

Obsessive-Compulsive Disorder: Puzzles and Prospects

Trevor W. Robbins,^{1,*} Matilde M. Vaghi,^{1,2,*} and Paula Banca^{1,*}

¹Department of Psychology, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, UK

²Present address: Max Planck UCL Centre for Computational Psychiatry and Ageing Research, 10-12 Russell Square, London WC1B 5EH, UK

*Correspondence: twr2@cam.ac.uk (T.W.R.), matilde.vaghi@gmail.com (M.M.V.), paula.banca@gmail.com (P.B.)

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Obsessive-compulsive disorder is a severe and disabling psychiatric disorder that presents several challenges for neuroscience. Recent advances in its genetic and developmental causation, as well as its neuropsychological basis, are reviewed. Hypotheses concerning an imbalance between goal-directed and habitual behavior together with neural correlates in cortico-striatal circuitry are evaluated and contrasted with meta-cognitive theories. Treatments for obsessive-compulsive disorder (OCD) tend to be of mixed efficacy but include psychological, pharmacological, and surgical approaches, the underlying mechanisms of which are still under debate. Overall, the prospects for new animal models and an integrated understanding of the pathophysiology of OCD are considered in the context of dimensional psychiatry.

Introduction

Most people have had intrusive thoughts or irresistible behavioral urges. When these tendencies become excessive and life disrupting, in the form of obsessions and compulsions, they may receive a diagnosis of obsessive-compulsive disorder (OCD), which is surprisingly common in the general population (2.5%–3%) and constitutes a major health-economic burden on society. OCD can be a severe and disabling disorder that is expressed in a bewildering variety of ways, including most obviously checking and washing, associated with excessive worrying and contamination fears. It has seriously afflicted numerous famous individuals, reportedly including Martin Luther, Samuel Johnson, Hans Christian Andersen, and Howard Hughes. One of the most remarkable facets of the disorder in many patients is their preservation of insight about what often presents as bizarre behavior. The mismatch between their subjective goals and their behavior is often called “egodystonia” and is one of many of the puzzles that OCD presents to the clinician or neuroscientist. Solving some of these questions and puzzles will undoubtedly advance the entire field of the cognitive neuroscience of mental health. Without attempting to review in detail all of the facets of OCD, we list below some of the major issues, and we will attempt to address them during the course of this article. Many of the classical references are to be found in the reviews provided in the monumental recent volume summarizing the massive amount of work in this field (Pittenger, 2017a).

Outstanding Research Questions for OCD

1. Does OCD invariably arise as a consequence of elevated anxiety? The common understanding of OCD is that the compulsive behavior is elicited by worrying obsessions as an attempt to alleviate anxiety. However, the DSM5 (American Psychiatric Association, 2013) classification recently moved OCD away from “anxiety disorders” into

a new home of “obsessive-compulsive and related disorders (ORCDSs),” suggesting that its relationship with other anxiety disorders was unclear.

2. How does OCD develop? Is there a genetic cause? Until very recently, there has been little consistent evidence, and by comparison with psychosis, there has been little progress in identifying plausible risk genes. By contrast, it has long been known that the syndrome can arise developmentally as an acute pediatric presentation following a streptococcal infection and possible basal ganglia neurodegeneration (Williams and Swedo, 2015).
3. To what extent is OCD a unitary syndrome? Its heterogeneous cognitive and behavioral phenotype, which can include behaviors as apparently distinct as hoarding, hair pulling (trichotillomania), and body dysmorphic syndrome, has led many investigators to suggest that these are separate disorders, distinguishing these subtypes. OCD is often also comorbidly associated with clinical depression and schizophrenia. Complementarily, obsessional thoughts and compulsive behavior are not unique to OCD and are symptoms of many other neuropsychiatric disorders, including compulsive gambling, eating disorders, or drug abuse (some of the main symptoms of which include “compulsive drug-seeking”) (Figure 1), suggesting a category of “impulsive-compulsive disorders.”
4. What are the neural correlates of OCD? Seminal work using positron emission tomography (PET) followed by structural and functional magnetic resonance imaging (MRI) emphasized overactivity of structures such as the orbitofrontal cortex (OFC), together with alterations in the basal ganglia, especially the caudate nucleus (Baxter et al., 1987). This is the “cortico-striatal-thalamic-cortical loop” hypothesis derived from the well-known characterization of functional pathways (Alexander et al., 1986; Haber, 2016) and supported by the efficacy of “psychosurgical”



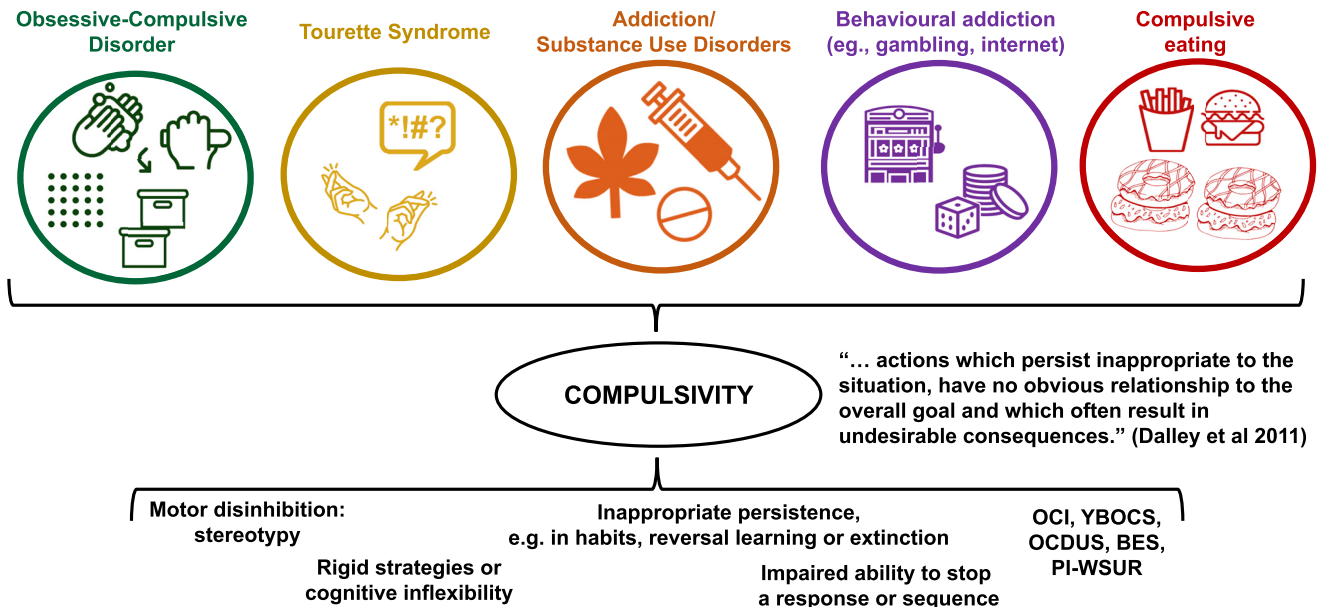


Figure 1. Compulsivity as a Transdiagnostic Dimension, Definition, and Measurement

The diagnoses can extend from OCD to Tourette tic disorder, drug addiction, eating disorders, and behavioral addictions such as compulsive gambling and compulsive internet use. Compulsivity as defined above can be measured in a variety of ways, including of stereotyped behavior, neuropsychological assessment of cognitive flexibility, inappropriate perseveration in reversal learning tasks, or response inhibition, and by questionnaires. BES, Binge-Eating Scale; OCI, Obsessive-Compulsive Inventory; OCDUS, Obsessive-Compulsive Drug Use Scale; PI-WSUR, Padua Inventory-Washington State University Revision; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

treatments of OCD such as cingulotomy and ventral capsulotomy (which probably affects fibers of the internal capsule).

5. What are the relevant psychological mechanisms underlying OCD? Theories have included impaired cognitive control (capturing the inability to regulate compulsive behavior), impaired cognitive flexibility (the inability to regulate thinking), and an impaired balance between goal-directed behavior and more automatic habit learning, in favor of the latter. A completely different approach considers possible meta-cognitive mechanisms, based for example on impaired processing of uncertainty in decision making. Interfacing with these are the possible contributions of anxiety and stress.
6. Which treatments work for OCD, and how? Cognitive behavioral therapy based on exposure combined with response prevention (ERP) appears to be the preferred psychological procedure, at least for compulsive behavior. Medication strategies employ drugs boosting serotonin (5-hydroxytryptamine, 5-HT) such as the selective serotonin reuptake inhibitors (SSRIs), the tricyclic drug clomipramine, and in more severe cases, dopamine (DA) receptor blocking agents. The precise rationale for SSRI treatment (which is moderately effective), especially at the high doses employed, is unclear, as it does not appear to be simply related to antidepressant effects.

Surgical approaches require a firmer neural circuit basis (Greenberg et al., 2010). For example, do anterior cingulotomy and ventral capsulotomy interrupt the same circuit at

different points? Similar considerations apply to the more modern use of deep brain stimulation (DBS) in OCD. Both ventral capsule (and ventral striatum) and subthalamic nucleus sites have been reported to be effective treatments for severe patients, often reducing clinical ratings by 35% or more. The neural circuit rationale for promising less invasive, neuromodulatory methods such as repetitive transcranial magnetic stimulation (rTMS) and direct current stimulation (tDCS) will require similar analysis.

7. Are current animal models of OCD useful? While much of the basic neuroscience underlying our present understanding of OCD has depended on animal experimentation (for example, the definition of functional neuroanatomical systems with their specific cell types, connectivities, and neurotransmitters), the utility of animal models for assessing etiological (e.g., genetic) factors, pathophysiological mechanisms, and possible treatments of simple repetitive behaviors is still being evaluated.

In this Review, we will address these various questions and assess the progress that is being made from a neuroscientific approach to OCD and related disorders.

Genetics of OCD

The position little short of a decade ago was that OCD is familial, with twin studies suggesting the involvement of genetic factors (Pauls, 2010). However, the mode of transmission was unclear, and the speculation was that OCD appeared to be a classic heterogeneous, polygenic neuropsychiatric disorder for which there was only suggestive evidence for genes of moderate-to-large

effect from linkage or candidate gene studies. A number of studies had identified the possible contribution of a gene (*SLCL1A1*) on chromosome 9 influencing the glutamate uptake transporter (Arnold et al., 2006; Dickel et al., 2006). There was at that time no information of the possible participation of common genes with small effects or copy-number variants, typically identified by genome-wide association studies (GWASs).

