Review

The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers

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Summary

Obsessive compulsive disorder (OCD) is a highly debilitating neuropsychiatric condition with estimated lifetime prevalence of 2–3%, more than twice that of schizophrenia. However, in contrast to other neuropsychiatric conditions of a comparable or lesser prevalence, relatively little is understood about the aetiology, neural substrates and cognitive profile of OCD. Despite strong evidence for OCD being familial, with risk to first-degree relatives much greater than for the background population, its genetic underpinnings have not yet been adequately delineated. Although cognitive dysfunction is evident in the everyday behaviour of OCD sufferers and is central to contemporary psychological models, theory-based studies of neurocognitive function have yet to reveal a reliable cognitive signature, and interpretation has often been confounded by failures to control for co-morbidities. The neuroimaging findings in OCD are amongst the most robust reported in the psychiatric literature, with structural and functional abnormalities frequently reported in orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus. In spite of this, our relative lack of understanding of OCD neurochemical processes continues to impede progress in the development of novel pharmacological treatment approaches. Integrating the neurobiological, cognitive, and clinical findings, we propose that OCD might usefully be conceptualised in terms of lateral orbitofrontal loop dysfunction, and that failures in cognitive and behavioural inhibitory processes appear to underlie many of the symptoms and neurocognitive findings. We highlight existing limitations in the literature, and the potential utility of endophenotypes in overcoming these limitations. We propose that neurocognitive indices of inhibitory functions may represent a useful heuristic in the search for endophenotypes in OCD. This has direct implications not only for OCD but also for putative obsessive-compulsive spectrum conditions including attention deficit hyperactivity disorder, Tourette's syndrome, and trichotillomania (compulsive hair pulling).
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1. Introduction

Obsessive compulsive disorder (OCD) is characterised by intrusive, troubling thoughts that are perceived as the product of one's own mind (as distinguished from thought insertion in patients with schizophrenia, for example) and/or repetitive, compulsive behaviours or mental rituals (DSM-IV, 1994). Obsessions typically include thoughts of harm or death occurring to a loved one, chronic doubting, fears of contamination, blasphemous or socially unacceptable thoughts or impulses, counting, and a preoccupation with symmetry. Compulsions include excessive hand washing, placing objects symmetrically, repeatedly checking (e.g. that lights are off), or following set routines. Though intrusive thoughts and ritualistic behaviours are frequently reported in the background population (Rachman and de Silva, 1978; Salkovskis and Harrison, 1984; Muris et al., 1997), those seen in OCD are considered psychopathological as they are time consuming, cause marked distress, or significantly interfere with everyday functioning (DSM-IV, 1994). In many ways they act against the best interests of the individual and are regarded as egodystonic. The majority of patients are aware of the irrationality of their thoughts and behaviours but have limited control over them (Marazziti et al., 2002). OCD has a lifetime prevalence of 2–3% (Robins et al., 1984; Myers et al., 1984; Weissman et al., 1994; Karno et al., 1988), more than twice that of schizophrenia (NIMH, 1999), and is thought to be more common in women than men (though this is not necessarily reflected in the relative proportions reporting to tertiary referral centres) (Fineberg and Roberts, 2001). OCD is a hugely debilitating disorder that causes significant impairments in everyday functioning (Leon et al., 1995; Koran et al., 1996), and is frequently hidden from friends and colleagues (Hollander, 1997). Mean age of onset has been estimated at around 20 years of age, though males tend to develop the disorder slightly earlier than females (Rasmussen and Eisen, 1990). The economic and social burden of the disease are difficult to quantify, though one study approximated the economic cost of OCD in the United States to be $8.4 billion in 1990 (DuPont et al., 1995).

In this selective review, we begin by discussing the heterogeneous nature of the symptoms and high frequency of co-morbidities found in people suffering from OCD. We move on to examine genetic studies, contrasting the findings in support of genetic contributions from twin and family studies with the failure to identify specific molecular genetic factors that may be of importance in the aetiology. As well as discussing the successes and limitations of modern treatment approaches, we review

key brain imaging studies, and cognitive studies, with the aim of bringing together what is known of the neurobiological and cognitive underpinnings of the disorder. Integrating the neurobiological, cognitive, and clinical findings, we propose that OCD might be usefully conceptualised in terms of lateral orbitofrontal loop dysfunction, and that failures in cognitive and behavioural inhibitory processes appear to underlie many of the symptoms and neurocognitive findings. Given the limitations in the existing research, we argue for a more endophenotype-centred approach towards the study of OCD. Endophenotypes represent intermediate measures (or markers) between top-level symptoms and bottom-level genetic contributions (see Gottesman and Gould (2003) for an excellent overview). Fundamentally, endophenotypes 'grounded in the neurosciences'—to use Gottesman and Gould's term—are by definition closer to the underlying neuropathology than top-level symptoms or clinical phenotype. The concept has in recent times been applied

with success to the study of psychiatric conditions including attention deficit hyperactivity disorder (ADHD; Castellanos and Tannock, 2002) and schizophrenia (Gottesman and Gould, 2003). We highlight the potential utility of neurocognitive tasks and neuroimaging techniques, including those designed to index inhibitory functions, in the search for OCD endophenotypes.

2. Symptom heterogeneity and co-morbidities

The diagnostic and statistical manual IV (DSM-IV; Fig. 1) and Yale–Brown obsessive compulsive scale (Y–BOCS; Goodman et al., 1989a,b) are well established indices of the presence and severity of OCD symptoms. However, the nature of the obsessions and compulsions can vary greatly between individuals with similar ratings of disease severity, and this has led some researchers to question the value of treating OCD as a single nosological

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A. Either obsessions or compulsions:

Obsessions as defined by (1), (2), (3), and (4):

(1) recurrent and persistent thoughts, impulses, or images that are experienced at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress

(2) the thoughts, impulses, or images are not simply excessive worries about real-life problems

(3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action

(4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions as defined by (1) and (2):

(1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly

(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Fig. 1. DSM-IV criteria for obsessive compulsive disorder (OCD).

entity. In order to address this issue, data-driven approaches have been used to delineate homogenous subgroups based on symptoms (Khanna and Mukherjee, 1992; Khanna et al., 1990; Calamari et al., 1999). Such approaches fail to address the ubiquitous issue in psychiatry that a given symptom may be attributable to various underlying neurocognitive or affective substrates. For example, it is unclear whether a given compulsion is best thought of as due to behavioural perseveration, motivational issues, or a host of other alternative explanations. Classic behavioural approaches towards OCD view anxiety as a core psychological component of the disorder (Rachman and Hodgson, 1980), and indeed OCD is categorised as an anxiety disorder in DSM-IV, though the role of anxiety in mediating symptoms is far from clear. Modern psychological approaches towards understanding the top-level symptoms in OCD include the thought-action-fusion (TAF) model (e.g. see Amir et al. (2001)). This model holds that people with OCD interpret thoughts differently to normal in that they believe thinking about a particular negative event makes it more likely to happen in reality, and thinking about a catastrophic event is on some level morally equivalent to letting the event take place in reality. It may in future be possible to investigate cognitive neurobiological mechanisms in OCD within psychological frameworks (such as TAF).

