfere with normal functioning. At some point in the course of the disorder, the affected individual must also recognise that the obsessions and compulsions are excessive or unreasonable. This criterion does not apply to children because they may not have sufficient cognitive awareness to make this judgment. Also, commonplace childhood rituals (eg, avoiding cracks on the pavement) are not compulsions, they are not distressing or debilitating, and they tend to be transient.

Search strategy and selection criteria

We searched Medline and PsychInfo from 2003 to 2008, with the search terms "obsessions", "compulsions", "obsessive-compulsive disorder", and "OCD". Although we focused on publications in the past 5 years, we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has space for.

Obsessive-compulsive disorder would not be diagnosed if obsessions and compulsions arose in the context of some other disorder such as schizophrenia. In such cases, the current diagnostic conventions (ie, *International Classification of Diseases* [ICD] and DSM) indicate that obsessive-compulsive symptoms are due to some other disorder (ie, schizophrenia). Here, we focus on obsessive-compulsive symptoms as they occur in what is currently called obsessive-compulsive disorder.

People with this disorder have varied insights into the senselessness of their symptoms,[1] with most acknowledging that obsessions and compulsions are at least somewhat unrealistic and excessive. Insight can be assessed by asking the patient how strongly he or she believes that the obsessions are realistic and that the rituals actually serve to prevent disastrous consequences.

Prevalence, demographic features, and comorbidity

Compared with people with other anxiety or unipolar mood disorders, those with obsessive-compulsive disorder are less likely to be married, more likely to be unemployed, and more likely to report impaired social and occupational functioning.[6] This disorder has a lifetime rate of 2–3% in the general population,[7] without sex differences in distribution, with the exception that in children the disorder is more common in boys than in girls.[8] Onset is usually gradual and, if untreated, the course is mainly chronic, with symptoms changing over time, often in response to life stressors.[9,10] The disorder is rarely limited to a single episode or to recurrent episodes. It usually arises in late adolescence or early adulthood, although onset in childhood or late adulthood can occur.[11] Clinical presentation of the disorder in children and adults is generally similar.[1]

Obsessive-compulsive disorder has been identified in many different ethnic groups.[12] Cross-national differences in prevalence are difficult to interpret because they could be due to various factors, including culturally influenced reporting biases such as reluctance to admit to suffering from a mental disorder. The main features of the symptoms seem to be consistent over time; for example, obsessions about violations of social taboos concerning sexual behaviour and aggression.[13,14] However, cultural background could affect the content of obsessions and compulsions.[15] For example, religious obsessions and compulsions (eg, blasphemous intrusive thoughts, compulsive praying, and cleansing compulsions) might be more common in ethnic groups that emphasise the importance of religious observance than in those in which religion has a less prominent role.[16]

Epidemiological surveys suggest that at least 50% of people with the disorder have at least one other psychological illness—most commonly a comorbid anxiety disorder (eg, social phobia) or a unipolar mood disorder (eg, major depressive disorder).[6,17] Alcohol abuse or dependence is also more common in people with obsessive-compulsive disorder than in the general population.[6] 20–30% of people with the disorder have a current or past history of tics.[1]

Pathophysiology

Neurochemistry and neuroanatomy

Obsessive-compulsive disorder has been linked to a disruption in the brain's serotonin system.[18] Serotonin dysregulation, however, has been implicated in many other psychological disorders, and whether these disorders differ from one another in the type of abnormality is unclear. Obsessive-compulsive disorder has been associated with hypersensitivity of postsynaptic serotonin receptors.[19] Individuals with the disorder might have a specific dysfunction in the genes encoding for the serotonin transporter (*5-HTT*) and serotonin receptor (*5HT2A*),[20] but these have not been consistently identified.[21] The glutamate system might also be dysfunctional in obsessive-compulsive disorder.[22] Preliminary research has implicated glutamate transporter genes—such as *Sapap3*[23,24] and *SLC1A1*—[25–27] in the disorder. Furthermore, the dopamine system might be abnormal in obsessive-compulsive disorder, although results have been inconsistent regarding which dopamine genes are associated with the disorder.[28]

Two common features of obsessive-compulsive disorder—excessive doubting and repetitive actions—suggest that specific brain regions are involved in the condition. In particular, the frontal orbito-striatal area (including the caudate nucleus) and the dorsolateral prefrontal cortex have been implicated in the inhibition of responses and in planning, organisation, and verification of previous actions.[29] Accordingly, a recent meta-analysis of brain imaging in adults has suggested that obsessive-compulsive symptoms might be implemented within the orbital cortex and the caudate nucleus.[30] Similar findings have been reported for children.[31] Preliminary evidence has shown white matter anomalies in frontal regions in people with obsessive-compulsive disorder, which is consistent with the hypothesis of a dysregulation in this and other brain regions.[32,33] Figure 1 shows the orbito-subcortical circuits that might connect regions of the brain associated with obsessive-compulsive symptoms. The direct pathway projects from the cerebral cortex to the ventromedial caudate, to the internal segment of the globus pallidus and substantia nigra, and then to the thalamus and back to the cortex. The indirect pathway is similar, but projects from the ventromedial caudate through various structures in the basal ganglia before returning to the direct pathway. Overactivity of the direct pathway is thought to be associated with obsessive-compulsive symptoms.

