From compulsivity to compulsion: the neural basis of compulsive disorders

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Abstract

Compulsive behaviour, an apparently irrational perseveration in often maladaptive acts, is a potential transdiagnostic symptom of several neuropsychiatric disorders, including obsessive-compulsive disorder and addiction, and may reflect the severe manifestation of a dimensional trait termed compulsivity. In this Review, we examine the psychological basis of compulsions and compulsivity and their underlying neural circuitry using evidence from human neuroimaging and animal models. Several main elements of this circuitry are identified, focused on fronto-striatal systems implicated in goal-directed behaviour and habits. These systems include the orbitofrontal, prefrontal, anterior cingulate and insular cortices, and their connections with the basal ganglia as well sensoriomotor and parietal cortices and cerebellum. Implications are considered for future classification of impulsive-compulsive disorders and their treatment.

[H1] Introduction

Pathological compulsions were first described by Esquirol in his treatise on insanity[1]. Today, they can be understood as behavioural manifestations of a deficit in inhibitory response control characterised by recurrent experiences of an irresistible, persistent urge [G] to perform an act, which persists even despite undesirable, negative consequences[2]. These attributes capture the two essential aspects of compulsions [G]; their subjective experience and their manifestation as maladaptive perseverative behaviour[2], both of which must be accommodated in any theory of their underlying basis (Box 1).

Compulsion-related symptoms are core diagnostic features of obsessive-compulsive disorder (OCD), which is characterised by the recurrence of intrusive thoughts (obsessions [G]) and the rigid engagement in specific behaviours (compulsions), that persist at the expense of other activities and lead to functional impairment[3]. Compulsion is also found across nosological boundaries as a central symptom of psychiatric and developmental disorders (Box 1). These include autism spectrum disorder (ASD), Tourette's syndrome, and trichotillomania [G] as well as behavioural addictions such as eating disorders, gambling and internet addiction. They also include substance use disorder (SUD; generally used to replace the popular term 'drug addiction') as several of the current qualifying symptoms listed by the Diagnostic and Statistical Manual (DSM5) — for example, "Persistent substance use despite knowledge that it may cause or exacerbate physical or psychological problems"[4] — encapsulate the rigid nature of the engagement in a specific behaviour that characterises compulsion. Compulsions can also emerge as a consequence of brain damage (for example, following stroke[5]), neurodegeneration (like in frontotemporal dementia[6]) or following pharmacological treatment (such as D2 dopamine receptor agonist treatment triggering gambling tendencies in people with Parkinson's disease[7,8]).

Whilst compulsive symptoms are important clinically, there are also compulsive elements of everyday behaviour. The dimensional trait [G] of compulsivity [G][9,10] characterises aspects of 'normal' or functional human behaviour and can be measured subjectively by several self-reported questionnaires (Box 2). Moderate compulsivity may contribute to adaptive, goal-directed activities like making accurate scientific measurements, proof-reading and sporting performance rituals. The realisation of its trait-like nature and its possible trans-diagnostic significance for many superficially distinct clinical disorders has encouraged a search for the neuropsychological basis of compulsivity.

In this Review, we discuss this rapidly evolving compulsive behaviour literature that encompasses functional imaging studies of human subjects and neural circuit mapping in animal models using state-of-the-art neuroscience techniques. First, we describe the neuropsychological basis of compulsive behaviour, taking into account its phenomenology and by reference to its major theoretical underpinnings in terms of psychological constructs and their associated brain systems. Then we perform an analysis and synthesis of the many relevant studies of human brain imaging of different disorders exhibiting compulsive behaviour to determine which circuits are implicated. Animal models are considered next, which throw additional light on underlying neural systems and causal mechanisms of compulsive behaviour. Finally, we summarise the major circuits associated with compuslivity across species and consider the ways in which they enable the development and occurrence of different manifestations of compulsion, and how these may be treated.

[H1] Neuropsychological basis of compulsive behaviour

[H2] Phenomenology

The necessary and sufficient qualities of compulsion are controversial, especially when reconciling its subjective and objective properties[2] (Box 1). For example, the word ‘action’ not only refers to overt behaviour such as hand-washing or grooming, but also encompasses covert 'mental acts' such as counting or praying. Compulsive behaviour is repetitive and hence 'excessive', which often (though not always) means that it is maladaptive and inappropriate to the immediate context or goals of the individual[2]. This quality of maladaptive, excessive repetition (or perseveration) helps to distinguish compulsivity from the more investigated trait of impulsivity [G], which has overlapping, but distinct neuropsychological attributes[11].

Although compulsive behaviour may be performed without a clear conscious rationale and can appear excessive, automatic, stereotyped and meaningless, both to its performer and others, it is commonly thought to represent an emotional regulation strategy gone awry (for example, to at least transiently relieve anxiety caused by persistent intrusive thoughts or obsessions)[4]. Compulsions may also arise from urges, often cued interoceptively (meaning bodily or visceral signals that are sensed and represented by the brain, ultimately in cortical structures such as the insula)[12]. Urges can be subjectively reported as manifestations of narrowing goal-selection including both ‘I want’ (as in craving [G] for drugs in absence of withdrawal) and ‘I need’ (as in craving for drugs in withdrawal), depending on which of the positive (incentive motivation [G]) or negative (anxiety or frustration) affective systems are predominantly recruited at the time[13,14]. Alternatively, subjective feelings can be directed to actual performance — for example, ‘I must-do’ — when they generate an internal struggle or obstacle against the ‘will’, hence causing ‘egodystonia’[15]. Egodystonia can be defined as the aversive subjective state, often reported in OCD, in which there is a failure of the individual to impose executive control over their own behaviour that prevents their volitional goals from being achieved. Another common subjective correlate of performance is the ‘not quite right’, perfectionist tendency in individuals with OCD[15], presumably arising from a failure in action monitoring (continuously checking that the action is being performed accurately so it can achieve its goal). While taking into account how urge and performance-related subjective correlates of compulsions can inform underlying theories, note that an individual's subjective rationale for their compulsive behaviour may be post hoc and hence not its primary driver[16] (depending on their level of insight[17]).

What types of behaviour can become compulsive? For individuals with OCD, the most common compulsion is checking [G][18], but hand-washing, counting, ordering [G] and perfectionism are also prevalent, sometimes in the same individual and sometimes at different stages of the disorder[15,18]. Whilst both are included in the OCD spectrum, body dysmorphic disorder (which includes constant checking of appearance and grooming) and hoarding may represent distinct diagnoses[9,5]. In humans, compulsive hoarding is associated with the excessive accumulation of items of limited value (such as old newspapers or clothes never worn). Rodents or other species are also said to compulsively hoard when they store food even in a caloric deficit state[19]. Eating disorders not only may include compulsive binge eating (bulimia), the persistence of eating high caloric food despite serious health problems[20,21], but also can be described as a compulsive tendency to exert control by relentless self-starvation and exercise (anorexia nervosa)[22].

In humans and other animals, innate or acquired coping [G] strategies can become compulsive in vulnerable individuals. These may involve body-focused behaviours, such as persistent skin picking, nail biting or hair pulling that characterise trichotillomania in humans, or self-grooming and barbering in rodents. For example, in the SAP90/PSD95-associated protein 3 (SAPAP3) mutant mouse, with genetic deletion of *Dlgap3* encoding SAPAP3 (SAPAP3$^{-/-}$ mice), such self-grooming can induce skin lesions and may parallel trichotillomania[23]. Moreover, acquired excessive coping strategies such as excessive polydipsia (hyperdipsia) induced by the intermittent presentation of small amounts of food — schedule-induced polydipsia [G] (SIP)[24,25] — in hungry rodents result in caloric waste (calories are used to bring ingested water to body temperature only to be immediately excreted by animals already in a state of caloric deficit). Similarly, psychogenic polydipsia — an uncontrollable urge to drink fluids in the absence of physiological thirst cues — can lead to hyponatremia (low plasma sodium and water intoxication) and both are relatively often observed in human mental health and neurodevelopmental disorders[26].

Substance use disorders most often result from compulsive drug-seeking and/or drug-taking behaviour (for example, drug foraging and self-administration despite adverse consequences[4] or following a state of urgency[13,27]). In rodents this is quantified as persistence of consuming — drinking — a drug (such as alcohol) despite adulteration by quinine[28,29] or as working for the opportunity to self-administer a drug (alcohol or cocaine) despite punishment by electric foot-shock[30-34]. Such preparatory (seeking) and consummatory (taking) behaviours are psychologically and neurally dissociable[33,35]. An important distinction in general can be made between compulsive consummatory behaviour, which terminates motivational sequences, and compulsive instrumental responding to acquire a goal (preparatory behaviour such as lever-pressing for a food reward); when compulsive instrumental responding becomes unduly perseverative, this may even prevent access to its actual goal. For example, if responding becomes 'hung up' by repetition on an initial element (such as lever pressing) of a behavioural chain or sequence, its actual goal will never be attained[36]. Thus, many laboratory paradigms possibly relevant to compulsive behaviour (Fig. 1) depend on measuring perseverative properties of instrumental responding following goal-devaluation [G], or when reinforcement contingencies have changed (as occurs in extinction (reward omission), contingency degradation [G] and reversal learning (overcoming a particular learned tendency in order to perform the alternative, previously inappropriate response)).

