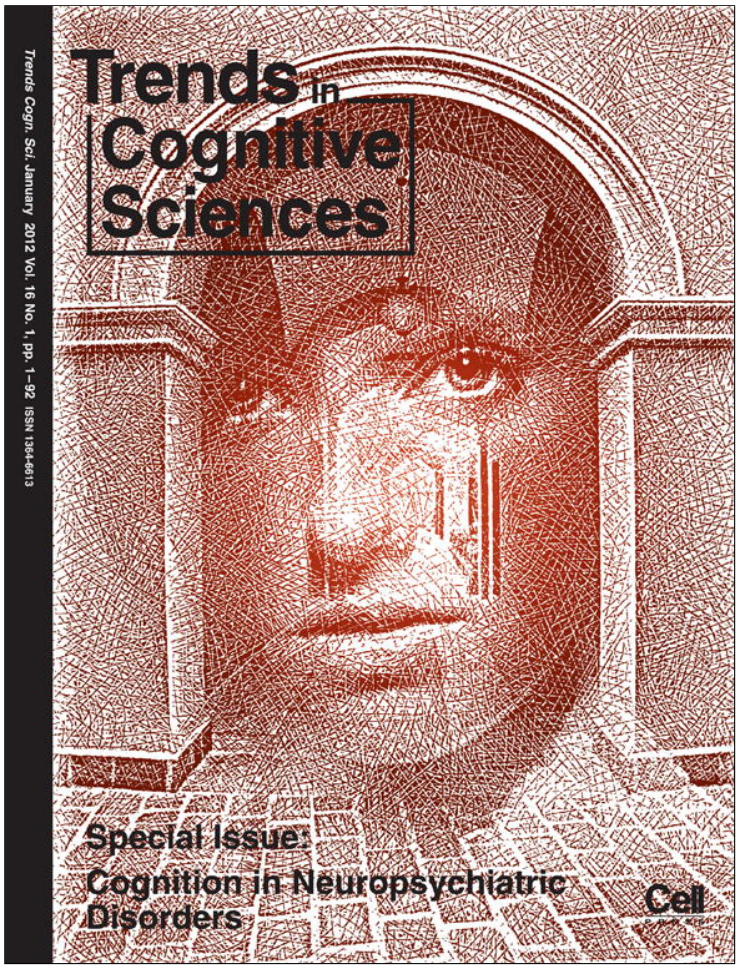

Review

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Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry

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A key criticism of the main diagnostic tool in psychiatry, the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV), is that it lacks a biological footing. In this article, we argue for a biological approach to psychiatry based on 'neurocognitive endophenotypes', whereby changes in behavioural or cognitive processes are associated with discrete deficits in defined neural systems. We focus on the constructs of impulsivity and compulsivity as key examples of the approach and discuss their possible cross-diagnostic significance, applying them to co-morbidities and commonalities across a range of disorders (attention-deficit/hyperactivity disorder, substance dependence, obsessive-compulsive disorder and eating disorders). We argue that this approach has important implications for the future classification of psychiatric disorders, genetics and therapeutics.

The case for biological psychiatry

Psychiatry is at a cross-roads, not only because of the continuing stigma of mental health disorders, which frustrates practitioners and patients alike, but also because of the way in which patients are diagnosed and treated [1]. Diagnosis, (for example, according to the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV)) has always been challenging due to the sheer complexity and heterogeneity of the symptoms that may occur in a particular disorder, the potentially confusing array of co-morbidities with other psychiatric disorders occurring in presenting patients, and the logical problem that there may exist neither necessary nor sufficient conditions for defining a particular category of disorder [2]. Thus, a patient can have the same diagnosis based on symptoms that are even opposite in nature (e.g., agitation and psychomotor retardation in depression). Moreover, some symptoms may be present in different diagnoses (e.g., apathy or delusions in both depression and schizophrenia).

Historically psychiatry had considerable success in a 'golden age' of psychopharmacology, with the sometimes serendipitous discovery of new drug treatments, such as the anti-psychotics (e.g., chlorpromazine and haloperidol, as well as lithium), anti-depressants (e.g., desipramine and fluoxetine) and anti-anxiety agents (e.g., the benzodiazepines). However, some of these advances have palled in recent years with the realisation of limited efficacy, major side-effects and a lack of novel mechanisms or compounds, few withstanding the crucial test of large phase-3 clinical trials [1,3]. The latter failures may reflect regulatory trends, but also perhaps the use of relatively poor means of neurocognitive and behavioural assessments, and the recruitment of patients with common DSM diagnoses, but widely disparate symptoms.

A common critique of DSM-IV is that, although it is a useful research instrument and invaluable clinical aid, its criteria appear based more upon the description of superficial behavioural signs and verbal reports of patients and associates than a firm biological footing [2]. Some of these concerns could conceivably have been allayed by revision of the DSM schemes. Moreover, in a process that has taken over a decade, the new version of the Manual, DSM-V, (http://www.dsm5.org) is set to be published in May 2013. Although there will be some undoubted improvements, including assessment of symptom severity and the incorporation of some biological criteria into the new edition, the progression to defining organic, as distinct from functional, syndromes has not been as rapid as would perhaps have been hoped, given the advances made in neurobiology, including cognitive neuroscience, and genetics.

This article addresses this difficulty by considering the utility of 'neurocognitive endophenotypes', such as impulsivity and compulsivity, derived from measures of brain as well as behavior, and using them 'transdiagnostically' across disorders, such as substance abuse, obsessive-compulsive disorder (OCD) and attention deficit /hyperactivity disorder (ADHD) to discern possible commonalities that may highlight new genetic or therapeutic avenues. Of course, it will also be important to determine what is different across such disorders, although these differences may not always be at the core of the disorder. However, by