Adding to the inherent difficulty in attempting to study OCD is the finding that co-morbidities are common. Motor tics (including Tourette's syndrome), trichotillomania (compulsive hair pulling), body dysmorphic disorder, and mood and anxiety disorders are frequently reported (Nestadt et al., 2001; Diniz et al., 2004). It is likely that the high frequency of co-morbidities can in some cases be explained in terms of overlapping aetiology, especially so with tic disorders (Diniz et al., 2004; Pitman et al., 1987; Leonard et al., 1992a,b; Leckman et al., 1994; Como, 1995). In exploring the neural substrates and cognitive dysfunctions central to OCD, studies have often failed to screen for and take into consideration the contribution of these co-morbidities (e.g. see Kuelz et al. (2004) for review in the context of cognitive findings)—a significant failing given that primary mood disorders for example are associated with broad and substantial cognitive deficits (Chamberlain et al., 2004; Elliott et al., 1996; Beats et al., 1996; Purcell et al., 1997; Sweeney et al., 2000). This frequent lack of screening for co-morbidities is unfortunate given that effective and well-validated clinical instruments are available for screening purposes, including the structured clinical interview for DSM-IV (SCID; Spitzer et al., 1996) or more rapid mini-international neuropsychiatric interview (MINI; Sheehan et al., 1998).

3. The genetics of OCD

Rutter and Silberg (2002) have argued that rapid progress has been made in the identification of genetic traits underlying monogenic mendelian disorders like cystic fibrosis, but that only limited progress has been made in complex psychiatric diseases which demand a sophisticated multi-tiered approach. Concordance rates for OCD symptoms are significantly higher for monozygotic versus dizygotic twins (Carey and Gottesman, 1981; Rasmussen and Tsuang, 1986), and the disorder is often demonstrably familial (Nestadt et al., 2000a; Jonnal et al., 2000; Bellodi et al., 1992; Pauls et al., 1995), with risk to first-degree relatives estimated at 3–12 times greater than for the wider population (Grados et al., 2003). Segregation analysis, in which mathematical modelling is used to accept or reject genetic models of inheritance, is suggestive of a major gene locus for OCD inheritance of greater importance in females than males (Alsobrook et al., 1999; Cavallini et al., 1999; Nestadt et al., 2000b). Researchers have investigated whether allelic variations in genes coding for enzymes, receptors, and reuptake transporters might contribute to the aetiology of OCD (see Grados et al. (2003) for review). However, these approaches are entirely dependent on the selection of candidate genes by researchers on the basis of our pre-existing understanding of the disorder, as genome wide scans have yet to be completed. For example, DSM-IV considers OCD to be an anxiety spectrum disorder, and there is evidence that a polymorphism in the promoter region for the serotoninergic reuptake transporter (5-HTTLPR promoter region) (Heils et al., 1995, 1996) accounts for a significant proportion of the variation in anxiety-related personality traits in the healthy background population (Lesch et al., 1996). Knock-out of this gene in mice causes abnormal behavioural phenotypes consistent with increased anxiety and reduced aggression (Holmes et al., 2003a,b). It is logical to question whether this polymorphism might contribute to the aetiology of OCD, especially given that selective serotoninergic reuptake inhibitors (SSRIs) represent a first-line pharmacological treatment (see later). Though McDougle et al. (1998) found preliminary evidence for a linkage disequilibrium between the long (l) allele of 5-HTTPLR and OCD in a familial study, and Bengel et al. (1999) found further evidence using a population based study, the findings from other studies are negative (Camarena et al., 2001; Chabane et al., 2004; Meira-Lima et al., 2004). Some studies have examined polymorphisms in serotonin receptor subtypes (Meira-Lima et al., 2004; Walitza et al., 2002; Di Bella et al., 2002; Mundo et al., 2002; Tot et al., 2003), leading Camarena et al. (2004) to the recent discovery that polymorphisms in the 5-HT-1D-beta receptor gene might contribute to disease severity. Other transmitter system components (e.g. Monoamine Oxidase A, Catechol-*O*-methyl transferase, and DRD4 dopamine gene mutations) have also been investigated, but positive results are seldom replicated between studies. This paucity of robust findings is probably largely attributable to the heterogenous nature of the condition, serving to highlight the need for the more

careful selection of research participants, on the basis of measures that are closer to the underlying pathology than overt symptomatology.

4. Pharmacological treatment approaches

Psychological treatment in the form of behaviour therapy (exposure and response prevention) has been used with success for some time in the treatment of OCD (Rasmussen and Eisen, 1997; Jenike, 2001). The use of pharmacological agents has also been explored, and serotonin reuptake inhibitors (SRIs) are now the first line pharmacological treatment at most centres (e.g. see Fineberg and Gale (2004); Fig. 2). The neurochemistry of OCD is nonetheless not well characterised (Graybiel and Rauch, 2000), and importantly 40–60% of OCD sufferers do not respond to appropriate courses of SRI treatment (Kaplan and Hollander, 2003; Davidson and Bjorgvinsson, 2003). This inevitably leads to speculation about whether pharmacological agents acting on other transmitter systems might have a role to play in the treatment of the disorder. Dopamine blockade via neuroleptic medication is a potential pharmacological augmentation strategy in treatment resistant forms of the disorder (Goodman et al., 1990; Zohar and Fineberg, 2001), and there is evidence for reduced dopamine receptor binding

in left caudate nucleus in OCD patients (Denys et al., 2004)—a region implicated in the neurobiology of OCD (see later). Given that the alpha-2 adrenergic agonist clonidine has been shown to reduce symptom severity in OCD (Knesevich, 1982; Hollander et al., 1991), noradrenergic dysfunction may also be important, though there is a lack of evidence that noradrenergic selective reuptake inhibitors are effective at ameliorating symptoms. A greater understanding of the neurobiological basis of OCD and the differential role of ascending modulatory transmitter systems in mediating symptoms, and in determining treatment response, may eventually contribute to the development of more effective pharmacological treatment algorithms.

5. Brain imaging techniques: identification of OCD neurobiology

5.1. Structural studies

Structural brain abnormalities, indexed by altered volumes in selected neural regions from magnetic resonance imaging (MRI) data, are frequently reported in people with OCD. For example, though some studies have reported normal caudate nucleus volume in OCD (Kellner et al., 1991; Aylward et al., 1996), other studies find altered
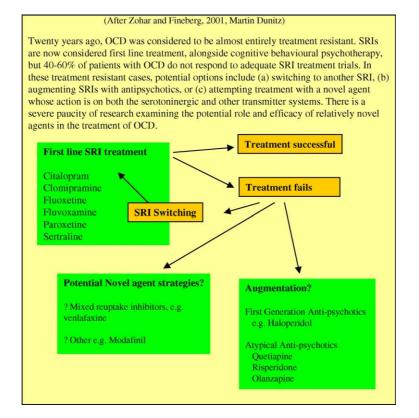

Fig. 2. Pharmacological treatment of OCD.

volume status (Scarone et al., 1992; Calabrese et al., 1993; Robinson et al., 1995). On the basis of studies using 'whole brain' approaches, rather than just focusing on specific regions, there is a broad consensus for widely distributed (albeit inconsistent) structural abnormalities involving frontostriatal circuits (e.g. see Jenike et al. (1996) and Pujol et al. (2004)). Some have tentatively suggested, based on the finding that streptococcal infection in susceptible children appears capable of causing OCD-like symptoms to develop (see later discussion), that volume abnormalities in these regions might be suggestive of immune mediated pathological processes. However, there is a lack of direct evidence for this hypothesis at the present time. In a review of the anatomical MRI findings in mood and anxiety disorders, Brambilla et al. (2002) concluded that orbito-frontal and basal ganglia regions are frequently reported to be anatomically abnormal in OCD, and represent distinct structural abnormalities to those reported in other anxiety disorders such as panic disorder and post-traumatic stress disorder.