Given this diversity of compulsive behaviours, it remains hypothetical as to whether there is a common underlying neural basis of compulsion irrespective of its behavioural manifestations or whether the compulsive quality of different behaviours arises from distinct mechanisms. Notwithstanding, present clinical diagnostic categories have been criticised for being fundamentally artificial and should not blind us to possible cross-diagnostic commonalities of phenomenology or mechanism.

[H2] Neuropsychological mechanisms and theories of compulsive behaviour

The two dominant theories of compulsive behaviour revolve around concepts of positive and negative reinforcement learning based on Thorndike's Law of Effect, which accounts for repetition of instrumental behaviour in terms of outcome feedback (positive reinforcement reproduces the rewarding outcome; negative reinforcement reproduces avoidance of the aversive outcome)[37]. If the positive reinforcement system is strongly engaged during training, then the trained behaviour can become so strong that it persists even when apparently disadvantageous, becoming perseverative and interfering with other goal-directed behaviours. Olds and Milner's discovery of intracranial self-stimulation in rats to the exclusion of other top priority goals (such as feeding and mothering pups)[38] first demonstrated persistent responding under positive reinforcement, recently emulated using response-contingent optogenetic [G] control of mesolimbic dopamine release in mice[39,40]. Thus, although foraging for drugs by individuals with SUD may even appear quite flexible in some cases, this drug-seeking behaviour, which is initiated relatively inflexibly, may be occurring in the context of a general narrowing of goal-selection, hence becoming perseverative. Such artificial activation of positive affective motivational systems (Fig. 2) may result in the pathological recruitment of 'wanting' urges perpetuated by an illusion of an impending reward[41] (which may have aberrantly high value). Moreover, this persistent 'wanting' behaviour may also be elicited by the response-contingent presentation of stimuli — conditioned reinforcers [G] — that formerly predicted reward through pavlovian association[42]. Money is an example of a conditioned reinforcer in real life, but such stimuli can also include incidental cues (such as needles used for intra-venous drug infusions) that become associated with the primary reinforcer (the drug of abuse).

Goal-directed instrumental responding — or action-outcome learning — often develops habitual qualities, by which instrumental responses are directly elicited by specific exteroceptive or interoceptive stimuli — stimulus-response associations — including the environmental context itself (Fig. 2a). Habits [G] are autonomous of goals, hence 'value-free' so habitual behaviour is less flexible than goal-directed behaviour [G][43]. Thus, instrumental habits, which develop under both positive and negative reinforcement[44,45], might contribute to the automatic quality of compulsive behaviour[46]. The neural systems mediating goal-directed behaviours and habits (Fig.2a), which implicate different fronto-striatal circuitries in the brain (Fig.2b), are generally co-ordinated in the overall expression of behaviour. This results in the need for efficient arbitration or control, especially when there is competition between the systems (Fig. 2a) which can result in intermediate pathological states[47]. There is also an element of hierarchical control over behavioural habits. For example, visual reversal learning impairments in experimental animals or humans are not necessarily due to perseveration in simple motor habits, but rather to persistent responding to a visual stimulus formerly predicting reward (see[48,49]); thus such impairments may be described as 'cognitive habits', perhaps analogous to obsessions. Excessive and perseverative responding in the absence of the primary reinforcer, which profoundly contributes to relapse — for instance an aberrant bout of drug-seeking behaviour following abstinence in animals with a prolonged history of cue-controlled cocaine seeking — may also result from the development of an incentive habit [G][50,51]. Such incentive habits, developing under control of conditioned reinforcers, can become self-reinforcing[51-53] and inflexible[36]. Hypothetically, some incentive motivational value of the conditioned reinforcer permeates the stimulus-response association such that the response itself may come to be imbued with motivational value. Proprioceptive or kinaesthetic feedback acting as conditioned reinforcers may also contribute to the self-reinforcing nature of incentive habits.

Some theories of OCD and addiction propose the goal-directed and habit systems are imbalanced in favour of the latter in the brain[54-56], which may be exacerbated by stress[57,58]. This imbalance can be conceptualised in neurocomputational terms of so-called 'model-based' and 'model-free' systems[59,60]; the model-based system provides an overall mental representation of the action-outcome contingencies that enable goal-directed planning and strategies whereas the model-free system operates on habit-based, simple reinforcement learning algorithms based on the Law of Effect principle. Using this theoretical scheme, Voon et al.[61] showed that individuals with OCD, stimulant drug use disorder (SDUD; the continued use of stimulants such as cocaine or amphetamine despite harm to user) and binge eating disorder all exhibited a bias to respond in a model-free manner, consistent with experimental evidence for OCD using other tests of goal-directed behaviour, including outcome-devaluation and contingency degradation[55].

An additional factor of dysfunctional top-down, executive control over behaviour stemming for example from impairments in frontal lobe circuitry, including fronto-parietal networks [G] and cingulo-opercular networks [G][62] is postulated to dysregulate the habit system and cause maladaptive repetition of habits, even in the face of negative consequences (Fig. 2a)[63]. Such deficits in executive function [G] could arise from genetic or developmental factors, or from environmental trauma like the neurotoxic effects of drugs of abuse such as cocaine and amphetamine[47]. For instance, in one addiction hypothesis, drug abuse chronicity leads to the development of compulsive drug seeking as a consequence of the progressive engagement of a dopamine-dependent dorsolateral striatal habit system coupled with the loss of top-down executive control from the frontal cortex[54], that results in an inability to relinquish the drug seeking habit when it leads to negative consequences[33].

Executive control (including what is sometimes called cognitive control [G]) comprises mechanisms such as inhibitory control, cognitive flexibility and working memory, and dysfunction in each mechanism may contribute to compulsive behaviour[64]. Inhibitory control mechanisms that constrain habitual responses which may develop in parallel to goal-directed responses, can be downgraded by fatigue or stress, including the need to respond quickly[65]. Such response scenarios are conducive to the emergence of negative urgency [G] mediated by fronto-insulo-striatal mechanisms[66-68] that lead to rapid decisions. An inflexible inhibitory control system could lead to inefficient arbitration between the goal-directed and habit systems in their dual control over behaviour, even though both systems themselves may be functioning normally (Fig. 2a)[69,70]. Recent evidence from individuals with OCD suggests that their ability to inhibit shifting to a model-free system of responding is impaired under conditions of uncertainty for implementing model-based strategies[71,72]. Moreover, impairments in behavioural monitoring, via motor working memory or corollary discharge-mediated feedback integration by the cerebellum could also lead to repetitive tendencies[73]. Indeed, individuals with OCD experience enhanced error-related negativity and larger prediction errors during learning (which may also include sensory prediction errors), leading to repetition of behaviour until ‘just right’[55]. Such uncertainty is a major factor leading to compulsive behaviour in OCD, with familiar environments affording the availability of everyday habits, such as checking or washing[73,74].

The engagement of the negative reinforcement system is another major potential underpinning mechanism of compulsive behaviour (Fig. 2a). Aversive outcomes or internal states are only partly avoided or mitigated by instrumental avoidance or escape 'coping' responses; the resultant persistence of the stressful state causes compulsive responding. This type of theory can be applied to the transient reduction of anxiety resulting from intrusive thoughts by compulsive rituals in individuals with OCD[4] and the regulation of the stress hormone corticosterone by SIP in rodents[24,75]. Avoidance (including coping) behaviour often becomes habitual in nature[45,56] and hence compulsions can again develop from what was initially goal-directed, instrumental responding. This is relevant to OCD which often begins in adolescence or earlier, as well as SUD: the mechanisms responsible for the initial acquisition of the behaviour that will subsequently become compulsive may be distinct from those mediating the consolidation and persistence of the compulsion[45,52,76].

These psychological theories prompt questions about the underlying circuitry of compulsive behaviour such as whether there is a general neural circuit implicated in different expressions of this behaviour, or whether the various factors implicate different circuits in compulsive responding, and also in its development and subjective manifestations. This issue can be investigated more directly by studies of the brain in relation to compulsive behaviour.

