Mapping Compulsivity in the DSM - 5 Obsessive Compulsive and Related Disorders: Cognitive Domains, Neural Circuitry And Treatment

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Abstract

Compulsions are repetitive, stereotyped thoughts and behaviors designed to reduce harm. Growing evidence suggests that the neurocognitive mechanisms mediating behavioural inhibition (motor inhibition, cognitive inflexibility) reversal learning and habit formation (shift from goal-directed to habitual responding) contribute toward compulsive activity in a broad range of disorders. In obsessive compulsive disorder (OCD), distributed network perturbation appears focused around the pre-frontal cortex, caudate, putamen and associated neuro-circuitry. OCD-related attentional set-shifting deficits correlated with reduced resting state functional connectivity between the dorsal caudate and the ventrolateral prefrontal cortex on neuroimaging. In contrast, experimental provocation of OCD symptoms reduced neural activation in brain regions implicated in goal-directed behavioural control (ventromedial prefrontal cortex (vmPFC), caudate) with concordant increased activation in regions implicated in habit learning (pre-supplementary motor area, putamen). The vmPFC plays a multifaceted role, integrating affective evaluative processes, flexible behavior and fear learning. Findings from a neuroimaging study of Pavlovian fear reversal, in which OCD patients failed to flexibly update fear responses despite normal initial fear conditioning, suggest there is an absence of vmPFC safety signaling in OCD, which potentially undermines explicit contingency knowledge, and which may help to explain the link between cognitive inflexibility, fear and anxiety processing in compulsive disorders such as OCD.

Cognitive Domains, Neural Circuitry and Treatment
Introduction

Compulsions are stereotyped behaviours, performed according to rigid rules and designed to reduce or avoid unpleasant consequences (Chamberlain et al., 2009). The newly created DSM-5 Obsessive Compulsive and Related Disorders (OCRDs) (APA 2013) are defined by the presence of compulsions. However, compulsive behaviours are observed in many other psychiatric disorders, particularly those involving deficient impulse control. For example, much of the behaviour associated with disorders of eating, substance addiction and ‘behavioural addiction’, such as pathological gambling or problematic internet usage (Ioannidis et al., 2016), is theorized to shift over the course of time from reward-driven impulsive (rapid, reckless) to compulsive activity (Everitt and Robbins, 2005; Robbins et al., 2012). These disorders share a profound experience of “lack of control”, thought to derive from the dysfunctional inhibition of thoughts and behaviours naturally prone to excess e.g. grooming, eating, purging, gambling and checking. As poorly understood ‘lifespan disorders’, they are difficult to treat and responsible for considerable psychiatric (depression, suicide) and somatic morbidity and cost to the individual and society as a whole (Hollander et al., 2016).

Regrettably, the development of new treatments in psychiatry is slowing, related, at least in part, to difficulties translating positive results from experiments using non-human illness-models to the clinical setting. These difficulties align with growing concern about the scientific utility of the existing diagnostic systems (ICD-10(1992), DSM-5 (APA 2013)) that tend to define psychiatric disorders according to symptoms and syndromes, and give less prominence to neuropsychological substrates. It is thought likely that the considerable biological heterogeneity that exists within the current taxonomy is hampering identification of
the underpinning mechanisms that may serve as new therapeutic targets. In response, the EU Roadmap for Mental Health Research in Europe (ROAMER) (Haro et al., 2014) and the US National institute of Mental health, Research Domain Criteria (RDoC) (https://www.nimh.nih.gov/research-priorities/rdoc, Insel et al., 2010) have called for new ways of classifying psychopathology to better support treatment-development, based on dimensions of observable behaviour with established biological validity, irrespective of diagnosis. Identifying the pathophysiological mechanisms underpinning ‘compulsivity’ as a trans-diagnostic, neuropsychological domain, would therefore be expected to advance the search for new treatment targets and support innovation in developing evidence-based treatments.

Many different compulsive disorders are found clustered within the same individual (comorbidity) or within the families of affected individuals, implying that vulnerability to these disorders is mediated via shared pathophysiological mechanisms (Fineberg et al., 2014). The investigation of ‘endophenotypes’ (intermediate phenotypes) that lie closer than do the expressed behaviours (phenotypes) to the genetic and environmental origins of compulsive disorders (Gottesman and Gould, 2003, Chamberlain and Menzies, 2009), such as changes in cognitive performance, or structural and functional brain imaging abnormalities, is expected to provide a clearer understanding of the biological processes underpinning these disorders.

Based on emerging data from the neurosciences, this narrative review, which was first delivered as a plenary lecture at the 2016 Annual Congress of the International College of Neuropsychopharmacology (Fineberg et al., 2016), appraises the results of a decade of research by the authors dedicated to exploring the neuropsychological underpinnings of the OCRDs, as examples of compulsive disorders, from the perspective of diagnosis, evidence-based treatments, candidate neuro-psychological endophenotypes and associated neural circuitry. The research builds upon previous and ongoing research by other groups and as it has progressed, has generated testable models of compulsivity as a biologically-relevant trans-diagnostic domain that could be expected to advance diagnostic classification and
identify new avenues for treatment including novel psychological, pharmacological and somatic treatment targets for these disabling and intransigent disorders.

The Obsessive-Compulsive and Related Disorders.

The DSM-5 OCRD cluster, comprising obsessive–compulsive disorder (OCD), body dysmorphic disorder (BDD), hoarding disorder, hair-pulling disorder and skin-picking disorder, represents some of the most costly, functionally disabling and treatment-resistant brain disorders. By gathering together diagnoses previously listed in the DSM-IV under Anxiety Disorders, Somatoform Disorders and Impulse-Control Disorders Not Elsewhere Classified, this new classification aims to advance the scientific study of the disorders, as well as to improve their clinical recognition and management. The disorders commonly occur together and yet are surprisingly poorly recognised, as individuals are often not forthcoming about their symptoms (for example, due to a sense of shame, or lack of knowledge that these problems constitute recognized mental disorders). As a result, there is usually a considerable time-lag - in the case of OCD, amounting to approximately 15 years, before the correct diagnosis is made and the correct treatments initiated. The duration of untreated illness represents one of the principal factors determining clinical and health outcomes (DellOsso et al., 2013), emphasizing the importance of early detection, especially for child and adolescent onset OCD (Fineberg et al., 2013a). It is to be hoped that by introducing this new classification, clinicians would be more likely to enquire about and detect the other disorders. It is fully expected that the forthcoming ICD revision will adopt a similar approach and may even include additional new diagnoses among the OCRD grouping, such as olfactory reference syndrome (Marras et al., 2016).
OCRDs are generally thought to be highly heritable (Hoarding Disorder; Iervolino et al., 2009; OCD, Nestadt et al., 2010; BDD, Monzani et al., 2012,), lifespan disorders (reviewed in Steketee G., 2011, APA 2013), though episodic forms of OCD, hair pulling and skin picking are seen. They are characterised by the irresistible urge to perform distressing and time consuming compulsive acts. Of these disorders, OCD has been subject to most study and is arguably the most well understood. OCD affects approximately 3% of the general population, though only a fraction of affected individuals present for treatment. Of considerable interest, sub-threshold OCD is found to be extremely common and such cases share a similar age of onset and symptom-trajectory as OCD, suggesting a natural continuum of compulsive behaviour exists affecting as many as 20% of the general population (Fineberg et al., 2013b).