The first GWAS of 1,465 early-onset cases found no single-nucleotide polymorphisms (SNPs) that achieved genome-wide significance, but there was an implication of methylation quantitative trait loci (QTLs) and frontal lobe expression (e) QTLs (Stewart et al., 2013). These findings were augmented in a follow-up investigation that focused on a signal near the *PTPRD* gene, a member of the receptor protein tyrosine phosphatase family that regulates transmembrane signaling molecules and that presynaptically promotes glutamate receptor differentiation (Mattheisen et al., 2015). Of many other suggestive findings in this latter study, the other most significant was in a region of cadherin clusters that have also been associated with autism spectrum disorder. Indeed, this possible genetic overlap is consistent with considerable association with other disorders such as anorexia, Gilles de la Tourette syndrome, and attention deficit hyperactivity disorder (ADHD), as well as with certain animal models.

This position has recently been updated by an investigation of 592 cases of OCD and 560 controls that sequenced 608 genes potentially contributing to OCD with their regulatory elements (Noh et al., 2017). Strongly associated genes were *NRXN1* and *HTR2A*, the former achieving genome-wide significance. *NRXN1* encodes the synapse cell-adhesion protein neurexin 1 α , a component of cortico-striatal neural pathway; 5-HT_{2A} receptor involvement is also consistent with SSRI treatment in OCD and other evidence. Two other regulatory genes that affect synaptic function were also identified. The fascinating contribution of this study was to demonstrate the genetic overlap with two animal models of compulsive behavior in excessively grooming mice and so-called canine compulsive behavior. However, the 5 genes these investigators found to be most associated with compulsive behavior in mice and dogs, including the well-known *Sapap3* model, were significantly enriched for rare variants in the human sample but did not attain statistical significance.

Results from a recent Consortium meta-analysis (Arnold et al., 2018) support some of the findings of two previous GWASs with 2,688 OCD patients. Robust findings include several glutamatergic system genes (*GRID2* and *DLGAP1*) to add to other consistently implicated genes affecting this neurotransmitter system (*GRIN2B49* and *SLCL1A1*). Further dissection of glutamatergic system genes with ever-increasing sample sizes will doubtless improve our understanding of the pathophysiology of OCD.

Overall, these findings appear consistent with evidence for the modal impairment of cortical-striatal function and possible glutamate-GABA imbalance in OCD in these circuits, but it is difficult to identify obvious molecular targets for novel treatments. An obvious goal is to seek evidence that may resolve the phenotypic and therapeutic heterogeneity of OCD to achieve more personalized medicine.

Defining OCD Phenotypes Developmental versus Adult Perspectives

As with many other psychiatric disorders, there is increasing emphasis on understanding early-onset (i.e., before puberty, mean age 11 years) versus late-onset adult expression (mean age 23 years), as these may indicate distinct etiological and biological factors, as well as clinical factors. Early-onset OCD tends to be more severe, more familial, and male predominant and is associated with tic disorders, other comorbidities, and poorer treatment response (Taylor, 2011). Other precise phenotypic differences and variation in brain network structure organization are more controversial. There are obvious difficulties in naive cross-sectional comparisons between the two populations. Thus, a brain region shown to be different in children with OCD may well be different from an adult expression simply because of investigating them at different stages of brain development. Taylor (2011) judged it unwise to make strong conclusions about differences in brain regions between early- and late-onset OCD, because none of the studies had adequate statistical power to do so, and the necessary longitudinal studies have been lacking. Similarly, unless duration of symptoms is equated, differences (e.g., in severity) may originate simply as a function of this greater exposure to the disorder, especially if untreated. A more intriguing and counterintuitive claim has been that early-onset OCD patients, despite greater clinical severity, have no evidence of “cold” cognitive deficits (e.g., Hybel et al., 2017). A recent study has shown not that adolescent OCD exhibits less severe cognitive deficits than those typically found in adult studies with similar tests but that the profile is different, with greater evidence of memory and learning than of “executive” impairments (Gottwald et al., 2018).

In terms of etiology, it is of course difficult to compare possible triggering effects of trauma and life-event stressors, because these are obviously so different between children and adults (e.g., perinatal complications versus divorce). The attractions of the pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) hypothesis have been offset because of large epidemiological studies (N = 678,862) showing no reliable association between streptococcal symptoms and later development of OCD (Schrag et al., 2009) and because of lack of evidence for shared environment contributing markedly to symptom severity on OCD development (Taylor, 2011). These considerations have potential implications for understanding the neurobiological and psychological basis of OCD.

We will undoubtedly understand more about the etiology of OCD when we have a greater understanding of functional brain development in humans. The ritualistic, repetitive behavioral patterns commonly evident in young children (Evans et al., 1997) may simply reflect differences in the ordered maturation of different neural structures such as the frontal lobes and basal ganglia and are not necessarily related to anxiety symptoms in large samples of 4-year-old twin pairs (Eley et al., 2003). It is still unclear whether a possible dimension of “compulsivity” is a biomarker or risk factor for future OCD and whether it occurs spontaneously, in the absence of anxiety or obsessions related to the compulsive behavior (Boileau, 2011). Scales such as the Obsessive-Compulsive Inventory (OCI) (Foa et al., 1998) were

developed partly to address the dimensionality of the spectrum, with OCD diagnosis being at the extreme, but the utility of this dimensional approach is still undergoing evaluation.

Seminal studies of the clinical phenomenology of pediatric OCD suggested a range of symptoms similar to those observed in adults, with washing, grooming, and checking or repeating rituals, as well as preoccupation with disease and danger, predominating (Swedo et al., 1989). Later studies confirmed this structural similarity, although Mataix-Cols et al. (2008) noted the particularly high incidence of hoarding in girls. Convincing evidence requires a longitudinal study in view of the high level of co-occurrence of compulsive responses in OCD and their fluctuating and evolving predominance.

To What Extent Is Anxiety Causal in OCD Symptoms?

What is especially important is the theoretical super-structure of the symptom clusters—in other words, the functional inter-relationships among anxiety, obsessions, and compulsions. When asked about the reasons they had for performing rituals, the most common response of children in the sample studied by Swedo et al. (1989) was that they “had no idea...children seemed to devise their explanation only after they saw themselves carrying out their peculiar rituals” (p 338). This is a significant observation, relevant to the common hypothesis that the compulsions develop to reduce anxiety; at least in children, this is not very evident. We have recently observed similar evidence of post hoc rationalization of compulsive-like behavior in experimental studies of adult OCD (Gillan et al., 2014a). In addition, 40% of children diagnosed with OCD deny that their compulsions are driven by obsessive thoughts (Karno et al., 1988; Swedo et al., 1989), and while OCD that develops during or after puberty is often associated with anxiety and depression, this is not the case for childhood-onset OCD (Mancebo et al., 2008). Douglass et al. (1995) reported for the Dunedin sample that scores of worrying and fearfulness from Rutter’s Child Behavior Questionnaire at ages 5, 7, 9, and 11 years did not predict OCD diagnosed at age 18 years. Given the fact that compulsions themselves may generate anxiety, it prompts the suggestion that OCD could also be rebadged as “COD,” thus acknowledging the difficulty of accepting rigid causal relationships between obsessive and compulsive symptoms.

Such considerations have undoubtedly contributed to the debate as to whether OCD should have been subsumed under or moved out of the traditional Diagnostic and Statistical Manual (DSM) category of anxiety disorders to its own classification, now termed ORCDs (Stein et al., 2010). While depression, anxiety, and obsessive-compulsive symptoms are frequently comorbid, there is evidence for distinct dissociations based especially on treatment. Non-serotonergic “anxiolytic” medications such as the benzodiazepines have no efficacy for OCD. Whether SSRI efficacy in OCD depends specifically upon possible anxiolytic or antidepressant actions remains unclear. Response prevention is an additional requirement for effective exposure therapy in OCD, further differentiating the disorders. Anxiety disorders other than OCD have not yielded to successful surgical treatment.

The functional relationship between obsessions and compulsions is also under further scrutiny from other perspectives. Compulsive hoarding frequently occurs in the absence of anxiety

or obsessional symptoms as measured, for example, by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). While this has suggested to some that hoarding is a disorder distinct from OCD, an alternative perspective is that it is a “pure” compulsion and therefore not dependent upon obsessions for its expression. Is there comparable evidence of “pure obsessions” in OCD in the absence of compulsions? This appears to be rare. Although compulsive behavior has proved to be relatively easy to define, covert, and verbally expressed obsessions have proven more controversial. For example, mental acts such as counting or repeated trains of thought could be considered to be incompletely expressed behavioral outputs. Williams et al. (2011) defined pure obsessions such as unacceptable or taboo thoughts (of aggressive, religious, or sexual content) but found them to be highly associated with reassurance-seeking behavior (i.e., the need to ask, tell, or confess to others, perhaps via the internet or the performance of self re-assurance rituals or compulsions). These considerations have encouraged a focus on understanding compulsions as a key to the neurobiological understanding and treatment of OCD, clearly compatible with animal models that necessarily employ behavioral measures (such as repetitive grooming) and neuropsychological theories that consider mental and behavioral output to be contingent on parallel (or sequential) cortico-striatal activity.

OCD Endophenotypes: Neurocognitive and Psychophysiological Biomarkers

The cortico-striatal systems and their modulation are implicated in virtually all of the major psychiatric disorders, and this might also help to explain common comorbidities of OCD such as depression and schizophrenia, which have also been linked to altered processing in such circuits. However, it is important to define the precise cortico-striatal substrates for OCD symptoms that differentiate it from other disorders. It is also important to determine which aspects of the functioning of these circuits are consequences of important “priors” such as genetics or past experience such as triggering stressors. Such evidence will have to depend on neuroimaging evidence from a number of modalities clearly linked to functional considerations; are these changes in structure or circuitry sufficient to produce the behavioral and cognitive sequelae of OCD? In order to link the evidence concerning heritability of OCD to these functional considerations in a theoretically coherent scheme, it may be necessary to define intermediate or endophenotypes of OCD (i.e., aspects that also appear in first-degree, clinically unaffected relatives).

Thus far, at least 5 main plausible endophenotypes of OCD have been identified, all of which are relevant to the dominant cortico-striatal theory, relating especially to its “dysexecutive” variant. They suggest OCD to be partly a consequence of dysfunctional circuits for response inhibition, cognitive flexibility, planning (and goal-directed behavior), working memory, and error monitoring. These deficits have been confirmed by meta-analyses of the salient neuropsychological assessments (e.g., Abramovitch et al., 2013), obtained using many different test instruments and heterogeneous OCD patient groups, with consequential variability and occasional inconsistency.