5.2. Resting state functional studies

Functional imaging studies using positron emission tomography (PET) and single photon emission tomography (SPECT) techniques have revealed glucose metabolism and regional cerebral blood flow (rCBF) abnormalities in people with OCD at rest. Multiple studies have identified such abnormalities in the basal ganglia (especially caudate), cingulate cortex, and orbitofrontal cortex (Edmonstone et al., 1994; Lucey et al., 1997; Crespo-Facorro et al., 1999; Busatto et al., 2000; Saxena et al., 2001a, 2004; Lacerda et al., 2003), and several of these studies included groups with different psychiatric disorders as well as healthy controls. Lucey et al. (1997) utilised SPECT and identified reduced caudate rCBF in OCD not only when compared to healthy controls, but also when compared to controls with panic disorder. Edmonstone et al. (1994) also using SPECT, found evidence for abnormal basal ganglia metabolism (in terms of reduced tracer uptake) in OCD that was absent in a group of clinically depressed controls matched for medication. Saxena et al. (2001a) were able to contrast baseline metabolic activity using PET in patients with OCD alone, major depressive disorder (MDD) alone, and OCD with co-morbid MDD. On the basis of the results, the authors argued that depressive episodes in OCD sufferers might have a different neurobiological basis to mainstream depression. A key limitation of these comparative neuroimaging studies is that the degree of neural dysfunction might be anticipated to be dependent on disease severity, yet it is difficult to see how groups with different psychiatric conditions can be matched on this basis. Additionally, it is foreseeable that chronic disease course and co-morbidities might signifi-cantly contribute to the findings. Collectively therefore, resting state studies are of limited utility in differentiating the neural underpinnings of OCD versus other anxiety

disorders and mood disorders. One potentially useful approach would be to examine resting state function in young medication-naïve adults with new onset OCD, and contrast the findings with data from studies using 'first episode' matched subjects with other conditions. However, this presents serious practical issues, as good community level screening for OCD is not routinely found.

5.3. Symptom provocation and stimulus exposure studies

It is possible to employ functional brain imaging techniques during the presentation of different types of stimuli, facilitating an examination of neural activity during symptom provocation in individuals with OCD. Rauch et al. (1994) utilised repeated PET to track rCBF in individuals with OCD both at rest (during exposure to innocuous stimuli), and during symptom provocation (exposure to individually tailored provocative stimuli). Increases in rCBF in right caudate, left anterior cingulate, and bilateral orbitofrontal cortex, were identified during symptom provocation compared to the baseline condition. Breiter et al. (1996) also employed a symptom provocation paradigm, this time in conjunction with fMRI, and replicated the finding of involvement of these—and other—neural regions (Breiter and Rauch, 1996). It has been suggested that brain reactivity to symptom provocation might be predictive of therapeutic outcome, and Hendler et al. (2003) employed SPECT to examine brain perfusion during symptom provocation before six months of sertraline treatment. They found that those who responded success-fully to treatment had significantly lower perfusion during symptom provocation prior to treatment in the right caudate, compared to non-responders. More recently, there has been an upsurge in research into whether there might be distinct neural correlates associated with different symptom dimen-sions. Recently, Mataix-Cols et al. (2004) have reported some very exciting findings using a symptom provocation paradigm and volunteers with different OCD symptom clusters in conjunction with healthy controls. Volunteers were scanned while observing blocks of emotional (wash-ing-related, checking-related, hoarding-related, or aversive, symptom-unrelated) and neutral pictures. Increased acti-vation compared to controls was identified in bilateral ventromedial prefrontal regions and right caudate nucleus in OCD volunteers with washing fixations; putamen/globus pallidus, thalamus, and dorsal cortical areas in OCD volunteers with checking fixations; and left pre-central gyrus and right orbitofrontal cortex in OCD volunteers with hoarding fixations. This seminal work highlights that different neural circuitry may be implicated in the manifestation of different symptom dimensions, and that it is necessary to consider OCD as a non-unitary entity.

An up-and-coming area of research involves the use of neuroimaging techniques to explore the role of 'disgust' in OCD. Stein et al. (2001) have reviewed the literature to identify core neural regions that are implicated in disgust

processing, and have argued that these processing regions share significant overlap with those cortico-subcortical circuits known to function abnormally in OCD. Phillips and Mataix-Cols (2004) explored the neural response to disgusting pictures in volunteers with OCD who had washing fixations or checking fixations, versus matched control volunteers. They found that exposure to normally disgusting pictures in OCD sufferers with checking concerns activated fronto-striatal regions—the same regions that have been implicated in the urge to perform rituals. Shapira et al. (2003) have investigated disgust-processing in OCD volunteers with contamination-fixations using a functional imaging paradigm. They found that the pattern of neural activation during threat-inducing stimulus exposure was similar between OCD volunteers and controls, whereas the pattern of activation during disgust-inducing stimulus exposure was different with greater increases in the right insula, parahippocampal region, and inferior frontal sites in OCD. Clearly, this is an area of study that merits further research.

5.4. Treatment response studies

It is interesting to consider whether the demonstrable functional abnormalities in neural regions including orbito-frontal cortex, anterior cingulate cortex, and caudate can be ameliorated by pharmacological intervention in people with OCD. One of the first studies to address this issue found that treatment with the tricyclic clomipramine led to a relative decrease in cerebral glucose metabolic rate in orbitofrontal cortex and left caudate, and increases in areas of the basal ganglia (Benkelfat et al., 1990). This 'normalisation' of orbitofrontal cortex dysfunction by clomipramine has been confirmed in another study using PET scanning in child-hood-onset OCD patients (Swedo et al., 1992). In a key study, Saxena et al. (1999) examined whether pre-treatment metabolic activity in orbitofrontal cortex was predictive of treatment response to the SSRI paroxetine (in terms of a reduction in symptom severity). They found that in patients who responded to 8–12 weeks of paroxetine treatment, there was a significant decrease in glucose metabolism in right anterolateral orbitofrontal cortex and right caudate nucleus. Further, lower pre-treatment metabolic activity in both left and right orbitofrontal cortex was found to be predictive of greater treatment response. Rauch et al. confirmed this finding using PET in contamination concerned people with OCD who underwent 12 weeks of fluvoxamine treatment (Rauch et al., 2002). Given the finding in major depression that successful psychological treatment may lead to the normalisation of dysfunctional neural circuitry akin to those changes seen in response to successful pharmacological intervention (Goldapple et al., 2004), it is interesting to question whether this might also be the case in the treatment of OCD. Nakatani et al. (2003) examined rCBF changes during successful treatment with behaviour therapy in OCD, and identified a reduction in right caudate rCBF that tended

to correlate with clinical improvement in symptomatology. These studies support the future utility of functional imaging techniques as a means of predicting likely response not only to pharmacological treatment, but also perhaps other forms of psychotherapeutic intervention. However, it is unclear whether the reported metabolic changes occurring over the course of successful treatment are simply a reflection of symptom reduction, or bear some more direct relationship to the correction of underlying brain pathology (for example, in terms of ascending monoaminergic transmitter systems).

5.5. Integration: orbitofrontal loop dysfunction

On the basis of earlier work by Alexander et al. (1986) supporting the idea that brain circuits connecting cortex to subcortical neural regions can be considered to be relatively functionally specialised, Graybiel and Rauch have argued that the cortico-subcortical circuits involved in OCD might be characterised in terms of abnormal habit forming mechanisms (see Graybiel and Rauch (2000) and Graybiel (1997) for further details). In this approach, the pathological obsessions and compulsions in OCD can be viewed as abnormal or maladaptive habits over which sufferers are unable to exert sufficient 'high level' control. The orbito-frontal cortex, anterior cingulate cortex, and caudate nucleus are integral to a 'lateral orbitofrontal loop', and it is useful to contrast this neural circuit to others such as a motor loop involving different structures (see Fig. 3). We therefore propose that the neurobiology of OCD might be usefully conceptualised in terms of lateral orbitofrontal loop dysfunction. Saxena et al. (1998) have argued that the manifestation of OCD symptoms might be best characterised by hyperactivation in cortico-subcortical circuits involving the orbitofrontal cortex, as evidenced by the symptom provocation and treatment response studies. Though this hyperactivation may represent a relatively disease-specific finding, abnormalities in structures within the lateral orbitofrontal loop have been reported in other psychiatric disorders with notably different symptomatology—including mood disorders, other anxiety disorders, and basal ganglia disorders. There is a growing body of evidence that obsessive-compulsive symptoms are found with unexpectedly high frequency in Tourette's syndrome (Como, 1995), Huntington's disease (De Marchi and Mennella, 2000), and perhaps also Parkinson's disease (see Alegret et al. (2001) and Maia et al. (2003)). Cortico-subcortical neural loops are not completely functionally segregated, and overlapping neurobiology may account for this overlap in symptoms. Therefore, though the concept of lateral orbito-frontal loop dysfunction represents a useful starting point, further research is needed to characterise the precise nature of the underlying neuropathologies between diseases.