Patients with OCD show difficulty in flexibly shifting attentional focus away from distressing intrusive, perseverative thoughts (obsessions) and behaviours (compulsions) (Fineberg et al., 2010, 2014). Washing, checking, ordering and arranging compulsions are extremely common. Whereas traditional learning-based psychological models of OCD posit harm-avoidance as the major re-inforcer of compulsive behaviours, some symptoms of OCD, especially those concerned with ordering and arranging to achieve symmetry, appear to reflect a need to make the environment ‘feel right’. Growing evidence suggests these symptoms represent a separate OCD subgroup, in which compulsions are driven by the urge to avoid an unpleasant a ‘not just right feeling’. The ‘not just right feeling’ has been found to be associated with an earlier age of OCD onset and the presence of sensory processing difficulties (Hellriegel et al., 2016), implicating the involvement of neuro-developmental mechanisms akin to autism spectrum disorder (ASD) in its aetiology.

Hoarding disorder is a separate, poorly understood and highly treatment refractory OCRD that involves the compulsive acquisition of new items and difficulty discarding owned items. These hoarding behaviours can also be viewed as an expression of the need to make the environment ‘feel right’. Typical responses when asking individuals what they would think/feel if we threw out a “treasured item”, which may be an old sweet paper, bus ticket etc.
are “it feels like I am missing part of me, it does not feel right” (Frost and Steketee, 2010). Hoarding compulsions are also commonly found in patients with OCD as well as those with neurodevelopmental disorders such as ASD. In young people with OCD, hoarding is associated with prominent executive function deficits (Park et al., 2016). Hair-pulling disorder and skin-picking disorder, on the other hand, are defined by more obviously disinhibited behaviour, in the form of repetitive, body-focused, grooming habits, that can be considered as either predominantly impulsive or compulsive, depending on the nature of the symptoms expressed (Chamberlain et al., 2007).

Other phenotypic signs of an altered neurodevelopmental trajectory are also commonly observed in patients with OCRDs, such as traits or symptoms of tic disorder, ASD and attention deficit hyperactivity disorder (ADHD). These comorbid traits and diagnoses appear to cluster in the same patient or within their family members, hinting that shared, heritable neuro-behavioural mechanisms contribute to the expression of many compulsive disorders (de Vries et al., 2016; Wikramanayake et al., 2017). Cases of tic-related OCD tend to have a male predominance (similar to ASD), an earlier age of onset and a higher proportion of OCD symptoms related to symmetry, “not just-right experiences,” and forbidden thoughts compared to non-tic-related OCD (Prado et al., 2008). Additionally, tic-related OCD shows a more favourable response to adjunctive treatment with dopamine antagonist drugs (Bloch et al., 2006). In response to the emerging evidence, the DSM-5 has highlighted the presence of tic as the first neuro-behavioural specifier of a clinically-relevant OCD subtype. Studies in patients with Tourette’s syndrome indicate a complex genetic relationship exists between tic disorder, OCD and ADHD. One such recent study (Darrow et al., 2016) identified two independent, heritable, symptom-based factors (one involving the urge to attain symmetry, the other involving behavioural disinhibition) as possible trans-diagnostic phenotypes of compulsive behaviour.
Evidence-Based Treatment of Obsessive-Compulsive and Related Disorders.

Figure 1 summarises the evidence-based treatment of the OCRDs, based on a systematic review (Grant et al., 2014). Apart from some studies of OCD and BDD, the pharmacotherapies were almost exclusively tested in small un-replicated trials and the psychotherapies were not rigorously tested against a matched control of fair comparison. Randomised controlled treatment trials of adequate size and power to enable the detection of predictive outcome markers are urgently needed to drive forward the clinical management of these disorders on an individualised basis.

**Figure 1 about here.**

OCD typically responds to pharmacological treatment with serotonin reuptake inhibitors (SRIs; clomipramine and selective SRIs, SSRIs) according to a dose-response relationship (higher doses needed for better clinical response) or to SSRIs combined with antipsychotic agents, and to cognitive behaviour therapy (CBT) involving exposure and response prevention (ERP) (Fineberg et al., 2015). Antipsychotics represent first-line treatment for Tourette’s syndrome and adjunctive antipsychotic may be preferentially effective in OCD with comorbid tics (Bloch et al., 2006). BDD has been studied less intensively than OCD but also shows a similar treatment response (Veale et al., 2014; Rashid et al., 2015; Phillips et al., 2016), though it remains less clear as to whether higher SSRI dosages and adjunctive antipsychotic are of value (reviewed in Reghunandanan et al., 2015). The compulsions associated with ASD also respond to SSRI, though the increased risk of SSRI-induced adverse effects in the autistic population, such as behavioural activation and agitation, warrant care in dosage titration and subject selection (Kolevzon et al., 2006). Hoarding
behaviour has been mainly studied in the context of comorbid OCD and may respond to SSRI or venlafaxine (Saxena & Sumner, 2014), but as yet no effective pharmacological treatment has been established for primary hoarding disorder. CBT, even when delivered intensively over long periods, has so far been found to produce only limited improvement in hoarding behaviour (Uhm et al., 2016). In hair-pulling disorder the data supporting the efficacy of SSRI and clomipramine are also not strong. Unlike OCD, but similar to impulse control disorders, SSRIs appeared to have a rapid onset of effect which was not sustained over time (Rothbart et al., 2013). Habit reversal therapy, rather than ERP, has emerged as the psychological therapy of choice (McGuire et al., 2014). Other data from single randomised controlled trials in hair-pulling disorder suggest that olanzapine (an antipsychotic agent) (Van Ameringen et al., 2010) and n-acetyl cysteine (an amino acid compound) (Grant et al., 2009) could be effective. Naltrexone, an opiate antagonist, produced substantial benefits in a small open-label study of children with hair pulling disorder (De Sousa, 2008), but the drug was not effective in a double-blind placebo-controlled study. However, those in this study with a family history of addiction showed a greater (but not statistically significant) decrease in the urge to hair-pull (Grant et al., 2014). Skin picking disorder has been barely studied to date, but as with hair-pulling disorder, shows some response to SSRI and n-acetyl cysteine (reviewed in Reghunandanan et al., 2015).

Approximately 40% of OCD patients fail to respond to standard forms of therapy (Fineberg et al., 2015). Of great interest, a wide range of pharmacological compounds have been tested in treatment-resistant OCD and some have found to be effective in small-sized trials, implicating a multiplicity of potential treatment targets and mechanisms (see figure 2).

**Figure 2 about here**

Thus, notwithstanding the limitations of the study data, some compulsive disorders (e.g. OCD, BDD) exhibit a strikingly similar treatment response to SSRIs, suggesting that the underpinning neural mechanisms may overlap significantly, and possibly also with those relating to anxiety and affective disorders. In contrast, hair pulling and skin picking disorders, which are also characterised by prominent impulse control and addictive symptomatology,
together with SRI-resistant OCD, respond better to combination treatment with drugs acting on dopamine, glutamate, opioid and noradrenergic systems, i.e. potentially more like impulse-control disorders or even behavioural addictions. Whereas those with prominent motor symptoms (tics, habits) may respond preferentially to adjunctive dopamine antagonists, known to modulate the cortico-striatal motor circuitry involved in Tourette’s syndrome and animal models of excessive habit behaviour (Fineberg et al., 2014, Furlong et al., 2014).