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Glossary

Basal ganglia: generic term for a collection of forebrain structures strongly connected to the cerebral cortex and to the motor output systems. These structures include the nucleus accumbens (ventral striatum), caudate nucleus and putamen (dorsal striatum).
Compulsivity: a hypothetical trait in which actions are persistently repeated, despite adverse consequences.
Cortico-striatal circuits: the topographical projection of different areas of cerebral cortical regions onto functionally inter-related regions of the striatum (a structure of the basal ganglia) to form parallel, functional 'loops'.
Delay discounting: preference of a smaller immediate outcome over a larger reward after a longer delay; implicated in waiting impulsivity and poor impulse control.
Endophenotype: quantifiable variable associated with genetic risk for a disorder; abnormal in patients with disorder, relatives of probands, and state-independent or trait-like.
Extra-dimensional shift: assessment of cognitive flexibility involving the ability to shift attention between stimulus dimensions.
Five choice serial reaction task (5CSRTT): a behavioural task used in animal models of impulsivity and inattention. Animals must wait for a light cue before performing a nose poke into one of five indicated boxes. Premature responses are measured as early nose pokes before the cue and are indicative of waiting impulsivity.
Fronto-striatal circuits: the topographical projection of different areas of prefrontal cortex regions onto functionally inter-related regions of the striatum (a structure of the basal ganglia). Generally, although there may be some overlap, different fronto-striatal circuits are implicated in impulsivity and compulsivity.
Functional connectivity: a method of analysis of brain imaging data that establishes the role of inter-connected neural structures in behaviour by inter-correlation of the magnitude of their metabolic responses, leading to a 'proxy' measure of anatomical connectivity.
Goal-directed behaviour: behaviour that is mediated by knowledge of the causal relationship between the action and its consequences (outcomes), and that is only performed when those consequences are in line with current needs and desires (i.e., when the consequences currently constitute a goal).
Habit: habitual responses (R) are directly triggered by environmental stimuli (S) regardless of the current desirability of the consequences. The S-R associations that mediate habits have been reinforced (strengthened) either by past experience with reward (positive reinforcement) or by the omission of an aversive event (negative reinforcement).
Impulsivity: the tendency to act prematurely, without foresight, despite adverse consequences (informal definition; for a formal definition, see the main text).
Learning theory: associative learning theory seeks to understand how environmental events produce expectancies and control instrumental behaviour (comprising goal-directed actions and habitual actions) by theorising about the nature of the underlying representations for these events and the relationships among them.
Neuroleptic drug: tranquilizing antipsychotic medication used in individuals with schizophrenia and bipolar disorder; effectively reduces delusions and hallucinations.
Reversal learning: the ability to flexibly alter behaviour based on negative feedback and respond to a previously incorrect stimulus.
Selective serotonin reuptake inhibitor (SSRI): psychotropic medication commonly used in the treatment of depression, anxiety and OCD. Works by blocking the reuptake of serotonin in the synapses back into the pre-synaptic cell, thereby increasing the level of extracellular serotonin in the synapse.
Stop signal reaction time (SSRT) task: behavioural task assessing stopping ability as an indicator of impulsivity and poor motor inhibitory control. Individuals must respond rapidly to a repeated visual stimulus; however, they must inhibit this ongoing response when a stop signal is suddenly presented, typically in the form of a tone accompanying the stimulus. Staircase functions are used to generate an estimate of the time that an individual needs to withhold an ongoing response (stop signal reaction time, SSRT). Participants are explicitly instructed to not wait for or anticipate the stop signal. Successful stops indicate adequate functioning inhibitory control, whereas impairments are suggestive of 'stopping impulsivity'.
Stroop task: a behavioural task requiring higher level cognitive control. Participants must read the font colour of a target word which spells either the same or different colour word as the font. Responses to incongruent colour-word combinations present a greater cognitive demand than the congruent pairings because of the interference of the pre-potent tendency to read words rather than assess their colour. The interference score indexes how well a person exerts cognitive control over an automatic behaviour (word reading) in favour of a more unusual behaviour (colour naming). The task can be adapted to measure emotional interference (e.g., for phobias or drug-related material in substance abusers).

defining the role of suitable dimensions, it may be feasible to provide a re-description of the disorder that is more objective and quantitative, while preserving the insight of the clinical assessments.

Neurocognitive endophenotypes

The concept of endophenotype, or 'intermediate phenotype,' has been well-known in psychiatry since the pioneering research of Gottesman and Shields on schizophrenia [4]. Endophenotypes may consist of changes in well-defined behavioural or cognitive processes associated with discrete deficits in defined neural systems, be present in first degree relatives of patients who do not have the psychiatric diagnosis, and also possibly enable early detection of a disorder before its full-blown expression. Neurocognitive endophenotypes would furnish more quantitative measures of deficits by avoiding the exclusive use of clinical rating scales, and thereby provide more accurate descriptions of phenotypes for psychiatric genetics or for assessing the efficacy of novel treatments. The use of such measures would likely also facilitate and improve the use of informative animal models in psychiatry by focusing on cognitive and neural processes that can often be investigated in parallel across species. Defining such endophenotypes might cut across traditional psychiatric classification, and hence begin to explain the puzzle of apparent co-morbidities.

The concept of cognitive endophenotypes is not new, and there have been many examples of attempts to define these, as well as attendant controversies [5,6]. Of more recent vintage are exciting attempts to associate these with particular brain systems, as has become feasible with the advent of modern neuroimaging [5]. However, the resultant neurocognitive endophenotypes must eventually explain psychiatric symptoms. Some examples of such candidate endophenotypes already exist for schizophrenia: prefrontal cortex-based working memory deficits (related to the cognitive deficits of schizophrenia [5]) and impairments in neural prediction errors derived from learning theory (related to 'incentive salience' and positive symptoms such as delusions), associated with altered dopaminergic function [7]. In this article, we focus on a broader range of psychiatric disorders including substance dependence, OCD and ADHD, as well as certain eating disorders, which might appropriately be labelled 'impulsive-compulsive disorders' on the basis of these predisposing traits, and which have proven especially amenable to translational approaches involving experimental animals.

Two trans-diagnostic themes: Impulsivity and compulsivity

Impulsivity (Figure 1) has been defined as a trait leading to 'actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences' [8]. It is a personality trait seen in healthy individuals but in more extreme forms excessive impulsivity is a component not only of juvenile and adult forms of ADHD but also mania, substance misuse disorders, behavioural addictions, such as gambling, anti-social behaviour, and related borderline personality disorders [9].

