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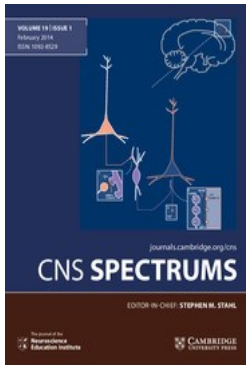

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REVIEW ARTICLE

New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity

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Impulsivity and compulsivity represent useful conceptualizations that involve dissociable cognitive functions, which are mediated by neuroanatomically and neurochemically distinct components of cortico-subcortical circuitry. The constructs were historically viewed as diametrically opposed, with impulsivity being associated with risk-seeking and compulsivity with harm-avoidance. However, they are increasingly recognized to be linked by shared neuropsychological mechanisms involving dysfunctional inhibition of thoughts and behaviors. In this article, we selectively review new developments in the investigation of the neurocognition of impulsivity and compulsivity in humans, in order to advance our understanding of the pathophysiology of impulsive, compulsive, and addictive disorders and indicate new directions for research.

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Introduction

Impulsivity may be defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others."[1,2] In contrast, compulsivity represents the performance of repetitive and functionally impairing overt or covert behavior without adaptive function, performed in a habitual or stereotyped fashion, either according to rigid rules or as a means of avoiding perceived negative consequences.[3–5] Impulsivity and compulsivity do not represent unitary phenomena; rather they represent useful conceptualizations that involve dissociable cognitive functions, which are mediated by neuroanatomically and neurochemically distinct components of cortico-subcortical circuitry. These constructs were historically viewed as diametrically opposed, with impulsivity being associated with risk-seeking and compulsivity with harm-avoidance. However, impulsivity and compulsivity have in common the profound feeling of "lack of control," and are increasingly recognized to be linked by shared neuropsychological mechanisms involving dysfunctional inhibition of thoughts and behaviors.[6]

Impulsive and compulsive mechanisms are implicated in many psychiatric disorders. However, there exist certain disorders in which impulsive and/or compulsive behavior seems, at least on phenotypic grounds, to be the essential and most damaging constituent. These often highly heritable and disabling lifespan disorders include those characterized mainly (but not exclusively) by compulsive acts, such as the newly created *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) Obsessive-Compulsive and Related Disorders (OCRDs) cluster that comprises obsessive–compulsive disorder (OCD; which is considered the archetypal compulsive disorder), body dysmorphic disorder (BDD), and hoarding disorder. Trichotillomania and skin-picking disorder, also classified with the OCRDs, are defined by body-focused repetitive behaviors or grooming habits that can be considered as either impulsive or compulsive, depending on the nature of the symptoms expressed in individuals, whereas attention deficit hyperactivity disorder (ADHD) appears to be characterized primarily by motor impulsivity. Of great interest, the pathological behavior associated with disorders of substance addiction (SA) and "behavioral addiction," such as pathological gambling (or gambling disorder in DSM-5[7]), appears, over time, to change from reward-driven impulsive responding to habit-related compulsive responding.[8–10]

Many of these disorders cluster together, either within the same individual (comorbidity) or within families, which implies the possibility of shared pathophysiological mechanisms.[11,12] Moreover, there is evidence of overlap in the treatment response across some disorders. For example, OCD and BDD typically respond to serotonin reuptake inhibitors (SRIs; clomipramine and selective SRIs, or SSRIs) and to SSRIs combined with antipsychotic agents,[13] as do the compulsions associated with autistic disorders.[14] However, unlike OCD, trichotillomania appears SSRI-unresponsive, and data from single randomized controlled trials suggest that monotherapy with olanzapine (an antipsychotic agent)[15] and n-acetyl cysteine (an amino acid compound) can be effective.[16] Antipsychotics represent first-line treatment for Tourette syndrome.[17] ADHD, on the other hand, responds to noradrenergic reuptake inhibitors as well as dopaminergic agents (eg, amphetamine), whereas substance-use and gambling disorders may share a therapeutic response to opiate antagonists.[18]

Traditionally, compulsive disorders such as OCD and impulsive disorders such as ADHD or addictions have been viewed at opposite ends of a single dimension; the repetitive compulsive acts that characterize OCD are designed to reduce or avoid harm and contrast with the reckless or reward-seeking behaviors that characterize impulsive disorders that invoke or disregard risk. However, the investigation of "endophenotypes" (intermediate phenotypes) that are thought to lie closer than the expressed behavior to the genetic and environmental origins of the disorders,[19,20] such as changes in cognitive performance, or structural and functional brain imaging abnormalities, increasingly suggests that rather than polar opposites, compulsivity and impulsivity may represent orthogonal factors that each contribute in varying degrees to the development of these disorders. A high level of comorbidity exists between impulsive and compulsive disorders across different cultures, and when these disorders occur together, they tend to be more severe.[21] Both impulsive and compulsive pathology may be underpinned by a shared tendency toward behavioral disinhibition, possibly resulting from failure in "top-down" cortical control of fronto-striatal brain circuits, or alternatively from over-activity within striatal neural circuitry.