The response inhibition hypothesis partly derives from evidence of impaired performance by OCD patients on such tests

as Go-NoGo performance and stop-signal inhibition (see Box 1, F). [Menzies et al. \(2007\)](#) found moderate, though significant, impairments in stop signal reaction time (SSRT) performance in OCD patients and in their unaffected relatives. These impairments of course are not specific to OCD ([Lipszyc and Schachar, 2010](#)), but they do apparently occur independently of “subtype” (or symptom dimensions) of OCD ([Lei et al., 2015](#)), hence suggesting a possible core deficit. Moreover, the deficits were correlated with evident structural changes in cortico-striatal regions. Specifically, inhibitory impairment was significantly associated with reduced gray matter in orbitofrontal and right inferior frontal regions and increased gray matter in cingulate, parietal, and striatal regions ([Menzies et al., 2007](#)). A novel permutation test indicated significant familial effects on the variation of these MRI markers of inhibitory processing. This analysis has been extended by an fMRI study ([de Wit et al., 2012](#)) that showed that patients with OCD exhibited decreased activity in the right inferior parietal and inferior frontal cortex and also that both OCD patients and their relatives had greater activity in the left pre-supplementary motor area during successful inhibition. These findings are consistent with current network analyses of the human response inhibition circuitry ([Aron et al., 2014](#)).

Whether this difficulty of response inhibition can be extended to include thoughts is an intriguing issue in view of possible evidence of neural commonalities in response and memory inhibition ([Anderson and Green, 2001](#)). [Morein-Zamir et al. \(2010\)](#) addressed this by using a variant of the SSRT task but only found evidence for cognitive rigidity rather than inhibition per se in suppressing cognitive responses; unintentional thought suppression as measured by repetition priming was intact.

SSRT deficits are in fact stronger in patients with trichotillomania, which is often considered as an “impulse control” disorder despite its evident compulsive properties, although a distinct cognitive impairment in cognitive flexibility was much more evident in OCD patients ([Chamberlain et al., 2007](#)).

The cognitive flexibility hypothesis of OCD is quite long-standing, beginning with neuropsychological evidence of impairments in a classic test of cognitive flexibility, the Wisconsin Card Sorting Test, and more recent demonstrations of impaired performance specifically at the extra-dimensional stage of the Cambridge Neurophysiological Test Automated Battery (CANTAB) attentional set-shifting task (see Box 1, E) in adult OCD patients and their clinically unaffected relatives ([Chamberlain et al., 2007](#)). Cognitive flexibility is a complex construct, and it has been shown in experimental animals, for example, that other forms of cognitive flexibility, such as those required in reversal learning (when the reward contingencies are switched in a discrimination learning task), depend on different sectors of the prefrontal cortex (PFC). Whereas reversal depends on the OFC in the marmoset monkey, extra-dimensional shifting depends on the lateral frontal cortex ([Dias et al., 1996](#)); analogous findings have been found for both rodents and humans ([Keeler and Robbins, 2011](#)). [Chamberlain et al. \(2008\)](#) found with an fMRI (“face-house” reversal learning) paradigm that patients with OCD and their unaffected relatives exhibited severely reduced blood-oxygen-level-dependent (BOLD) activation of lateral orbitofrontal

and posterior parietal cortex during reversal learning compared to healthy controls. In a recent study, using resting state multi-echo acquisition, [Vaghi et al. \(2017a\)](#) focused on the attentional set-shifting deficit in OCD and found that impaired performance outside the scanner correlated with reduced functional connectivity in OCD patients. The relevant circuits included the ventrolateral (Brodmann area [BA] 10, 11, and 47) and medial (BA 9) PFC, with reduced bilateral connectivity with the body of the caudate and putamen, quite consistent with the evidence in experimental animals (e.g., [Dias et al., 1996](#)).

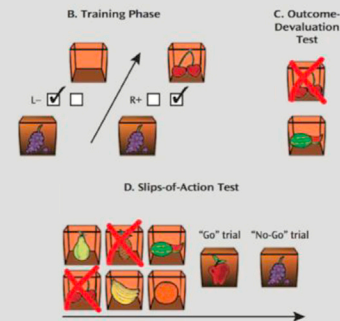
In the same study, [Vaghi et al. \(2017a\)](#) also found evidence for a distinct pathway of reduced functional connectivity associated with planning performance on the Stockings of Cambridge version of the Tower of London task in OCD but for a dorsolateral PFC (dlPFC) and putamen circuit, thus providing “doubly dissociable” effects with those for cognitive flexibility. The finding for planning agreed with earlier fMRI investigations of the Tower of London task in OCD by [van den Heuvel et al. \(2005\)](#), who found a similar dlPFC-striatal hypo-responsiveness in 22 medication-free OCD patients (although with apparently compensatory heightened activity in the anterior cingulate cortex [ACC] and ventrolateral PFC). Most recently, [Vaghi et al. \(2017b\)](#) extended the analysis in another fMRI study that confirmed dl-PFC-striatal (putamen) hypoactivity that correlated with poor (slow and inaccurate) performance on the Tower but also showed similar effects in first-degree relatives of OCD patients, thus supporting a possible endophenotype. As with cognitive flexibility, the deficits did not relate in a significant manner to clinical severity; however, that is not a requirement of a trait, as distinct from a state, factor. The precise psychological basis of this endophenotype needs further specification. One obvious point is that planning a route to a goal is a key component of goal-seeking behavior, and OCD patients have deficits in this domain (see below). It also requires working memory. A study of visuospatial n-back performance has shown a complex pattern of changes in OCD and first-degree relatives that included compensatory fronto-parietal hyperactivity in both patients and relatives, as well as increased task-related connectivity between frontal regions and the amygdala ([de Vries et al., 2014](#)). In resolving what may appear to be contradictory findings, these authors suggest that the heightened fronto-parietal activity reflects inefficiency in this network.

Taken together, the findings for candidate neuro-endophenotypes for OCD suggest a broad set of fronto-executive impairments leading to problems in response inhibition, cognitive flexibility, planning, and working memory. One issue is whether these impairments are relatively nonspecific and occur in many psychiatric disorders. In this vein, it is important to note that cognitive flexibility, as measured by the attentional set-shifting task, is not apparently an endophenotype for patients with schizophrenia ([Ceaser et al., 2008](#)), although this is less clear for working memory deficits.

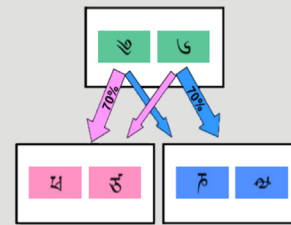
A relatively specific impairment in OCD may be shown by their tendency to heightened error-related negativity (ERN) responses, a negative deflection of the event-related potential when subjects make an error ([Falkenstein et al., 1991](#)) and hence a putative measure of enhanced performance monitoring. This response might capture the “not quite right” subjective report

Box 1. Description of the Behavioral Tasks Measuring Psychological Mechanisms of Relevance to OCD Manifestation**Balance between goal-directed and habitual behavior**

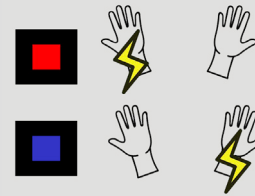
A. The Fabulous Fruit Game task measures whether actions are goal directed and habitual via the experimental manipulation of outcome devaluation. Initially, if pressing the right key (right for grapes), the subject is rewarded with a specific outcome (cherry). The outcome is then devalued (red cross), so that the subject knows that the specific outcomes (cherry) are no longer worth any points. In the final and crucial test, subjects are asked to press the correct key when a stimulus signals the availability of the still-valuable outcome and refrain from responding if the outcome has been devalued. A supplementary test assesses whether the subject can recall the action-outcome associations, another index of goal-directed behavior (adapted from Figure 1, [Gillan et al., 2011](#)).



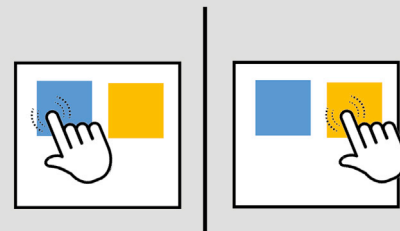
B. The two-step task is used to assess goal-directed (model-based) learning. In the first stage, subjects choose between two stimuli, which determine common or rare transition to the pink or blue second stage. In the second stage, subjects choose between two stimuli, each of which associated with a distinct probability of reward. A purely habitual (hypothetically, model-free) agent only shows sensitivity to whether or not the trial was rewarded or not reward. A goal-directed (model-based) agent exhibits sensitivity to not only reward but also transition type, as is more likely to repeat the action (e.g., select the same stimulus at the first stage) after reward only if the transition was common (adapted from Figure 1, [Daw et al., 2011](#)).



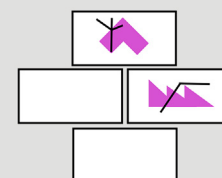
C. The avoidance task measures goal-directed versus habitual behavior in avoidance. Subjects are first trained to produce an action to avoid shocks to either the right or left wrist for specific stimuli (blue predicts shock to right wrist; left predicts shock to left wrist). At devaluation, the electrodes on one wrist (e.g., right) are disconnected from their connector so that the shock is not delivered anymore. Subjects behaving in a goal-directed manner should not respond to the stimulus that predicted the devalued outcome (e.g., blue) but maintain responding to avoid the valued outcome (e.g., red) ([Gillan et al., 2014a](#)).

**Cognitive control**

D. The reversal learning task measures the ability to learn the best course of action and flexibly alter behavior. For example, visual discrimination tasks can be employed where subjects initially learn to respond to stimuli that are deterministically (i.e., 100:0 reward for the 2 alternatives) or probabilistically (e.g., 80:20) rewarded with positive or negative outcomes. The subject should learn to respond to the stimulus most often correct. At reversal, the subject has to adapt to the opposite stimulus-reward pairing. In these situations, subjects have to adapt their behavior and respond to a previously incorrect stimulus, which is now most often rewarded (e.g., [Remijne et al., 2006](#)).



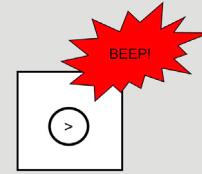
E. The Intra-Extra Dimensional Set-Shifting task measures the ability to form an attentional set (i.e., selecting the correct stimulus based on one dimension such as shape) and shifting attention to another, previously irrelevant dimension (i.e., line). It is a measure of cognitive flexibility. This construct is also assessed by the category shift in the classic Wisconsin Card Sorting Task (e.g., [Chamberlain et al., 2007](#)).