There are several tiers of evidence beyond the brain imaging data already discussed implicating lateral orbito-frontal loop circuitry in the manifestation of OCD

| Motor Loop | Lateral Orbitofrontal Loop |

Supplementary motor area → Putamen → Pallidum / Substantia nigra → Thalamus

Arcuate premotor area
Motor cortex
Somatosensory cortex

Dysfunction may underlie motor symptoms in:
• Parkinson's Disease
• Huntington's Disease
• Tourette's Syndrome

Lateral orbitofrontal cortex → Head of caudate → Pallidum / Substantia nigra → Thalamus

Anterior cingulate cortex
Superior temporal gyrus
Inferior temporal gyrus

Dysfunction may underlie symptoms in:
• OCD
• Depression
• Mania

Basal gangliathalamocortical loops link cortical and subcortical neural structures, and can be considered to be relatively segregated. Two examples of these loops are the motor loop and lateral orbitofrontal loop (above). Several structures within the lateral orbitofrontal loop are implicated in the neurobiology of OCD (highlighted in dark grey) as evidenced by structural and functional brain imaging data. Though some have argued that the functional findings in OCD are relatively disease-specific, there is overlap with other conditions including mood and anxiety disorders.
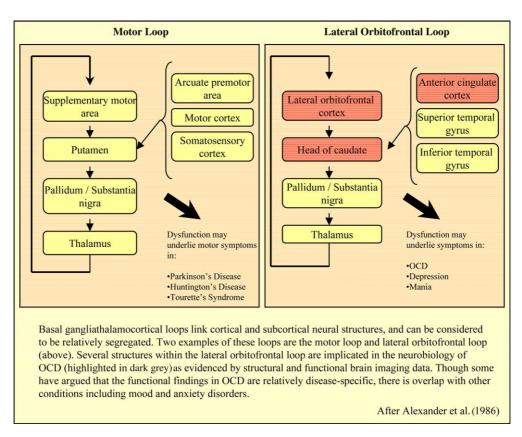
After Alexander et al. (1986)

Fig. 3. Basal ganglia-thalamocortical loops.

symptoms. Firstly, Graybiel and Rauch have cited evidence from animal studies that components of the orbitofrontal and anterior cingulate cortices have links to the striosomal system in the head of the caudate (Eblen and Graybiel, 1995), a structure that appears to be differentially active when animals perform repetitive stereotyped behaviour after dopamine receptor agonist administration (Graybiel and Rauch, 2000). Secondly, traumatic brain injury to local regions of neural tissue can cause OCD to develop in adults with no prior history of symptoms (Berthier et al., 2001; Hiott and Labbate, 2002; Stengler-Wenzke et al., 2003), and in severe cases focal contusions can be visualised within lateral orbitofrontal loop structures (Berthier, 2000; Berthier et al., 1996, 2001). Thirdly, SSRIs are able to alleviate symptom severity, and this may relate to normalisation of dysfunctional regions including orbitofrontal cortex, most likely via modulation of ascending neurotransmitter pathways (especially serotoninergic). Lastly, in paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) there is reasonable evidence for a causal pathway between streptococcal infection in susceptible children, autoimmune mediated damage to basal ganglia structures, and the development of OCD-like symptomatology (Swedo et al., 1992, 1994; Giedd et al., 2000; Swedo, 2002; Snider and Swedo, 2003; Pavone et al., 2004). However, the wider relevance of

these findings to mainstream OCD is far from clear. Several human leukocyte antigen (HLA) types have been established to be associated with autoimmune disorders (see Ebringer and Wilson (2000) and Wilson et al. (2000)), and it may be that research can identify certain HLA or other genetic markers for PANDAS susceptibility in children, facilitating preventative intervention.

In all, the available evidence suggests that the neurobiology of OCD may be characterised by abnormal processing within cortico-subcortical neural networks, including the lateral orbitofrontal loop. Further work is needed to characterise the nature of this abnormal processing, and the relationship to different ascending monoaminergic transmitter systems.

6. Cognitive functioning

Given the structural and functional abnormalities in orbitofrontal cortex, anterior cingulate gyrus, and the basal ganglia (especially caudate) (Saxena et al., 2001a,b; Saxena and Rauch, 2000), it is logical to hypothesise that OCD patients would show impaired performance on neurocognitive tasks sub-served by these brain regions. Contemporary clinical models of OCD emphasise the central role of 'idiosyncrasies' in cognition (Salkovskis, 1985, 1989, 1999; Salkovskis et al., 1998, 2000;

Salkovskis and Westbrook, 1989), and the everyday behaviour of people with OCD is suggestive of cognitive dysfunction. The development of advanced computerised cognitive testing batteries, such as cambridge neuropsychological test automated battery (CANTAB) has facilitated the profiling of abnormalities in a diverse array of psychiatric and neurological disorders. Modern cognitive tests allow for hypothesis-driven dissection of different domains of cognition, and can be utilised in patients with focal neurosurgical lesions and in conjunction with brain imaging techniques, facilitating the identification of neural substrates of task performance. These approaches hold advantages over more traditional 'pen and paper' methods, in that they can be more readily administered between study sites, and can enable more automated and accurate data collection. Kuelz et al., in a comprehensive review of cognitive functioning in OCD (Kuelz et al., 2004), found evidence for frequent but inconsistent deficits across several cognitive domains. They argued that failures to control for co-morbidities probably accounted for many of the inconsistencies in the OCD neurocognitive findings. Here, we focus on some key findings in the available literature.