Genetic factors

Probands with obsessive-compulsive disorder are more likely to have first-degree family members who suffer from the same disorder than are matched controls who

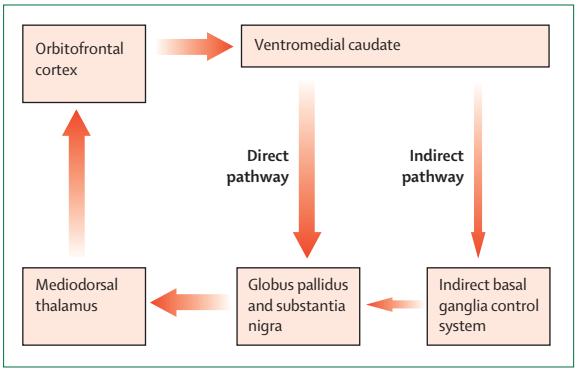

Figure 1: **Direct (thick arrows) and indirect (thin arrows) pathways of the orbito-subcortical circuit connecting neuroanatomical structures hypothesised to be associated with symptoms of obsessive-compulsive disorder**

do not have the disorder.[34] Twin studies of adults suggest that obsessive-compulsive symptoms are moderately heritable, with genetic factors contributing 27–47% of variance in scores on measures of obsessive-compulsive symptoms.[35,36] The remaining 53–73% of the variance is attributed to environment factors. In studies of obsessive-compulsive symptoms in children, genetic factors account for 45–65% of variance.[36] No sex differences exist in heritability. However, there might be a stronger familiarity in childhood-onset obsessive-compulsive disorder than in cases in which the disorder develops later in life.[37,38] The first genome-wide association study of obsessive-compulsive disorder is currently underway by the international obsessive-compulsive foundation genetics collaborative. This study might provide further information about genetic vulnerability to the disorder.

Autoimmunity

Some cases of childhood-onset obsessive-compulsive disorder might be a consequence of streptococcal infection, which causes inflammation to the basal ganglia. Such cases are grouped within a set of clinical conditions called paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).[39] In such cases, obsessive-compulsive symptoms are sometimes successfully treated with antibiotics, if the intervention occurs early in the course of the disorder.[40] Infection-related obsessive-compulsive disorder might account for no more than 10% of early-onset disorder,[41] suggesting that there could be several causal pathways for acquiring the disorder.

Biological models

An issue for any model of obsessive-compulsive disorder is the symptomatic heterogeneity of the disorder, raising the question of whether the disorder is aetiologically heterogeneous. Indeed, different models might be needed to account for different classes of obsessive-compulsive symptoms. Biological models of the disorder have some support from empirical studies, although these models have so far failed to explain why a person develops, for example, contamination obsessions and washing compulsions, whereas another develops symmetry and ordering obsessions and compulsions, and another develops both classes of symptoms. Learning experiences might be important in determining the symptoms in individuals with putative biological abnormalities. If this is the case, then biological models need to be refined to account for the interplay between environmental events and biological systems.

Cognitive and behavioural models

Of the contemporary psychological models of obsessive-compulsive disorder, the one with the most empirical support is the cognitive-behavioural approach, which proposes that obsessions and compulsions arise from certain types of dysfunctional beliefs, the strength of which affects the risk that a person will develop obsessions and compulsions.[42–44] The basis for this model is the well-established finding that unwanted cognitive intrusions (ie, unpleasant thoughts, images, and impulses that intrude into consciousness) are experienced by most people in the general population.[45] These intrusions typically have similar contents to clinical obsessions.

For example, they might consist of intrusive thoughts of poisoning one's family, or unwanted thoughts of uttering obscenities to people in authority. Research studies indicate that these commonplace intrusions develop into obsessions when they are appraised as personally important, highly unacceptable or immoral, or as posing a threat for which the individual is personally responsible.[46,47] For example, consider the unwanted, intrusive image of stabbing one's child with a carving knife. Most people experiencing such an intrusion would regard it as an unpleasant but meaningless event, with no harm-related implications—ie, flotsam in the stream of consciousness. According to the cognitive-behavioural model, such an intrusion develops into an obsession if the person appraises it as being highly important or threatening: "Having images of stabbing my child means that I will lose control and kill her". Such an appraisal evokes distress and motivates the affected individual to try to suppress or remove the unwanted intrusion (eg, by trying to replace the unwanted image with a pleasant image), and to attempt to prevent any harmful events associated with the intrusion (eg, by avoiding knives and continually asking other people to check on the safety of the child).

From this perspective, compulsive rituals develop as efforts to remove intrusions and to prevent any perceived harmful consequences. The cognitive-behavioural model proposes that compulsions become persistent and excessive because they are reinforced by immediate distress reduction and by the temporary removal of the unwanted thought (negative reinforcement), and because they prevent the affected individual from learning that

their appraisals are unrealistic (eg, the affected individual fails to learn that unwanted harm-related images do not lead to acts of harm).

Compulsions affect the frequency of intrusions by serving as reminders of intrusions, thereby triggering their reoccurrence. For example, compulsive hand-washing can remind the affected individual that he or she may have become contaminated. Attempts at distracting oneself from unwanted intrusions could paradoxically increase the frequency of intrusions, possibly because the distractors become reminders (retrieval cues) of the intrusions. Compulsions can strengthen one's perceived responsibility—ie, the absence of the feared consequence after having the compulsion reinforces the belief that the person is responsible for removing the threat. Figure 2 shows the cognitive-behavioural model of obsessive-compulsive disorder.