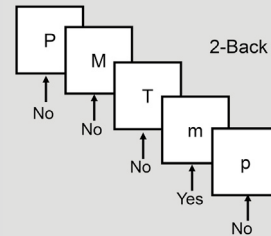
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Box 1. Continued

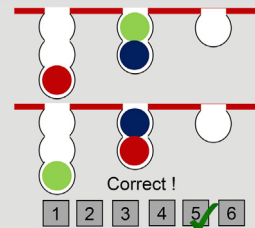
F. The Stop-Signal task (SST) is a version of classic Go/NoGo measuring response inhibition/motor inhibitory control. In the SST, subjects press a left or right hand button when a corresponding arrow pointing to the left or right is presented. On a random selection of the trials, a stop signal is presented after a variable delay and participants have to withhold their response to the stimulus on those trials. Staircase functions are used in the SST to estimate the time that a subject needs to withhold a response providing an estimate of the time needed to a participant to withhold an ongoing response (e.g., [Menzies et al., 2007](#)).



G. The N-back task measures working memory. Participants are presented a sequence of stimuli one by one. For each stimulus, they need to remember if the current stimulus is the same as the one presented N trials ago. The N can be 1 trials, 2 trials, 3 trials, etc. The higher the number, the more difficult the task (e.g., [de Vries et al., 2014](#)).

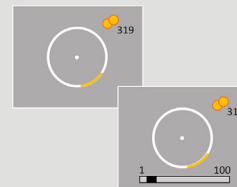


H. The Tower of London task is used to assess high-level visuospatial planning. It requires participants to rearrange a set of colored balls to match a target configuration according to specific rules. The aim is to solve each problem in the minimum number of moves. Planning abilities are indexed by the number of correct responses and by latencies to give the answer to a specific problem. Difficulty can be varied parametrically, depending on the number of moves necessary to arrange the balls according to the target or goal display (e.g., [Vaghi et al., 2017b](#)).

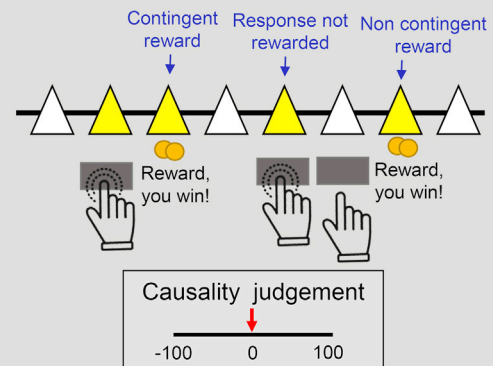


Metacognition

I. The predictive inference task measures the ability to update action and confidence based on environmental information. On each trial, subjects select a position of the bucket (orange segment) to catch coins flying from the middle of screen and score their confidence in their prediction on a bar appearing thereafter. Subjects are asked to gauge the value of a new piece of information and differentiate periods of time in which unexpected outcome should be ignored as noise and those in which abrupt changes require updating of actions and beliefs ([Vaghi et al., 2017c](#)).



J. The contingency degradation task measures goal-directed versus habitual behavior by reducing the causal link between action and obtained outcome. It also tests subjective accounts of the causal relationship between action and outcome. In some blocks, rewards are mostly obtained upon performance of an action (e.g., pressing the space bar). However, when the contingency is degraded, outcomes can also come “for free,” without the action being necessary. A goal-directed agent would press more often when obtaining an outcome is solely dependent on the action. In contrast, behavior persisting even when the causal link is reduced provides an index of habitual behavior. Subjective accounts of the causal understanding the agent has of their behavior are assessed at the end of each block (adapted from Figure 2, [Vaghi et al., 2019](#)).



of the typical OCD patient. [Ullsperger et al. \(2014\)](#) and [Gillan et al. \(2017\)](#) recently reviewed the large number of studies, beginning with [Gehring et al. \(2000\)](#), in which elevated ERN responses in the vicinity of the ACC in OCD patients were not paralleled consistently in other patient groups to any great

extent, including depression, schizophrenia, social anxiety disorder, ADHD, autism, or addiction, although a few studies of patients with generalized anxiety disorder also exhibited such enhancements. The ERN is often reduced in magnitude in schizophrenia and in impulsive behavior. A larger ERN response

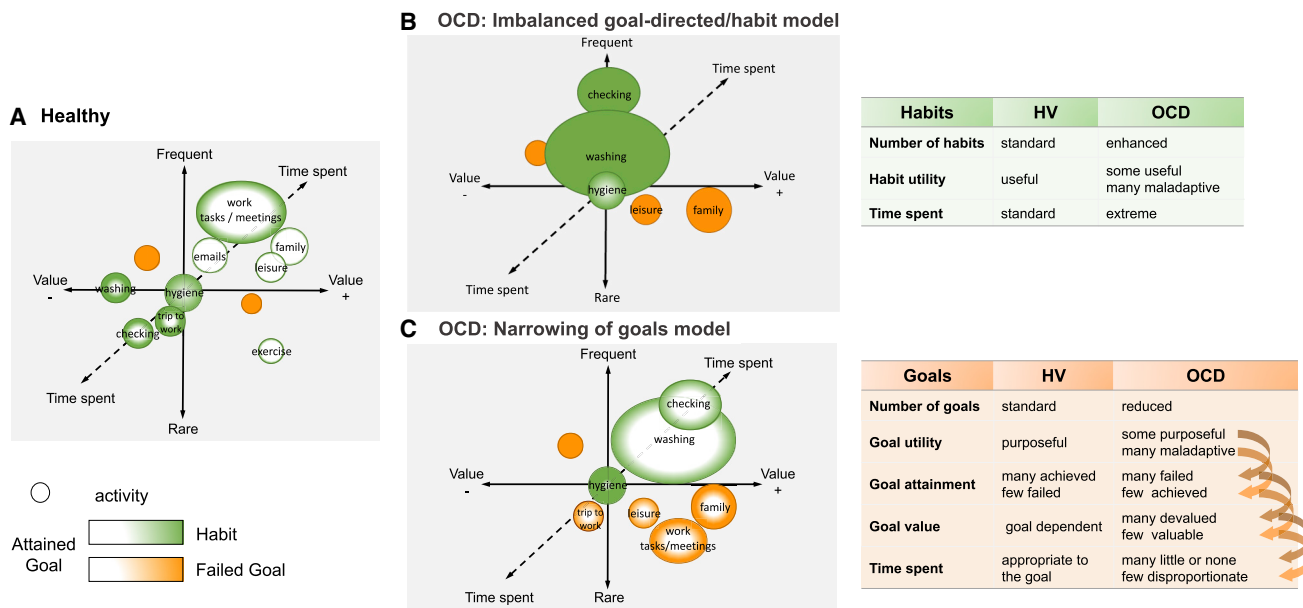


Figure 2. Hypothetical Models of OCD

Schematic representation of activities on a typical day described according to 3 axes: their frequency, time spent, and personal value. Individual activities are represented by circles, the size of which depicts their time spent. The activities vary in their degree of goal-directedness (white) and habitual control (green). Some of the activities attain their goals and are successful, whereas others fail (orange).

(A) An example of typical healthy pattern of successful and unsuccessful activities throughout the day.

(B) The current “habit” model for OCD, in which compulsions have no goal or purpose and the valence of the action is only attributed post hoc, as a rationalization of compulsive behaviors. Most goals fail due to a deficient goal-directed system, and compulsions are consequently hypothesized as maladaptive habits. Behavioral output is dominated by compulsions to the detriment of many goal-directed activities (this may represent the extreme case of severe OCD). These compulsions are mediated almost exclusively by habitual control, exacerbated over many years of repetition.

(C) Schematic representation of a speculative “narrowing of goals model.” Behavioral output is still dominated by compulsions, with many failed goal-directed behaviors. There is a narrowing in the number of goals attempted, with some of the compulsions having an abnormally strong, goal-directed nature. Although the valence of these compulsions is positive, this could arise as a consequence of avoidance relief.

Note that these theories in (B) and (C) are not necessarily mutually incompatible: (1) it could reflect different developmental stages or degrees of severity of the disorder, and (2) a hybrid model between (B) and (C) is possible, to include a narrowing of goals but also a tendency toward increased habit learning.

is found in adolescent OCD to be related to age of symptom onset and a tendency toward developing depression (Fitzgerald and Taylor, 2015; Hanna et al., 2018). Thus, this electrophysiological response may prove to be an effective biomarker of OCD and certain affective disorders. However, to be related to OCD symptoms, the ERN response requires a more accurate and precise behavioral interpretation; whether for example it is related to internal conflict, as in a Stroop task, or to feedback in learning tasks with prediction errors (Ullsperger et al., 2014). Moreover, the activity of the ACC in performance monitoring as exemplified by the ERN in OCD has to be understood in the context of alteration in activity of an entire network for error processing that includes the ventromedial PFC (vm-PFC) and dl-PFC and anterior insula (Fitzgerald and Taylor, 2015).

Neuropsychological Theories of OCD

OCD as a Disorder of Goal-Directed Behavior versus Maladaptive Habits

Two decades ago, the conceptualization of OCD as a product of maladaptive habit learning emerged (Graybiel and Rauch, 2000), partly from a growing consensus concerning a pivotal role for the striatum in the disorder. This theory contrasted with the classical metacognitive account that postulated compulsions as goal-directed behaviors, driven by irrational thoughts and cognitive

biases (Salkovskis, 1985). Taking a lead from theorizing about transitions between goal-directed and habitual actions underlying the compulsive drug-seeking behavior characterizing addiction (Everitt and Robbins, 2016), we began to consider the hypothesis that compulsions in OCD might arise from excessive habit formation or habit dysregulation, which may be exacerbated by anxiety or stress (cf. Schwabe and Wolf, 2009), also potentially leading to subjective post hoc rationalization that could in turn further fuel obsessions (Gillan and Robbins 2014).

Much evidence from both experimental animals and human studies has been adduced to support the existence of two neural systems in control of behavioral output that are coordinated to some extent but that may also compete under certain conditions: a goal-directed system and a habit-based system (Balleine and O’Doherty, 2010). An imbalanced and dysregulated frontostriatal functional circuitry in control of goal-directed versus habitual actions, favoring the latter, has been hypothesized as a fundamental mechanism underlying compulsions in addiction and OCD (Figure 2B). The theory of maladaptive habits has thus become a prominent model of compulsivity in dimensional psychiatry. It has been suggested to be a quantifiable transdiagnostic trait relevant for many disorders (Gillan et al., 2016), possibly including eating disorders and gambling, as well as addiction and OCD (e.g., Meunier et al., 2012; Voon et al., 2017).

Two experimental methods have been conventionally used across species to probe the dominance of habits over goal-directed actions: outcome devaluation (Box 1, A and C) and contingency degradation (Box 1, J). These methods are based on the notion that animals or humans are sensitive to changes in motivational values. In an outcome devaluation procedure (most commonly used), animals or people must flexibly update behavior by ceasing responding when previously yielded valuable outcomes become devalued and undesired. If a response persists despite devaluation, this is interpreted as not being goal directed and hence under control of the habit system. In the contingency degradation test, the extent to which an action is mediated by a representation of its relation to an outcome is assessed. Here, the detection of habits is assessed by degrading (i.e., reducing) the contingency between an action and an outcome, thus degrading control exerted on environmental outcomes. Again, if the instrumental behavior continues when the action-outcome relationship is reduced, then it is hypothesized to be in habit mode (Dickinson and Balleine, 1994).