6.1. Memory

There is a substantial body of evidence to suggest that OCD patients show impaired performance on a number of different memory tasks. Additionally, aspects of the behaviour seen in people with OCD might be argued to be suggestive of memory problems. For example, many patients engage in repetitive checking behaviour—e.g. that the gas stove is off—arguably suggestive of attentional problems or a failure to appropriately encode memories for self-actions. However, studies indexing reality monitoring and memory for self-actions in OCD patients fail to find evidence of impairments in these areas (McNally and Kohlbeck, 1993; Constans et al., 1995; Hermans et al., 2003). Non-verbal memory has been assessed by the Rey complex figure test (RCFT; Osterrieth, 1944) and Benton visual retention test (BVRT; Benton, 1974). In the RCFT, subjects copy a complex line diagram from a stimulus card and later re-draw it from memory, and in the BVRT (version A), a series of cards with simple geometric designs are exposed for ten seconds and the subject must then draw the designs one at a time immediately after each has been covered up. There is broad agreement that an impairment exists in recall performance on these tasks in OCD, but many have argued that this impairment is due to failures in the employment of appropriate organisational strategies (Kuelz et al., 2004; Martinot et al., 1990; Savage et al., 1999; Savage and Rauch, 2000; Deckersbach et al., 2000; Kim et al., 2002). The suggestion that performance deficits occur in situations where strategy is important is also supported by the finding that verbal memory is generally unimpaired in OCD patients (Christensen et al., 1992; Martin et al., 1995; Mataix-Cols et al., 1999), except in tasks requiring stimuli to be semantically clustered (Savage and Rauch, 2000; Cabrera et al., 2001). The CANTAB testing battery (CANTAB) includes the pattern recognition memory (PRM), spatial recognition memory (SRM), and spatial working memory (SWM) tasks (see Fig. 4 for descriptions). Purcell et al. (1998) identified SWM and SRM impairments in OCD but not PRM impairment. Barnett et al. (1999) confirmed SRM deficits in another study using OCD patients. Nielen and Den Boer (2003) replicated the finding of SRM impairment and no PRM impairment, but in contrast to the findings of Purcell et al. their results indicated no statistically significant SWM impairment. In an fMRI study using a different spatial working memory task, medication-free individuals with OCD were found to perform worse than controls at harder levels of difficulty and demonstrated heightened activation in anterior cingulate cortex (compared to controls) at multiple levels of task difficulty (van der Wee et al., 2003). The authors concluded that their findings were suggestive of executive dysfunction rather than a deficit in spatial working memory system per se. Given that SWM is strategy-dependent, and that we believe many subjects utilise strategy on the SRM task, studies to date suggest that performance on spatial recognition and spatial working memory tasks may be impaired in individuals with OCD consequential to strategy failures. Further decomposition of the component cognitive processes of task performance will help to refine our understanding of the basis for the apparent mnemonic failures.

6.2. Planning

The original Tower of London (CANTAB) (TOL) cognitive task (e.g. see Purcell et al. (1998b)) requires subjects to rearrange a set of snooker balls in pockets on a computer screen to match the appearance of another set determined by the computer, within the confines of the game rules. The aim is to solve each problem in the minimum possible number of moves (indicated by a number on the screen). The outcome measures from this task include 'number of perfect solutions', and latency data for reaction and thinking times. To our knowledge, four OCD studies have been conducted with the TOL task, and ability to meet the minimum number of moves requirement was found to be impaired in one (Nielen and Den Boer, 2003) but not the other studies (Purcell et al., 1998a; Veale et al., 1996; Watkins et al., in press). Watkins et al. (in press) have argued that cognitive planning, as indexed by the CANTAB TOL, appears generally unimpaired in people with OCD. They contrast this with the finding from multiple studies that people with depression tend to be impaired on CANTAB TOL planning measures.

Collectively, though the studies utilising CANTAB TOL in OCD find limited support for pure planning deficits, there is strong evidence for abnormal psychomotor slowing (as indexed by lengthened latency/thinking

Pattern Recognition Memory (PRM) Task

In the PRM task, the subject views a sequence of patterns that are presented consecutively on the screen (left figure), and then has to select the pattern present in the original set from a forced choice of two (right figure). This is a test of ability to recognise patterns that are designed to be difficult to semantically encode, and is thought to represent a relatively pure measure of memory function that is not dependent on strategy.

Spatial Recognition Memory (SRM) Task

In the SRM task, subjects are asked to remember the positions of consecutively presented boxes on the screen (e.g. left figure). They are then given a forced choice of two positions, and asked to select the box that is in the same position as one of the original boxes (e.g. right figure). Spatial recognition memory is thought to be dependent on relatively frontal neural circuitry.

Spatial Working Memory (SWM) Task

In the SWM task, subjects have to search for tokens hidden behind boxes by selecting them one at a time. Tokens are collected to complete a particular task. The key rule is that once a token has been hidden behind a particular box, it will not be hidden behind that same box again on that part of the exercise. By varying the colour, location, and number of the boxes, this task examines working memory at several levels of difficulty.
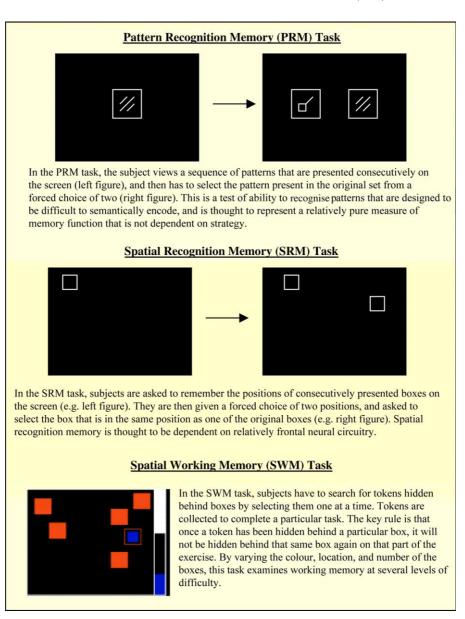
Fig. 4. CANTAB memory tasks of use in exploring OCD (see www.camcog.com).

times compared to controls) in at least a subset of sufferers. However, further research is needed to delineate the cognitive underpinnings of this slowing phenomenon, as the nature of this slowing has been found to be inconsistent between studies (e.g. see Purcell et al. (1998) for discussion). It may be that lengthened latency times on the TOL task are consequential to strategy failures, attentional problems, and/or chronic doubting in situations where the subject is informed via computer feedback that they have just made an error (negative feedback).

6.3. Decision-making

The ability to make reasoned judgements on the basis of available information is integral to everyday living. It has

been suggested that the compulsive behaviours in OCD may be conceptualised as failures in decision-making (Cavedini et al., 2002). The Iowa Gambling Task (Bechara et al., 1994) mimics real life decision-making, has been employed in the investigation of many neuropsychiatric conditions (Bechara et al., 1994, 1999; Wilder et al., 1998; Schmitt et al., 1999), and is sensitive to ventromedial prefrontal cortical damage (Bechara et al., 1999, 2000). In this task, there are several decks of cards and the goal is to maximise profit by making a series of card selections. The examiner schedules rewards and punishments such that decision-making can be objectively quantified by examining the tendency of the subject to select advantageous versus disadvantageous card decks overall. The available studies utilising this task in individuals with OCD provide mixed findings (Cavedini et al., 2002; Nielen et al., 2002), and

there is some evidence that decision-making impairments on this task may represent a marker for treatment resistant forms of the disorder (Cavedini et al., 2002). Watkins et al. (in press) utilised a different decision-making task (see Rogers et al. (1999) for task description), and replicated the finding of intact decision-making in OCD. More research using a variety of decision-making tasks, in conjunction with an understanding of neural correlates of performance derived from functional imaging studies, is likely to be of value.

6.4. Set-shifting

Set-shifting represents the ability to switch attention from one aspect of a stimulus to another in an ongoing task, in accordance with changing reinforcement contingencies. Given the perseveration and repetition demonstrable in the clinical behaviour, set-shifting impairments might be expected to represent a core feature of the neurocognitive profile of OCD. There are several cognitive tasks that can be used in the exploration of set-shifting (see Fig. 5 for overview). The Wisconsin Card Sorting Task (WCST; Berg, 1948) is known to be sensitive to brain lesions, and performance has been found to be particularly dependent on dorsolateral prefrontal cortical integrity (Lombardi et al., 1999). Some studies have identified set-shifting deficits in OCD using the WCST (Hymas et al., 1991; Okasha et al., 2000), but others have not identified such deficits (Abbruzzese et al., 1995, 1997; Moritz et al., 2001, 2002). The object alternation test (OAT; Freedman, 1990) and delayed alternation test (DAT; Freedman and Oscar-Berman, 1986) measure a distinct aspect of set-shifting: behavioural reversal, in which a rule is learnt and then subsequently needs to be inhibited and reversed in order to maintain good performance. These tasks appear to be more dependent on orbitofrontal rather than dorsolateral prefrontal cortical function (Freedman et al., 1998; Zald et al., 2002). Set-shifting performance (in terms of behavioural reversal) in OCD sufferers has been found to be impaired on both of these tasks (Abbruzzese et al., 1997; Aycicegi et al., 2003). The intra-dimensional/extra-dimensional (IDED) set-shifting task (CANTAB) is an automated computerised task, utilising conceptually distinct stages such as the intra-dimensional shift (examining rule generalisation when there are novel stimuli) and extra-dimensional shift (in which the relevant stimulus dimension alters). Veale et al. (1996) found that individuals with OCD recruited mainly from inpatient settings made more errors than controls on multiple stages of this task. In contrast, Watkins et al. (in press) identified selective deficits at the ED stage (using people with OCD recruited from outpatient settings) that were not found in patients with Tourette's syndrome and have not been found in separate studies involving patients with Depression. A feasible explanation for the broader IDED set-shifting deficits found in Veale et al.'s study is that these volunteers are likely to have had