With its focus on person-specific intrusive thoughts, beliefs, and behaviours, along with the emphasis on learning experiences, the cognitive-behavioural model accounts for the heterogeneity and idiosyncratic nature of obsessions and compulsions. For example, a person with a strict religious upbringing could become highly distressed by the occurrence of unwanted blasphemous thoughts, and therefore is at risk of developing religious obsessions. However, such an upbringing would not confer risk for other symptoms, such as symmetry obsessions and ordering compulsions. The cognitive-behavioural approach has received empirical support in cross-sectional, experimental, and prospective studies.[46,47] However, the available evidence suggests that dysfunctional beliefs and the misappraisal of intrusive thoughts do not explain all cases of obsessive-compulsive disorder, because some people with the disorder have essentially normal scores on measures of such beliefs and appraisals.[48] Because both cognitive-behavioural and biological models have some empirical support, a comprehensive model of obsessive-compulsive disorder might come from an integration of these theoretical approaches.[49]

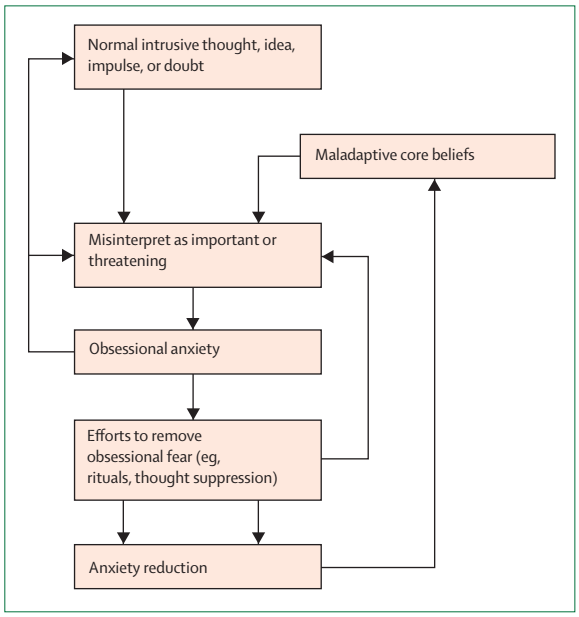

Figure 2: **Cognitive-behavioural model of obsessive-compulsive disorder**

***Panel:* Obsessive-compulsive-related disorders, as proposed for DSM-V[50]**

- Obsessive-compulsive disorder
- Obsessive-compulsive personality disorder
- Tourette's syndrome
- Grooming disorders
  - Trichotillomania
  - Excoriation (skin picking)
  - Nail biting
- Body dysmorphic disorder
- Eating disorders

Classification controversies

Some authors have proposed that obsessive-compulsive disorder should not be grouped in the DSM-IV class of anxiety disorders.[50] They argue that in forthcoming revisions to the diagnostic manuals—DSM-V and ICD-11—the disorder should be moved from this category and integrated into a new category called obsessive-compulsive-related disorders (panel). This proposal does not imply that people with obsessive-compulsive disorder are not anxious; but that the disorder has more similarity to obsessive-compulsive-related disorders than to anxiety disorders. Although the concept of obsessive-compulsive-related disorders was initially developed on the basis of the apparent similarity of symptoms of some disorders (eg, repetitive thinking and repetitive behaviour), its proponents assert that these disorders also overlap in their neurobiology, patterns of comorbidity, familial patterns, and effective treatments.[50]

There is considerable disagreement—on both conceptual and empirical grounds—regarding the creation of a separate category for obsessive-compulsive-related disorders, and the way in which the category is defined.[51] Proponents of this category suggest that obsessive-compulsive disorder and the putatively related disorders share common types of symptoms. For example, both obsessive-compulsive disorder and Sydenham's chorea are characterised by repetitive behaviours. However, the behavioural characteristics of these repetitive symptoms vary considerably across the proposed obsessive-compulsive-related disorders. In Sydenham's chorea, for example, which has been regarded as a possible obsessive-compulsive-related disorder, the repetitive behaviours are sudden, uncoordinated, rapid jerking movements devoid of purpose. By contrast, in obsessive-compulsive disorder the repetitive behaviour is deliberate

and often done according to certain rules with the intention of reducing anxiety. Patterns of comorbidity also fail to support a distinct category for obsessive-compulsive-related disorders.[52,53] In fact, obsessive-compulsive disorder is more commonly associated with mood and anxiety disorders than with the putative obsessive-compulsive-related disorders.[54]

In contrast to obsessive-compulsive disorder, in which repetitive behaviour occurs to alleviate anxiety, the repetitive behaviour in impulse control disorders (eg, trichotillomania) is pleasure-seeking.[55] Repetitive behaviours in some neurological disorders (eg, Tourette's syndrome) are more similar to involuntary reflexive muscle movements than to intentionally performed compulsive rituals. The link between obsessive-compulsive disorder and putatively related disorders is also not supported in terms of neurobiological correlates,[56,57] familial aggregation,[52] and response to pharmacological and cognitive-behavioural treatment. Treatments that are effective for obsessive-compulsive disorder (ie, serotonin reuptake inhibitors and cognitive-behavioural treatment involving exposure and response prevention) are quite different from those for some of the obsessive-compulsive-related disorders. For example, studies of trichotillomania have shown no beneficial effect of serotonin reuptake inhibitors.[58–60]

Treatment

Pharmacotherapy

Randomised controlled trials[61] have indicated that efficacious pharmacotherapies for obsessive-compulsive disorder include serotonin reuptake inhibitors, such as clomipramine, and some selective serotonin reuptake inhibitors. However, these medications are effective only in some patients. A comprehensive meta-analysis of the pharmacotherapy publications for obsessive-compulsive disorder[61] found that the mean effect size for obsessive-compulsive symptoms across 18 randomised controlled trials of serotonin reuptake inhibitors was 0·91, which is a large effect. However, most treatment responders showed residual symptoms after an adequate trial of treatment. Relapse after medication discontinuation is another issue. Relapse rates varied from 24% after discontinuation of sertraline[62] to 31–89% after discontinuation of clomipramine,[63,64] values which are much higher than the 12% relapse after completion of exposure and response prevention therapy.[65] Many patients with obsessive-compulsive disorder have a good response to medication, but this is usually only a partial response.