The pharmacological treatment response may be of particular value for parsing psychiatric disorders, and defining the boundaries of diagnostic groups, as it depends on underpinning biological mechanisms. As the treatment trial data for the OCRDs accrues, it is possible that for some disorders more convincing similarities will be found with disorders classified elsewhere in the DSM, such as the behavioural addictions (e.g. pathological gambling), impulse control disorders (e.g. intermittent explosive disorder) or even neurodevelopmental disorders (e.g. autism spectrum disorder), challenging their classification within the OCRDs grouping. Alternatively, by taking a dimensional (impulsive-compulsive-habit) approach to the psychopharmacology of the OCRDs, the emerging evidence may instead be interpreted to support the inclusion of some of these other disorders into an expanded OCRDs grouping.

**Neuro-psychological Endophenotypes**

Psychiatric symptoms and cognitive deficits can be conceptualised as disordered structure, connectivity and function in large-scale neural networks. A series of evolutionarily well conserved, parallel, cortico-striato-thalamo-cortical (CSTC) circuits are believed to underpin the expression of compulsive behaviours (Alexander et al., 1986; Cummings et al., 1993; Groenewegen & Uylings 2000). These circuits include direct (positive feedback) and indirect (negative feedback) pathways, projecting from specific cortical areas to the corresponding sub-regions of the striatum and thalamus with recurrent projections to the cortex. They are involved in diverse computational activities, including reward processing, action selection, habit formation and motor control (Arnsten et al., 2011; Robbins et al., 2012). They play an
important role in recognizing behaviourally significant stimuli (and in error detection) and in regulating goal-directed responses (Lovinger, 2010) and may therefore be particularly important for OCRDs. The anatomical overlap and functional interplay between these circuits may explain why compulsive behaviour occurs in so many psychiatric syndromes.

Historical Perspectives

Early indications that the compulsive behaviours seen in OCD and other compulsive disorders may be mediated by CSTC circuits came from work showing an association between post-encephalitis parkinsonian and obsessive-compulsive symptoms occurring together with striatal lesions (Cheyette & Cummings, 1995). OCD symptoms occurring in a range of other neurological disorders with striatal involvement, including Tourette’s syndrome, Sydenham’s chorea, Huntington’s disorder and Parkinson’s disorder, were also documented early on (Pitman et al., 1987; Rapoport, 1989, Stein et al., 1994). OCD patients have subsequently been found to demonstrate abnormalities in a broad series of measures used in neuropsychiatric (e.g. neurological soft signs, olfactory identification, evoked potentials, intra-cortical inhibition) and neuropsychological (e.g. executive function) research (Stein et al., 1994; Purcell et al., 1998a). These abnormalities have consistently pointed to CSTC dysfunction and impaired control of the inhibition of thoughts and behaviours (reviewed in Morein-Zamir et al., 2010), and some evidence has suggested that they are relatively specific to OCD (Purcell et al. 1998b) and disorders characterized by compulsive behaviors (Phillips et al., 2010).

Advances in brain imaging have provided persuasive neuroanatomical data for OCD (Rauch & Baxter, 1998; Graybiel & Rauch, 2000; Whiteside et al., 2004, Mataix-Cols & van den Heuvel, 2006; Menzies et al., 2007, Milad & Rauch, 2012), as well as Tourette’s syndrome (Groenewegen et al., 2003), trichotillomania (Chamberlain et al., 2009), impulse control disorders in Parkinson’s disease (van den Heuvel et al., 2010), and addictive disorders (Everitt & Robbins, 2005). Functional imaging in OCD has demonstrated increased activity
in CSTC circuits connecting the orbitofrontal cortex, cingulate cortex and striatum, both at rest and especially during exposure to feared stimuli. Somewhat different circuits may be involved in mediating different OCD symptom clusters such as hoarding (Saxena et al., 2004; Mataix-Cols et al., 2005). The use of sophisticated cognitive and affective paradigms has generated new heuristics regarding the role of these circuits (Fitzgerald et al., 2004; Remijnse et al., 2006); for example during implicit learning, OCD subjects failed to show an expected increase in striatal activity, and instead activated temporal cortex regions (Rauch et al., 2001). The observation that some behavioral challenges, such as exposure to OCD cues, induce over-activation of the orbitofrontal cortex on functional imaging and others induce under-activation (e.g. Chamberlain et al., 2008) may be explained by functional segregation within the orbitofrontal cortex.

Pediatric imaging research has also supported the involvement of CTSC circuits in OCD, and potentially offers the promise of being able to determine the evolution of brain abnormalities in different regions over time (Rosenberg & Keshavan, 1998, Rosenberg et al., 2011). Abnormal structure or function in other brain regions such as the temporal lobe structures involved in memory and fear processing (Hugo et al., 1999; Zungu-Dirwayi, 1999, Szeszko et al., 1999), the supra marginal gyrus and the parietal lobe involved in the initiation and flexible control of instrumental behavior (Chamberlain et al., 2008; Meunier et al., 2012), have less commonly been found in OCD. However, a recent meta- and mega-analyses of structural imaging data from OCD sites worldwide found distinct patterns of subcortical abnormalities in pediatric and adult OCD patients. The hippocampus as well as the pallidum seemed to be of importance in adult OCD, whereas the thalamus was involved in pediatric OCD (Boedhoe et al., 2017).

Both successful SRI pharmacotherapy and behavioural therapy have been shown to normalize activity in CSTC circuits (Baxter et al., 1992). Baseline structure or activity may differentially predict response to pharmacotherapy and to psychotherapy (Brody et al., 1998; Hoexter et al., 2013), so that different modalities may be effective via different mechanisms. Neurosurgical interruption of CSTC circuits may also reduce symptoms and decrease striatal
volume (Rauch, 2000). Magnetic resonance spectroscopy has demonstrated alterations in glutamate metabolites in CSTC circuits (Rosenberg et al., 2004; Whiteside et al., 2006; Yucel et al., 2007), in some cases normalizing after successful treatment with an SSRI (Rosenberg et al., 2000). Evidence from the relatively few PET ligand studies so far performed in OCD have identified abnormal binding of the serotonin transporter in cortical and subcortical areas (Reimold et al., 2007; Matsumoto et al., 2010; Hesse et al., 2011) and of the striatal post-synaptic dopamine D2 receptor (Moresco et al., 2007; Perani et al., 2008; Denys et al., 2013), which normalized after treatment with SSRI (Moresco et al., 2007).

Techniques combining gene variants and brain imaging have been used to enhance the imaging findings. Several gene variants have been associated with structural and functional alteration in CSTC circuits relevant to OCRDs. For example, genetic variation in the serotonin transporter was demonstrated to be associated in OCD with (a) reduced orbitofrontal cortex volume as measured by MRI (Atmaca et al., 2011; Hesse, 2011) and (b) the availability of the serotonin transporter in the putamen, nucleus accumbens and hypothalamus as measured by [11C] DASB PET) (Hesse et al., 2011).