[H1] Neural basis of compulsivity and compulsion

[H2] Human neuroimaging studies of functional networks

[H3] Orbitofrontal-striatal interaction. An early clue towards the neural basis of compulsive behaviour came from observations of apparent increased glucose metabolic activity in the orbitofrontal cortex (OFC) and head of the caudate nucleus, as measured using positron emission tomography [G] (PET) in individuals with OCD[77]. This heightened activity was subsequently mitigated following successful intervention with cognitive-behavioural therapy [G] or administration of selective serotonin reuptake inhibitors [G] (SSRI)[78,79]. These observations formed the basis of the original fronto-striatal hypothesis[80] which ultimately ascribed OCD symptoms to alterations in cortico-striatal loop pathways, through increased activity of the striatal striosomal [G] system, relative to direct and indirect striatal matrix output pathways (but see 'Circuit and neurochemical basis of compulsive behaviours in animal models'). Early studies of symptom provocation [G] using functional magnetic resonance imaging (fMRI)[81] and resting state functional connectivity [G] (rs-fc) confirmed a special role for the OFC in compulsive behaviour. One study showed that local connectivity of the OFC

related to symptom severity in OCD, consistent with the PET findings[82]. A second study identified two major areas of cortical dysconnectivity within the OFC in both OCD and SDUD, particularly in the right medial OFC (mOFC) (Brodmann areas [G] (BA) 10 and 11)[83]. The overlap in dysconnectivity — for example with dorsomedial prefrontal cortex (PFC) — between these two distinct clinical disorders was striking. More striking still was that the dysconnectivity correlated with clinical measures of obsessive-compulsive and addiction symptoms as assessed by the Yale-Brown obsessive-compulsive scale (YBOCS) and obsessive compulsive drug use scale (OCDUS), respectively (Fig. 3; Box 1), suggesting the existence of a common neurobehavioural construct of compulsion. Considering the pivotal role of the OFC, including adjacent structures in the ventromedial PFC (vmPFC), in regulating goal-directed behaviour[84], this also suggests that compulsive behaviour stems from a deficit in the goal-directed system. The finding of reduced connectivity in the vmPFC associated with the OCDUS score in SDUD also converges with similar negative correlations with grey matter volume [G] (GMV)[85].

Although structural and functional neuroimaging measures can thus yield comparable results there are often problems in defining precise mechanisms arising from human neuroimaging studies. Neither metabolic activity (PET) nor rs-fc derived from fMRI BOLD signals is directly related to neuronal activity, and other measures from different neuroimaging modalities, such as structural indices of grey and white matter and neurochemical indices from magnetic resonance spectroscopy (MRS), may provide different mechanistic perspectives.

Reductions in structural measures, such as grey matter in the OFC and vmPFC assessed with voxel-based morphometry [G]) in OCD[86,87] may be accompanied by enhanced activity of the same structure[88], and the ultimate functional interpretation hinges on how this interplay manifests behaviourally, including the possibility of functional compensation (for example, see de Vries et al.[89]). Moreover, the vmPFC and OFC are complex regions comprising several Brodmann areas, each likely serving distinct functions. Findings from functional neuroimaging studies (as well as evidence from experimental animals) suggest anatomical specificity and even opponent processing within OFC medial and lateral (BA 12,47) regions[90-92]. This medial-lateral distinction also extends to correlations with the symptom severity in OCD, with mOFC hyperconnectivity being positively associated with symptom severity, whereas lateral OFC (lOFC) connectivity exhibits the opposite effect[93].

The primate OFC also has distributed topographic projections to the ventral striatum [G] — including the nucleus accumbens (NAc), ventral caudate and ventral putamen — in addition to the dorsal striatum [G], including more central regions of the caudate and putamen[94]. These dorsal and ventral striatal circuitries can also apparently be differentially affected in OCD[95]. Several rs-fc studies found enhanced connectivity between the mOFC (BA10) or anterior cingulate cortex (ACC; BA 24 and 32) and different components of the ventral striatum including the nucleus accumbens, ventral caudate and ventral putamen[93,95-98], sometimes related to severity of symptoms measured by the YBOCS (Fig 3). Note also, however, examples of where hyperconnectivity of the dorsal putamen is correlated with YBOCS scores[82] (Fig 3). The ventral striatal connectivity is potentially related to impaired reward processing caused by maladaptive narrowing of goal-selection[99] (Fig. 3**)**. A focused hyperconnectivity of the nucleus accumbens sometimes occurs with the ACC even when it exhibits global hypoconnectivity with other brain regions, including the PFC, in individuals with OCD, also suggesting restricted top-down influence[95].

There is also evidence of a more general disruption of the goal-directed behaviour system in OCD from a recent multi-modal neuroimaging study combining structural, diffusion tensor and resting state fMRI imaging, which showed reduced structural and functional connectivity in a 'goal-directed' network (comprising the caudate and several PFC and ACC regions), with structural connectivity correlating significantly with compulsion[100]. Intriguingly, changes in connectivity in a 'habit subnetwork' (comprising putamen, insula and regions of motor cortex) correlated with obsessions[100]. A comparable investigation in individuals with SDUD and their unaffected siblings also showed hypoconnectivity between various frontal regions (OFC, mPFC and ACC) and the ventromedial caudate[101]. The apparent differences between these rs-fc findings and those described above, which sometimes indicated increased rs-fc connectivity in the caudate, may reflect different neurobehavioural mechanisms underlying compulsive behaviour.

Furthermore, a developmental study using magnetisation transfer methods indicated that young persons with high compulsive traits as measured by OCI and the Padua scale, express slower maturational myelin-related changes in a fronto-striatal network comprising the ACC and the ventral striatum[102]. Such structural changes possibly underlie the abnormal functional hyperconnectivity between the left hemispheric nucleus accumbens and a cluster of premotor cortex and right middle frontal gyrus activity observed in both children with OCD and children with ASD, which positively correlated with measures of their repetitive behaviour[103].

[H3] Lateral frontal-parietal-striatal interaction. Although OCD symptoms measured by the YBOCS sometimes correlate with heightened connectivity of the caudate and putamen[95,97,], (being consistent with enhanced caudale or putamen GMV[104,105]) some studies have shown reduced rs-fc between distinct lateral PFC projections to the dorsal striatum, relevant to executive control and goal-directed behaviour[98,106]. For example, hypoconnectivity between ventrolateral PFC (vlPFC) and the caudate related to impairments in cognitive flexibility (Fig.3) whereas hypoconnectivity between the dorsolateral PFC (dlPFC) and the putamen linked to deficits in goal-directed planning[107].

Moreover, these findings relating OCD symptoms to rs-fc measures are consistent with relevant established task-related fMRI paradigms and the neuropsychology of OCD[108]. Substantial evidence in OCD (and in other compulsive disorders such as SUD[101,109,110]) of impaired executive control exists, including examples of deficits in cognitive flexibility and inhibitory response control linked to impaired functioning of lateral fronto-parietal networks. First, activity in the lOFC (BA 12 and 47) and the parietal cortex is reduced during tasks involving reversal learning (in both individuals with OCD and their first-degree relatives)[111]. Second, dlPFC and dorsal caudate are hypoactivated during tasks involving goal-directed planning[112] and task-set switching[113]. Last, inferior PFC (iPFC) and parietal activity is reduced during tasks involving stop-signal inhibition[114]. Together, these examples point to reduced lateral PFC and lOFC influence over the dorsal striatum, in concranialt to the possible enhanced mOFC and vmPFC control over the ventral striatum previously discussed (see 'Orbitofrontal-striatal interaction'). A recent study with a large sample of adolecents found that higher levels of compulsivity were linked to a less pronounced developmental change in the overall connectivity between striatum and fronto-parietal regions, including dlPFC[115].

Within the general domain of executive control, recent emphasis has been placed on the investigation of the arbitration mechanism governing optimal selection of the goal-directed or habit system (Fig. 2a)[69-71,116]. There is emerging consensus that impaired connectivity between arbitrator regions such as the iPFC and vlPFC with areas of the habit system such as the putamen and supplementary motor area (SMA) underlies the shift from model-based to model-free behaviour (and the bias towards habit) observed in individuals with OCD. This may account for the lack of firm evidence of dysfunction within the habit system per se in some studies (see[100] for an example). A recent neurostimulation study targeting the vlPFC has confirmed the pivotal role of this arbitrator region in the dynamic coordination of the goal-directed and habit systems[117]

[H3] ACC, vmPFC and insula-striatal interaction. Several fMRI tasks are also associated with hyperactivation of the vmPFC, dorsomedial PFC, ACC and the insula — the portion of the cerebral cortex implicated in sensing and representing interoceptive inputs, that give rise to bodily feelings; divided into anterior and posterior regions; the former having cognitive-behavioural functions — in individuals with OCD[108,114,118-122]. These include threat or avoidance conditioning and conflict monitoring tasks in addition to other functional paradigms able to detect negative prediction errors. However, we note that some inhibitory tasks may show reduced activation in ACC[105]. An elegant study using an avoidance paradigm which initially trained individuals with OCD to respond to avoid an aversive electric shock but then removed the threat of the latter, thus rendering the avoidance behaviour redundant, revealed that habitual avoidance behaviour is linked to an elevated BOLD response in the caudate nucleus,

along with a tendency towards experiencing subjective urges to respond[118]. Such habitual responding involving caudate hyperactivity was shown to be reciprocally modulated by enhanced sub-genual ACC and diminished right hemispheric iPFC activation. The potential relevance of these findings to compulsive responding has been substantiated directly by symptom provocation fMRI studies, which typically indicate heightened activation of the ACC and vmPFC during compulsions related to washing, checking and hoarding[123]. Banca et al.[124] demonstrated, in a sample of individuals with OCD, that their urge to engage in an avoidance or escape response in reaction to provocative stimuli led to a reduction in vmPFC hyperactivity, whilst also increasing putamen and insula activation, perhaps reflecting the interoception-bound habitual nature of the avoidance response.