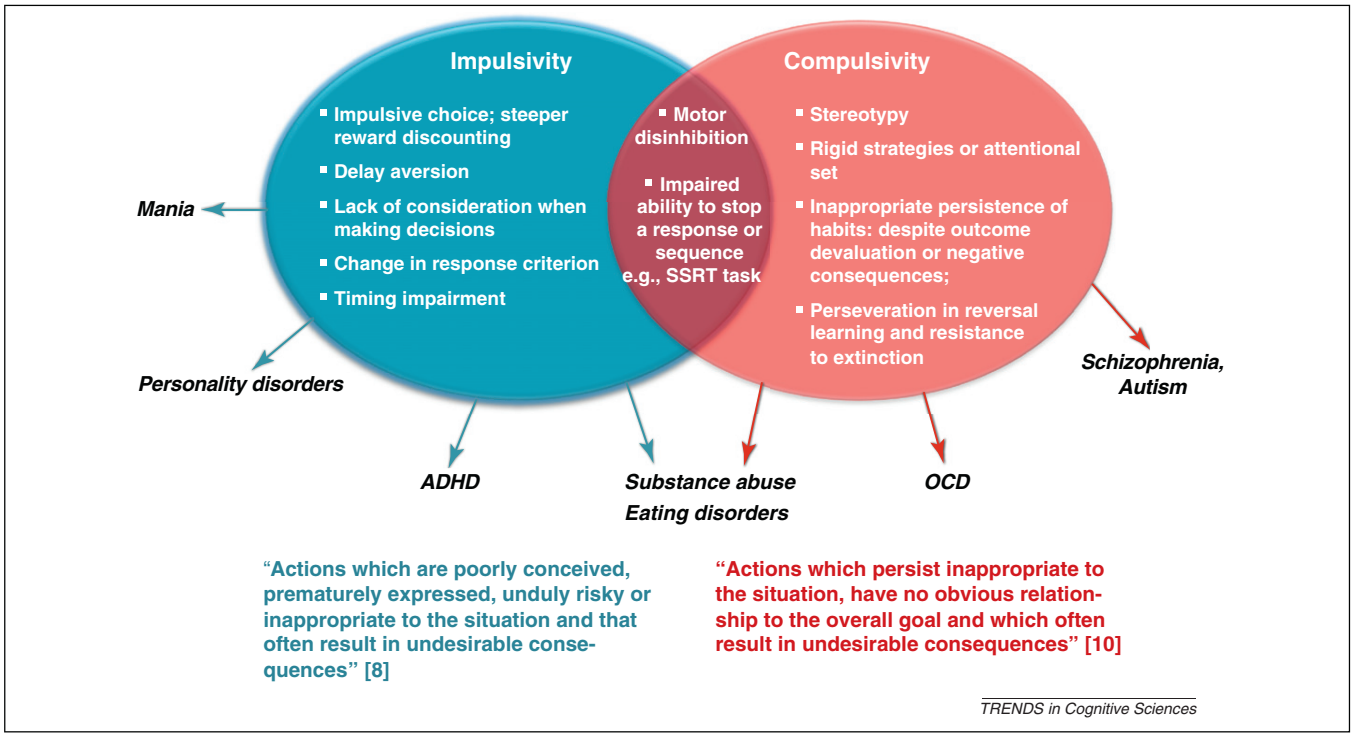

Figure 1. The impulsivity and compulsivity constructs. The diagram describes possible psychological mechanisms underlying the two constructs. Note that this schematic summary includes some possibilities not mentioned in the text: for instance, impulsivity could arise from impaired timing mechanisms, from an aversion to delays in discounting paradigms, or from changes in the decisional criteria for making a response. Equally, compulsivity could arise from enhanced resistance to extinction or the tendency to perform simple stereotyped movements, as well as the other mechanisms alluded to in the text. It would appear that these different measures likely do not inter-correlate well, which would argue against a unitary construct for either impulsivity or compulsivity, but this issue is still actively being researched. Note possible overlap in tasks and hence possibly mechanisms: the stop signal reaction time task (SSRT) could be considered as tapping both impulsivity and compulsivity traits, on the basis of its measurement of the capacity to inhibit an initiated response. Moreover, both impulsivity and compulsivity involve motor/response disinhibition, but at different stages of the response process.

Given the complexity of its definition, which includes elements of response dyscontrol, sensitivity to reward anticipation and poor planning, it seems reasonable to ask whether impulsivity is a unitary construct [10]. Different aspects of impulsivity are assessed by specific measures such as the stop-signal reaction-time (SSRT) task [11] for behavioural dyscontrol, and delay discounting tests [12] of reward anticipation. The Barratt Impulsiveness Scale (BIS-11) [16] is a widely-used self-report measure of trait-impulsivity which captures aspects of inattention, spontaneous actions and lack of forethought. Whether these different objective and subjective measures relate to a unitary construct of impulsivity is controversial [9,10], but a greater understanding of these dimensions and their inter-relationships may very well be brought to bear on the expression of impulsivity in so many apparently distinct disorders. The expectation is that this analysis may help to develop an even more refined, dimensional approach to diagnosis that will allow greater understanding and treatment of the symptoms.

Compulsivity is sometimes confused with impulsivity, but appears quite different in nature (Figure 1). Both constructs have been hypothesized to result from failures of response inhibition or 'top-down' cognitive control (10). However, compulsivity can be characterised by a modification of the above definition of impulsivity, that is, as leading to actions inappropriate to the situation which persist, have no obvious relationship to the overall goal and often result in undesirable consequences [10]. One theoretical interpretation, based in part upon this definition, is that compulsivity reflects the aberrant dysregulation of stimulus-response habit learning (relative to goal directed, action-outcome learning) (Box 1).

Thus, compulsivity is considered as a maladaptive perseveration of behaviour, which, in contrast to impulsivity, does not so obviously fall within the range of normal behaviour. There exist few tests measuring the individual variation in compulsivity that we suspect is present in normal populations; those measures that have been developed are disorder-specific. The Yale-Brown Obsessive-Compulsive Scale (YBOCS) [13] for example, measures the frequency and the duration of persistent maladaptive behaviours as well as their interference with normal life. The scale has been adapted to specific maladaptive behaviours such as drug-taking, drinking (OCDUS, [14]), or eating. These scales are clinically useful and endorse an underlying concept of compulsivity, although some of the items (see Table 1) could equally relate to items on the BIS-11, which measures impulsive behaviour.

However, compulsivity like impulsivity, can also be measured objectively in different ways (see Figure 1) and the two constructs may be differentiated in part by their engagement with different aspects of response control (compulsivity being related to terminating actions and impulsivity to initiating them) mediated by related, but distinct, cortico-striatal circuitries [10,15] (see Figure 2).

Box 1. Goal-directed actions and stimulus-response habits: does compulsivity in addiction and OCD reflect dysregulated habit-learning?

Goal-directed behaviour is mediated by knowledge of, and desire for, its consequences. In contrast, habits are controlled by external stimuli through stimulus-response associations that are stamped in through behavioural repetition [91,92]. Habits are thus commonly formed after considerable training, can be automatically triggered by stimuli, and are defined by their insensitivity to their outcomes. Evidence suggests that behavioural output is controlled by a balance between dual, sometimes competing, neurobehavioural systems [93]. In both rodents and humans, an action-outcome learning system for instrumental behaviour has been identified that depends on the ventromedial prefrontal cortex and caudate, and a habit system that implicates the putamen [94–96] (see Figure 2).