A meta-analysis of nine double-blind randomised controlled studies (a total of 278 adult patients) showed that, for patients with obsessive-compulsive disorder who fail to fully respond to at least 3 months of treatment with serotonin reuptake inhibitors at their maximal tolerated dose, outcome can be significantly improved by adding an antipsychotic medication.[66]

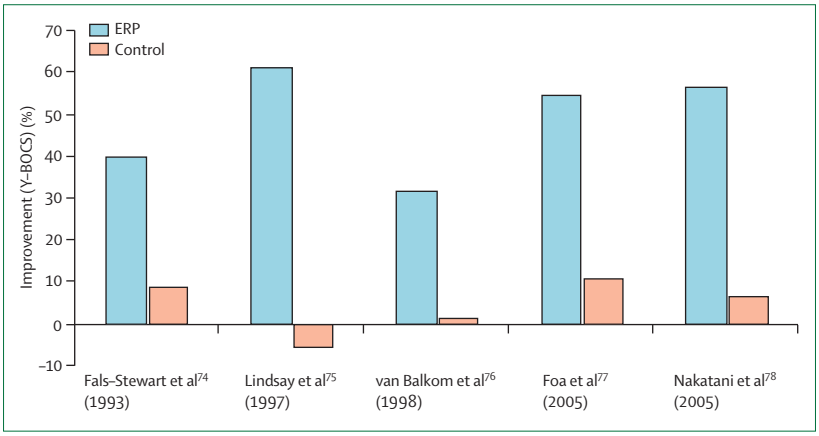

Figure 3: **Improvement of exposure and response prevention and control groups on the Yale-Brown obsessive-compulsive scale in five randomised controlled studies**
Control group in each study was as follows: Fals-Stewart et al=progressive muscle relaxation; Lindsay et al=anxiety management training; Nakatani et al=autogenic training; all others=pill placebo. ERP=exposure and response prevention. Y-BOCS=Yale-Brown obsessive-compulsive scale.

Risperidone and haloperidol had additive effects that were especially beneficial for affected people with comorbid tics. Although these findings are encouraging, only a third of treatment-refractory patients with obsessive-compulsive disorder show a clinically meaningful response to antipsychotic medication.

Pharmacotherapy of paediatric obsessive-compulsive disorder has also been assessed in a meta-analysis,[67] in which four serotonin reuptake inhibitors (paroxetine, fluoxetine, fluvoxamine, and sertraline), together with clomipramine, were investigated. This study showed that, although treatment was effective compared with placebo, the effect sizes were generally modest (mean effect size=0·46), suggesting that these treatments were only partially effective.

Evidence exists that the glutamate system is also dysregulated in obsessive-compulsive disorder. Accordingly, the efficacy of antiglutamatergic agents has been investigated, so far, with small uncontrolled trials of riluzole.[68,69] Preliminary findings suggest that riluzole is associated with a modest reduction in obsessive-compulsive symptoms.[68,69]

Psychological treatments

The only empirically supported psychological treatment for obsessive-compulsive disorder is cognitive-behavioural therapy involving exposure and response prevention.[70] Exposure entails systematic, repeated, and prolonged confrontation with stimuli that provoke anxiety and the urge to perform compulsive rituals. In situational exposure, the patient encounters actual feared stimuli—eg, toilets, cemeteries, and knives. In imaginal exposure, the patient confronts anxiety-provoking obsessional images (eg, of molesting a child), thoughts (eg, of a loved one's death), and doubts (eg, "I might have hurt an innocent person by mistake"). Response prevention means refraining from performing

compulsive rituals. For example, a patient who fears the number 13 because it will bring bad luck would practise writing this number and imagining causing bad luck. He or she would also refrain from performing any rituals to reduce anxiety or the chances of bad luck (eg, saying prayers, checking for reassurance). The aim of exposure and response prevention is to teach patients with obsessive-compulsive disorder that his or her obsessional anxiety does not persist indefinitely, and that avoidance behaviour and compulsive rituals are unnecessary for averting harm.[71] Although exposure and response prevention is the only empirically supported psychological treatment for obsessive-compulsive disorder, additional motivational interventions are sometimes necessary for patients with very severe symptoms or for those with a limited ability to perceive that behaviours arising from obsessions are senseless.[72]

The Yale-Brown obsessive-compulsive scale (Y-BOCS)[73] is regarded as the gold standard measure of obsessive-compulsive symptom severity and is used in most treatment trials. Figure 3 shows the results of randomised controlled trials using this measure. These studies[74–78] consistently demonstrated that exposure and response prevention was better than other forms of psychotherapy and placebos. Meta-analyses[79–81] found large effect sizes, ranging from 1·16 to 1·72 in trials of exposure and response prevention with adults[79–81] and children.[82,83] Although often effective, exposure and response prevention provokes anxiety in patients, and therefore approximately 25% of patients drop out of treatment.[84] For patients who undergo exposure and response prevention, the effects of this treatment often last up to at least 2 years.[70]