A role for the insula in compulsive disorders has recently been highlighted by a large meta-analysis of fMRI studies in OCD, SUD and internet gaming disorder[125]. Despite notable differences among these three compulsive syndromes, OCD and SUD shared dysregulation in the anterior insula (AI), consistent with other evidence based on reduced GMV[126]. As a consequence of reduced GMV in the AI, Conti et al.[127] implicated an associated insensitivity to punishment as a contributor to compulsive nicotine abuse. Further studies have revealed that urges in SUD, subjectively experienced as craving, are associated with[128] and dependent on[129] the insula, whereas others have proposed that compulsive behaviours relate to enhanced insula and putamen coupling[105,124,130,131]. Thus, the insula's functional importance may lay in the mediation of negative interoceptive states to subjective urges and to action (Fig. 2a,b), common in compulsive behaviour[132].

[H3] Putamen-sensorimotor cortex interaction. A large recent meta-analysis of OCD rs-fc studies failed to reveal definitive evidence of fronto-striatal changes described above, perhaps because of patient heterogeneity[133]. Instead, it highlighted evidence in OCD of possible relevant changes in structures implicated in motor behaviour outside the fronto-striatal circuitry, including the parietal cortex, thalamus and cerebellum (see also[88,95,105,106,134]). However, that meta-analysis did point towards hypoconnectivity within a cortical sensorimotor network (partly confirmed by Yang et al.[88]), which the authors related to the cortico-striatal habit system and repetitive behaviour. Putamen GMV has been positively related to a (sub-clinical) compulsivity trait[135] and to 'OCD-like repetitive behaviour' in ASD[136] (Fig 3) but any underlying relationship with habits has not been determined. A multi-modality study of binge eating and bulimia nervosa revealed alterations in putamen connectivity with SMA (and other PFC and ACC regions) in sensorimotor networks, which correlated with stimulus-bound compulsive overeating in individuals with eating disorders, which the authors interpreted in terms of involvement of the habit system[137] (Fig. 2 and Fig. 3).

Two additional recent studies have delved into the relative bias toward habitual tendencies using 7-Tesla MRS to measure glutamate function in the habit system. Ersche et al.[138] found that individuals with SDUD exhibit enhanced habitual behaviour, as assessed both by a questionnaire and a laboratory paradigm of contingency degradation. They linked this automatic habitual tendency to compulsivity scores — from obsessive-compulsive inventory (OCI) self-report questionnaires — and reduced glutamate turnover in the putamen, suggesting that participants' compulsivity is linked to a dysregulation of habitual control caused by their chronic cocaine use. Another study[139] found that glutamate levels in the SMA positively correlated not only with YBOCS scores in individuals with OCD (Fig. 3), but also to OCI scores and a contingency degradation index of habit in both these atypical participants and typical controls. Moreover, this habit index score also correlated with a glutamate to gamma-amino-butyric acid (GABA) ratio score in the ACC in individuals with OCD (consistent with evidence in non-human primates specifically implicating BA 24[140]). Together, these studies are consistent with a role for putamen-sensorimotor cortex (and ACC) circuitry in an habitual component of compulsive behaviour[139].

In summary, from the analysis in this section it is apparent that although the general circuitry for compulsivity is emerging from human studies (Fig. 2b), further advances providing mechanistic detail will probably depend on basic neuroscience research with experimental animals. Thus, cross-species comparison is crucial because it allows for more precise manipulations and measurements, particularly in rodents and non-human primates, although with homological constraints on interpretation in terms of cortical regions, and with the added requirement of suitable translational behavioural paradigms (Fig. 1).

[H1] Circuit and neurochemical basis of compulsive behaviours in animal models

Several animal models capitalise on innate behaviours supposedly capturing a dimension of compulsion. Examples include barbering (the repetitive plucking of fur or whiskers from themselves or cage mates by group housed mice)[141] and seemingly aberrant innate body-focused behaviours like compulsive self-grooming manifested by several murine genetic knock out models, including *Spred2*$^{-/-}$, *Hoxb8*$^{-/-}$ and SAPAP3$^{-/-}$ mice[142-144]. SAPAP3 is involved in the organisation of post-synaptic scaffolding at excitatory glutamatergic synapses, and is highly expressed in the striatum[142]. Thus, SAPAP3$^{-/-}$ mice display alterations of cortico-striatal, (but not thalamo-striatal) glutamatergic synapses[142,145], accompanied by a strengthening of the input from the rodent secondary motor area (M2) (the functional equivalent of the SMA in humans) onto dl striatal fast spiking interneurons[146] (Fig. 4). They also exhibit abnormal lOFC activity[147] associated with persistent grooming (standard clinical treatments for OCD, SSRI medication[148] or deep brain stimulation (DBS) of the internal capsule[149], reduce grooming). In addition, they exhibit alterations in GABAergic interneuron control of a lOFC circuit that drives dorsal striatal dopamine D1 receptor expressing medium spiny neurons (MSN; a particular class of projecting striatal GABAergic neurons)[150]. This circuitry underlies impaired cognitive flexibility in reversal learning in SAPAP3$^{-/-}$ mice[150], which is also restored by SSRI treatment[148]. These findings, although not entirely in line with the striosomal dysfunction hypothesis[80] (see also[151]) have substantial cross-species relevance, given the extensive evidence that reversal learning depends on intact serotonin functioning in the lOFC of both rats[48] and non-human primates[49]. Reversal learning is impaired in both OCD[152] and SDUD[47,109], in the former case being ameliorated by SSRI medication[168].

Optogenetic activation of lOFC, which enhances feedforward inhibition in dorsal striatal circuitry, profoundly decreased compulsive grooming in SAPAP3$^{-/-}$ mice[153]. Conversely, chronic photostimulation of mOFC inputs into the ventral striatum induced excessive grooming in wild-type mice[154]. These results, combined with evidence that SAPAP3$^{-/-}$ mice develop habits faster than wild-type animals[155], suggest an alteration in two OFC-striatal circuits involved in goal-directed behaviours (vmOFC-ventral striatum pathway) and inhibitory control (lOFC-dorsal striatum pathway) in SAPAP3$^{-/-}$ mice: which thus contribute to distinct facets of compulsive behaviour, analogous to the situation in humans (Fig. 4).

Recent analysis of the repetitive motor twitches of SAPAP3$^{-/-}$ mice has suggested that it may be better conceptualised as a mouse model of repetitive, uncontrolled movements and, perhaps, trichotillomania or Tourette's Syndrome, than of OCD[155] (especially as it is unclear to what extent excessive grooming represents a coping response). By contrast, when rodents are exposed to the anxiogenic[156] and stress-inducing effects of the SIP procedure[24,75] they often engage in copious drinking that is initially anxiolytic[45] and decreases hypothalamic-pituitary axis activation[24], consistent with an instrumental negative reinforcement account[45]. Moreover, individual differences in the development of hyperdipsia in rodents[45,157] are predicted by high impulsivity trait[156], and associated with impaired behavioural flexibility[158]. The acquisition of this excessive coping response depends upon the ventral striatal dopamine system[159] and the AI[156], and its further development into a compulsive behaviour on the recruitment of noradrenergic mechanisms[75,160]. The excessive manifestation of polydipsia (or hyperdipsia) associated with compulsive coping is ultimately mediated by the dopamine-dependent dorsolateral striatal (dl-striatal) habit system[45], and is also associated with increased volumes of the amygdala, mPFC[161] and lOFC[162]. These neuroanatomical changes, which resemble those associated with the phenotype of SAPAP3$^{-/-}$ mice, are accompanied by alterations in serotoninergic activity in both the amygdala[163] and the prelimbic cortex (PLc)[164] and also with impaired PLc glutamatergic output[164]. The PLc is the part of the rodent mPFC considered to be (the homologue [G] of BA 32 in primates, and is implicated in rodents in goal-directed behaviour[84].

Some analogous patterns of neural system involvement exist in rodent models of compulsive eating disorders, whether of anorexia nervosa or binge eating[165,166]. For example, in the activity-based-anorexia model[167], rats choose apparently compulsive wheel-running exercise over homeostatic energy balance. Chemogenetic inhibition of mPFC-NAc shell activity reversed the consequent pathological weight loss, whereas chemogenetic activation of that circuit exacerbated it[168]. With respect to compulsive eating, rats working for palatable high-fat food exhibited a significant correlation of binge intake with instrumental responding for a food-paired visual-auditory-olfactory cue acting as a conditioned reinforcer[169]. Chemogenetic activation of the AI reduced both binge eating and this exteroceptive cue reactivity[169]. Last, rats with a history of binge-like exposure to highly palatable food exhibited habitual tendencies during a goal devaluation test, consistent with increased c-fos (a protein indicator of neural activity) in the dl-striatal and associated cortical regions[170] (but see also ref.[171]).