Everitt and Robbins [43] hypothesised a role for a dysregulated habit system in producing compulsive behaviour in drug addiction, and evidence has recently been provided of an underlying over-reliance on stimulus-response habits in OCD [24]. One of the striking features of OCD is that patients experience an intense urge to perform stereotypic, ritualistic acts, despite having full insight into how senseless and excessive these behaviours are, and having no real desire for the outcome of these actions (as for stimulus-response habits). In the case of drug addiction, although initial drug use is thought to be voluntary and linked to trait impulsivity [97], stimulant-dependent individuals gradually lose control over drug-seeking and drug-taking behaviour, which becomes compulsive.

Given that goal-directed actions are relatively cognitively demanding, for daily routines it is adaptive to rely on habits that can be performed with minimal conscious awareness. The question arises why only a subset of vulnerable individuals forms these highly specific compulsive habits. For drug addiction, impulsive traits and a dysfunctional reward system may confer a propensity towards drug use and abuse, and the involvement of the habit system may be a means by which this eventually becomes compulsive. For OCD, a general propensity towards habit may be expressed solely as avoidance, deriving from the co-morbid anxiety that OCD patients typically report. In the context of high anxiety, superstitious avoidance responses may offer relief, which reinforces the behaviour. Stress and anxiety may enhance the formation of habits, whether appetitively or aversively motivated [98]. However, as the habit becomes progressively compulsive, the experience of relief may no longer be the driving force and instead the behaviour comes under external control. Therefore, although a propensity to habits may not be the only vulnerability factor for OCD, it is likely the main maintaining factor.

The prototypical disorders of compulsive behaviour include OCD (as well as tic-related disorders), substance dependence, eating disorders and other examples of behavioural 'addictions'.

Compulsivity and impulsivity as endophenotypes for psychiatric disorders

Compulsive behaviour in OCD and related disorders

OCD is heterogeneous in terms of symptom presentation, co-morbidity, underlying neurocognitive profile, and therapeutic responsiveness [17,18]. Recent clinical commentary has suggested that OCD might better be described as part of a larger group of obsessive-compulsive spectrum disorders and that different patients with OCD diagnoses may lie at very different ends of this spectrum [19]. However, compulsions appear to be the most prominent feature of OCD [20] and are unrelated to self-reported levels of impulsivity ([22], Ersche *et al.*., unpublished manuscript). These excessive, inflexible behaviours are often thought to be carried out in order to neutralize anxiety or distress evoked by particular obsessions (but see Box 2). The YBOCS has demonstrated sensitivity to symptom changes following treatment with selective serotonin reuptake inhibitors (SSRIs) and its scores are also associated with a lack of both structural and functional integrity in the orbitofrontal cortex [21,22]. The most common types of compulsions are checking (a person repeatedly checks whether an activity has been completed adequately) and cleaning compulsions. Paradoxically, although OCD patients feel compelled ('must do!') to perform these behaviours, they are often aware that they are more disruptive than helpful. Therefore, rather than conceptualising compulsive

Table 1. A categorical comparison of compulsivity symptom questionnaires, spanning obsessive-compulsive disorder, compulsive drug seeking and taking, and compulsive binge eating

	YBOCS [13]	OCDUS/BES [14]	PI-WSUR [57]
	Used as a clinical diagnostic tool. More adept at identifying severe single symptom problems in patients with OCD. Not useful for identifying obsessions and compulsions in the broader population.	Nearly identical format to YBOCS. Measures severity of drug-related thoughts and behavioural urges. Includes versions for cocaine, alcohol, heroin, and binge eating.	List of specific obsessions and compulsions common to OCD. More sensitive to obsessions and compulsions in the general population. Has potential to overweight mild, broad-ranging concerns as compared to singular, more severe obsessions.
Assessment Item	**YBOCS**	**OCDUS/BES**	**PI-WSUR**
Frequency of thoughts associated with obsession	X	X	X
Level of anxiety due to these thoughts	X	X	X
Frequency of urges to perform behaviour		X	X
Distress over being unable to perform urge		X	
Time spent resisting these thoughts/ behaviours	X	X	
Time spent performing compulsive behaviours	X		X
Life interference due to thoughts/behaviours	X	X	
Control over thoughts/behaviour	X	X	