more clinically severe psychopathology given their inpatient status. While Purcell et al. (1998) failed to report statistically significant deficits in OCD on this task, it is worth noting that their OCD and control groups differed in terms of the ED stage trials to criterion measure, but that this did not meet a priori significance criteria ($p = 0.04$). Nielen and Den Boer (2003) failed to identify statistically significant set-shifting deficits using this task in another group of OCD patients, both before and after a course of pharmacological treatment. It may be that the expression of set-shifting deficits in OCD is related to clinical disease severity or disease progression, highlighting the potential usefulness of set-shifting tasks as candidate markers for different manifestations of the condition. Clearly further studies are required, with larger sample sizes, careful patient selection, monitoring of co-morbidities, disease severity, and medications. Switching tasks, in which subjects undertake two or more tasks that run alternately in a rapid fashion, may help to clarify the nature of deficits in cognitive flexibility in OCD.

6.5. Response inhibition

The term 'response inhibition' (RI) refers to cognitive processes enabling executive control over pre-potent motor responses in accordance with changing situational demands (e.g. see Logan et al. (1984) and Aron et al. (2003)). Initial evidence for RI deficits in OCD came from studies using oculomotor tasks that required the suppression of eye movements. Failures of inhibition were identified in treatment naïve children and adults with OCD (Rosenberg et al., 1997a,b). In Go/No-Go tasks, subjects have to make a simple motor response (such as pressing a button) as quickly as possible when target stimuli are presented, and withhold the motor response when non-target stimuli are presented. Bannon et al. (2002) found that OCD patients made significantly more commission errors than matched panic disorder control subjects in a computerised task necessitating the inhibition of responses on a proportion of trials—OCD patients tended to make inappropriate motor responses to non-target stimuli. Aycicegi et al. (2003) utilised a computerised task with different stimuli, and identified impaired performance on conflict blocks compared to healthy matched controls, consistent with Bannon et al.'s findings. Similar deficits have been identified in Tourette's syndrome complicated by co-morbid OCD (Muller et al., 2003). Recently, Watkins et al. (in press) utilised a computerised Go/No-Go task in which response contingencies were reversed on some blocks of trials. This enabled the quantification of switching cost, in terms of reduction in correct responding on reversal blocks. They found that the OCD group had an abnormally high switching cost compared to both matched healthy controls and volunteers with Tourette's syndrome. Tasks that examine switching performance may be useful not only in examining response

Wisconsin Card Sorting Task (WCST) (Berg, 1948)

In the original version of the WCST, subjects receive a deck of 60 cards, each of which has one to four identical symbols printed on it: star, cross, triangle, or circle. The experimenter decides on a rule for 'correct' sorting and gives feedback to the subject after they place each card underneath one of the four stimulus piles. Thus, the subject has to learn a sorting rule in order to succeed. In the example (right), the subject needs to place the card (X) underneath one of the stimulus cards A/B/C/D. The correct rule, for example, might be 'same shape', in which case the correct pile would be 'B'. By altering the rule when certain criteria are met, this task examines aspects of cognitive flexibility and perseverative tendencies (see Neuropsychological Assessment, Lezak et al., Oxford University Press).

Object Alternation Task (OAT) (Freedman, 1990) and Delayed Alternation Task (DAT) (Freedman and Oscar-Berman, 1986)

In these tasks, the experimenter and subject sit opposite each other with a curtain between them so that between each trial the experimenter can move objects without the subject seeing. In the OAT, there are two objects of different appearance, under which money can be hidden. The subject can choose to reveal the contents of only one object per trial, and the aim is to accumulate as much money as possible. On the first trial, both objects contain money and thus the subject is automatically correct. For subsequent trials, the money is hidden under the object not previously chosen, or under the same object if the subject chose the wrong location. The location of the objects is varied left versus right in a pseudorandom fashion. Total perseverative errors can be calculated, in which subjects choose the incorrect object two or more times consecutively before shifting strategy. The DAT (see diagram below) is similar to the OAT task except that rather than money being hidden under two different objects, there are two identical cups and the side (left or right) is the important variable. Following a correct response, the money is shifted to the opposite side, otherwise the money is kept hidden under the same side.

CANTAB 2D IDED Task (www.camcog.com)

In the CANTAB IDED task, subjects are told that they will see two patterns on screen at a time, that there is a rule they can learn to get the task right every time, and that when the computer decides that they know the rule, the rule will be changed. It is made clear that these rule changes will not happen very often. This task enables performance to be compared over multiple different stages and thus helps to fractionate out different aspects of set-shifting. For example, at the extra-dimensional shift stage, the rule changes so that a previously irrelevant stimulus dimension becomes important – e.g. the number of lines might become important rather than the shape of the main item in the pattern.
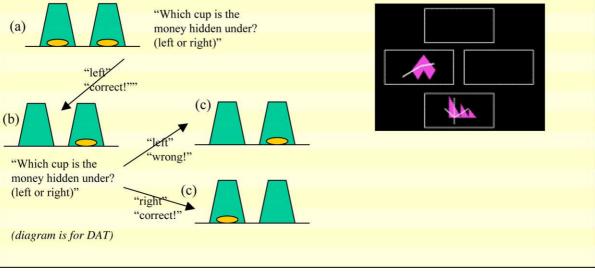
Fig. 5. Set-shifting tasks of use in exploring OCD.

inhibition failures but also set-shifting, as per our previous suggestion.

In a recent pilot study using seven adults with OCD recruited from the community (rather than from outpatient clinics), RI was examined using a stop-signal task in which subjects had to make a motor response to a green 'x' on-screen but withhold motor response if this green 'x' changed to red (the stop signal) (Krikorian et al., 2004). Contrary to expectations, the authors report superior inhibitory control in their OCD sample compared to controls. However, the length of the stimulus display intervals, and the proportion of 'stop' compared to 'go' trials, are important in determining the physiological validity and sensitivity of such tasks. We would argue that

a neurocognitive task such as the stop signal reaction time (SSRT) task originally developed by Logan et al. (1984) that uses stepwise tracking algorithms to determine measures of inhibitory control, represents a technically superior model of this aspect of cognitive functioning (e.g. see Aron et al. (2003)). The development of different neurocognitive tasks that model pre-potent inhibition processes will be of use in further exploring cognitive deficits in OCD.