Use of these methods provides support for the two distinct but interactive aforementioned neural systems controlling behavior. The medial PFC and the caudate nucleus are suggested to underlie goal-directed actions (Valentin et al., 2007), whereas the putamen and motor cortical regions are proposed to mediate habits (Tricomi et al., 2009; Yin et al., 2004).

Applying similar diagnostic methods for habits in OCD (for review, see Gillan and Robbins, 2014), multiple findings converge onto dysfunctional goal-directed control and putatively maladaptive habit formation in OCD. First, deficits in OCD patients' ability to inhibit previous learnt stimulus-response associations as consequence of change in outcome values were found using both appetitive (earning points) and avoidance (avoiding shocks) outcome devaluation tasks (Gillan et al., 2011, 2014a). When using contingency degradation, evidence was found for continued responding in OCD patients in face of reduced instrumental contingency (Vaghi et al., 2019). A symptom-provocation fMRI paradigm designed to induce autobiographical symptoms in OCD patients also found reduced neural activation in brain regions implicated in goal-directed behavioral control (vmPFC and caudate nucleus) and increased activation in regions involved in habit learning (pre-supplementary motor area [pre-SMA] and putamen) during exposure (Banca et al., 2015a). Importantly, putamen and vm-PFC/OFC were shown to be key structures modulating urges and compulsions. Neuroimaging evidence has revealed larger volume changes in the anterior-ventral putamen in older or more severe OCD patients, consistent perhaps with the ability of extended experience of compulsions (or habit training) to affect this striatal region (Radua and Mataix-Cols, 2009).

The possible contribution to compulsions of aversive habits arising from instrumental avoidance behavior to OCD (Gillan et al., 2014a, 2015a) is persuasive, given that avoidance behavior has an especial tendency to become susceptible to habitual tendencies, particularly as the transition from goal-directed to habitual control is exacerbated by exposure to stress (Schwabe and Wolf, 2009) as well as by top-down executive deficiency. Thus, behavior that begins as natural avoidance tendencies can evolve gradually into compulsive rituals (see Figures 2B and 2C).

An alternative motivational stimulus to habitual actions is by Pavlovian-instrumental transfer (PIT). In this paradigm, superimposed Pavlovian conditioned stimuli (CS) increase behavioral output. Transfer can be either outcome specific or general (if acquired by conditioning with a different reinforcer). Outcome-specific transfer may thus represent goal-directed decision making, while general transfer may be an affective driver of habitual behavior (Dolan and Dayan, 2013). Some authors (Bradfield et al., 2017) suggested that OCD symptoms may result from a failure to integrate these Pavlovian and instrumental influences over behavior, perhaps via a failure of lateral OFC activity over striatal outflow, given the putative roles of these structures in Pavlovian and instrumental learning, respectively (Balleine and O'Doherty, 2010).

Critique of the “Habit” Hypothesis

While the habit account of OCD is promising, several caveats are in order before it can provide a convincing neuropsychological model of compulsivity. Habit perseveration in OCD has not been measured directly but inferred, based on failures in goal-directed control. The evidence for such goal-directed failures in OCD is strong not only behaviorally but also in neural terms: (1) hyperactivity in the caudate nucleus (not the putamen) was related to devaluation failures for avoidance behavior in OCD, and its strength was parametrically associated with urges to perform devalued actions (Gillan et al., 2015a); and (2) reduced sensitivity to instrumental contingencies recently found in OCD also reinforces a deficient goal-directed system in this disorder (Vaghi et al., 2019). However, the implicit assumption that if the behavior is not under goal control then it must be a habit (or vice versa)—i.e., that this is “a zero-sum game” (Robbins and Costa, 2017)—is questionable, especially given their dissociable neural substrates. Indeed, recent studies have shown that while goal devaluation reduces model-based behavior, it does not necessarily enhance model-free responding (Gillan et al., 2015b). Furthermore, individual differences in stimulus-response strength are primarily determined by differences in the goal-directed neural system (decreased activity in the inferior parietal lobule and vm-PFC predict higher habit acquisition strength) and not the habitual system (posterior putamen and premotor cortex) (Zwosta et al., 2018).

These findings argue against the hypothetical simple reciprocity between the two systems of behavioral control and question the use of devaluation strategies to probe habits. Perhaps habit learning (or urges in OCD) and habit perseveration (compulsions) are governed by distinct neural circuitries and we have not yet been able to target the latter experimentally. A failure of value-updating observed in goal-directed tests may represent only a first stage of habit formation (the cognitive stage) and the strengthening of stimulus-response links (the autonomous stage), governed possibly by a separate and distinct neural pathway could occur later, as a function of training duration. Only a direct probe of such “habit circuitry” underlying this autonomous stage could elucidate potential dysfunction in OCD and possible relations between maladaptive habits and compulsions.

To achieve this, a key strategy might be to manipulate habit training duration. Despite the classic evidence that habit learning requires extended training (Adams, 1982), an exhaustive program of five separate experiments, using both approach and

avoidance learning procedures in humans, has recently shown that extended training does not always enhance habit learning (de Wit et al., 2018). These studies fail to replicate the Tricomi et al. (2009) study, in which 3 days of training of an operant appetitive response led to habitual behavior in humans. However, strong habits in humans may take months or years to develop, and it might therefore seem unreal to experimentally probe them over such short periods. A possible approach might be to study action sequences, investigating their “chunking” (Graybiel, 1998). Like skills or routines, the performance of one action facilitates the next (presumably via proprioceptive or kinaesthetic feedback in a stimulus-response or automatic manner) and extensive training of sequential actions may more rapidly and efficiently boost the habit system. This approach considers possible relationships between habit and skill learning, which may be relevant to the need for compulsions to be performed in a “just right” manner, akin to skill learning, including implicit sequence learning (Rauch et al., 1997), and in OCD conceivably implicating interactions between fronto-striatal and fronto-parietal-cerebellar circuitry (Anticevic et al., 2014; Vaghi et al., 2017a).

Metacognitive Theory of OCD

Metacognition refers to awareness of one’s own abilities and thoughts. In contrast to the habit account of OCD, the metacognitive model (Myers and Wells, 2005) proposes that compulsions originate as a consequence of intrusive thoughts due to patients’ overestimation of the credibility of their thoughts. Within this framework (Rachman, 1993), OCD patients regard intrusive thoughts (for example, the thought of a forbidden action) in the same way as performing the action. Due to this metacognitive impairment, patients overestimate the credibility of their thoughts and consequentially engage in compulsions. Some studies also extend this deficit to memories, whereby repetitive compulsions arise from low confidence in memory of one’s actions, causing their repetition (Hermans et al., 2008; Tolin et al., 2001). The Salkovskis (1985) model similarly conceptualizes a negative interpretation of intrusive thoughts at the core of the disorder, so that patients have an inflated sense of responsibility for their actions. This construct of “responsibility” does not correspond to metacognition per se. On the other hand, egodystonic features of OCD, in which patients recognize their actions as irrational or at least exaggerated, is at odds with both of these models, pointing nevertheless to metacognitive deficits, whereby performance of actions and their subjective accounts are detached from one another.

At the empirical level, evidence of such dissociation has been provided via different experimental methods. Excessive actions have been observed in OCD patients despite degraded instrumental contingencies, meaning that patients performed an action even if there was a diminished causal link between the action and the obtained outcome (Vaghi et al., 2019). However, patients reported intact and accurate subjective judgments of the relationship of the causal link between action and outcome. In addition, there was evidence for a dissociation between increased behavior and correct appraisal on the need of performing such behavior, as assessed by subjective report on action-outcome relationships. A related “illusion of control” task with no causal link between the action and the outcome found lower but more accurate estimates of control in OCD patients, again supporting

correct insight concerning the consequences of their actions (Gillan et al., 2014b). In similar vein, in a predictive inference task, OCD patients only took into consideration recent, noisy evidence, leading to excessive actions. Excessive action was dissociated from subjective confidence about their outcomes, equivalently to control subjects (Vaghi et al., 2017c). These studies thus identify dissociation between subjective reports and action output in favor of a form of metacognitive deficit whereby the subjective appraisal of the action is similar to that of healthy controls and hence apparently intact, despite action output being exaggerated. On the other hand, a distinct form of metacognitive impairment was shown in another study in which high-compulsive subjects (with no formal diagnosis of OCD) exhibited reduced ability to judge the correctness of their decision, as well as higher decision thresholds when compared to low compulsive subjects (Hauser et al., 2017), which is in line with findings with formally diagnosed OCD patients (Banca et al., 2015b).

The OCD Brain

Neural Correlates of OCD

Early studies of the abnormalities of the OFC and the caudate in association with OCD (Baxter et al., 1987; Saxena et al., 1999) have largely been confirmed by meta-analyses of a variety of neuroimaging indices over the years (Whiteside et al., 2004) and are consistent with the implication of fronto-striatal “loops” (Alexander et al., 1986) in OCD (see van den Heuvel et al., 2016). Direct estimates of brain connectivity features have been obtained relatively recently with resting state approaches. Hypothesis-driven analyses directed at the fronto-striatal circuits have shown an imbalance between reciprocal pathways, with reduced functional connectivity of the caudate and increased functional connectivity of the ventral striatum in OCD patients to their associated cortical regions (Harrison et al., 2009; Vaghi et al., 2017a) (Figure 3A). Therefore, the longevity of the initial neuroanatomical model has been maintained by independent evidence of altered neuroanatomical connectivity between the basal ganglia and frontal cortex in OCD. However, while initial imaging studies mostly pointed to caudate abnormalities, the nucleus accumbens (NAc) (and adjacent structures in the ventral capsule) has recently apparently been a successful target of DBS for therapeutic intervention in OCD, leading to symptom reduction (Denys et al., 2010). Such intervention has functional implications, with normalization of NAc activity in OCD patients during a reward anticipation task and reduction of excessive functional connectivity to cortical areas correlating with greater reductions of obsessions and compulsions (Figeo et al., 2013). The NAc receives main cortical afferent projections from the ACC, also successfully targeted by cingulotomy for otherwise treatment-resistant OCD (Dougherty et al., 2002; Rauch et al., 2001). However, the physiological mechanisms leading to symptomatic improvement are unclear.

Lateral versus Medial Fronto-striatal Imbalance in OCD?