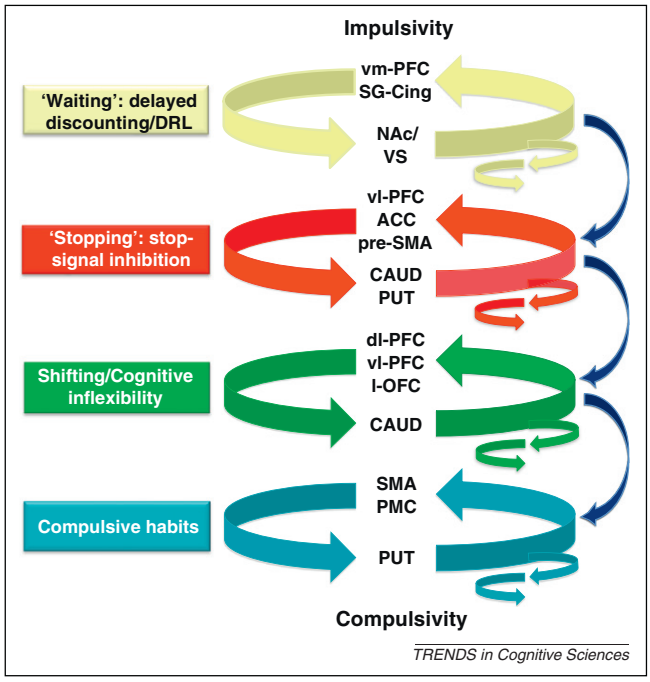

Figure 2. Highly schematic and speculative depiction of four different 'fronto-striatal loops' putatively associated with aspects of impulsivity and compulsivity. The diagram is based on extensive primate anatomical evidence and nomenclature (e.g., [100]) but also incorporates evidence from rodent studies based on plausible homologies (e.g., subgenual cingulate cortex (SG-cing) = Brodmann Area 25 = infra-limbic cortex in the rat). The diagram only shows the cortical and striatal components of the loops (see also [100] for further details). There is probably extensive cross-talk between them and one general flow of information is from ventral to dorsal striatal structures, as depicted. The loops are also not closed, as shown. Two 'loops' are depicted relevant to impulsivity: the ventral striatal 'loop' associated with discounting of reward and some aspects of waiting for reward (DRL= differential reinforcement of low rates of responding timing paradigm, also relevant to the premature responding in the 5CSRTT) and the dorsal striatal 'loop' associated with stop-signal inhibition. Extensive evidence for the separate existence of these two 'loops' is provided in [10], including rodent and human neuroimaging and lesion data. Additional references supporting these functional anatomical mappings can be found in the supplementary material online or to patient data cited in the text (e.g. [21–23,33,34,39,43,47,49,52–55,66,72–74,78]). Note that the ventromedial prefrontal cortex/rat prelimbic cortex- caudate is also implicated in instrumental (goal-directed) conditioning [95,96], but this is not shown in this diagram. For compulsivity, some of the best evidence of the anatomical basis of shifting deficits comes from non-human primate data on reversal learning (e.g.[15]). The OFC is implicated in human reversal learning (e.g. [39]). Finally, the anatomical substrates of habit learning have been mapped in rodents and humans [94,95], but mainly refer to the putamen/dorsolateral striatum, and only invoke cortical motor outputs on anatomical grounds of connectivity. Note that the analysis is not exhaustive and makes no attempt to assimilate negative evidence. Abbreviations: vm-PFC: ventromedial prefrontal cortex; SG-Cing: subgenual cingulate cortex; NAc: nucleus accumbens; VS: ventral striatum; vl-PFC ventrolateral prefrontal cortex (including inferior PFC); ACC: anterior cingulate; pre-SMA: pre-supplementary motor area; CAUD: caudate nucleus; PUT: putamen; dl-PFC: dorsolateral prefrontal cortex; dl-PFC: dorsolateral prefrontal cortex; l-OFC: lateral orbitofrontal cortex; SMA: supplementary motor area; PMC: premotor cortex.

behaviour as goal-directed action, these repetitive, stereotypic rituals might be better understood in the framework of aberrantly strong stimulus-response habit formation [23]. Indeed, OCD patients tend to rely on stimulus-response habit learning even after minimal behavioural repetition [24].

In line with the hypothesized role of habits, behavioural interventions appear to be quite effective in treating OCD. For example, exposure and response prevention (ERP), the most common form of behaviour therapy for OCD, involving graded exposure to anxiety-provoking stimuli/situations and prevention of the associated avoidance compulsions, is thought to have its therapeutic effect by breaking the pattern of compulsive avoidance, which not only confers dominant control to the external environment (such that the sight of a door elicits checking), but also maintains inappropriate anxiety [25].

Motor tic disorders, including Tourette's Syndrome (TS) are much more prevalent in OCD patients and their families compared with the general population [26]. The presence of tics in OCD is associated with early-onset OCD, which is generally more severe and is also associated with greater familial OCD rates [27,28]. One of the most obvious differences between the two categories of disorder is that tic disorders are treated most effectively with neuroleptic agents [29], whereas SSRIs are the first-line choice for OCD [30]. However, for refractory OCD, neuroleptics are often used as an adjunct to SSRIs [31]. Moreover, 'habit reversal therapy' in TS has obvious similarities to response prevention therapy for OCD [32].

Although OCD and TS may have distinct neurochemical underpinnings, they share some common dysfunctions in fronto-striatal circuits, regions known to be involved in inhibiting compulsive behaviour [33–36]. In both disorders, deficits in inhibiting behaviour are evident not only in terms of clinical phenotype but also in tests of neurocognitive

Box 2. OCD or COD?

The current DSM-IV definition of OCD describes compulsions as repetitive behaviours that a patient feels driven to perform in response to an obsession. By describing the condition thus, the DSM may be falling victim to the same fallacy as the patients, that is, attributing undue importance to obsessive thoughts. However, clinical observations that compulsive behaviour often occurs in the absence of obvious obsessional or anxiety symptoms, and indeed that such symptoms may be a consequence rather than a precursor of compulsions, suggest a need to revise that view. In cognitive and treatment terms, it might then better to consider the sequence 'C-O-D' rather than 'O-C-D.' In accordance with this perspective, it has long been established that disturbing intrusive obsessions are not unique to OCD, but rather are equally prevalent in the general population, differing only in terms of frequency, intensity and duration [20]. Furthermore, recent evidence suggests that the 'pure obsessional' subtype of OCD may in fact not exist: by computing a factor analysis using the Yale-Brown Obsessive-Compulsive Checklist (YBOCS-SC), Williams *et al.* [99] found that the 'pure obsessional' subtype loaded heavily with mental compulsions and reassurance seeking. As these types of mental compulsions are often erroneously classified as obsessions, this may explain the apparent misnomer of the 'pure obsessional' OCD. Preliminary support for the 'COD' hypothesis comes from the data demonstrating that OCD patients have a deficit in goal-directed learning, causing them to over-rely on their habit system (Box 1) [24]. These habitual responses were correlated with symptom severity, suggestive of the importance of the habit/goal-directed system for OCD. Moreover, the fact that compulsive responding can be instilled in the absence of antecedent obsessions suggests a much greater role for compulsivity in OCD than previously described. Instead of considering compulsions as behavioural reactions to abnormal obsessions, the reverse may be true: obsessions in OCD may in fact be a *post hoc* rationalisation of otherwise inexplicable compulsive urges.

This account of the functional relationship between compulsions and obsessions makes a case for the use of integrative evidence from both neurocognitive and basic learning theory research, as opposed to presumptions encouraged by a categorical diagnostic system.

function. OCD patients and their first-degree relatives exhibit deficits in cognitive flexibility (attentional or extra-dimensional set-shifting) and motor inhibition (SSRT performance) [37,38], processes thought to rely on the inhibition of regions of the basal ganglia by the prefrontal cortex, which potentially contribute to their compulsivity. OCD patients and their first-degree relatives also show reduced activation of the orbitofrontal cortex (OFC) during reversal learning in an fMRI paradigm [39]. These changes in the capability for response inhibition and cognitive flexibility may thus provide examples of neurocognitive endophenotypes for OCD. The attentional set-shifting deficits in OCD are not evident in the OCD-spectrum disorder trichotillomania (compulsive urge to pluck out one's own hair) but the SSRT impairment is greater in trichotillomania [37], suggesting that these disorders differentially involve 'top-down' control over attention and motor response inhibition. However, TS patients (unlike OCD) do not show clear deficits in SSRT performance [40] but have similar deficits to OCD in both extra-dimensional set shifting and a go/no go reversal learning task [18]. Although the precise pattern of deficits is still being defined for the OCD spectrum, it is apparent that tests of response inhibition and 'cognitive rigidity' may provide the spectrum with possible neurocognitive endophenotypes. Whether the recently demonstrated bias to habit learning [24] might also provide such an endophenotype remains to be tested.