6.6. Attentional bias and vigilance

Attentional and information processing biases are commonly reported in affective (Chamberlain et al., 2004; Tavares et al., 2003) and anxiety disorders (Summerfeldt and Endler, 1998)—both of which are frequent co-morbidities in OCD (Diniz et al., 2004). The clinical symptoms of OCD are suggestive of processing biases, such as fixations with potential contamination sources or stimuli that would not normally evoke emotional responses. It is important to consider whether processing bias can be indexed by cognitive tasks, given the finding of abnormal neural activity in lateral orbitofrontal loop structures in OCD during symptom provocation. The Stroop task is a classic measure of attentional processing and executive control, in which subjects are asked to name the ink colour of printed words that have an interfering semantic content—for example, the word 'RED' written in green ink (or equivalent on a computer screen). By examining average reaction times in different conditions, the 'cognitive' cost of interfering semantic content can be quantified. Though an abnormal interference cost has been identified in at least one study using OCD patients (Hartston and Swerdlow, 1999), other studies report no abnormalities (Martinot et al., 1990; Schmidtke et al., 1998). Modified versions of the Stroop using emotionally relevant words have been utilised to seek out attentional biases, but it is not easy to quantify and control for the variable relevance of stimulus words to individual patients' obsessive and compulsive foci. This perhaps accounts for the lack of evidence for common attentional biases in OCD using this type of task (Lavy et al., 1994; Kampman et al., 2002; Moritz et al., 2004). In dot probe paradigms, word pairs are typically presented on a computer screen in a vertical arrangement, and then both words disappear and a 'dot' appears in place of one of the words. The aim of each 'dot probe' trial is to give an appropriate motor response corresponding with whether the dot is in the top or bottom position. By recording the average response times when the dot probe is preceded by different classes of words, attentional vigilance to particular types of stimuli can be recorded. Tata et al. (1996) employed a version of the dot probe task using social anxiety threat, contamination threat, and neutral words, in OCD patients with contamination fixations. They found increased vigilance towards contamination threat words in the OCD patients, increased vigilance towards social threat words in high anxiety healthy controls, and a lack of such heightened vigilance in low anxiety healthy controls. The findings are consistent with selective attentional bias and increased vigilance towards contamination related words in this subtype of OCD patient not simply attributable to a state of anxiety. Tata et al. have argued that the dot probe paradigm has fewer interpretative problems than the Stroop, and therefore further studies using this paradigm would be of interest.

In directed forgetting (DF) tasks, subjects typically view a series of words presented sequentially on a computer screen. Immediately after each word presentation they receive an instruction to remember or forget that particular word. Subjects then undergo free recall and recognition tests for all words irrespective of the original instructions they received. Wilhelm et al. (1996) used negatively valenced (sad), positively valenced (happy), and neutral words in OCD patients and matched controls. They found that the OCD group had difficulty forgetting information when it was negative: they recognised more negative words they were instructed to forget than other types of words compared to controls. The results were interpreted in terms of OCD patients inappropriately encoding negatively valenced stimuli. However, it is noteworthy that the authors reported 25% of their OCD group to suffer from co-morbid Major Depressive Disorder (whereas controls were free of any DSM-IV axis-I psychiatric condition). On this basis, we would argue that the abnormal encoding of negative words reported in this study might have been consequential to depressive mood status rather than OCD per se. Tolin et al. (2002) utilised a similar approach to explore directed forgetting in the case of OCD related stimuli, by asking each OCD subject to generate their own word lists at least 24 h prior to the experiment proper. By providing OCD participants with forms containing blank spaces, and a list of sample words, idiographic stimulus selection was made for four categories: OCD relevant positive (happy) words, OCD relevant negative (unpleasant) words, OCD non-relevant positive words, and OCD non-relevant negative words. Those with OCD were found to be impaired in their ability to forget words that were relevant to their OCD state (whether negative or positive), but had no impairments in forgetting other types of words (whether negative or positive). By yoking to anxious and non-anxious healthy control groups, the effects were again found to be OCD specific rather than attributable to a state of anxiety per se. The lack of apparent bias towards negative or positive words, irrespective of OCD relevance, supports our contention that Wilhelm et al.'s finding may have been attributable to depressive mood rather than OCD. In summary, there is evidence for abnormal processing bias towards OCD relevant stimuli on paradigms such as dot-probe and directed forgetting. However, it is evident that the ability to demonstrate these processing biases is highly dependent on the relevance of task stimuli to individual OCD concerns.

7. The importance of failures in cognitive and behavioural inhibition processes

The top-level symptoms seen in OCD are strongly suggestive of inhibitory failures. OCD is characterised by intrusive, troubling thoughts that are perceived as the product of one's own mind and/or repetitive, compulsive behaviours or mental rituals. The content of intrusive thoughts experienced by healthy people shares significant overlap with the content of obsessions in OCD patients (Rachman and de Silva, 1978; Salkovskis and Harrison, 1984), and ritual-like behaviours are commonly found in the background population (Muris et al., 1997). The differences between 'normal' and 'OCD' cognitions are that the latter are more frequent, more intense, and elicit more resistance and subjective discomfort, such that they may impair activities of daily living and quality of life (see DSM-IV criteria, Fig. 1). OCD cognitions might be best characterised in terms of failures to inhibit, or shift attention from, these ongoing thoughts or motoric activities towards other more pleasant, or less distressing, cognitions. Tolin et al. (2002) have argued that cognitive behavioural psychological models of OCD are suggestive of such inhibitory failures. Given that inhibitory failures appear integral to aspects of the symptoms and psychology of OCD, it is necessary to ask whether inhibitory failures might also underlie the reported cognitive deficits, and whether the abnormal neural circuitry implicated in OCD is involved in physiological (normal) inhibitory functions. We propose that it may be useful to differentiate between two types of inhibition processes: (a) cognitive inhibition, representing control over internal cognitions (e.g. intrusive thoughts, mental rituals, or inappropriate strategies); and (b) behavioural inhibition, representing control over externally manifested motoric activities (e.g. ritualistic checking behaviour; Fig. 6). Though this may represent a useful conceptual distinction, common cognitive and neural processes may of course be implicated in both thoughts and actions. As discussed earlier, Mataix-Cols et al. (2004) have recently reported in a seminal study that different symptom dimensions in OCD have distinct neural correlates. Bilateral ventromedial prefrontal regions and right caudate nucleus were implicated in washing symptoms; putamen/globus pallidus, thalamus, and dorsal cortical areas in checking; and left
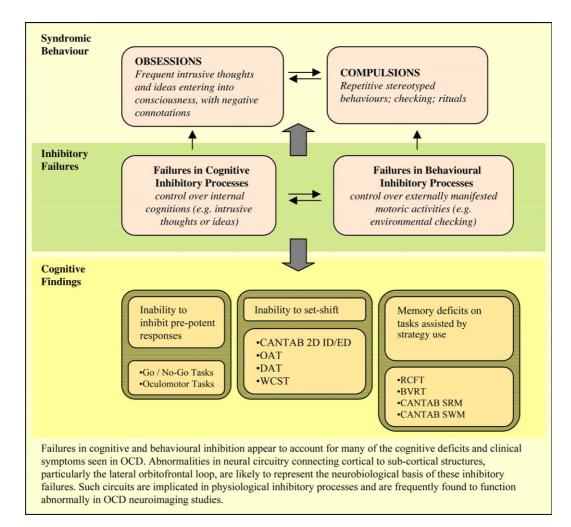

Fig. 6. The importance of inhibitory failures in OCD.

pre-central gyrus and right orbitofrontal cortex in hoarding. Given that different types of inhibitory failure may underlie different symptoms, it follows that neurocognitive indices of such inhibitory failures may ultimately be useful in sub-grouping patients.