Thus, in OCRDs, distributed network perturbation appears focussed around the pre-frontal cortex, caudate, putamen and associated neuro-circuitry. In OCD, convergent evidence points to a. a deficit in ‘top-down’ inhibitory control in the pre-frontal cortex nodes within this circuitry, coupled with the hijacking of flexible, contingency-dependent instrumental behaviour in favour of excess habit generation mediated by dysfunction within the dorsal striatum (reviewed in Fineberg et al., 2014; Gillan et al., 2016a). Abnormal activation in the dorsal striatum, especially the head of the caudate nucleus and the putamen, is well replicated in the OCD literature (reviewed in Reghunandan et al., 2015) - implicating the cognitive fronto-striatal loop communicating with the dorsolateral prefrontal cortex driving action selection and the motor loops driving goal directed and habitual responses (Gillan et al., 2014). This neuro-anatomical model goes some way to explain the link between compulsive acts and harm related thoughts and activities. Involvement of the putamen may be particularly relevant for the development of sensorimotor symptom such as tics. However,
imaging research suggests that a wider range of CTSC circuits are involved in OCD, including systems responsible for reward processing more usually associated with addiction (Klanker et al., 2013).

Surgical disconnection of this circuitry via stereotactic capsulotomy, cingulotomy or limbic leucotomy, has been used to treat severe, intractable OCD for several decades, with some evidence of success. A double-blind sham controlled trial has recently produced limited evidence of the efficacy and tolerability of ventral capsulotomy using gamma radio-surgery (Lopes et al., 2014, 2015; Batistuzzo et al., 2015). Promising results from a small number of treatment-studies using invasive (deep brain stimulation) or non-invasive (transcranial magnetic stimulation, transcranial direct current stimulation) methods of neuro-modulation to target either cortical (orbitofrontal cortex, pre-supplementary motor area (pre-SMA)) or subcortical (nucleus accumbens, sub-thalamic nucleus) nodes within this frontal-striatal circuitry (reviewed in Senco et al., 2015) indicate new treatment-possibilities for refractory obsessive-compulsive disorders. There is experimental evidence that deep brain stimulation targeted to the nucleus accumbens reduced excessive fronto-striatal connectivity within that circuit (Bourne et al., 2012). The degree of such normalization correlated with reduced severity of symptoms in OCD (Figee et al., 2013).

**Neuro-cognitive models of OCRDS**

Neurocognitive changes are likely to be of great value for studying the neurobiology of psychiatric disorders, as they are theoretically more directly linked to brain structure and function than are the more complex higher level phenotypes such as compulsive symptoms (Fineberg et al., 2014). They are also more tractable to exploration across animal species (Dalley et al., 2011) and are invaluable for clinicians and patients, providing a richer understanding of the phenotype. Of the available instruments, computerised cognitive tests have several advantages over pen and paper assessment. To date, a number of tasks derived from the Cambridge Automated Neurocognitive Test Battery (CANTAB;), which
includes tests that are adaptable for translational work in animals and for application during brain-imaging, have shown considerable utility in fractionating cognitive processes in OCRDS and in localising neural and neurochemical substrates.

Growing evidence from human and animal research using tests such as the CANTAB suggests that the neurocognitive mechanisms mediating behavioural inhibition (motor inhibition, cognitive inflexibility) and habit formation (shift from goal-directed to habitual responding) variably contribute toward vulnerability to compulsive activity in a broad range of compulsive disorders (reviewed in Fineberg et al., 2014). Moreover, some of these deficits can be found in unaffected healthy relatives of OCD probands, suggesting they represent vulnerability or ‘trait’ markers of compulsivity that also exist in non-patient groups.

A. Motor inhibition

Multiple tiers of evidence, ranging from functional magnetic resonance imaging (fMRI) of individuals with focal frontal lobe lesions to animal research, have demonstrated that the inhibitory control of motor acts is sub-served by a neural network that encompasses the right inferior frontal gyrus (RIFG) and its sub-cortical (including sub-thalamic) connections (Rubia et al., 2003). Motor inhibition can be reliably tested using the stop-signal reaction time (SSRT) task (Aron et al., 2005). Pharmacological manipulations in rats and in humans suggest that motor response inhibition, as operationalised by the SSRT, falls under the neuro-modulatory influence of the noradrenaline/norepinephrine system (Chamberlain et al., 2006b, 2007a, 2013). In contrast, serotonin appears not to be centrally involved in this particular measure of impulsivity (Clarke et al., 2005a, Chamberlain et al., 2006b). Paradoxically, compared with the SSRIs, there is only weak evidence to suggest that drugs acting to increase norepinephrine in the synaptic cleft, such as the SNRIs venlafaxine and duloxetine (Hollander et al., 2003; Dell’Osso et al., 2008; Dougherty et al., 2015; Mowla et al., 2016), are beneficial in OCD.

In a series of experiments using the SSRT (Chamberlain et al., 2006a; Odlaug et al., 2011) evidence of significant impairment in motor inhibition, compared to healthy controls, was
found in separate groups of patients with OCD, hair-pulling and gambling disorder. However, this deficit was not seen in a study of community respondents with obsessive compulsive personality traits but without OCD (Fineberg et al., 2015), suggesting that this form of inhibitory failure represents a concomitant of compulsive motor acts. In the case of OCD, SSRT performance was also highly significantly impaired in unaffected first degree relatives (Chamberlain et al., 2007b). In a MRI study of OCD families that included unaffected first degree relatives (Menzies et al., 2007), reduced cortical grey matter volume, coupled with increased basal ganglia grey matter volume, was found to correlate with SSRT indices of increased motor dis-inhibition. This study produced some of the earliest evidence of a structural imbalance in inhibitory cortico-striatal circuitry as a neurocognitive endophenotype of motor-impulsivity in OCD. A more recent fMRI study demonstrated trait-dependent compensatory hyperactivity in the pre-SMA during the performance of the SSRT in both medication-free patients with OCD and unaffected siblings versus healthy controls, representing another neurocognitive endophenotype of motor impulsivity, in this case possibly related to inefficient neural processing within the pre-SMA in those vulnerable to OCD (de Wit et al., 2012).

B. Cognitive Inflexibility.

The intradimensional-extradimensional (ID-ED) shift task examines different components of attentional flexibility, including reversal learning, set formation and inhibition, as well as shifting attention between stimulus dimensions (ED shift). Studies have demonstrated that ED shift is impaired in OCD and additionally in the unaffected first-degree relatives of OCD subjects (Chamberlain et al., 2006a, 2007b; Vaghi et al., 2016), suggesting that this aspect of cognitive inflexibility represents an endophenotype for OCD-related compulsivity. Moreover, ED shift impairment has been identified in patients with other obsessive-compulsive spectrum disorders including obsessive-compulsive personality disorder (Fineberg et al., 2015), schizophrenia with OCD (Patel et al., 2010) and BDD (Jefferies et al., 2016). In a study of OCD hoarders compared with compulsive hoarders without OCD,
significant EDS changes versus healthy controls were found in the OCD hoarders only, suggesting that the comorbid group is associated with greater cognitive inflexibility (Morein-Zamir et al., 2014). Interestingly, another study found that hair-pulling disorder was not associated with EDS impairment, though OCD was, suggesting that cognitive inflexibility is not an essential component of repetitive acts of grooming (Chamberlain et al., 2006a).