The hallmark finding of a hyperactive OFC in OCD has been further supported by findings that lower pretreatment metabolic activity is associated with better pharmacological responses to SSRIs (Saxena et al., 1999; Swedo et al., 1992). Although this finding of a hyperactive OFC has proven valid, this region is not functionally and anatomically homogeneous (Kringelbach

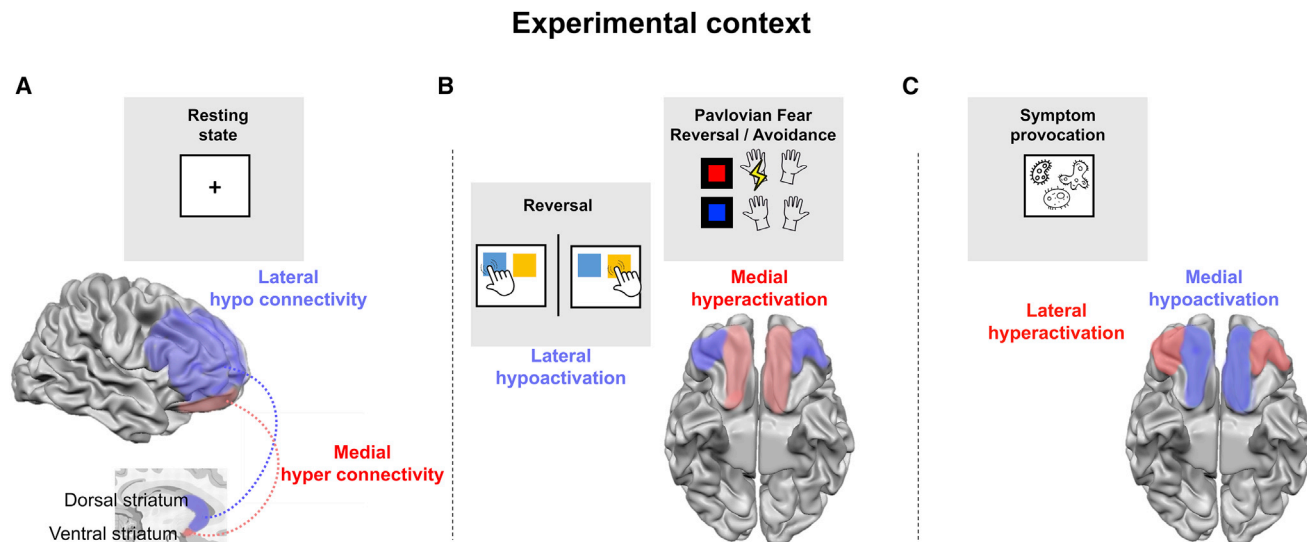


Figure 3. Neural Correlates of OCD

Highly schematic diagram showing pattern of context-dependent modulation of brain areas included within cortico-striatal loops consistently implicated in OCD. The diagram depicts a qualitative analysis from the lowest level of stimulation (i.e., resting state) to the highest level of stimulation (i.e., symptom provocation). Task-related brain activation is illustrated for a cognitive control task (i.e., reversal learning) with low emotional valence (i.e., points) and a task with high emotional valence (i.e., shock) measuring the balance between goal-directed and habitual behavior (i.e., active avoidance) or the ability to assign safety to stimuli.

(A) During the resting state, hypoconnectivity of a lateral circuit is observed with patterns of reduced connectivity between the lateral PFC and dorsal striatum. Hyperconnectivity is observed for a medial circuit with patterns of increased connectivity between medial cortical regions (vm-PFC including medial OFC) and the ventral striatum.

(B) Reversal learning requiring cognitive flexibility is characterized by hypoactivation in the lateral portions of the OFC (which may have trait features [see text]); in contrast, when required to reverse stimulus values in an aversive setting (Apergis-Schoute et al., 2017) or when learning to avoid aversive stimuli (Gillan et al., 2015a), hyperactivation of the vmPFC including medial OFC occurs.

(C) This pattern is reversed for symptom provocation, whereby presentation of salient, OCD-related stimuli leads to hyperactivation of the lateral OFC. Although findings for the medial OFC are less consistent in symptom provocation studies, a recent ecologically valid symptom provocation study identified hypoactivation of the medial OFC in OCD patients (Banca et al., 2015a). The dorsal striatum includes both the caudate and putamen; the ventral striatum includes regions of the nucleus accumbens and portions of the caudate and putamen. The schematic is based on available neuroimaging data from the literature, but the analysis is not exhaustive and the conclusions speculative.

and Rolls, 2004; Zald and Rauch, 2006). A primary distinction is between its lateral and medial OFC compartments as indicated by resting-state (Kahnt et al., 2012) and task-related functional connectivity (Zald et al., 2014) as well as by functional considerations (Dias et al., 1996; Hampshire and Owen, 2006). Moreover, a lateral and medial PFC distinction is relevant to functional neuroimaging findings in OCD, as pointed out by Milad and Rauch (2012).

The lateral portion of the OFC is hypoactive in OCD patients during reversal learning, when a change in behavior is required (Remijnse et al., 2006), and in their first-degree unaffected relatives (Chamberlain et al., 2008). Moreover, recent studies of attentional set-shifting and planning show reduced connectivity, respectively, with reduced ventrolateral PFC-caudate and dl-PFC-putamen functional connectivity (Vaghi et al., 2017a, 2017b) (Figure 3B). The lateral OFC is also consistently implicated in symptom provocation studies of OCD according to meta-analytic studies (Rotge et al., 2008, 2009, 2010a; Simon et al., 2010). Notably, in this specific experimental context, the BOLD response was *increased* rather than reduced (as observed during reversal). Hyperactivity of the lateral OFC during symptom provocation normalized over the course of behavioral therapy for OCD (Morgiève et al., 2014). In addition, lower metabolism of the lateral OFC, as measured by fluoro-deoxyglucose (FDG) with PET, during symptom provocation

correlated with superior symptom improvement upon pharmacological manipulation (Rauch et al., 2002) (Figure 3C). Therefore, although the lateral OFC is consistently implicated in OCD, two orthogonal aspects merit consideration: (1) the precise role of the experimental context in modulating its activity (leading to either hypo- or hyper-activation) and (2) whether its activity represents trait-like (i.e., endophenotype) or a state-like OCD features, given its sensitivity to pharmacological intervention.

An important role of the vm-PFC is the ability to flexibly update values of stimuli that cease to be threatening (i.e., Pavlovian fear conditioning) (Fullana et al., 2016; Schiller and Delgado, 2010). The clinical manifestation of OCD is characterized by elevated fear and anxiety, consistent with functional imaging studies of shock-avoidance learning in OCD, showing elevated vm-PFC-caudate activity (Gillan et al., 2015a) (Figure 3B). Recent findings further show a lack of a safety signal computed by the vm-PFC in OCD patients when required to flexibly update the value of stimulus previously threatening but then becoming safe (Apergis-Schoute et al., 2017). This signal was possibly attenuated by sustained vm-PFC hypermetabolism and could be interpreted as the underlying cause of inflexible threat beliefs. vm-PFC hyperactivity is also linked to similar hyperactivity of the caudate, ACC, insular, and thalamus (Apergis-Schoute et al., 2017). In another study, however, patients with OCD

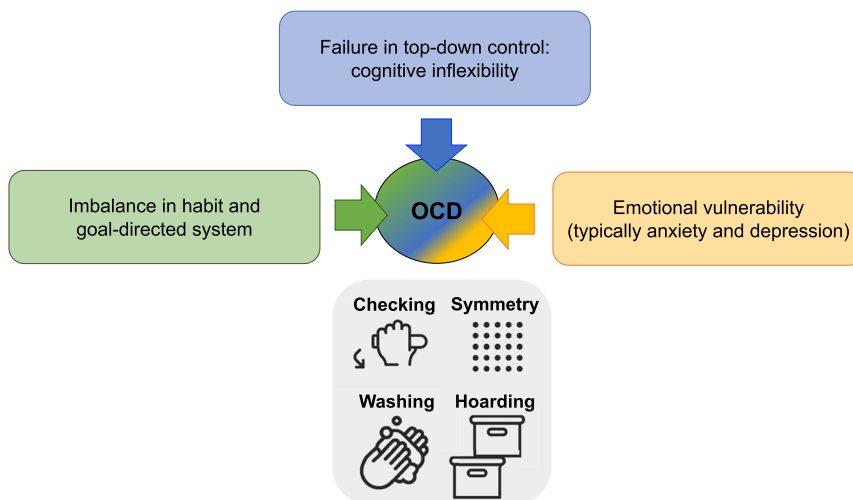


Figure 4. Dimensions and Subtypes of OCD

A dimensional account of OCD, which is suggested to arise from the interaction of three main factors: anxiety or emotional vulnerability, cognitive inflexibility, and an imbalance between goal-directed and habitual control over behavior (toward the latter). This interaction is assumed to be at the core of OCD subtypes such as checking, washing, ordering, and hoarding.

showed *hypoactivity* of the vm-PFC when required to recall a memory initially conditioned to fear but then extinguished (Milad et al., 2013). Therefore, the neural mechanism underlying the ability to flexibly respond in the context of learned fear might be relevant to understanding the symptoms of OCD (Milad and Rauch, 2012), with implications for current behavioral therapies for the disorder. Banca et al. (2015b) also showed *reduced* activation of the vm-PFC including medial OFC during symptom provocation, apparently paralleling the relative *increases* in the lateral PFC regions described above (see Figure 3C). However, in interpreting these results, it must be pointed out that (1) no single study has yet directly compared medial and lateral OFC regions in a symptom provocation design; (2) the vmPFC region is complex, with several distinct regions, including the medial OFC, the functions of which are still being defined (Zald and Rauch, 2006); and (3) these regions are technically difficult to differentiate because of significant lack of signal due to imaging artifacts.

Nevertheless, the lateral and medial PFC imbalance appears to be context dependent, perhaps related to the degree of emotional salience of the situation. This may have further important implications for neuropsychological theories of OCD concerning goal-directed behavior and habits. Thus, the hyper-medial PFC versus hypo-lateral PFC pattern in OCD appears to contradict a simple version of the reduced goal-seeking and increased habit learning theory of OCD symptoms, insofar that the medial regions projecting to the caudate nucleus have generally been reported as hyperactive (Gillan et al., 2015a) and the lateral regions projecting to the putamen as hypoactive (e.g., Vaghi et al., 2017a). Naively, one might have expected the opposite pattern of findings given what is known about the neural mediation of goal-directed behavior and habits (Balleine and O'Doherty, 2010), unless increased BOLD activity in the case of vm-PFC-caudate function represents an impairment of goal-directed behavior (Gillan et al., 2015a).