For OCD, rodent models of symptoms other than hyperdipsia and compulsive grooming (presumably relating to compulsive coping and compulsive washing, respectively) have been developed. One OCD model in rats derives from a decision-making paradigm where dopamine D2 receptor agonism or sign-tracking tendencies[172], the proclivity to approach pavlovian cues associated with altered nucleus accumbens D2 receptor activity, may elicit excessive checking behaviour[173]. Such behaviour is exacerbated by excitotoxic lesions [G] of m-PFC or NAc[174]. Another rat model[175], based on negative reinforcement, measures the persistent instrumental avoidance of cues incorrectly associated with negative outcomes (possibly reflecting persistent habitual behaviour)[118]. Pathways from the AI or lOFC to the rostral PLc were causally associated with extinction of such persistent behaviour, presumably reinstating effective goal-directed responding[175]. In general, a systematic comparison of the neural substrates of these promising models of compulsive eating and OCD would be desirable to parallel comparisons to the respective human disorders.

Preclinical models of compulsive drug seeking or taking[175-183] also reveal neural circuitries underpinning SUD (Fig. 4) including serotoninergic modulation[184]; and drug seeking models often depend critically on drug-associated conditioned reinforcers[32,34,51,52,185,186]. Both alcohol drinking during SIP (as a coping mechanism) or compulsive alcohol seeking (measured as persistence of alcohol seeking despite electric foot-shock[34]) are associated with devolution of behavioural control to the dopamine-dependent dl-striatal habit system[33,34,187], and underpinned by an inability to disengage this system under punishment[33]. This inflexibility of habitual alcohol seeking may be driven by alterations in GABAergic mechanisms in the central nucleus of the amygdala[188] and alterations of vmPFC projections to dopamine D1 receptor expressing MSNs in the NAc[189]. Long term histories of stimulant or opioid seeking also tend to recruit dl-striatal circuitry[185,186,190,191], consistent with compulsive drug use being associated with habitual tendencies[192].

Compulsive, punishment resistant cocaine seeking in rats is also associated with neuronal hypoactivity in the PLc[177] (Fig. 4). Such behaviour is normalised by optogenetic activation of PLc, possibly reflecting restoration of the balance between goal-directed and habit systems modulated by the reciprocal arbitrating influences of PLc and infralimbic cortex (ILc; the part of the mPFC below the PLc; implicated in rodents in arbitrating between goal-directed and habitual behaviour and may be the homologue of BA 25 in primates)[193,194]. An MRI study of rats taking methamphetamine under punishment has also shown underactivity of PLc projections connecting with the ventrolateral striatum[195]; in contrast to an active mOFC to dorsomedial striatal (DMS) circuitry[176], and somewhat aligning with findings observed in human methamphetamine abusers[176,196]. A recent prospective longitudinal study in rats demonstrated an association between the vulnerability to develop compulsive cocaine-seeking habits in drug naïve rats and reduced functional connectivity of the PLc-posterior DMS and ACC-posterior DMS circuits (normally associated with goal-directed behaviour) that correlated with an index of value-free repetitive instrumental responding (which may reflect habitual tendencies), suggesting that such imbalances in cortico-striatal networks actually predate drug exposure[32]. The same study also showed structural alterations in insula to ventral striatal circuitry associated with impulsive responding, previously shown to predict compulsive forms of SIP, eating[21] and cocaine self-administration[197]. Together, with the evidence for its role in the development and maintenance of hyperdipsia, binge eating, and compulsive drug self-administration, these data suggest that the insula is pivotal in driving transitions towards several forms of compulsive behaviour in animals[156,181,183,198,199] through its interactions with the OFC, PLc and ventral striatum (Fig. 4). This prompts the question of how the insula's role actually affects behavior. Human cognitive neuroscience suggests that AI contributes to the urge for action[132], which may explain how the interoceptive cues of negative urgency, resulting from the thwarting of an incentive cocaine-seeking habit, trigger substantial levels of relapse in rats[51].

[H1] Conclusion: Towards a multi-faceted neural circuit theory of compulsivity

Overall, these human neuroimaging and animal model findings offer new prospects for a generalised neural circuit account of compulsive behaviour. In this Review, we discussed what are essentially four major neurobehavioural elements of a new theory (involving the six neural systems described in Fig. 3), that attempts to account for both subjective and behavioural aspects of compulsion, and which we outline below.

First, evidence indicates both enhanced and reduced connectivity between structures implicated in a broadly conceived cortico-striatal goal-directed system that includes both positive and negative affective systems (Fig. 2), with changes in either affective system (i.e approach and avoidance) potentially producing compulsions. Specific mOFC or vmPFC circuits may exhibit increased activity and connectivity with their projection targets in the ventral striatum and caudate, potentially mediating excessive goal-directed (or model-based) behaviour, coupled however, with a maladaptive narrowing of goal options[99] (Fig. 5a). The fact that compulsions may occur in conjunction with either increases or decreases in functional connectivity linking the different components of the positive or negative affective system that contribute to goal-directed behaviour, is suggestive of dysfunctional nodes in fronto-striatal loop circuitry that either drive exaggerated goal-directed behaviour or impair it (ultimately by disrupting connectivity). Loss of connectivity in the goal-directed system may result, by default, in the expression of dyscontrolled habits (which can also be aberrantly strengthened within the habit system itself) resulting in compulsive behaviour. Goal narrowing could thus be a precursor to a general loss of goal-directed behaviour, as subsequently reduced cortico-striatal activity in this goal-directed (or model-based) system may lead to an imbalance in favour of activity in a habit (or model-free) system that includes the putamen and its cortical sensorimotor influences (Fig. 5b). Furthermore, apparently enhanced local functional connectivity within the mOFC, vmPFC or basal ganglia regions can be correlated with measures of compulsivity[82,200]. By contrast with between-region functional connectivity, enhanced local connectivity in such regions as the mOFC and putamen, could possibly reflect excessive attractor network [G] activity[201], which could conceivably reflect exaggerated goal representations or autonomous action sequences which characterise compulsions. The tendency to form such attractor networks may reflect trait compulsivity. Second, top-down executive control or specific arbitration influences of lateral fronto-parietal networks (especially under uncertain or stressful circumstances) that normally optimise goal-directed behaviour and regulate habits are generally lost. Third, insula networks hypothetically provide interoceptive triggers for habits that have developed from negative reinforcement mechanisms. Last, the ACC and sensorimotor cortical regions monitor whether actions match their intended motor targets via prediction errors (which may also involve the cerebellum).

This proposal of neurobehavioural systems that underlie compulsivity poses critical questions for how the systems may interact dynamically over time to produce compulsive behaviour. The transition from goal-directed actions to habits (Fig. 2 and Fig. 5) represent critical dimensions of the staging and time-course of a compulsive disorder. On the basis of both cross-sectional and longitudinal studies some theories have proposed that changes may not only occur in relation to predisposing endophenotypes, but also during the course of a compulsive disorder. Chronic effects of stimulant self-administration affecting cortical control circuitry over the striatum are one example of the latter[202,203]. Evidence of shifts from ventral to dorsal striatal control[63] mediated in rats by the amygdala[204] and via cascading loop circuitry that connects these striatal domains via recurrent connections with dopaminergic neurons in the ventral tegmental area and the substantia nigra pars compacta are another[186,205]. Little investigation of longitudinal changes in human neuroimaging has tested this notion, although a recent study of ventral to dorsal striatal shifts in alcohol use disorder[206] and internet gambling disorder[207] demonstrate important future research initiatives. Comparative life course studies of OCD indicate that several of the neuroimaging changes observed in adults are present in adolescents[105], although it is notable that increases in putamen volume appear to occur as a function of age, against other trends for decline, suggesting that the compulsive behaviour is self-reinforcing. In addition, compulsive behaviour may be exacerbated by additional stressors experienced throughout one's life, including lived experience with the mental disorder itself. Different forms of compulsive behaviour could also emerge from pathophysiological changes within any of these four neurobehavioural systems, which in combination would lead to severe compulsive symptoms (Fig. 5). The precise qualitative presentation of compulsive behaviour, for example as SUD or OCD, probably depends in part on prior life events or dispositions, as well as genetic factors; investigating the genetic basis of compulsivity is only just beginning[208].