From impulsivity to compulsivity in drug addiction

Drug dependence is characterised by persistent maladaptive behaviour to obtain and consume an increasing amount of drugs at the expense of the individual's health, social and personal life. Impulsivity and compulsivity are both evident in substance dependence. An analysis of the processes contributing to the induction of dependence to stimulant drugs, such as amphetamine and cocaine, both in experimental animals and in human stimulant drug abusers, provides insight into the possible interplay between impulsivity and compulsivity [10,41]. Rats with a consistent tendency to respond prematurely (designated 'high impulsives') in a continuous performance test of attention (the 5-choice serial reaction time task, 5CSRTT) also tended to escalate intra-venous cocaine self-administration, would tolerate foot-shock in order to 'seek' the drug (the latter being an 'adverse consequence' of the type defined by DSM-IV as a key criterion of compulsive drug-seeking behaviour), and would show enhanced relapse of cocaine self-administration behaviour following abstinence [10]. In other words, in this animal model of addiction, high levels of impulsivity are predisposing for the development of compulsive drug-taking. This appears to also be reflected in stimulant-dependent individuals: cocaine users who report high levels of trait-impulsivity also score highly on cocaine-related compulsivity (Ersche, K.D. *et al.,* unpublished manuscript). Moreover, Hogarth *et al.* [42] demonstrated in smokers that high impulsivity is predictive of a tendency to over-rely on habit learning. In agreement with Everitt and Robbins [43], they propose that accelerated habit formation may underlie the transition of high-impulsive individuals to compulsive smoking behaviour.

Moreover, in addition to premature responding in the 5CSRTT, 'high impulsive' rats also exhibit steep discounting in a choice between a small immediate and large delayed reward [44]. This convergence of two measures, also referred to respectively as 'impulsive action' and 'impulsive choice', encourages the notion of 'impulsivity'. However, it is often the case that these measures can also be dissociated, for example, following brain lesions or treatment with drugs [45]. Moreover, the 'high impulsives' did not exhibit impulsiveness as measured by the ability to stop an initiated response (measured with the SSRT task), suggesting a distinction between 'waiting impulsivity' and 'stopping impulsivity'. This distinction is also supported by findings of different underlying neural circuitries involving the ventral and dorsal striatum respectively [10] (see Figure 2).

These findings have stimulated research aimed at defining the relationship between impulsivity and human stimulant drug abuse. Impulsivity is a proposed endophenotype for substance dependence, serving as a predisposing risk factor, as well as a possible consequence of prolonged drug use. In a recent endophenotype study investigating impulsive and compulsive traits in substance dependent individuals and their biological siblings, both groups reported greater impulsive tendencies (as assessed by the BIS-11) in comparison to healthy controls [41]. These behavioural results confirm the earlier findings of increased impulsivity (though using different measures [46]), suggesting a heightened familial vulnerability for impulse control disability. However, it should be noted that drug users were still significantly more impulsive than their siblings according to the BIS-11, which indicates either a potential additional incremental effect of the stimulant drugs themselves on impulsivity, or alternatively the drug-using siblings had an even greater propensity for impulsivity, relative to their siblings [41].

A recent exciting finding is that the drug users and their siblings are also highly and almost equivalently impaired on a precise test of response inhibition, as demonstrated through greater difficulty stopping on an SSRT task associated with changes in white matter in the vicinity of the right inferior frontal cortex [47]. Underlying impulsive tendencies in first-degree relatives have also been demonstrated in other familial studies of drug and alcohol abuse. For example, children of alcohol dependent individuals display cognitive control impairments on a Stroop task, with corresponding abnormalities in the inferior frontal gyrus [48]. By contrast, drug-related compulsivity, as assessed by the OCDUS, has been shown to be associated with both structural and functional integrity of the orbitofrontal cortex [22,49], as in OCD. Figure 2 illustrates possible different fronto-striatal loop circuitry in the control of impulsive and compulsive behaviour.

Impulsivity in ADHD

Impulsivity (alongside inattention and hyperactivity) is a key symptom in ADHD. The possibility of an impulsivity endophenotype for substance abuse raises obvious comparisons with ADHD. Certainly, ADHD patients (especially with concomitant conduct disorder) have a propensity for drug abuse [50]. The nature of the impulsivity in ADHD

appears to include both the hypothesised 'waiting' and 'stopping' forms. However, there is often little correlation between the measures for 'delayed gratification' and 'stop-signal inhibition' [51] although both were shown to contribute significantly to the variance of a large ADHD population. The lack of correlation is consistent with the hypothesis that they depend on different neural circuitries (e.g. ventral versus dorsal striatum) [52] (see Figure 2), which are potentially susceptible to varying degrees across the spectrum of ADHD.

Compulsivity, impulsivity, and commonalities across disorders

Parallels between OCD and stimulant drug dependence

The incidence rates of drug addiction, pathological gambling and eating disorders are no higher in OCD than in the general population [26]. However, this apparent lack of comorbidity amongst these disorders should not obscure the possible interpretation that they all reflect a behavioural tendency that stems from a common 'compulsivity' endophenotype, despite the fact that the tendency is expressed in superficially contrasting ways (hence, resulting in largely non-overlapping diagnoses).

The compulsive nature of drug abuse is supported by similarities in brain structural and functional abnormalities in both substance dependent individuals and OCD patients. Decreases in OFC gray matter density and brain metabolism, as well as reductions in striatal dopamine (DA) D_2 receptor binding have previously been reported in both groups [33,49,53–55]. In a recent study [22], resting state magnetic resonance imaging (MRI) for both stimulant-dependent individuals and OCD patients showed significantly decreased connectivity of both the right inferior and superior OFC as compared to healthy controls. This dysconnectivity was also associated with increased self-reported compulsivity and compulsive drug taking in patients with OCD and substance dependent individuals respectively, suggesting a common construct of 'compulsivity' (Figure 3). However, OCD patients displayed additional dysconnectivity between the OFC and dorsal pre-motor regions, as well as the posterior cingulate. These regions have been implicated in motor planning and goal-directed actions. In contrast, substance dependent participants had significantly higher ratings of impulsivity as compared to OCD patients, confirming a neurobiological distinction between these two groups, despite their significant overlap [22].

It remains likely that, as with the impulsivity construct, compulsivity itself can be fractionated into several subtypes, based on dissociations amongst its different measures (Figure 1). An obvious additional distinction is between compulsive behaviour driven by positive versus negative reinforcement. Thus, OCD compulsions are often considered to resemble avoidance behaviour driven by the need to ameliorate anxiety caused by obsessional thinking, although there may be reasons to doubt this simple relationship (Box 2). Both positive and negative reinforcement may potentially contribute to substance dependence, as continuing drug use may occur even after it is no longer deemed pleasurable, to avoid the aversive state of withdrawal.