According to a recent fMRI analysis, compared to healthy controls, patients with OCD when tested in a resting state, irrespective of treatment status, showed reduced functional connectivity in circuits linking the dorsal caudate nucleus and its anatomical cortical projections (Vaghi et al., 2016). In addition, reduced connectivity between the left dorsal caudate and the ventrolateral prefrontal cortex, an area of cortex known to be associated with EDS in healthy controls (Rogers et al., 2000), was associated with reduced OCD-related EDS performance. The reduced functional connectivity within this circuitry may account for the deficits in shifting attentional focus away from inappropriate intrusive thoughts and rituals, resulting in the perseverative behaviour seen in OCD and acting as a potential biomarker of OCD.

Perseverating on a behaviour that was once rewarded, but is later associated with negative consequences, may reflect a lack of contingency-related cognitive flexibility. Exerting flexibility in learning and unlearning behaviour based on (probabilistic) contingencies (“probabilistic reversal-learning”) may be particularly relevant for the development of compulsive tendencies. Contingency-related flexibility is dependent on serotonin systems (Clarke et al., 2005b) and has been linked to OFC function (Rubia et al., 2003). Reduced activation of the OFC, lateral PFC, and parietal cortex was observed using task-related fMRI during reversal learning, not only in patients with OCD but also in their unaffected, never-treated relatives (Rejminse et al., 2006, Chamberlain et al., 2008). Reversal-learning–related hypofunction, therefore, appears to be another candidate endophenotype for compulsivity that exists in people at increased genetic risk of OCD.

The identification of cognitive endophenotypes, such as those reflecting failures in motor inhibition and cognitive flexibility, opens up new perspectives for the development of bio-
markers that may be objectively quantified and used to ‘parse’ compulsive disorders into more biologically homogeneous groups and that may even enable the development of personalised forms of treatment tailored to the individual (see figure 3). For example, a small-sized randomised placebo-controlled trial in patients with skin picking disorder found that whereas lamotrigine was not efficacious in the group as a whole, benefit was seen in a subset of patients who exhibited relatively impaired cognitive flexibility on the EDS (Grant et al., 2010). Results such as these highlight the need for randomised controlled studies of adequate power to prospectively examine the role of cognitive endophenotypes as predictors of treatment response across the full spectrum of compulsive disorders.

Figure 3 about here.

C. Habit learning

Compulsions are characterised by the persistence of activities that become disconnected from the prevailing environmental contingencies and lack an obvious relationship to the overall goal of the activity. In OCD, many patients are fully aware that their compulsive behaviours bear little to no relation to desirable outcomes, yet despite this knowledge, they continue to perform them. They often describe their compulsions as unwanted habits.

According to associative learning theories of instrumental behaviour (Balleine & Dickinson, 1998, de Wit et al., 2009), actions are supported by at least two separate neural systems: a goal-directed system and a habitual system. When controlled by the goal-directed system, actions are purposeful inasmuch as they are flexibly performed in order to obtain desired goals or to avoid undesired events. In contrast, habitual behaviours are lower order behaviours, performed as a routine response to specific environmental triggers and are insensitive to changes in environmental contingency (i.e. whether the action is contextually appropriate) or the outcome value of the behaviour (i.e. whether the goal is actually desirable). After multiple repetitions, the habit system begins to render purposeful behaviour rigid and automatic (Adams et al., 1981, 1982), allowing simple acts to be conducted without effort. Exaggerated habit formation is consistent with the ego-dystonic stimulus-driven
aspects of compulsivity. Compulsivity may thus arise from a shift from goal-directed action to habit, rendering behaviour insensitive to its outcome or to the prevailing environmental contingencies.

The caudate nucleus is pivotally involved in OCD, and in the dynamic regulation of goal-directed contingency learning, under the prevailing influence of the ventromedial prefrontal cortex (vmPFC), which tracks the current value of outcomes. In contrast, habitual acts involve the posterior lateral putamen, where stimulus-response associations are stored (Balleine & O’doherty, 2010; Gillan et al., 2011). In a recent fMRI study (Banca et al., 2015), the experimental provocation of autobiographical compulsions in OCD patients was shown to reduce neural activation in brain regions implicated in goal-directed behavioural control (vmPFC, caudate nucleus) with concordant increased activation in regions implicated in habit learning (pre-SMA, putamen). This finding contrast with previous evidence of generalised fronto-striato-limbic hyperactivation during OCD symptom evocation and provocation. This is likely due to differences in task nature and design. The cited study used a highly ecological symptom provocation paradigm, which overcame some of the limitations of previous studies, as well as, for the first time, subject-driven feedback which enabled the authors to specifically address the link between symptom provocation and compulsive urges i.e. the “motor component” of OCD. The hyperactivation of caudate and medial prefrontal cortex found in previous studies could represent OCD-related changes in other cognitive domains such as imagery or autobiographical memory recollection, which are also processed in the medial prefrontal cortex (Lin WJ et al., 2015).

Stronger support for a shift toward habitual responding is derived from the following series of studies that investigated the extent to which patients with OCD showed a bias towards performing stimulus-response habits and away from goal-directed activities. In the first of these studies (Gillan et al., 2011), subjects were trained to respond to cues to press computer keys to win valuable points on a computer game. Next, some of the keys were devalued i.e. they were no longer linked to a valuable outcome, and subjects were told not to
press them when cued to do so. Yet, the OCD patients continued to habitually press in response to the cue, even after the keys had ceased to be linked to a reward.

The next study attempted to more closely model the development of compulsions as behaviours designed to avoid harmful consequences (as opposed to gain appetitive outcomes), using a shock-avoidance task (Gillan et al., 2014). Subjects were trained to lever-press in response to a computer signal in order to avoid a mildly painful electric shock indicated by the signal. After over-training on the task, the electric wire was obviously disconnected and the subjects instructed not to press in response to the signal. As predicted, however, patients with OCD continued to lever-press to the ‘devalued’ stimulus that explicitly no longer predicted a shock, and did so significantly more than did a healthy control group (Gillan et al., 2014). In a subsequent study, this habitual ‘shock-avoidance’ behaviour was directly related to fMRI evidence of hyperactivity in both the vmPFC, during the initial acquisition of the goal-directed avoidance behaviour, and in the caudate, during the performance of the habitual avoidance behaviours (Gillan et al., 2015). In addition, more OCD patients than controls reported experiencing a premonitory urge to perform the shock-avoidance habits, the urge intensity of which correlated with the performance of the habits and with the strength of the fMRI caudate hyperactivity. These findings provide compelling support for the hypothesis that compulsions in OCD result from a shift from goal-directed to habitual behavioural control and are underpinned by changes in activity focussed around the vmPFC, caudate nucleus and the associated fronto-striatal neural circuitry.