This multi-faceted account also predicts that several future treatments for severe compulsive symptoms will be required for remediation. These interventions may include cognitive-behavioural therapy and mindfulness[209,210], each targeting a different aspect of emotion regulation and inhibitory control. In addition, they might involve the use of pharmacological agents aimed at modulating monoamines or the glutamate to GABA balance [G]. Moreover, neuromodulatory techniques, such as DBS[211,212] or repetitive transcranial magnetic stimulation [G] (rTMS)[213-216], may be employed to target specific neural circuits. Demonstrating therapeutic effects of such interventions on specific circuits would help to further the evidence of the causal involvement of such neural systems in compulsions that is emerging from preclinical research[149,217]. The singular success of surgical dorsal anterior cingulotomy or anterior capsulotomy — procedures that disrupt bidirectional signalling between the ACC, OFC and the striatum — in the treatment of severe treatment-refractory OCD is certainly consistent with our account[218]. Neuromodulation by either DBS or rTMS also has evident promise in this regard as notable therapeutic benefits have been observed for OCD targeting structures such as the ACC, SMA, OFC, and basal ganglia. For example, a recent study demonstrated equivalent therapeutic benefits, albeit with an impact on different symptoms of OCD, by targeting the mOFC and ACC or the vlPFC as two distinct sites for DBS[219]. Based on connectomics analysis, it is possible that such distinct effects are integrated in a unified circuitry to achieve therapeutic success[220,221].

rTMS targeting lPFC, vmPFC or, most recently, frontopolar cortex is being deployed with some success to improve executive control and reduce compulsive cocaine seeking in stimulant use disorder[215,216]. Pharmacological MRI, MRS or PET will be necessary to determine how existing and novel drug treatments (such as psychedelics) interact with these proposed neural networks to produce their clinical effects; again there are some promising clues concerning loci of action of SSRIs[222] and ketamine[223] for OCD. However, there is still much scope for translating how possible serotoninergic, dopaminergic and noradrenergic mechanisms revealed in preclinical studies contribute to compulsive behaviour in humans[33,45,51,75,184,224,225]. A possible future development to achieve modulation of specific circuits may involve a combined neurosurgical-pharmacological strategy in the form of chemogenetics [G]. This method would enable the eventual definitive testing of the causal role of each hypothesised circuits underlying compulsion, as well as their functional interaction in the development and pathological maintenance of compulsive behaviour.

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Fig. 1 | Behavioural models of perseverative and compulsive behaviour

Several animal models of compulsion have been developed that rely on aberrant manifestations of innate behaviours (such as self-grooming or hoarding) or preparatory (instrumental) (**a-d, f & h**) and consummatory (**e, g & i**) responses that are repetitive, excessive and/or persistent in the face of adverse consequences. **a-b** | A seeking-taking heterogeneous chained reinforcement schedule with punishment investigates the tendency to persist in seeking (**a**) alcohol or (**b**) a drug of abuse (cocaine or heroin) under the threat of punishment. Individuals are trained to respond on a seeking lever under a 60 second variable interval schedule of reinforcement (VI) — under which a response is reinforced after unpredictable intervals, thereby promoting relatively low rates of responding under a relatively weak response-outcome contingency, which facilitates the development of habitual control over behaviour — which provides access to a second, taking lever, a response on which delivers the drug reinforcer intravenously or via drinking from an exposed spout. Compulsive drug seeking is assessed by persistent seeking lever responding when the seeking response results in the presentation of an electric footshock instead of the taking lever on 25% of the trials. **c** | Drug seeking under control of drug-paired cues (conditioned reinforcers) is operationalised under second order schedules of reinforcement (SORs) — which enables the measurement of the influence of the conditioned reinforcing properties of Pavlovian cues on seeking behaviour — that lead to the development of persistent incentive habits under punishment (footshock). Under a typical SOR, the outcome is delivered when an instrumental response on the active lever is produced after a 15 min interval (FI15) has elapsed (either from the start of the session or since receiving the previous outcome) but during this interval every ten lever presses (FR10) result in the contingent presentation of the outcome-paired conditioned stimulus (yellow bulb), thereby acting as a conditioned reinforcer. The compulsive nature of the cue-controlled drug seeking habits that develop after several weeks of training under a SOR (coined compulsive incentive habits) is assessed as the persistence of responding despite contingent presentation of electric footshocks every 16th active lever press (FR16). This procedure uniquely enables the assessment of compulsive drug seeking in a drug-free state. **d** | Impairments in behavioural flexibility are assessed by the tendency to perseverate responding during reversal learning (the ability to overcome a particular learned tendency in order to perform the alternative, previously inappropriate response). **e** | In contrast to drug seeking models (**a-c**), compulsive drug taking is operationalised for stimulant drugs as persistent self-administration (SA) in the face of footshock punishment. In the seminal procedure developed by Belin and colleagues[31,197], rats trained to self-administer cocaine under a fixed ratio 5 schedule of reinforcement (FR5) are challenged on their propensity to persist in self-administering the drug despite contingent presentation of electric footshocks. In this challenge session the first active lever press (ALP) of a sequence of five results in the presentation of a shock-paired cue (green light). Some animals will stop responding then, thereby demonstrating sensitivity to conditioned suppression. If the rat persists in it's behavioural sequence and reaches the fourth lever press, then it receives a footshock. More than 50% of any population of rats would stop responding then. However, compulsive individuals will press another time within a minute. These rats will then receive another footshock followed by an infusion of cocaine alongside the presentation of the cocaine-paired cue (yellow light). **f** | Resistance to extinction (reinforcer omission), for example for food reinforced-behaviour, is another commonly used index of perseveration. **g** | Compulsive alcohol drinking is manifested by persistent drinking of adulterated alcohol (with bitter tasting quinine), an example of resistance to the devaluation of the goal. **h** | Contingency degradation. Persistence in instrumental responding when the contingency between action and outcome is uncoupled, for example by free presentation of the reinforcer (for example, a food pellet), reflecting habitual control. **i** | Schedule-induced polydipsia. Hyperdipsia following the occasional delivery of small quantities of food in food deprived rats, a putative compulsive coping response. FR1, each active lever press or any such instrumental response results in outcome delivery (also called continuous reinforcement); FT, fixed time schedule of outcome delivery in which the outcome is delivered every n seconds (usually 30 or 60) irrespective of the organism's behaviour.

Fig. 2 | Neural systems of compulsive behaviour: insights from cognitive neuroscience

Compulsive behaviour is considered to involve six major neurobehavioural systems, each mediated by a specific neural network. **a-b** | The executive control (fronto-parietal) system (purple)[64,110] comprises the inferior frontal gyrus (IFG; BA 44 and BA 45), dorsolateral prefrontal cortex (dlPFC; BA 9 and BA 46), ventrolateral prefrontal cortex (vlPFC; including BA 47), rostral prefrontal cortex (rostral PFC; encompassing BA 10) and parietal cortex. The positive affective system (blue)[226], comprises the ventral tegmental area (VTA), substantia nigra pars compacta (SNc), nucleus accumbens (NAc), amygdala (Amyg) and ventromedial prefrontal cortex (vmPFC, including the orbitofrontal cortex (OFC)). The anterior insula, amygdala, anterior cingulate cortex (ACC), habenula (not displayed), VTA, SNc, caudate nucleus and vmPFC encompasses the negative affective system (pink)[227]. The interoception system (yellow)[228] comprises the insula and the ACC. The goal-directed (action-outcome, A-O) component (dark green) of the instrumental system[84,229] comprises the vmPFC (including the medial OFC), the ACC (including BA 24 and BA 32) and the caudate nucleus whereas the habit (stimulus-response, S-R) component (orange) comprises the posterior putamen, supplementary motor area (SMA) and premotor andmotor cortices. Action monitoring (light green) is under the control of a system involving the ACC, somatosensory cortex, cerebellum and their interaction with the basal ganglia (not shown). The interoceptive system influences the positive and negative affective systems as well as the instrumental system, while informing the executive control system, which exerts top-down inhibitory control over all the other systems. Both the positive and negative affective systems feed into the instrumental system to promote reward seeking and coping behaviours, respectively, which can be mediated by either actions or habits. The control over behaviour by actions or habits is balanced, or arbitrated by the executive control system. Upon engagement of one or the other of the two branches of the instrumental system, the action performance system ensures appropriate motor performance integrating sensory feedback within ongoing motor programmes. Alterations in any of the functional relationships between these systems, such as, for instance, lack of arbitration over the goal-directed and habit systems, or an imbalance in the influence of interoception on the negative affective and the executive control systems, contribute to compulsion.

Fig. 3 | Human neuroimaging and compulsion

Orbitofrontal-striatal, lateral PFC-dorsal striatal and putamen-motor neural networks directly associated with human compulsive behaviours across various disorders including obsessive compulsive disorder (OCD), stimulant drug use disorder (SDUD), binge eating disorder (BED) and autism spectrum disorder (ASD). Multimodal neuroimaging methodologies including voxel-based morphometry (VBM; pink triangle and central bar plot), resting state functional connectivity (rs fMRI; red and blue triangles), magnetic resonance spectroscopy (MRS; yellow triangle) and positron emission tomography (PET) identified activity in these networks. Hyperconnectivity (solid red) and hypoconnectivity (dashed blue) highlight the apparent opponency of circuits dependent on ventromedial PFC (orbitofrontal-striatal) versus ventrolateral PFC (lateral PFC-dorsal striatal) in individuals with compulsive behaviours. Most of the studies depicted here provide a measure of functional connectivity. However, two studies used other indices of network activity such as glutamate concentration and regional cerebral blood flow (rCBF). All studies presented here identify correlations between brain activity and measures of compulsivity, with the exception of Vaghi et al 2017[107]. DEBQ, Dutch eating behaviour questionnaire; dmPFC, dorsomedial prefrontal cortex; EDS, extra dimensional set shift; mOFC, medial orbitofrontal cortex; NAc, nucleus accumbens; OCDAS,