A relatively large number of individuals entering drug treatment also report symptoms of OCD [56]. One scale for assessing the spectrum of obsessive-compulsive behaviour is the PADUA inventory (PI-WSUR [57] Table 1). Not only drug-dependent individuals but also their non-dependent siblings report elevated levels of obsessive-compulsive behaviour [49]. There are also some evident differences between stimulant abusers and patients with OCD. For example, impulsive and compulsive traits are significantly correlated in stimulant dependence, but not in patients with OCD (Ersche K.D. *et al.* unpublished manuscript). Substance dependent individuals also demonstrated a significant increase in perseverative responding on a probabilistic reversal learning task (associated with reduced

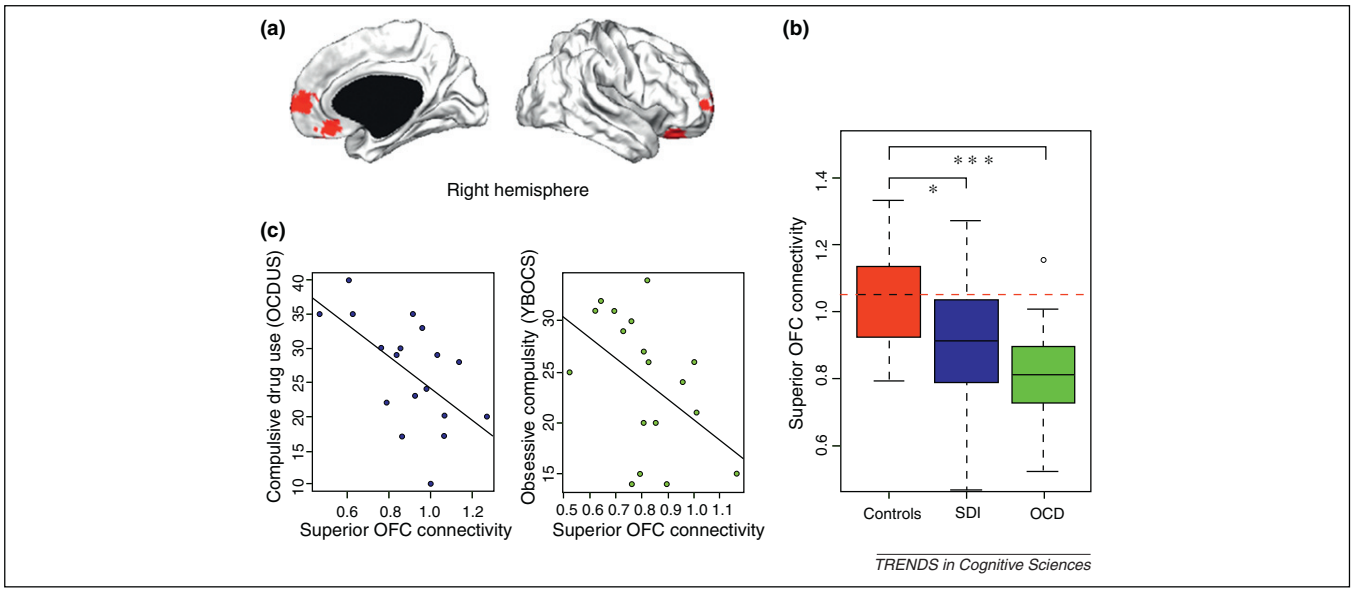

Figure 3. Neural connectivity inferred from resting state data in a magnetic resonance scan. **(a)** Superior and inferior orbitofrontal cortex sites were the only areas to show significantly reduced connectivity, following **(b)** correlational analysis of activity across all 50 regions of interest within the cerebral cortex in both patients with OCD and stimulant-dependent individuals. **(c)** Degree of connectivity in one OFC region correlated significantly negatively with compulsivity scores in stimulant-dependent individuals (OCDUS scores) and in patients with OCD (YBOCS scores). Reproduced, with permission, from [22].

activation of the anterior head of the caudate nucleus and remediated by D_2 agonist treatment), whereas individuals with OCD did not [58].

Taken together, these results suggest that although there is a substantial neurocognitive overlap between the two disorders, drug addiction may stem from an additional propensity to impulsivity, which contributes to the impaired decision-making and impetuosity, which can instigate risk taking, leading to drug-seeking behaviour.

Parallels between compulsive eating disorders, substance abuse and OCD

An analysis of impulsive-compulsive tendencies should not be limited to substance abuse and OCD, given the growing acceptance of the existence of such 'behavioural addictions' as gambling, eating, sexual and internet addiction [9]. Moreover, there have been a number of comparisons over the last decade between drug addiction and compulsive eating (demonstrated both in obese individuals and in patients with binge eating disorder) [59,60].

For these individuals, food-seeking may possibly be governed by similar mechanisms as drug-seeking in substance-dependence individuals [60], inspiring the term 'food addiction'. For example, exposure to food-associated stimuli, such as particular wrappers, can induce snacking, binge-eating and a failure to commit to dietary restrictions [61,62]. Ultimately, these external stimuli may become triggers of maladaptive eating habits that are performed despite apparent satiety and adverse health consequences. Therefore, as in drug addiction, aberrant habit formation develops [60].

There is also co-morbidity between drug use and binge eating, and the two conditions share numerous behavioural and physiological similarities [63–65]. Diagnostic criteria for substance dependence and binge eating disorder are also similar, with the characteristic components of addiction including loss of control, tolerance, withdrawal and cravings being present in both disorders [63–65].

In terms of brain mechanisms, both conditions are characterised by altered activity of the midbrain DA system. Individuals with substance dependence and obese individuals with and without binge eating disorder are known to have decreased DA D_2 receptor availability in the striatum, possibly signifying lower DA-ergic activity, which can be manifested as a tendency for natural rewards to lose their value in these populations [66,67] as well as enhanced impulsivity [63,68–70]. Such impairments can be expressed via deficits in delay discounting, where immediate smaller rewards hold greater salience than larger future gains [69,70]. These neurocognitive findings are in line with the neurobiological data presented above, a down-regulation in striatal DA D_2 receptors hypothetically producing a faulty reinforcement system [60,66,67] and a tendency towards impulsive responding [10].