These considerations might lead to a more sophisticated version of the psychological hypothesis of OCD, namely that there can be *enhanced* goal-seeking, especially in specific

aversive situations, to the detriment of other goal-directed activities and also coupled with an overall narrowing of goals (Figure 2C). This revised hypothesis may also help to explain the coexistence of context or state-dependent hyperactive and hypoactive PFC regions described above. It is also not necessarily contradictory to the original hypothesis,

because it is possible that it represents a less severe, or earlier, stage of the illness (Figure 2C versus Figure 2B).

Neural Networks for OCD

Integrating evidence from neuroimaging and neuropsychological studies, an “extended circuit” for OCD has been proposed (Menziés et al., 2008). Even though abnormalities within OFC-striatal regions are clearly supported by the literature, the introduction of whole-brain-based imaging techniques has allowed a more comprehensive investigation of other neural circuits implicated in the disorder. In addition to the inferior PFC, ACC, and insular cortex, the mid-occipital, posterior cingulate, temporal lobe, parietal cortex, and cerebellum have all been implicated (e.g., based on a mega-analysis of cortical thickness in 780 patients; Fouché et al., 2017).

Some of this rather extensive pattern of neural deficits in OCD might correspond to the heterogeneity of the disorder in terms of its various subtypes, such as checking, washing and symmetry, and hoarding (Figure 4). Thus, van den Heuvel et al. (2009) relates washing and contamination to reduced gray matter in the caudate nucleus and white matter volume in the parietal lobe. By contrast, checking is related to changes in white matter volume in the temporal lobe, and “ordering” is related to widespread structures. It does seem likely that the expression of these behaviors may well have distinct neural substrates; however, many studies showing common changes in tests of fronto-striatal functioning (e.g., Morein-Zamir et al., 2014) and specific laboratory tests of responses such as “checking” across the subtypes (e.g., Morein-Zamir et al., 2018) suggest that there are core neural features that relate to fundamental psychological deficits for all of these variants (Figure 4). Possible substitutability of the main compulsive behaviors in some patients is also consistent with this viewpoint.

An extended network model is further supported by neuropsychological evidence of impaired performance on a host of executive functions broadly involving regions of the PFC extending beyond the OFC to the parietal cortex (see above). Due to prominent anxiety symptoms, the role of the limbic system, particularly the amygdala, has been matter of controversy. Some investigations have emphasized possible fronto-amygdala

Table 1. Animal Models of OCD and Related Disorders

Model	Phenotype	Putative Mechanism
Genetic		
HoxB knockout mouse	excessive auto-grooming	neuronal development, immune involvement
Slitrk5 knockout mouse	excessive auto-grooming, anxiety	striatal neuronal differentiation and neurotransmission
Sapap3 knockout mouse	excessive grooming, anxiety	postsynaptic scaffolding protein at excitatory synapses highly expressed in the striatum
5-HT2C receptor knockout mouse	putative compulsive behaviors but reduced anxiety	possible 5-HT involvement
Aromatase knockout mouse	excessive auto-grooming, wheel running in males	connection between estrogen and low COMT activity
Pharmacological (Rats)		
Serotonin Treatments		
5-HT1B agonist (systemic and intra OFC)	perseverative locomotor patterns	impaired fronto-striatal function
Mcpp, 8-OHDPAT agonists	reduced alternation, increased checking	–
5-HT2C receptor agonist	increased self-grooming	–
5-HT2A receptor antagonist	impaired reversal learning	–
Neonatal repeated clomipramine	reduced alternation, impaired reversal, increased marble burying	limpaired cortico-striatal function and altered 5-HT and DA modulation
Dopamine D2 Receptor		
Sub-chronic quinpirole	increased checking	DA-dependent striatal function
Ethological		
Canine lick dermatitis (dogs)	excessive grooming	putative striatal involvement
Barbering in mice	excessive grooming	–
Stress Induced (Rat)		
Schedule-induced behavior under food restriction	compulsive drinking and other adjunctive behaviors	striatal involvements

Examples of the main classes of models for OCD. See [Camilla d'Angelo et al. \(2014\)](#) for references. COMT, catechol-O-methyl-transferase.

connectivity ([Subirà et al., 2016](#)), for example implicated in response inhibition functions of the inferior frontal cortex, modulated by emotional factors such as anxiety ([Subirà et al., 2016](#); [van Velzen et al., 2015](#)). There has been no consistent evidence for activation of the amygdala or other limbic structures in meta-analyses of investigations of metabolism at rest ([Whiteside et al., 2004](#)) or during aversive conditioning ([Apergis-Schoute et al., 2017](#)). However, a recent meta-analysis of 25 fMRI studies (comprising 571 patients and 564 healthy controls) of emotional processing showed increased activation for OCD patients in the bilateral amygdala as well as in the middle temporal and left inferior occipital cortices during emotional processing (though also involving fronto-striatal systems) ([Thorsen et al., 2018](#)). Right amygdala hyperactivation was most pronounced in unmedicated patients. Symptom severity was related to increased activation in the OFC, ACC, and precuneus. Greater comorbidity with mood and anxiety disorders was associated with higher activation in the right amygdala, putamen, and insula as well as with lower activation in the left amygdala and right vmPFC.

Data-driven approaches, including analysis using graph theory, have also revealed abnormalities of cerebellar connectivity ([Anticevic et al., 2014](#); [Vaghi et al., 2017a](#)) in line with anatomical evidence of overlap of fronto-parietal and fronto-striatal circuitry

with the cerebellum ([Bostan et al., 2010](#)). Increasing evidence for a role of the cerebellum in higher-order cognitive functions ([Buckner, 2013](#)) may have important implications for some of the abnormalities in OCD related, for example, to skill learning.

Neural Mechanisms of OCD Animal "Disease" Models

Work with experimental animals has played a major role in shaping our current understanding of the neuropsychological basis of OCD at both the neural systems and neurochemical modulatory levels (see the section [Treatments for OCD: Neuroscientific Basis and Future Prospects](#)). A number of animal "disease" models of the disorder have also emerged from a variety of sources, including ethology, pharmacology, and neuroscience ([Camilla d'Angelo et al., 2014](#)). One serendipitous example is the naturally occurring canine acral lick dermatitis, in which excessive licking of paws or flank can produce ulcers requiring medical treatment ([Rapoport et al., 1992](#)). Of relevance to impoverished 5-HT and excessive DA theories of OCD symptoms (see below), knockout of the 5-HT2C receptor gene is implicated in apparently compulsive behaviors such as increased chewing of non-nutritive kaolin clay and perseverative head-dipping ([Chou-Green et al., 2003](#)). Sub-chronic treatment with the DA D2/3 receptor agonist quinpirole in rats also produces enhanced

checking behavior measured in the open field (Szechtman et al., 1998) or in an operant task that defines checking as information seeking and becomes excessive and maladaptive after quinpirole treatment (Eagle et al., 2014).

Alternatively, genetic discoveries have produced a variety of murine models in which knockouts usually produce excessive grooming behaviors, including barbering reminiscent of trichotillomania (Table 1). Foremost among these is the knockout of the *Sapap3* gene (which normally produces a post-synaptic scaffolding protein) that leads to excessive auto-grooming and anxiety, ameliorated by treatment with an SSRI (Welch et al., 2007).

More recently, two novel complementary “neural” models were produced by use of optogenetic inhibition applied to the rodent OFC. In the study by Ahmari et al. (2013), infusion of an adenovirus-associated vector carrying the gene encoding channelrhodopsin (ChR2) into the medial OFC led to functional ChR2 expression in projections from the medial OFC to the ventromedial striatum (VMS). Repeated optogenetic stimulation of this OFC-VMS pathway progressively increased grooming, which persisted beyond the time the stimulation was on. The excessive grooming was remediated by sub-chronic administration of the SSRI fluoxetine (Ahmari et al., 2013). A parallel study by Burguière et al. (2013) used a related, though distinct, approach by applying optogenetic stimulation to the pathological grooming of the *Sapap3* mouse. They successfully conditioned grooming to a cue signaling a water drop delivered to the forehead and found that the *Sapap3* mice persisted in this response. This persistent grooming was inhibited by optogenetic stimulation of the lateral OFC neurons projecting to the striatum (Burguière et al., 2013). Fast-spiking activity in the striatum was associated with the development of this compulsive grooming, suggesting a pathophysiological mechanism of some forms of compulsive behavior in OCD, notably trichotillomania, arising from neurological changes in the striatum. Taking the two studies together, there is an intriguing complementarity of the medial and lateral OFC in the regulation of grooming corresponding to imbalance emerging from the human neuroimaging literature, as discussed above.

A consideration that applies to many genetic animal models in psychiatry is how much of the syndrome can possibly be related to single gene loci? More recently, Manning et al. (2018) have extended the *Sapap3* model to show that the reversal learning deficits shown in this mouse correlate with increased *c-fos* activity in the medial PFC, which they associate with the impaired fear reversal exhibited by OCD patients associated with elevated vmPFC activity (Apergis-Schoute et al., 2017). However, although this may highlight some of the cognitive impairments associated with OCD, the deficits in reversal did not correlate with the compulsive grooming of the *Sapap3* model. Further validation of the *Sapap3* model is provided by the demonstration by Pinal et al. (2018) that DBS of the internal capsule successfully reduced excessive grooming, paralleling the effects seen in OCD.

Toward a Molecular Pathophysiology of OCD

Initial work focused on the abnormalities in the cortico-striatal-thalamic-cortical loop pathways and, guided by therapeutic indications, their neuromodulation by DA and 5-HT, using neuro-

imaging studies (see the section **Treatments for OCD: Neuroscientific Basis and Future Prospects**). However, more integrative hypotheses (Rotge et al., 2010b) have taken into account glutamate dysregulation, possibly related to the recent genetic findings, overactivity of certain cortical regions in OCD, and immunological factors. Glutamate is also an immunomodulator and an important regulator of T cell function via their surface mGluR-1 receptors. Rotge et al. (2010b) summarized evidence that activation of T cells by specific antigens, such as the Borna disease virus (BDV) antigen, may promote cytokine production in OCD (for review, see Frick and Pittenger, 2016). In addition, such antigens may increase activity in structures such as the ACC via thalamocortical pathways by increasing glutamate levels, with consequential effects on hyperactivity and also possible neurodegeneration caused by excitotoxicity. An unusual aspect of this theory is the focus on the ventro-anterior thalamic nucleus, which projects to key regions responsible for the symptoms of OCD, the ACC and OFC. This contrasts with theories based on optogenetic models of striatal dysregulation in OCD (Ahmari et al., 2013; Burguière et al., 2013) but may, of course, also complement them. Rotge et al. (2010b) also speculate that differential effects of BDV infections at different ages might be responsible for the differences between early- and late-onset OCD. This theory and other possible variants may be tested in future by a combination of immunological and magnetic spectroscopic studies, aimed at quantifying changing glutamate/GABA levels at different stages of the development of OCD (Brennan et al., 2013).