Pharmacotherapy versus exposure and response prevention

Researchers have investigated the efficacy of medications versus exposure and response prevention. Foa and colleagues[77] compared exposure and response prevention with clomipramine, the combination of exposure and response prevention and clomipramine, and placebo. Exposure and response prevention reduced Y-BOCS scores by 55%, whereas clomipramine alone reduced it by 31%. The combination of exposure and response prevention and clomipramine reduced Y-BOCS scores by 58%, which was significantly greater than the effect of clomipramine alone, but not of exposure and response prevention alone. All active treatments were superior to placebo (11% Y-BOCS reduction).

Overall, the findings from randomised controlled trials suggest that exposure and response prevention—whether delivered in daily or weekly sessions—substantially improve obsessive-compulsive symptoms, and its effect is more than that produced by pharmacotherapy. Evidence also exists that symptom reduction is due to the specific techniques used in exposure and response prevention (ie, exposure to fear-provoking stimuli while refraining from rituals) over and above the non-specific factors (eg, expectations, attention) that are common to all psychological treatments.

Psychotherapy and pharmacotherapy: D-cycloserine

Despite the hope that the combination of serotonin reuptake inhibitors and exposure and response prevention would lead to a more pronounced reduction of symptoms than that achieved with either monotherapy, this result has not been obtained. A meta-analysis of randomised controlled trials[85] comparing combined treatments with monotherapies of serotonin reuptake inhibitors or exposure and response prevention showed no clear benefit of combined treatment over either monotherapy alone.

A novel approach that combines exposure-based treatments with medication involves the search for pharmacological agents that facilitate fear extinction. Animal research suggests that the *N*-methyl-D-aspartate (NMDA) glutamate receptors are important for the expression of conditioned fear responses in the basolateral amygdala and of conditioned fear extinction in the amygdala.[86] These findings are consistent with the view that fear extinction, similar to fear acquisition, is a form of learning. Accordingly, NMDA agonists, administered before an exposure task, might facilitate the extinction of fear responses.

One such compound is D-cycloserine, which has been used for years in humans to treat tuberculosis and is not associated with significant side-effects. Animal research has shown that this compound facilitates fear extinction after either systemic administration or intra-amygdala infusion.[86] Research on humans suffering from either animal phobia or social anxiety disorder has provided preliminary evidence that D-cycloserine, administered shortly before an exposure session, can facilitate (ie, speed up) fear extinction.[87,88] With regard to obsessive-compulsive disorder, three studies have compared exposure and response prevention (10–12 sessions) with D-cycloserine (100–250 mg) to exposure and response prevention with a placebo.[89–91] D-Cycloserine was not better than placebo in reducing obsessive-compulsive symptoms either immediately after treatment or at 1–3-month follow-up. However, in two studies[90,91] that assessed outcome at the midpoint of exposure, D-cycloserine was superior to placebo—ie, it improved symptoms more rapidly. A limitation of all three trials was the small number of participants in each treatment group (10–14 per group), which reduces the statistical power of these studies.

Overall, preliminary results suggest using D-cycloserine as a method for accelerating the effects of exposure and response prevention, especially in the early phases of treatment. Further research on large samples is needed to replicate these findings and to determine the optimal dose of D-cycloserine. Research on patients with acrophobia (ie, phobia of heights) suggests that as little as 50-mg

D-cycloserine is effective.[88] Moreover, animal research indicates that high doses of D-cycloserine can desensitise NMDA receptors, thereby attenuating the effects of the drug.[92] Accordingly, a narrow therapeutic range might exist for D-cycloserine when used to augment exposure and response prevention.[90]

Brain stimulation and surgical interventions

Surgical interventions for obsessive-compulsive disorder involve cutting the tracts (circuits) between structures that might be important in the disorder (eg, the sectioning of tracts connecting the orbital frontal cortex and anterior cingulate).[93] These procedures include anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy. Surgical treatments are usually reserved for patients who have failed to respond to pharmacological or psychological treatments for obsessive-compulsive disorder. However, even for these patients, safety and efficacy of surgical interventions remain controversial, and there has been a growing interest in alternative, non-ablative surgical procedures.[93] One such intervention is deep brain stimulation of the basal ganglia, through surgically implanted electrodes.[94] Although initial results are promising, this intervention should be adequately assessed for safety and efficacy in the treatment of obsessive-compulsive disorder.[93] A non-surgical brain stimulation method is repetitive transcranial magnetic stimulation, in which electrical activity in the brain is altered by placing an external electromagnet over certain brain regions. Although this stimulation has not been extensively assessed in obsessive-compulsive disorder, available data do not support its therapeutic efficacy for this condition.[95]

Conclusions

Biological models of obsessive-compulsive disorder posit abnormalities of some neurotransmitter systems, such as the serotonin system, and dysfunctional circuits in the orbito-striatal area. These models still fail to account for symptom heterogeneity. The cognitive-behavioural model of obsessive-compulsive disorder emphasises the importance of dysfunctional beliefs and appraisals. This model has some empirical support but is insufficient to fully explain the disorder. Thus, despite some promising models, what causes obsessive-compulsive disorder remains unknown. A combination of cognitive and neurobiological factors might be needed to fully explain the disorder. Because of the heterogeneity of obsessive-compulsive disorder in terms of symptoms, the main symptom patterns might have different origins.