Various neurocognitive deficits have been identified across several domains in OCD, including memory, set-shifting, response inhibition, and attentional processing. There is direct evidence for response inhibition failures as indexed by Go/No-Go and oculomotor tasks, in which there is a need to inhibit pre-potent motor responses (Aycicegi et al., 2003; Rosenberg et al., 1997b; Bannon et al., 2002; Muller et al., 2003). As Aron et al. report (Aron et al., 2004), inhibition as a cognitive function has been associated with neural substrates including the dorsolateral prefrontal cortex, inferior frontal cortex, and orbitofrontal cortex. Horn et al. (2003) for example, found inhibition to be associated with activation of multiple regions on a Go/No-Go task in healthy volunteers, including orbitofrontal cortex, superior temporal gyrus, cingulate gyrus, and inferior parietal lobule. Bokura et al. (2001) used event-related potentials to indicate increased orbitofrontal cortex activity during inhibition of responses in the 'no go' condition. Therefore, the inhibitory failures demonstrated by individuals with OCD on these neurocognitive tasks are consistent with lateral orbitofrontal loop dysfunction, particularly in orbitofrontal cortex. Set-shifting is classically regarded as a distinct cognitive function to inhibition, and some have argued that dorsolateral prefrontal cortex is important in set-shifting whereas orbitofrontal cortex is more important in response inhibition. At first sight the finding of set-shifting deficits in OCD patients from multiple neurocognitive studies (Veale et al., 1996; Watkins et al., in press; Abbruzzese et al., 1997) in the absence of imaging evidence for dorsolateral prefrontal cortical dysfunction might be surprising. However, as Evans et al. (2004) have argued, set-shifting not only requires the ability to adopt a new rule or attend to a different stimulus dimension, but also the inhibition of responding to the previously acquired rule. Human patients with focal lesions to the orbitofrontal cortex are impaired on a probabilistic behavioural reversal learning task, which shares cognitive requirements in common with the behavioural reversals necessary on some of these set-shifting tasks (Berlin et al., 2004). Additionally, lesions to orbitofrontal cortex in animals have been shown to lead to abnormal perseveration on equivalent animal tests (de Bruin et al., 1983; Rolls, 1996; Chudasama and Robbins, 2003). Therefore, inhibitory failures arising from dysfunction in the orbitofrontal cortex are likely to be important in mediating the set-shifting deficits reported in OCD patients.

Greisberg and McKay (2003) were amongst the first researchers to suggest that cognitive deficits in people with OCD are most consistently found on tests requiring the use of organisational strategies in conjunction with short and long term memory. It is possible that most, if not all, of the memory deficits reported in OCD could be accounted for by non-mnemonic processing failures, in particular the rigid implementation of inappropriate strategies (Kuelz et al., 2004; Martinot et al., 1990; Savage et al., 1999; Savage and Rauch, 2000; Deckersbach et al., 2000; Kim et al., 2002). Savage et al. (1999) and Savage and Rauch (2000) have argued that the orbitofrontal cortex is implicated in the initialisation of effective behavioural strategies in novel or ambiguous situations (such as when undertaking a memory task for the first time). It will be important for future research to examine whether failures in the inhibition of response strategies could account for these apparent deficits on strategy and memory tasks. In particular, it will be useful to investigate whether people with OCD have difficulty inhibiting inappropriate strategies when novel (more effective) strategies are suggested on neurocognitive tasks.

8. Future research directions

In reviewing the available data, we have identified several significant limitations in our current understanding of OCD: specific genetic contributions have not been identified, current treatment algorithms fail to help a significant proportion of sufferers, studies have frequently failed to control for co-morbidities, and cognitive deficits, though frequently reported, are highly variable. We have proposed that lateral orbitofrontal loop dysfunction is important in understanding the neurobiology of OCD, though clearly further work is needed to explore the nature of any underlying pathology. We have built on the work of other researchers by suggesting not only that the symptoms seen in OCD are strongly suggestive of failures in cognitive and behavioural inhibitory functions, but also that many of the cognitive deficits seen in the available literature are suggestive of such failures (Fig. 6). These failures are consistent with what is known of the role of lateral orbitofrontal loop circuitry in cognition.

At the present time, the diagnosis of OCD, sub-typing of patients, and tracking of treatment response, are facilitated by top-level clinical measures such as DSM-IV diagnostic criteria (DSM-IV, 1994) and the Yale–Brown obsessive compulsive scale (Goodman et al., 1989a,b). In the field of psychiatry, it is becoming increasingly evident that approaching psychiatric entities only in terms of top-level overt symptoms is unsatisfactory (Gottesman and Gould, 2003). Many have proposed that endophenotypes may be useful in this regard. Central to this search is the idea that intermediate measures of disease (termed endophenotypes), grounded in the neurosciences, are by definition closer than the underlying pathology of a given psychiatric condition than the top-level symptoms (see Gottesman and Gould (2003) for discussion). The endophenotype concept may be of significant utility in overcoming the limitations that we have identified in our current understanding.

The available literature is suggestive of future research directions in the search for candidate endophenotypes.

As discussed previously, Mataix cols et al. have recently identified specific neural substrates underlying different symptom dimensions in OCD (Mataix-Cols et al., 2004; Phillips and Mataix-Cols, 2004)—ventromedial prefrontal regions and right caudate nucleus are implicated in washing, putamen/globus pallidus, thalamus, and dorsal cortical areas in checking, and left pre-central gyrus and right orbito-frontal cortex in hoarding. These regions are implicated in physiological cognitive and behavioural inhibitory processes, as indexed by neurocognitive tasks (see earlier discussion). We propose that neurocognitive tasks designed to tap these cognitive and behavioural inhibitory processes therefore represent a useful heuristic in the search for candidate endophenotypic markers, especially when coupled with functional imaging techniques.

It will be interesting to compare neurobiological markers of inhibitory functions between OCD and other conditions that have been suggested to constitute an obsessive-compulsive spectrum of conditions, including ADHD, Tourette's syndrome, and trichotillomania (compulsive hair pulling). These disorders share co-morbid overlap with OCD—especially when symptoms are conceptualised in terms of failures in impulse control (e.g. see Phillips (2002) and Richter et al. (2003) for discussion). Gilbert et al. (2004) have argued that OCD, ADHD, and Tourette's syndrome may be considered as hyperkinetic disorders involving excess excitatory output from basal ganglia to cortical regions. It is noteworthy that failures in pre-potent inhibitory functions have been implicated in the neurocognitive and symptomatological findings in all of these conditions (see earlier discussion; also see Castellanos and Tannock (2002) and Muller et al. (2003)) though of course pre-potent motor inhibition represents just one aspect of inhibitory function. The development of neurocognitive tasks capable of tapping different cognitive and behavioural inhibitory processes is likely to have relevance not only to our neurocognitive understanding, but also to the nosology of these complex psychiatric conditions.

9. Conclusions

Research into OCD has been hindered by the hetero-genous nature of the symptoms as indexed by clinical measures including DSM-IV and Y–BOCS, and by the high frequency of co-morbidities. Robust genetic contributions to the aetiology have not been identified, and significant limitations in current treatment algorithms are evident. In reviewing the neural, cognitive, and clinical findings in OCD, we find that failures in cognitive and behavioural inhibition processes appear integral to the neuropsycho-pathology of the disorder. Additionally, a heuristic explanation in these terms is consistent with the neurobiology of OCD, as structures within the lateral orbitofrontal loop appear to be important in the physiological control of inhibition processes, as evidenced by lesion and functional imaging studies. We propose further that the identification, validation, and refinement of neurocognitive endophenotypic OCD markers may be of utility in assessing the efficacy of existing and novel pharmacological interventions, optimising diagnosis, assessing disease severity, and isolating the genetic contributions of this severely debilitating and prevalent disorder. An approach founded in terms of inhibitory failures is likely to represent a useful starting point for these developments, particularly as failures in inhibitory control are collectively implicated in the putative obsessive-compulsive spectrum of conditions, including OCD, Tourette's syndrome, and ADHD.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neubiorev. 2004.11.006

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