D. Safety Signaling

The vmPFC plays a complex role in fear learning and safety-signaling and is closely involved in integrating the evaluative processing of environmental cues with flexible behaviour. Abnormal vmPFC activation has been implicated in anxiety disorders (Schiller et al., 2008; Cha et al., 2014,) as well as in impaired fear retention in OCD (Milad et al., 2013). Dysfunctional processing within the vmPFC therefore represents a plausible mechanism by
which explicit contingency knowledge related to safety and harm is undermined, leading to the failure to flexibly update fear responses and the persistence of rigid, ‘habitual’ compulsive activity. Further studies in OCD patients are therefore under way to clarify the neuro-psychological relationship between fear and anxiety processing in the vmPFC on the one hand and cognitive flexibility in the caudate nucleus on the other. A recent neuroimaging study of Pavlovian fear reversal found that OCD patients failed to flexibly update fear responses, as measured by skin conductance changes, despite normal initial fear conditioning. This inability to update threat estimation was significantly correlated with vmPFC hyper-activation during early fear learning. The findings suggest that there is an absence of vmPFC safety signaling in OCD that potentially undermines explicit contingency knowledge, and that may go some way to explain the link between cognitive inflexibility, fear and anxiety processing in compulsive disorders such as OCD (Apergis Schoute et al., 2017).

**Figure 4 about here**

Compulsive-Obsessive Disorder

In the shock avoidance studies by Gillan et al (2014, 2015), post-hoc explanations for continuing to respond to the devalued stimulus (e.g. “why did you press?”) were described as irrational threat beliefs by many of the OCD patients (e.g. “I thought I might still be shocked”). Like obsessions these beliefs were directly contradictory to the patients’ explicit knowledge of threat and their ratings of shock expectancy. Thus, in OCD subjects faced with aversive situations, dysfunctional activation of the vmPFC and dorsal striatum may disrupt normal goal-directed behaviour, leading to the generation of harm-avoidance habits that readily become compulsive or “urge-driven” and that may go on to create ego-dystonic, irrational fears (obsessions) with the effect of perpetuating the compulsive behaviour. According to this ‘compulsive-obsessive disorder’ model, the compulsive behaviours of OCD play a key role in ensuring the persistence of the obsessions.

Consistent with this model, behavioural therapy using exposure and response prevention (ERP), representing the standard psychological therapy for OCD (www. NICE.org.uk), requires patients to undergo symptom provocation via exposure to relevant stimuli or
situations and to learn to resist the urge to perform the compulsions. ERP has been found not only to produce a reduction in compulsive responding, but also concurrently causes the urge to respond and the associated obsessive thoughts to attenuate (Foa et al., 2005). Our data suggest that suppressing compulsions e.g. using ERP should remain a key therapeutic intervention in OCRDs, and hint that habit reversal therapies (Morris et al., 2013) that are designed to break habitual associations between exposure-related cues and compulsive responses and that are currently used to treat hair-pulling disorder (Rothbart et al., 2013), may also have value in OCD e.g. by augmenting the clinical response to ERP.

Disorders of compulsivity: a common bias towards learning habits?

A number of computational modelling techniques (e.g. the two-step sequential discrimination task, Daw et al., 2011) have been developed to infer the prevailing balance between goal-directed and habitual behavioural control by assessing a person's decision-making tendencies (respectively, model-based versus model-free). These questionnaires have the added advantage of being readily disseminated on-line and therefore available to test very large numbers of subjects. In one of the earliest studies that applied this methodology to compulsivity, Voon et al (2015a) tested a trans-diagnostic group of subjects with diagnoses involving both natural reward (binge eating disorder), artificial reward (methamphetamine/cocaine abuse), and OCD and compared them to healthy controls. The results showed a common bias across all these disorders away from model-based (goal-directed) learning. In addition, the habit formation bias was associated with lower grey matter volumes in the caudate and medial orbitofrontal cortex on structural MRI.

The findings suggested that dysfunction in a neuro-computational mechanism favouring model-free habit learning may underlie the repetitive behaviours that ultimately dominate in diverse disorders involving compulsion. In a further study (Voon et al., 2015b) that compared performance on the two-step task under conditions of reward and loss, OCD subjects compared with healthy volunteers were less goal orientated (model-based) and more habitual (model-free) to reward outcomes with a shift towards greater model-based and
lower habitual choices to loss (punishment) outcomes. These results highlight the importance of motivation for learning processes in OCD and suggest that distinct clinical strategies based on reward valence may be warranted.

Most recently, Gillan et al (2016b) applied computational modelling to investigate whether a dimensional approach could better delineate the clinical manifestations of goal-directed learning deficits using large-scale online assessment of psychiatric symptoms and neurocognitive performance in two independent general-population samples. Nearly 2,000 people completed the on-line self-report questionnaires measuring decision–making preferences as well as symptoms of various mental health conditions. As expected, people demonstrating reduced goal-directed control on the two-step task (Daw et al., 2011) also reported higher rates of compulsive symptomatology related to OCD and also eating disorder, impulse control disorder and addiction symptoms – further demonstrating the generalizability of the deficits across multiple compulsive disorders.

By leveraging an online methodology to collect such a large dataset, Gillan et al (2016b) were also able to deal with a key limitation of standard case-control research – the question of specificity. While the demonstration of a degree of generalizability of cognitive deficits across compulsive disorders that are similarly characterised by a loss of control over behavior, alcohol addiction, eating disorders and impulsivity is of great interest, without establishing the specificity of this deficit to at least this class of symptoms (and not depressive symptoms, for example), the findings are quite limited. By carrying out a factor analysis on their large data-set, Gillan and colleagues identified that the self-report data from nine different questionnaires could be explained neatly in terms of three separate trans-diagnostic symptom-dimensions; ‘compulsive behaviour with intrusive thought’, ‘anxious-depression’ and ‘social withdrawal’. Critically, they found that when the individual disorders (OCD, eating disorder, impulse control disorder, addiction) were replaced with the compulsive factor, the deficits in goal-directed control were captured even more strongly. Moreover, this association was highly specific when compared to the other non-compulsive aspects of psychopathology. These data indicate that deficits in goal-directed control,
conferring vulnerability for developing rigid habits, may have a specific role in driving the compulsive behaviours that characterise diverse disorders such as OCD, eating disorder, substance abuse and addiction.

**Integrating neuropsychological models with treatment models.**

Based on these and other emerging findings, it is possible to draw inferences about the neuropsychological mechanisms underpinning the response to standard treatments in disorders such as OCD (Gillan et al., 2016a). Increased stress is known to induce a tendency to form habits (Schwabe & Wolf, 2009). It has therefore been suggested that SSRIs may act in OCD by restraining anxiety and reducing the effects of punishment, thereby helping the OCD patient to switch from habitual towards goal directed behaviour and indirectly attenuating the need to perform compulsions (Morein-Zamir et al., 2013). This effect of SSRI could also enhance the capacity to benefit from CBT with ERP (Gillan et al., 2016a).