As part of the preparation of DSM-V and ICD-11, whether obsessive-compulsive disorder is an anxiety disorder has been debated. Some have suggested that it should be regarded as a new obsessive-compulsive-related disorder. However, this proposal is controversial. Further research is needed to determine whether such a reclassification of the disorder would improve the understanding of the causes and treatment of this severe, debilitating, and chronic disorder.

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC, 2000.

2 McKay D, Abramowitz J, Calamari J, et al. A critical evaluation of obsessive-compulsive disorder subtypes: symptoms versus mechanisms. *Clin Psychol Rev* 2004; **24:** 283–313.

3 Mataix-Cols D, Rosario-Campos M, Leckman J. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry* 2005; **162:** 228–38.

4 Stewart SE, Rosario MC, Baer L, et al. Four-factor structure of obsessive-compulsive disorder symptoms in children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 763–72.

5 Abramowitz J, Wheaton M, Storch A. The status of hoarding as a symptom of obsessive-compulsive disorder. *Behav Res Ther* 2008; **46:** 1026–33.

6 Torres A, Prince M, Bebbington P, et al. Obsessive-compulsive disorder: prevalence, comorbidity, impact, and help-seeking in the British National Psychiatric Comorbidity Survey of 2000. *Am J Psychiatr* 2006; **163:** 1978–85.

7 Kessler R, Berglund P, Demler O, Jin R, Walters E. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 593–602.

8 Geller D. Obsessive-compulsive and spectrum disorders in children and adolescents. *Psychiatr Clin North Am* 2006; **29:** 353–70.

9 Mataix-Cols D, Rauch S, Baer L, et al. Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. *Am J Psychiatry* 2002; **159:** 263–68.

10 Stewart S, Geller D, Jenike M, et al. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. *Acta Psychiatr Scand* 2004; **110:** 4–13.

11 Heyman I, Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *Int Rev Psychiatry* 2003; **15:** 178–84.

12 Fontenelle LF, Mendlowicz MV, Versiani M. The descriptive epidemiology of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30:** 327–37.

13 Spitzer M, Sigmund D. The phenomenology of obsessive-compulsive disorder. *Int Rev Psychiatry* 1997; **9:** 7–14.

14 Alvarenga PG, Hounie AG, Mercadante MT, Miguel EC, Conceicao M. Obsessive-compulsive disorder: a historical overview. In: Storch EA, Geffken GR, Murphy TK, eds. Handbook of child and adolescent obsessive-compulsive disorder. Mahwah, NJ: Erlbaum, 2007; 1–15.

15 Pallanti S. Transcultural observations of obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165:** 169–70.

16 Vishne T, Misgav S, Bunzel ME. Psychiatric disorders related to menstrual bleeding among an ultra-Orthodox population: case series and literature review. *Int J Soc Psychiatry* 2008; **54:** 219–24.

17 Steketee G, Barlow D. Obsessive-compulsive disorder. In: Barlow DH, ed. Anxiety and its disorders. 2nd edn. New York: Guilford, 2002; 516–50.

18 Lopez-Ibor J, Lopez-Ibor M. Research on obsessive-compulsive disorder. *Curr Opin Psychiatry* 2003; **16** (suppl 2)**:** S85–S91.

19 Gross R, Sasson Y, Chopra M, Zohar J. Biological models of obsessive-compulsive disorder: the serotonin hypothesis. In: Swinson RP, Antony MM, Rachman S, Richter MA, eds. Obsessive-compulsive disorder: theory, research, and treatment. New York: Guilford, 1998; 141–53.

20 Greenberg B, Benjamin J, Martin J, et al. Delayed obsessive-compulsive disorder symptom exacerbation after a single dose of serotonin antagonist in fluoxetine-treated but not untreated patients. *Psychopharmacology* 2000; **140:** 434–44.

21 Saiz P, Garcia-Portilla M, Arango C, et al. Association study between obsessive-compulsive disorder and serotonin candidate genes. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 765–70.

22 Griest JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 1995; **52:** 53–60.

23 Chakrabarty K, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. *Neuropsychopharmacology* 2005; **30:** 1735–40.

24 Welch JM, Lu J, Rodriguiz RM, et al. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature* 2007; **448:** 894–900.

25 Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene *SLC1A1* associated with obsessive-compulsive disorder. *Arch Gen Psychiatry* 2006; **63:** 769–76.

26 Dickel DE, Veenstra-VanderWeele J, Cox NJ, et al. Association testing of the positional and functional candidate gene *SLC1A1/EAAC1* in early-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 2006; **63:** 778–85.

27 Stewart SE, Fagerness JA, Platko J, et al. Association of the *SLC1A1* glutamate transporter gene and obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B:** 1027–33.

28 Camarena B, Loyzaga C, Aguilar A, Weissbecker K, Nicolini H. Association study between the dopamine receptor D-sub-4 gene and obsessive-compulsive disorder. *Eur Neuropsychopharmacology* 2007; **17:** 406–09.

29 Rauch S, Whalen P, Dougherty D, Jenike M. Neurobiologic models of obsessive-compulsive disorder. In: Jenike MA, Baer L, Minichiello WE, eds. Obsessive-compulsive disorders: practical management. St Louis, MO: Mosby, 1998; 222–53.