Some of the first evidence for inflammation in adult OCD was in fact recently reported following PET studies of a ligand for the translocator protein (TSPO), the density of which increases when microglia are activated (Attwells et al., 2017). Significant elevations of ~30% were observed in a number of cortico-striatal sites, that in the OFC correlating significantly with the distress caused by preventing compulsions. Animal models may point the way to further immunological treatments. For example, in *Hoxb8* mutant mice, defective microglia underlie compulsive grooming (Chen et al., 2010) and show cortico-striatal circuit defects (Nagarajan et al., 2018). Moreover, reducing levels of tissue necrosis factor alpha (TNF- α) in progranulin knockout mice abolished excessive self-grooming and the associated hyper-excitability of medium spiny neurons of the NAc (Krabbe et al., 2017).

Treatments for OCD: Neuroscientific Basis and Future Prospects

The currently used most effective treatments for OCD are cognitive behavior therapy (CBT) including ERP and high doses of SSRIs (Bloch et al., 2010; Skapinakis et al., 2016). The latter, however, are only effective in ~40%–60% of patients and do not generally achieve full remission. It may be important to resolve this heterogeneity using a pharmacogenomic approach that has been relatively understudied for OCD (Zai et al., 2014) but could conceivably aid more “personalized” medicine.

Psychological Treatments

ERP involves a systematic (progressive and repeated) exposure to stimuli that would normally induce fear and trigger obsessions and compulsions, followed by response prevention of compulsive rituals. This combined strategy enables anxiety and the

urges to perform compulsions to eventually dissipate. The necessity for response prevention is an important component of the psychological treatment given the perspective that compulsions are often manifested as avoidance habits. CBT by itself may be less effective, because it addresses only cognitive aspects of OCD. Although this psychological technique is effective in reducing not only the urges to perform compulsions but also the obsessive thoughts, ~50% of patients are resistant to such treatment due to lack of motivation and engagement (Reghunandan et al., 2015). The neural mediation of successful CBT remains fully to be elucidated; a classical study showed that behavior therapy in OCD had effects comparable to those of medication with the 5-HT agent clomipramine in influencing caudate nucleus metabolism (Baxter et al., 1992). In an animal model of exposure with response prevention, a subset of rats exhibiting persistent avoidance could be treated by pharmacological inactivation of the lateral OFC (Rodriguez-Romaguera et al., 2016).

Perhaps new technologies and approaches will be beneficial, such as the use of apps that blunt an individual's urge to compulsive behavior (such as washing) by having them instead view a brief video of their own performance of that behavior (Jalal et al., 2018). New psychological treatments have a different focus, consistent with notions that automatic habits underpin compulsive behaviors in OCD. Such methods as "implementation intentions" (Gollwitzer, 1999) or "habit reversal" (Azrin and Nunn, 1973) attempt the difficult task of counteracting them by substitutive strategies that seek to replace rather than suppress the habit in the specific contexts in which it is normally elicited. This technique has been shown to be more effective than ERP in treating trichotillomania and excoriation (Wilhelm et al., 2003), but to our knowledge, it has not been attempted in OCD.

Pharmacological Medication

Mechanisms of the therapeutic actions of SSRIs, both behavioral and molecular, remain obscure. The main evidence for possible 5-HT deficiency in OCD comes, in fact, from effects of treatment with relatively high doses of SSRIs (Soomro et al., 2008). Evidence for neurochemical changes in OCD consistent with changes in 5-HT function is more limited. Thus, there is no consensus on the evidence of significant 5-HT_{2A} receptor changes in the caudate nucleus and neocortex using PET in unmedicated patients with OCD (Adams et al., 2005; Perani et al., 2008; Simpson et al., 2011). Possible behavioral mechanisms may be through anxiety reduction in which automatic cycles of thoughts and actions (enhanced by stress; e.g., Schwabe and Wolf, 2009) subsequently diminish and patients become more capable of engaging in CBT. However, this hypothesis seems unlikely given the inefficacy of other anxiolytics such as benzodiazepines in treating OCD. An alternative hypothesis is that SSRIs may exert their effect in OCD by re-engaging the goal-directed brain system, thus boosting patients' capability to resist compulsive behavior (Palminteri et al., 2012). A third possibility is that 5-HT modulates certain fronto-executive functions such as cognitive flexibility. 5-HT is also known from animal studies to modulate reversal learning in the OFC (Barlow et al., 2015; Clarke et al., 2007), which also depends on DA-dependent striatal outflow via the caudate and putamen (Clarke et al., 2011; Groman et al., 2013). 5-HT depletion can cause perseveration in

reversal learning, analogous to a form of compulsive behavior (Barlow et al., 2015; Clarke et al., 2004) consistent with reversal deficits in OCD (Remijnse et al., 2006; Chamberlain et al., 2008). Transient central 5-HT downregulation in humans caused by acute dietary tryptophan depletion impairs reversal (Rogers et al., 1999) and also goal-directed behavior under reward (accompanied by increases in appetitive habits), though not goal-directed avoidance behavior, which may even be boosted (Worbe et al., 2016). This valence-dependent imbalance between goal-directed behaviors and habits, with the former being stronger for aversive motivation, remains to be tested further in OCD patients.

El Mansari et al. (1995) attributed the special requirement of high doses of SSRIs to the desensitization of the terminal 5-HT autoreceptor, specifically in the OFC, following chronic treatment with the SSRI paroxetine in the guinea pig, presumably increasing post-synaptic 5-HT transmission. Chronic SSRI treatment may also influence DA transmission (e.g., reducing striatal DA in mice; Morelli et al., 2011), and PET studies in OCD patients showed increases in striatal D₂ receptor availability changes after repeated SSRI (fluvoxamine) treatment suggestive of DA downregulation (Moresco et al., 2007). This may be consistent with reports of loss of D₂ receptor availability in the striatum of OCD patients, interpreted as indicating relatively increased DA transmission (Denys et al., 2013; Perani et al., 2008).

A future focus on glutamate mechanisms may be timely, given that SSRIs also regulate cortical glutamate transmission. Pittenger (2017b) has recently reviewed the possible efficacy of various modulators of glutamate transmission, including the NMDA receptor noncompetitive antagonists memantine and ketamine, and D-cycloserine, an agonist at the glycine site of the NMDA receptor, with no clear evidence in favor. The latter agent has been used effectively in certain anxiety disorders in conjunction with CBT, and Pittenger (2017b) suggests this might be an interesting future avenue to explore for OCD. Given the presumed hyper-glutamatergic state of certain circuits in OCD, it might be predicted that a different approach that reduces glutamate transmission may work better, and Graat et al. (2017) discuss several possible existing strategies to effect this, including the use of topiramate and lamotrigine. Reduction of glutamate transmission by mGluR_{2/3} receptor agonists acting at inhibitory presynaptic receptors may be a more direct means by which to achieve this end.

Surgical and Neuromodulatory Treatments

Surgical treatment is perhaps more successful in OCD than in any other psychiatric disorder but is only employed in severe, treatment-resistant cases (Greenberg et al., 2010). The relative efficacy of both cingulotomy and ventral capsulotomy (affecting white matter connections between the basal ganglia and cortex) in OCD is consistent with cortico-striatal involvement but has not yet elucidated underlying behavioral mechanisms contributing to OCD. More recently, the efficacy of ventral capsule surgery has been exploited using instead DBS of this region, which is also efficacious in OCD (e.g., Figeo et al., 2013). Although the electrodes may extend into the NAc, the most effective sites on the electrode generally lie outside this structure, suggesting effects on fibers of passage. Another effective location has been established in the subthalamic nucleus (STN) (Mallet et al., 2008),

which has been a preferred site for treating Parkinson's disease, raising the question of whether the same neural network circuitry is being affected in both cases at different loci or, alternatively, whether the two sites are delivering different therapeutic effects. Evidence for this has recently been reported in a small study of 6 well-studied severe OCD patients who were implanted bilaterally in both regions for direct comparison (Tyagi et al., 2019). DBS at both sites significantly and dramatically reduced Y-BOCS scores. However, this may have been for different reasons; whereas DBS in the ventral capsule site improved mood on the MADRS depression scale, DBS in the STN significantly improved cognitive flexibility using the attentional set-shifting task. The two stimulation sites were shown by tractography to affect relatively medial frontal sites (ventral capsule) and lateral region of the PFC in the case of STN DBS. Therefore, the two sites appear to ameliorate two distinct classes of symptoms of OCD that are mediated by distinct circuits. It is possible that this principle could be useful in the context of burgeoning use of rTMS (Zhou et al., 2017) and tDCS (Brunelin et al., 2018), relatively novel, noninvasive “neuromodulatory” treatments for OCD.

Summary and Conclusions

OCD can be regarded as a “model” psychiatric disorder for neuroscience researchers focusing their efforts on impacting mental health. Its symptoms are fascinating, though their provenance is seemingly baffling and heterogeneous. Original and testable hypotheses are emerging on all fronts about its psychological, neural, genetic, and immunological basis. Animal models appear plausible both from an etiological (genetic) perspective and from their contribution to the elucidation of underlying neuropsychological themes, such as cognitive control, cognitive flexibility, emotional vulnerability, and the goal-directed and habit imbalance. The egodystonic nature of the disorder poses intriguing questions about the relationship between behavior and its subjective or metacognitive correlates, relevant to theories of cognitive control. Although the “modal hypothesis” of dysregulation of cortico-striatal-thalamic-cortical pathways is being extended to include other structures, advances have been made in understanding how its symptoms can be related to the fundamental functions of these networks and their interactions and regulation. The triad of effective cognitive-behavioral, pharmacological, and surgical treatments is unusual in psychiatry, although much needs to be done to improve therapeutic efficacy. OCD is relevant to a modified “R.Doc” perspective (Cuthbert and Insel, 2013) that seeks to define the contribution of primary dimensions such as compulsivity and their mechanistic basis. How many interactive neurocognitive (e.g., cognitive flexibility) or neuroaffective (e.g., anxiety) factors (or “dimensions”) might be necessary to simulate compulsivity or full-blown OCD (see Figure 4)? What should be their respective loading to account additionally for the comorbidities associate with the disorder and its relationship with other “categorical” disorders, including general anxiety disorder, depression, drug addiction, and eating disorders? This may be a suitable problem for computational psychiatry to solve. OCD can indeed be understood as a prototypical disorder of compulsivity and perhaps a prime example of a “behavioral addiction” (Robbins and Clark, 2015), and hence its broader relevance for understanding

many other, possibly related, mental health disorders should be clear.

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