obsessive compulsive disorder analogue scale; OCDUS, obsessive compulsive drug use scale; OCI, obsessive-compulsive inventory; PC, posterior cingulate cortex; PUT, putamen; SMA, supplementary motor area; TP, typical participants; vlPFC, ventrolateral prefrontal cortex; VS, ventral striatum; YBOCS, Yale-Brown obsessive compulsive scale. *,R value not available. The plots shown are schematic, but based on published findings (counterclockwise from the top left: refs 83,85-87, 77, 96, 93, 82, 107, 139). Sources of data are shown beneath the plots; for the bar chart, data are from (second left to right) refs. 151, 102, 103 and 101. References:
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Fig. 4 | Neural circuits of compulsive behaviour: insights from animal models

a-b | The basic layout of overlapping orbitofrontal-striatal and medial PFC-striatal neural circuits, and sensorimotor cortex-dorsolateral striatal habit and insula-dependent interoceptive systems identified across several animal models of compulsion, including self-grooming, hyperdipsia under schedule-induced polydipsia (SIP), compulsive drug seeking or taking, and their functional or structural alterations. In contrast to basal (**a**), increased thickness of the connections represent increased or decreased functional connectivity within circuits in compulsion (**b**), whereas as alterations in the size of a given brain region represents structural changes (yellow arrows show change direction). **Orbitofrontal-striatal circuits**. Compulsive grooming, hyperdipsia under SIP and compulsive reward seeking are all associated with increased functional connectivity in a dual lOFC striatal pathway (nucleus accumbens and dorsomedial striatum, DMS), involved in goal-directed behaviours, that is aberrantly modulated by enhanced mesolimbic dopamine activity[230]. Hyperdipsia under SIP is also associated with structural changes, namely enlargement, of the lOFC (displayed with arrow). **Medial PFC-striatal circuits**. Compulsive drug seeking and hyperdipsia under SIP are associated with altered structure and/or function of the prelimbic-striatal circuits involved in executive control, such as alterations of PLC projections to D1-receptor containing MSNs in the NAc in compulsive alcohol seeking, hypofunction of the mPFC in compulsive cocaine seeking and enlargement of the PLc in hyperdipsia under SIP. **Sensorimotor cortex-dorsolateral striatal circuits**. Compulsive grooming, drug seeking and hyperdipsia under SIP all depend on the cortico-dorsolateral striatal circuits that underlie habits. For instance, compulsive self-grooming is associated with alterations of cortico-striatal glutamatergic synapses accompanied by a strengthening of the secondary motor area (M2) input onto striatal fast spiking interneurons. The rigid functional engagement of the dl-striatum-dependent habit system, mediated by dopamine-dependent ascending spiralling circuitry, also subserves incentive drug seeking habits, hyperdipsia and alcohol drinking under SIP, as well as compulsive alcohol seeking. Functional engagement of the dopamine-dependent dl-striatum habit system is controlled by the amygdala the basolateral territory of which (BLA), enlarged in hyperdipsic individuals, contributes the development of incentive drug seeking habits while its central nucleus (CeN) is involved in the maintenance of incentive habits and compulsive alcohol seeking and drinking. **Insula-dependent circuits.** Compulsive feeding and drug seeking as well as hyperdispia under SIP are all associated with alterations of interoception-related insula circuits, especially those involving the OFC and the striatum circuits, thereby demonstrating the important contribution of alterations in interoception to compulsion. While the ACC has long been implicated in compulsive disorders in humans, there is a relative paucity of experimental evidence in the rat[31] but some in the marmoset[140].ACC: anterior cingulate cortex, BLA: basolateral amygdala, CeN: central nucleus of the amygdala, DLS: dorsolateral striatum, DMS: dorsomedial striatum, ILc: infralimbic cortex, MC: motor cortex, MSN: medium spiny neuron, OFC: orbitofrontal cortex, PLC: prelimbic cortex, VTA: ventral tegmental area,.

Fig. 5 | The anatomy of a compulsive action: a theoretical model of the psychological underpinnings of compulsive disorders

In compulsive disorders, an action that is originally goal-directed — under action-outcome (A-O) control, whether maintained by positive or negative reinforcement — becomes excessive and exclusively focused on a goal and such behaviour may eventually transition to become habitual. This action, which eventually turns out to be sub-optimal or inappropriate, results from an impaired top-down executive control system (purple). Such executive dyscontrol not only results in a failure to inhibit an urge — the subjective experience of an intrusive burst of positive (blue) or negative (pink) motivation subserved by interoceptive mechanisms — but also in a failure to update representations based on negative experiences, thereby leading to perseverative engagement in urge-driven acts. In addition, impairments in response monitoring (grey) lead to uncertainty about action performance and a failure to achieve a 'just right' feeling, thereby contributing to behavioural repetition. **a** | For one type of compulsion, the action (A) is goal directed, mediated by an action-outcome association (A-O). It results from an urge directed towards the attainment of the exclusively focused goal (or outcome), which is pursued (green arrow) at the expense of other potential outcomes (narrowing of goals; arrows pointing towards a unique goal — dark grey circle —, within the light grey circle representing all potential goals). The urge is subjectively reported to be directed towards an exteroceptive or interoceptive goal as 'I want' and the action can be reinforced by either positive (exteroceptive reward, blue) or negative (interoceptive relief or avoidance; pink) processes, or both. Relief often accompanies the attainment of an exteroceptive goal albeit covertly, being less accessible to subjective representations. Thus, relief may not be perceived as the primary source of motivation even when it is the case, as in compulsive eating that derives from comfort eating. **b** | For likely more common and severe compulsions, instrumental behaviour is habitual, mediated by stimulus-response associations (S-R) rather than goal-directed. Habits are then triggered by interoceptive (urge) or exteroceptive (environmental) stimuli. Although the immediate transient relief brought about by engaging in the habit (blue arrow) is diminished (compared with the situation illustrated in panel a), the overall goal has become the behaviour itself. The individual is then compelled to engage in the behaviour and the subjective urge is verbalised as 'I must', irrespective of potential consequences, experienced subjectively as 'never mind'. Fulfilment of the instrumental response, which is negatively and transiently reinforced by covert relief, now leads to more severe aversive consequences. However, as in the situation described in panel a, the behaviour will be repeated because of executive dyscontrol and deficits in action monitoring which may facilitate repetitive behaviours due to a failure to achieve a 'just right' feeling, leading to uncertainty and further negative internal states to which the habit is bound. Together, although panel b might represent a transition from panel a, they encapsulate four major types of compulsion (positive versus negative and goal-directed versus habitual).

Box 1 | Definitions of compulsive behaviour and possible transdiagnostic compulsivity in clinical syndromes

Luigjes et al.[2] have recently called for an accurate, transdiagnostic definition of compulsive behaviour. They describe three main categories of definition: phenomenological (subjective feelings), observational (behavioural descriptions such as excessive, maladaptive, persistent, repetitive) and explanatory (reducing stress or avoiding harm). Their consensual definition is that compulsive behaviour "consists of repetitive acts that are characterized by the feeling that one has to perform them while one is aware that these acts are not in line with one’s overall goal”[2]. However, stringent adherence to this definition may be problematic when investigating its componential neuropsychological processes. For instance, the notion of "one's overall goal" is vague; the compulsive behaviour could in theory be goal-directed in a very restricted manner, and hence nevertheless maladaptive. The criterion of experienced feelings is also problematic as experimental animal models used for investigations of underlying neuropsychological processes have necessitated a more operational approach. Furthermore, subjective accounts in humans may only provide reasons for behaviour that are sometimes post hoc*,* as well as highly variable, and hence somewhat unreliable as explanations in terms of underlying processes. Luigjes et al. also accept that such subjective feelings are insufficient in themselves as definitions of compulsive behaviour, which necessarily have to include the component of maladaptive repetitive behaviour. A plausible psychological model of this component is the distinction afforded by goal-directed behaviour and habits[84]. Thus, one hypothesis is that compulsions derive in part from the dyscontrol of habits[63] (and not that compulsions are simply habits).

Hence, compulsive behaviour hypothetically has several interacting components that may depend on different neural systems, requiring separate investigation. Thus, it is necessary to consider a range of repetitive, maladaptive behaviours that occur both clinically and in experimental situations to establish whether there are common neural, computational and psychological mechanisms. The list of disorders below illustrates the transdiagnostic diversity of compulsions, each with their own clinical scale of measurement. One clinical outcome could be a common therapeutic intervention, blind to diagnosis. Another outcome could be diagnosis of a variety of different forms of compulsive behaviour each requiring their own treatment. Our own viewpoint is intermediate between these extremes; that different manifestations of compulsive behaviour may depend on several shared, interactive neuropsychological processes that may, however, have differential involvement. Although common neural circuits may become dysfunctional in different compulsive behaviours, these may also be subject to distinct aetiological factors and molecular mechanisms.