30 Whiteside S, Port J, Abramowitz J. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatr Res Neuroimag* 2004; **132:** 69–79.

31 MacMaster FP, O'Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 1262–72.

32 Menzies L, Williams GB, Chamberlain SR, et al. White matter abnormalities in patients with obsessive compulsive disorder and their first-degree relatives, *Am J Psychiatry* 2008; **165:** 1308–15.

33 Nakamae K, Narumoto J, Shibata K, et al. Alteration of fractional anisotropy and apparent diffusion coefficient in obsessive-compulsive disorder: a diffusion tensor imaging study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 1221–26.

34 Hettema J, Neale M, Kendler K. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry* 2001; **158:** 1568–78.

35 van Grootheest D, Cath D, Beekman A, Boomsma D. Genetic and environmental influences on obsessive-compulsive symptoms in adults: a population-based twin-family study. *Psychol Med* 2007; **37:** 1635–44.

36 van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive-compulsive disorder: a review. *Twin Res Human Genet* 2005; **8:** 450–58.

37 Rosario-Campos MC, Leckman JF, Curi M, et al. A family study of early-onset obsessive-compulsive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2005; **136B:** 92–97.

38 Nestadt G, Samuels J, Riddle M, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry* 2000; **57:** 358–63.

39 da Rocha FF, Correa H, Teixeira AL. Obsessive-compulsive disorder and immunology: a review. *Prog Neuropsychopharm Biol Psychiatry* 2008; **32:** 1139–46.

40 Swedo S. Genetics of childhood disorders: XXXIII. Autoimmunity, part 6: poststreptococcal autoimmunity. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 1479–82.

41 Trifiletti R, Packard A. Immune mechanisms in pediatric neuropsychiatric disorders: Tourette's syndrome, OCD, and PANDAS. *Child Adolesc Psychiatr Clin N Am* 1999; **8:** 767–75.

42 Rachman S. A cognitive theory of obsessions. *Behav Res Ther* 1997; **35:** 793–802.

43 Rachman S. A cognitive theory of obsessions: elaborations. *Behav Res Ther* 1998; **36:** 385–401.

44 Salkovskis P. Obsessional-compulsive problems: a cognitive-behavioral analysis. *Behav Res Ther* 1985; **23:** 571–83.

45 Gibbs N. Nonclinical populations in research on obsessive-compulsive disorder. *Clin Psychol Rev* 1996; **16:** 729–73.

46 Abramowitz J, Khandker M, Nelson C, Deacon B, Rygwall R. The role of cognitive factors in the pathogenesis of obsessions and compulsions: a prospective study. *Behav Res Ther* 2006; **44:** 1361–74.

47 Abramowitz J, Nelson C, Rygwall R, Khandker M. The cognitive mediation of obsessive-compulsive symptoms: a longitudinal study. *J Anxiety Disord* 2007; **21:** 91–104.

48 Taylor S, Abramowitz JS, McKay D, et al. Do dysfunctional beliefs play a role in all types of obsessive-compulsive disorder? *J Anxiety Disord* 2005; **20:** 85–97.

49 Abramowitz JS. Understanding and treating obsessive-compulsive disorder: a cognitive-behavioral approach. Mahwah, NJ: Erlbaum, 2006.

50 Hollander E, Braun A, Simeon D. Should OCD leave the anxiety disorders in DSM-V? The case for obsessive compulsive-related disorders. *Depress Anxiety* 2008; **25:** 317–29.

51 Storch E, Abramowitz J, Goodman W. Where does obsessive-compulsive disorder belong in DSM-V? *Depress Anxiety* 2008; **25:** 336–47.

52 Bienvenu O, Samuels J, Riddle M, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. *Biol Psychiatry* 2000; **48:** 287–93.

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

54 Nestadt G, Samuels J, Riddle M, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. *Psychol Med* 2001; **31:** 481–87.

55 Grant J, Potenza M. Impulse control disorders: clinical characteristics and pharmacological management. *Ann Clin Psychiatry* 2004; **16:** 27–34.

56 O'Sullivan R, Rauch S, Brieter H. Reduced basal ganglia volumes in trichotillomania measured via morphometric MRI. *Biol Psychiatry* 1997; **42:** 39–45.

57 Stein D, Coetzer R, Lee M. Magnetic resonance brain imaging in women with obsessive-compulsive disorder and trichotillomania. *Psychiatr Res* 1997; **74:** 177–82.

58 Christenson G, Mackenzie T, Mitchell J, Callies A. A placebo controlled, double-blind crossover study of fluoxetine in trichotillomania. *Am J Psychiatry* 1991; **148:** 1566–71.

59 Ninan P, Rothbaum B, Marsteller F, Knight B, Eccard M. A placebo-controlled trial of cognitive-behavioral therapy and clomipramine in trichotillomania. *J Clin Psychiatry* 2000; **61:** 47–50.

60 Van Minnen A, Hoogduin K, Keijsers G, Hellenbrand I, Hendriks G. Treatment of trichotillomania with behavioral therapy or fluoxetine: a randomized, waiting-list controlled study. *Arch Gen Psychiatry* 2003; **60:** 517–22.

61 Eddy KT, Dutra L, Bradley R, Westen DA. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev* 2004; **24:** 1011–30.

62 Koran L, Hanna G, Hollander E, Nestadt G, Simpson H. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry* 2007; **164** (suppl 7)**:** 5–53.