The finding from a non-randomised study that goal-directed learning under both reward and punishment conditions was enhanced in OCD patients receiving SSRI (Palminteri et al., 2012), provides some support for this hypothesis. Further support is derived from more recent findings in healthy volunteers that acute tryptophan depletion, which reduces serotonin transmission, induced a shift from goal-directed to habitual responding on a slips-of-action test and also had a deleterious effect on model-based learning (Worbe et al., 2015, 2016).

However, if the mechanism of effect of SSRI in OCD depended upon anxiety reduction, benzodiazepines and other anxiolytics would also be expected to show evidence of efficacy, which they do not. Moreover, SSRIs are at their most efficacious in OCD at dosages higher than is typically recommended for anxiety disorders (Fineberg et al., 2013c; Skapinakis et al., 2016). An alternative hypothesis, therefore, proposes that SSRIs exert a therapeutic effect in OCD by bolstering goal-directed behaviour through direct pharmacological actions in those areas of cortex implicated in safety signalling and goal-directed control, including the vmPFC and the medial orbitofrontal cortex (El Mansari & Blier, 2006; Gillan et al., 2015;...
Voon et al 2015a,). El Mansari and Blier (2006) reviewed the effects on 5-HT release and the adaptive changes in pre- and postsynaptic 5-HT receptor sensitivity induced by SRI treatment in rodent brain structures involved in OCD including analogues of the orbito-frontal cortex (OFC). The time course of increased 5-HT release and terminal 5-HT1D desensitization aligned with the course of the therapeutic response to SRI in OCD. In addition, consistent with the dose-dependent therapeutic effect of SRIs, a greater dose of SRI induced greater reuptake inhibition, which played an essential role in this phenomenon. The authors hypothesized that enhanced 5-HT release in the OFC is mediated by the activation of postsynaptic 5-HT2-like receptors and underlies the therapeutic action of SRI in OCD. This cortical region is among the most consistently implicated in OCD (Whiteside et al., 2004) and shares overlapping functional connectivity abnormalities with those seen in addicted individuals at rest (Meunier et al., 2012).

Antipsychotics are used to treat stereotyped or self-injurious behaviour in patients with ASD. It has been proposed that antipsychotics may also work in OCD by reducing habitual or stereotyped behaviour patterns. The anti-OCD effect of antipsychotic agents, when co-administered with SSRI, has been shown to positively correlate with the drugs’ inherent dopamine D2 receptor antagonist affinities (Ducasse et al., 2014). However, whereas studies in rodents have identified a link between dopamine in the dorsal striatum and the flexible modulation of learnt behaviour (Lovinger et al., 2010; Furlong et al., 2014), studies of dopamine receptor agonists and antagonists in human models of compulsive behaviour have produced ambiguous findings (reviewed in Gillan et al., 2016a).

ERP for OCD involves repeated exposure to the fear-inducing stimuli that would ordinarily trigger a compulsive response, and resistance to the urge to perform the compulsion, so that the urge eventually dissipates. However, ERP usually involves weeks of practice, few people manage to drop all their compulsions and about half of those with the condition aren’t helped at all (Reghunandan et al., 2015). The finding that, in OCD, patients may fail to flexibly update threat perception through faulty vmPFC safety signaling (Apergis-Schoute et al., 2017) may explain some of the difficulties that many experience in extinguishing OCD-
related fears and offers exciting new treatment heuristics. The failure to recognize when a feared situation has become safe may explain why people with OCD find ERP so difficult and the treatment takes so long to work. Clinicians may therefore find these results helpful in their discussions with their patients, who could be persuaded of the importance of sticking with the therapy rather than giving up prematurely. This may even explain why co-administration of SSRI with ERP is found to be helpful. In addition, the new findings indicate the need to explore new methods of strengthening attention to safe situations during ERP in order to enhance fear-extinction, e.g. through the use of psychopharmacological, cognitive or neuromodulation strategies.

Another way in which the efficacy of ERP for OCD can be explained is via the systematic breaking of habitual (stimulus-response) associations between exposure-related cues and compulsive responses, through repeated response-prevention exercises (Gillan et al., 2016). Brain-imaging measures of hyperactivity in the caudate nucleus of OCD patients were found to correlate both with goal-directed deficits and subjective urges to respond habitually (Gillan et al., 2014). In other studies, caudate abnormalities were found to be remediated when OCD patients respond to ERP (Baxter et al., 1992; Whiteside et al., 2012). These results suggest ERP may exert a direct effect on caudate hyperactivity. Abstinence in addiction, which results in a reduction in craving, may also work by breaking stimulus-response associations between cues and drug-taking behaviour. However, both ERP and abstinence are experienced as aversive and drop-out rates are high, reflecting the need to develop more clinically acceptable ways to deliver this form of treatment. Moreover, as the habitual behaviours are strengthened with repetition (Tricomi et al., 2009), OCD and addictions become even more difficult to treat over time, emphasising the importance of detection and intervention at the earliest stage (Fineberg et al., 2013a; Gillan et al., 2016a).
Conclusions

The data presented serve to highlight the potential of a dimensional, biologically-grounded approach to psychiatry research. They suggest that vulnerability to compulsive activity can be predicted by a spectrum of neuropsychological mechanisms, including, inter alia, impaired motor inhibition, cognitive inflexibility (attentional set-shift, reversal learning) and an imbalance in goal-directed versus habit learning. In OCD, abnormal safety signaling may undermine accurate safety learning, resulting in inflexible threat beliefs, with important implications for exposure-based therapies that rely on robust safety memories and new treatment development (Apergis- Schoute et al., 2017).

Avoidance habits, acting via disrupted goal-directed learning, represent a plausible model of chronic OCD-related compulsivity. Furthermore, emerging evidence implicates disrupted goal-directed learning in an extended group of DSM disorders characterised by compulsive behaviours and intrusive thoughts, and maps with specificity onto a trans-diagnostic compulsive symptom-dimension. Distributed network perturbation associated with these cognitive changes, affecting the prefrontal cortex (vmPFC, lateral PFC), the dorsal striatum (caudate) and the associated neuro-circuitry modulating emotional, cognitive and motor control, has been identified in OCD. Networked studies investigating multiple disorders under the same conditions, head-to-head, are needed to determine the extent to which these changes overlap with or differentiate other disorders of compulsive behaviour.

Empirical evidence suggests that the psychopathology of OCRDs becomes more habitual over time. Mega-analysis in OCD suggests that illness-related structural brain changes differ in pediatric and adult cases. Longitudinal studies are now needed to explore the effect of duration of untreated disorder on the mediating neurobiology. These findings would have the potential to inform (1) the development of biomarkers to enable the detection of compulsive disorder at the earliest opportunity – crucially, in children, adolescents and young adults, before it becomes entrenched, as well as (2) the development of new treatments with novel mechanisms of action designed to strengthen goal directed behaviour and top–down cognitive strategies for controlling urges with better efficacy and tolerability. Agreement on a
standardised set of validated clinical measures of compulsivity that could be used trans-diagnostically would represent a rational next step.

Disclosures.

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genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 57: 1285–1292.

Abbreviations; SMA-supplementary motor area, VMPFC-ventromedial prefrontal cortex; CANTAB-Cambridge
Neuropsychological Test Automated Battery; OCPD-obsessive compulsive personality disorder; ? - findings not


International College of Obsessive Compulsive Spectrum Disorders (ICOCS) ICOCS group.