Disorder	Clinical scale of measurement	Ref
Obsessive-compulsive disorder	Yale Obsessive-Compulsive Scale (YBOCS)	231
Trichotillomania	Psychiatric Institute Trichotillomania Scale	232
Tourette's syndrome	The Gilles de la Tourette Quality of Life Scale	233
Gambling Disorder	Gambling Symptom Assessment Scale	234
Substance Use Disorder	Obsessive-Compulsive Drug Use Scale (OCDUS)	235
Autism	Repetitive Behavior Scale	236
Eating Disorder	Compulsive Eating Scale	237
Internet Addiction	Internet Addiction Test	238
Gereralised Anxiety Disorder	Anxiety Disorder Interview Schedule (checking item)	239
Fronto-Temporal Dementia	Stereotypic and Ritualistic Subscale of Neuropsychiatric Inventory	240

Schizophrenia (comorbid with OCD)	YBOCS	231

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Box 2 | Measuring the dimensional trait of compulsivity

Measuring compulsivity by self-report in typical populations as well as patients has a long history.

A frequently used, reliable scale is the Padua inventory[241]. A revised (PI-WSUR) scale[242] comprises 39 items (5 subscales). The Padua scales have surprisingly poor correlations with the clinician-rated YBOCS[231]; probably because of how the clinical scale characterises symptom severity.

The obsessive-compulsive inventory-revised (OCI-R)[243] is an 18-item inventory — a set of questions (but often a questionnaire) with a theoretical basis — with 6 subscales: washing; checking and/or doubting; obsessing; mental neutralising; ordering; and hoarding. There is good cross-correlation with the Padua scales. Some statements from the various scales (which also measure obsessionality) that require responses include:

"I am sometimes late because I keep on doing certain things more often than necessary"

"I wash my hands more often and longer than necessary"
"I check and recheck gas and water taps and light switches after turning them off"
"I feel compelled to count while I am doing things"
"I collect things I don't need"
"I need things to be arranged in a particular order"

Rather few attempts have tested whether measures of compulsivity correlate with objective experimental test measures of behavioural performance. Gillan et al.[244] related a bias to 'model free' over 'model based' responding to a factor defined as "compulsive behaviour and intrusive thought", which they derived from multiple self-report questionnaires including OCI-R and a broad range of self-report questionnaires including for anxiety, schizotypy and impulsivity. Another study related Padua score to cognitive inflexibility measured by intra-dimensional-extra-dimensional set-shifting[245].

Recent interest has focused on the heritability of compulsivity. The Toronto Obsessive-Compulsive Scale was used to investigate trait compulsivity in a large sample of Canadian youths including 220 twin pairs (60 monozygotic, 160 dizygotic). There was evidence of heritability in all six of the factor dimensions (cleaning and/or contamination; symmetry ordering; rumination; counting and/or checking and hoarding)[246]. The estimated heritability for the total score was 74%, each trait dimension being heritable as well as co-heritable. Even less phenotypically correlated trait dimensions such as hoarding shared genetic risk.

Glossary

arbitration: A resolution of conflict between alternative strategies
attractor network: A computational term referring to a network of neuronal nodes, often recurrently connected, whose dynamic relations over time settle into a stable pattern of activity
Brodmann areas: Regions of the brain in defined in terms of histological characteristics and denoted by numbers, such as BA 9.
checking: Repeated monitoring of behavior caused in part by uncertainty.
chemogenetics: A method of manipulating neuronal activity in specific circuits using otherwise inert drugs that activate engineered receptors expressed in identified (genetically or otherwise) cells
cingulo-opercular network: A neural system that includes the cingulate cortex, inferior prefrontal cortex and insula implicated in executive functions and thought to be a major mediator of urgency affecting action.
cognitive-behavioural therapy: A general set of psychological treatments by which the patients are instructed to adhere to certain cognitive strategies to combat their mental symptoms. In OCD, often combined with a special technique of 'response prevention'.
cognitive control: A set of executive operations that optimises behaviour mediated in part by frontal lobe circuitry; almost synonymous with executive control
compulsion: A strong feeling of wanting or having to do something repeatedly that is difficult to control
compulsivity: A trait that refers to a tendency toward repetitive behaviour
conditioned reinforcer: A conditioned stimulus (associated with a primary reward) that reinforces those actions by which it is produced
contingency degradation: An experimental manipulation that uncouples the predictive relationship or correlation between an instrumental action and its outcome or consequence. Persistent instrumental responding then indicates mediation by habitual (stimulus-response) tendencies.
coping: A response, whether behavioral, cognitive or neuroendocrine, associated with reducing stress via negative reinforcement
craving: An overwhelming desire for the drug, frequently expressed by individuals with SUD as "I want".
deep brain stimulation: A form of invasive neuromodulation by implanted electrodes increasingly used in some mental health disorders including OCD and addiction as well as its original application to Parkinson's disease
dorsal striatum: That part of the basal ganglia of the brain that comprises the dorsal caudate nucleus and dorsal putamen in primates and their homologues in rodents
dorsolateral striatum: That region of the striatum in rodents generally assumed to be homologous with part of the primate putamen and alongside the infralimbic cortex, central nucleus of the amygdala and pre/motor cortex, part of the so-called habit system
dorsomedial striatum: That region of the striatum in rodents generally assumed to be homologous with part of the the primate caudate nucleus and alongside the prelimbic cortex and the basolateral amygdala, part of the so-called goal-directed system

excitotoxic lesion: Cell-body specific lesions of brain regions, produced by glutamatergic agonist drugs.that spare nerve fibres of passage (connections)

executive function: A set of cognitive operations, including working memory, attention, inhibitory control, cognitive flexibility and monitoring that optimise behaviour. Largely synonymous with cognitive control.

fronto-parietal network: A neural system, especially including the lateral prefrontal cortex and its connections with the parietal cortex, and thought to be a major component of the executive control system.

Glutamate to GABA balance: Hypothetical relationship between excitatory (glutamate) and local inhibitory (GABA) neurons in the cerebral cortex.

goal-directed behaviour: A sequence of purposeful, motivated instrumental actions whose initiation is predicated on a clear conscious representation of a goal

goal-devaluation: An experimental manipulation that reduces the value of a goal or an outcome produced by instrumental behaviour (such as reducing food value by satiation or poisoning). Persistent instrumental responding assessed under extinction conditions then indicates performance mediation by habitual (stimulus-response) tendencies.

grey matter volume: The volume of nerve cells established by voxel-based morphometric methods in neuroimaging

habit: An instrumental response generally elicited by internal or external environmental stimuli in the absence of any prior conscious representation of the primary goal

homologue: Neuroanatomical structure of common developmental and evolutionary history over species.

urge: An urgent feeling (often called an impulse) that a behavior must be performed imminently

impulsivity: A trait that refers to a tendency to premature, risky behavior

incentive motivation: invigoration of instrumental responding either by conditioned stimuli (pavlovian-instrumental transfer) or by incremental changes in value of the primary goal.

incentive habit: a habit in which a response has acquired inherent motivational value (and hence can be a goal on its own) through its development under the pavlovian incentive influence of conditioned reinforcers (either exteroceptive or interoceptive) that enable the incentive value of pavlovian cues to transfer to the setting-bound (stimulus-response) response itself.

negative urgency: An aversive motivational state associated with urges to respond

obsession: A persistent intrusive line of thought, often aversive

optogenetics: A method of manipulating neuronal activity in specific circuits using the photo-stimulation of a light-sensitive channel ectopically expressed in genetically or otherwise identified cells.

ordering: imposing organisation on a scene or objects

positron emission tomography: Neuroimaging technique using radioactive tracers to detect specific chemicals (often receptors) and metabolic or chemical changes in brain

resting state functional connectivity: A particular form of fMRI using inactive participants performing no task. Correlations of resultant fluctuations of the oxygenated haemoglobin response are made across functionally coherent brain regions to produce a proxy measure of connectivity. Hypoconnectivity, diminished BOLD responses; hyperconnectivity, enhanced BOLD.

schedule-induced polydipsia: Excessive drinking caused by intermittent, but predictable, delivery of small food rewards, generally in food deprived rodents.

serotonin selective reuptake inhibitor: a class of drugs used for the treatment of depression and OCD that selectively inhibit serotonin reuptake and directly bind to the BDNF trkB receptor.

striosomal: refers to one of two complementary neurochemically defined compartments within the striatum visualized by staining for immunocytochemical markers (that receives limbic inputs)

symptom provocation: Attempt to generate a patient's symptoms by specific environmental challenge or by presenting a stimulus associated with those symptoms (for example, by visual imagery or touch).

Trichotillomania: The continual pulling out of one's own hair, resulting often in baldness

trait: A behavioural disposition, generally assumed to be of genetic origin

repetitive transcranial magnetic stimulation: A form of non-invasive neuromodulation employing magnetic stimulation applied to the scalp.

ventral striatum: That part of the basal ganglia of the brain comprising the nucleus accumbens (including both its core and shell sub-regions), the olfactory tubercle and sometimes (in primates) the ventral caudate and ventral putamen. The region is often defined in terms of its anatomical projections from the limbic system, associated with emotional behaviour.

voxel-based morphometry: a neuroimaging method that investigates focal differences in brain anatomy.