63 Ravizza L, Barzega G, Bellino S, Bogetta F, Maina G. Drug treatment of obsessive compulsive disorder: long term trial with clomipramine and selective serotonin reuptake inhibitors. *Psychopharmacol Bull* 1996; **32:** 167–73.

64 Pato M, Zohar-Kadouch R, Zohar J, Murphy D. Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. *Am J Psychiatry* 1988; **145:** 1521–25.

65 Simpson H, Liebowitz M, Foa E, et al. Post-treatment effects of exposure therapy and clomipramine in obsessive-compulsive disorder. *Depress Anxiety* 2004; **19:** 225–33.

66 Bloch M, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken M, Leckman J. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry* 2006; **11:** 622–32.

67 Geller DA, Biederman J, Stewart SE, et al. Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. *Am J Psychiatry* 2003; **160:** 1919–28.

68 Coric V, Taskiran S, Pittenger C, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry* 2005; **58:** 424–28.

69 Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 2007; **17:** 761–67.

70 Abramowitz J. The psychological treatment of obsessive-compulsive disorder. *Can J Psychiatry* 2006; **51:** 407–16.

71 Abramowitz J, Taylor S, McKay D. Exposure-based treatment for obsessive-compulsive disorder. In: Steketee G, ed. New York: Oxford University Press, in press.

72 McKay D, Taylor S, Abramowitz JS. Obsessive compulsive disorder. In: McKay D, Abramowitz JS, Taylor S, eds. Cognitive behavior therapy for refractory cases: turning failure into success. Washington, DC: American Psychological Association, in press.

73 Goodman W, Price L, Rasmussen S, Mazure C, Delgado P, Heninger G, Charney D. The Yale-Brown obsessive compulsive scale: validity. *Arch Gen Psychiatry* 1989; **46:** 1012–16.

74 Fals-Stewart W, Marks A, Schafer J. A comparison of behavioral group therapy and individual behavior therapy in treating obsessive-compulsive disorder. *J Nerv Ment Disord* 1993; **181:** 189–93.

75 Lindsay M, Crino R, Andrews G. Controlled trial of exposure and response prevention in obsessive-compulsive disorder. *Br J Psychiatry* 1997; **171:** 135–39.

76 Van Balkom A, De Haan E, Van Oppen P, Spinhoven P, Hoogduin K, Van Dyck R. Cognitive and behavioral therapies alone versus in combination with fluvoxamine in the treatment of obsessive compulsive disorder. *J Nerv Ment Disord* 1998; **186:** 492–99.

77 Foa E, Liebowitz M, Kozak M, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2006; **162:** 151–61.

78 Nakatani E, Nakagawa A, Nakao T, et al. A randomized trial of Japanese patients with obsessive-compulsive disorder: effectiveness of behavior therapy and fluvoxamine. *Psychother Psychosom* 2005; **74:** 269–76.

79 Abramowitz J, Franklin M, Foa E. Empirical status of cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analytic review. *Rom J Cogn Behav Psychother* 2002; **2:** 89–104.

80 van Balkom AJLM, van Oppen P, Vermeulen AWA, van Dyck R, Nauta MCE, Vorst HCM. A meta-analysis on the treatment of obsessive-compulsive disorder: a comparison of antidepressants, behavior therapy, and cognitive therapy. *Clin Psychol Rev* 1994; **14:** 359–81.

81 Abramowitz J. Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. *J Consult Clin Psychol* 1997; **65:** 44–52.

82 Abramowitz J, Whiteside S, Deacon B. The effectiveness of treatment for pediatric obsessive-compulsive disorder: a meta-analysis. *Behav Ther* 2005; **36:** 55–63.

83 Watson HJ, Rees CS. TMeta analysis of randomized controlled treatment trials for pediatric obsessive-compulsive disorder. *J Child Psychol Psychiatry* 2008; **49:** 489–98.

84 Franklin M, Abramowitz J, Foa E, Kozak M, Levitt J. Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples. *J Consult Clin Psychol* 2000; **68:** 594–602.

85 Foa, E, Franklin M, Moser J. Context in the clinic: how well do CBT and medications work in combination? *Biol Psychiatry* 2002; **51:** 989–97.

86 Walker D, Ressler K, Lu K, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J Neurosci* 2002; **22:** 2343–51.

87 Hofmann S, Meuret A, Smits J, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry* 2006; **63:** 298–304.

88 Ressler K, Rothbaum B, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobics to facilitate extinction of fear. *Arch Gen Psychiatry* 2004; **61:** 1136–44.

89 Storch E, Merlo L, Bengtson M, et al. D-cycloserine does not enhance exposure–response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007; **22:** 230–37.

90 Wilhelm S, Buhlmann U, Tolin D, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165:** 335–41.

91 Kushner M, Kim S-W, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry* 2007; **62:** 835–38.

92 Boje K, Wong G, Skolnick P. Desensitization of the NMDA receptor complex by glycinergic ligands in cerebellar granule cell cultures. *Brain Res* 1993; **603:** 207–14.

93 Aouizerate B, Rotge J-Y, Martin-Guehl C, et al. A systematic review of psychosurgical treatments for obsessive-compulsive disorder: does deep brain stimulation represent the future trend in psychosurgery? *Clin Neuropsychiatry* 2006; **3:** 391–403.

94 Kopell B, Greenberg B. Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci Biobehav Rev* 2008; **32:** 408–22.

95 Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. *Psychol Med* 2007; **37:** 1645–49.