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**Figures**

**Figure 1. Evidence-based treatments for OCRDS**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rx</th>
<th>Psychotherapy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCD</td>
<td>SSRI</td>
<td>CBT with ERP</td>
<td>Cingulotomy</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td></td>
<td>Capsulotomy</td>
</tr>
<tr>
<td></td>
<td>Adjunctive antipsychotic (haloperidol, risperidone, quetiapine, olanzapine, aripiprazole)</td>
<td></td>
<td>Deep brain stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rTMS</td>
</tr>
<tr>
<td>BDD</td>
<td>SSRI</td>
<td>CBT with ERP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoarding Disorder</td>
<td>SSRI (in comorbid OCD)</td>
<td>CBT for hoarding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-pulling Disorder</td>
<td>Clomipramine</td>
<td>Habit reversal therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N-Acetyl Cysteine</td>
<td>ACT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Dialectical BT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress Reduction</td>
<td></td>
</tr>
<tr>
<td>Skin picking Disorder</td>
<td>SSRI</td>
<td>Habit reversal therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N-Acetyl Cysteine</td>
<td>ACT- enhanced BT</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Grant J, Chamberlain S, Odlaug B, Clinical Guide to OCRDs, Oxford, 2014

Treatments with robust evidence of efficacy derived from randomised controlled trials of fair comparison are highlighted in bold black type. Rx = medication, SSRI = selective serotonin reuptake inhibitor, CBT = cognitive behavior therapy, BT = behavior therapy, ERP = exposure and response prevention, ACT = acceptance and commitment therapy. rTMS = repetitive transcranial magnetic stimulation.
### SSRI-Resistant OCD:
Small-sized Randomized Controlled Trials Showing Efficacy Vs. Placebo

<table>
<thead>
<tr>
<th>Compound</th>
<th>Study</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-amphetamine (single dose)</td>
<td>Insel et al 1983</td>
<td>Double-blind RCT</td>
<td>D-amphetamine/placebo</td>
</tr>
<tr>
<td></td>
<td>Joffe et al 1991</td>
<td></td>
<td>D-amphetamine/placebo methylphenidate/placebo</td>
</tr>
<tr>
<td>Ketamine (IV) (single dose)</td>
<td>Bioch et al (2012)</td>
<td>Open-label RCT</td>
<td>No responders at 3d</td>
</tr>
<tr>
<td></td>
<td>Rodriguez et al 2013</td>
<td>Double-blind RCT</td>
<td>Ketamine placebo et 7d</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Koran LM et al 2008</td>
<td>Double-blind discontinuation</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Aniracetamole + SSRI</td>
<td>Sayah et al. 2012</td>
<td>Double-blind RCT</td>
<td>Aniracetamole/placebo</td>
</tr>
<tr>
<td></td>
<td>Muscatello et al 2011</td>
<td></td>
<td>Aniracetamole/placebo</td>
</tr>
<tr>
<td>Lamotrigine + SSRI</td>
<td>Bruce et al. 2012</td>
<td>Double-blind RCT</td>
<td>Lamotrigine/placebo</td>
</tr>
<tr>
<td>Topiramate + SSRI</td>
<td>Berlin HA et al 2010</td>
<td>Double-blind RCT</td>
<td>Compulsions sig. Total Y-BOCS NS</td>
</tr>
<tr>
<td></td>
<td>Movia et al 2010</td>
<td></td>
<td>Topiramate/placebo</td>
</tr>
<tr>
<td>Memantine +SRI</td>
<td>Highgi et al 2013</td>
<td>Double-blind RCT</td>
<td>Memantine/placebo</td>
</tr>
<tr>
<td>N-acetyl cysteine +SRI</td>
<td>Afshar et al 2012</td>
<td>Double-blind RCT</td>
<td>N-acetyl cysteine &gt; placebo</td>
</tr>
<tr>
<td>Granisetron +SSRI</td>
<td>Askar et al 2012</td>
<td>Double-blind RCT</td>
<td>Granisetron/placebo</td>
</tr>
</tbody>
</table>
Figure 3

HPD - hair-pulling disorder; SPD-skin-picking disorder; BDD-body-dysmorphic disorder; OCD-obsessive-compulsive disorder; OCPD-obsessive compulsive personality disorder; schizo-OCD = schizophrenia with OCD

DSM disorders can be differentiated using tests of inhibitory failure, though considerable intra-class heterogeneity exists.
Figure 4. Subdividing compulsive disorders according to neurocognitive domains: Task performance, neural and neurochemical correlates.

<table>
<thead>
<tr>
<th>Neurocognitive Domain</th>
<th>Definition</th>
<th>Task</th>
<th>Neural system</th>
<th>Neurochemistry</th>
<th>Compulsive disorders showing abnormalities in this domain compared to healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor inhibition</td>
<td>pre-potent motor disinhibition</td>
<td>stop signal reaction time task</td>
<td>right inferior frontal cortex, SMA and subcortical connections, including subthalamic nucleus</td>
<td>norepinephrine</td>
<td>OCD (and unaffected 1st degree relatives), BDD, hair pulling disorder, hoarding disorder, skin picking disorder, gambling disorder, binge-eating disorder</td>
</tr>
<tr>
<td>Contingency related cognitive inflexibility</td>
<td>inability to adapt behavior after negative feedback</td>
<td>reversal learning tasks</td>
<td>orbitofrontal cortex and subcortical connections</td>
<td>Serotonin, Dopamine?</td>
<td>OCD (and unaffected 1st degree relatives), pathological gambling</td>
</tr>
<tr>
<td>Attentional inflexibility</td>
<td>inability to switch attention between stimuli</td>
<td>extra-dimensional attentional set-shifting (CANTAB)</td>
<td>Vventro-lateral PFC- humans. Lateral PPC - primates and subcortical connections</td>
<td>Dopamine</td>
<td>OCD, BDD, OCD with schizophrenia, OCPD, Anorexia nervosa, Binge eating disorder</td>
</tr>
<tr>
<td>Inflexible fear learning</td>
<td>Inflexible fear learning and inadequate safety signalling</td>
<td>Pavlovian fear reversal</td>
<td>VMPFC, caudate, insula, anterior cingulate cortex</td>
<td>?</td>
<td>OCD</td>
</tr>
<tr>
<td>Habit learning</td>
<td>Lack of sensitivity to goals, contingencies or outcomes of actions</td>
<td>Habit formation tasks testing appetitive or avoidance habit learning under outcome devaluation. Two-step sequential discrimination task; model-based (goal directed) versus model free (habitual) decision making</td>
<td>Fronto-striatal circuits: Habit activity involves connections between SMA and posterior putamen Goal-directed activity involves connections between VMPFC and caudate</td>
<td>Dopamine, Serotonin?</td>
<td>OCD, Binge-eating disorder, Methamphetamine or cocaine abuse</td>
</tr>
</tbody>
</table>

Abbreviations; SMA-supplementary motor area, VMPFC-ventromedial prefrontal cortex; CANTAB-Cambridge Neuropsychological Test Automated Battery; OCPD-obsessive compulsive personality disorder; ? - findings not assured