Similar to the OFC dysfunction seen in chronic drug abuse and OCD, obese individuals also exhibit reductions in both prefrontal cortical grey matter volume and OFC blood glucose metabolism [71–73]. Furthermore, significant differences were observed in the brains of normal and overweight or obese individuals, particularly in the inferior frontal gyrus, and body mass index (BMI) was shown to have a significant negative correlation with gray matter volume [71,72]. This finding applies not only to obese individuals, but also extends to patients suffering from binge eating disorder and bulimia nervosa [71,74].

Greater levels of compulsivity, as assessed by self-report questionnaires, have also been demonstrated in patients suffering from bulimia nervosa, who exhibit impulsive binge eating symptoms as well as obsessive and compulsive thoughts about weight restriction and compulsive compensatory purging [75–77]. Bulimia nervosa patients also demonstrate impaired performance and blunted cortico-striatal activity on an inhibitory task activating the prefrontal cortex, anterior cingulate and ventral and dorsal striatum [78]. These impairments may stem from abnormalities in the brain's serotonin system, which is implicated in both impulsive and compulsive disorders [79]. Furthermore, treatment with SSRIs is common in both bulimia nervosa and OCD, suggesting a potential commonality in neurochemical status between the two disorders.

Due to the significant overlap of neurocognitive deficits, compulsive tendencies, neuroanatomical abnormalities, and familial endophenotypes among substance users, compulsive eaters and patients with OCD, we argue that there is a strong case for an underlying link between these disorders. A primary distinction between these three is the nature of the focus of their compulsive tendencies, as well as the incorporation of impulsive traits in substance dependent individuals and patients with binge eating disorder. Note that compulsive eating can be mirrored by compulsive rejection of food, as in anorexia nervosa, and that there is also considerable co-morbidity between childhood OCD and anorexia [80].

Concluding remarks

Impulsive and compulsive symptoms occur in many neuropsychiatric disorders and may even help to define them. They may also co-exist in the same condition, but the nature of their relationship is less clear. For example, impulsivity appears to constitute a vulnerability factor for compulsive stimulant drug-seeking, but does not obviously contribute to the compulsive behaviour of OCD (although further developmental studies of their possible inter-relationship may be warranted).

In order to better characterise impulsivity and compulsivity, we have advocated a psychological approach, based largely on cognitive and learning theory, combined with neural and neurochemical analyses to further define these neurocognitive endophenotypes. This 'trans-diagnostic' approach (see also [81]) can be extended to several other conditions. There are current queries, for example, about the precise relationship of hoarding behaviour in OCD and compulsive hoarding in the absence of OCD symptoms. Both will be included under OCD spectrum disorder in the new DSM-V manual, but do they represent common symptoms of compulsive hoarding or distinct nosological entities? OCD can also be co-morbid with other neuropsychiatric disorders such as schizophrenia, and it is striking that cognitive flexibility (as measured by extra-dimensional set-shifting) is particularly impaired in schizophrenia with co-morbid OCD, as compared with either disorder alone [82].

Impulsivity and compulsivity can also occur in neurological disorders where they are not normally a major symptom: for example, compulsive gambling can be a consequence of dopaminergic medication overdose in Parkinson's disease [83].

We identified in the introductory section possible functions of endophenotypes in predicting vulnerability to a future neuropsychiatric disorder (thus highlighting the potential need for interventions to prevent this) and also in targeting behavioural and pharmacological treatments more effectively. Impulsivity and compulsivity appear to have distinct, though possibly overlapping, neural and neurochemical substrates, and this may lead to the identification of transdiagnostic treatments that can be used across what appear to be very different diagnostic entities, such as ADHD and OCD. Thus, for example, noradrenaline reuptake inhibitors appear to be effective agents in the treatment of impulsivity [84,85], possibly contrasting with serotoninergic agents for treating compulsive behaviour.

Understanding the different behavioural nature of the deficits in goal-directed control over habits and impulsive behaviours that is evident in drug abusers and OCD patients alike may also be important for the implementation of new, theory-based treatment strategies. Behavioural training strategies that involve enhancing response inhibitory control may be effective in the treatment of impulse control. Likewise, ERP is a well-validated treatment for OCD [86]. In contrast, current addiction treatment programmes tend to advocate total avoidance of drug cues, rather than exposure. While this strategy is effective in promoting initial abstinence, total avoidance is often not feasible long term, and contact with drug-cues can trigger relapse. Despite the considerable advances in animal research in the area, exposure therapy trials for addiction have yielded disappointing results thus far [87]. Future research is needed to harness and translate advances in animal models of addiction to exposure work in the clinic, with particular attention to context effects on extinction (i.e., when reward or reinforcement is withdrawn for a conditioned response), with implications for both OCD and addiction [88,89].

However, there is much more to ADHD than impulsivity, for example, and so an effective specific treatment for this dimension alone may be less effective than a pharmacological 'cocktail' (such as methylphenidate) with many potential therapeutic actions. In order to adequately redefine the nature of neuropsychiatric disorders, it will be important to characterise all of the contributory dimensions of deficit, as well as their relative contributions in the individual patient, in this trans-diagnostic approach. A similar position should be taken in the search of specific genes that may underlie disorders: genetic influences on impulsivity and compulsivity should be studied in parallel with other dimensions or neurocognitive endophenotypes. 'Dimensions' such as impulsivity and compulsivity might themselves not be unitary, and could be further fractionated. One useful distinction has already been made between 'waiting' and 'stopping' forms of impulsivity [10]. Another consideration is the interaction of impulsivity with motivational factors to produce either positive (appetitive) or negative (aversive) urgency [90]. This division by motivational valence may also help provide more precisely defined phenotypes of compulsivity. The possible utility of these approaches will have to be decided on the basis of further evidence (see also Box 3). Finally, it is to be hoped that, eventually, refined tests of compulsivity and impulsivity may enrich diagnostic systems, such as DSM-V, by providing objective, quantitative assessment of the nature and severity of impulsive-compulsive syndromes, with possible aetiological relevance.

Box 3. Questions for future research

- Can impulsivity/compulsivity be further fractionated based on finer-grained neuropsychological analysis?
- Are traits of impulsivity/compulsivity observed in patients on a continuum with similar traits observed in the healthy population?
- What are the possible causal relationships between impulsivity/compulsivity and symptoms in neuropsychiatric disorders?
- How can studies of the first-degree relatives of patients and prospective longitudinal studies assist in the investigation of the possible status of impulsivity/compulsivity as endophenotypes of psychiatric disorders?
- What are the neural and neurochemical substrates, as well as the genetic basis, of the impulsivity/compulsivity endophenotypes?
- How can measures of impulsivity/compulsivity best be used to supplement traditional diagnostic criteria?

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tics.2011.11.009.

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