The U.S. National Institute of Mental Health Strategic Plan calls for the development, for research purposes, of new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures.[22] Its aim is to define basic dimensions of function to be studied across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined. The intention is to translate results from basic neurobiological and behavioral research to an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders. In line with this strategy, in

this article we selectively review new developments in the investigation of the neurocognition of impulsivity and compulsivity in humans, in order to advance our understanding of the pathophysiology of impulsive and compulsive disorders. We focus on the following key questions:

1. Can we define the neuropsychological and associated neuroanatomical and neurochemical mechanisms that contribute to impulsive and compulsive responses in humans?
2. How do these mechanisms differentially contribute to impulsive disorders (eg, ADHD), compulsive disorders (eg, OCD), and addictive disorders (eg, substance-use and gambling disorders)?
3. Can we link genes with the neuropsychological changes that underpin impulsive and compulsive behaviors and disorders?
4. Does the presence of impulsivity or compulsivity have prognostic implications for treatment response?
5. What are the next steps for research?

Theoretical Models of Impulsivity and Compulsivity

Impulsivity and compulsivity are each multidimensional constructs. They involve disruption within a wide range of neural processes, including attention, perception, and coordination of motor or cognitive responses. These processes are thought to be underpinned by separate but intercommunicating "impulsive" and "compulsive" cortico-striatal neurocircuitry, with each circuit modulated by different neurotransmitters.[18,23]

According to current neuroanatomical models, at least 2 striatal nodes (one impulsive and one compulsive) *drive* these behaviors, while 2 corresponding prefrontal nodes *restrain* them. Thus, the impulsive circuit may comprise a striatal component (ventral striatum/nucleus accumbens) that drives the impulsive behaviors, while a prefrontal component (anterior cingulate/ventromedial prefrontal cortex, VMPFC) exerts inhibitory control. Similarly, in the compulsive circuit, a striatal component (caudate nucleus/putamen) may drive compulsive behaviors, and a prefrontal component (orbitofrontal cortex, OFC) may exert inhibitory control. Other important areas for cortical control include the lateral PFC, especially on the right side, and increasingly (but mainly in social cognition or hyperbolic discounting choice procedures), the dorsolateral (DL)-PFC. Hyperactivity within the striatal components or abnormalities (presumably hypoactivity) in the prefrontal components may result in an increased automatic tendency for executing impulsive or compulsive behaviors, depending on the subcomponent that is affected. Current understanding suggests that OCD demonstrates over-activation (hyperactivity) during resting state, and symptom provocation and even error monitoring. However, there are many studies involving cognitive function that clearly indicate hypoactivation, ie, reduced activity in areas such as the DLPFC and OFC during executive functions.[24–27] In addition, overlap between these functional systems is likely to exist, so that what starts out as a problem in the impulsive circuit may end up as a problem in the compulsive circuit and vice versa, thereby contributing to an "impulsive–compulsive diathesis" model.[18,28,29] In the same patient, deep brain stimulation of the nucleus accumbens may reduce compulsivity at certain voltages and elicit impulsivity at others,[30] suggesting that under different contingencies, nodes within the same circuitry may direct both forms of behavior. Other prevailing influences on cortico-striatal activity, eg, diminished striatal activation to rewards during engagement in reward-related behaviors, may also contribute to seemingly impulsive or compulsive behaviors.[31]

Impulsivity: Neurocognitive Components and Role in Impulsive and Compulsive Disorders

Data indicate that impulsivity may derive from several distinct neurocognitive mechanisms, each with separate neuroanatomical and neurochemical bases. Debate currently exists regarding the number and identity of domains into which impulsivity might fractionate, with 2 or more domains typically identified.[32] Proposed domains may include (i) a tendency to pre-potent motor disinhibition (motor impulsivity), (ii) a tendency towards decision-making deficits (decision-making impulsivity), (iii) difficulty in delaying gratification and choosing immediate small rewards despite negative long-term consequences (choice impulsivity), and (iv) insufficient information sampling before making a choice (reflection impulsivity). It should be noted that these represent working forms of impulsivity that are defined not clinically but rather on the basis of a number of cognitive tests, described below. Thus defined, different forms of impulsivity can co-occur within a given disorder, and may even overlap in terms of what is being measured. See Table 1.

Motor impulsivity

Motor impulsivity, also termed response or rapid-response impulsivity, refers to impairment in the ability to stop motoric responses following changes in environmental circumstances. This is typically operationalized in the laboratory using go/no-go (GNG) and stop-signal reaction time (SSRT) tasks.[33,34]

In GNG tasks, subjects perform motor responses to go cues but should refrain from responding when a no-go cue is presented. On SSRT tasks, subjects make

TABLE 1. Subdividing impulsivity: abbreviated summary of neurocognitive domains, tasks, and neural and neurochemical correlates

Neurocognitive domain	Definition	Task	Neural system	Neurochemistry	Pharmacological probes
Motor impulsivity	Impaired ability to stop motor responses following environmental change	Go/no-go (GNG) for stopping responses before they have been initiated Stop signal reaction time task (SSRT) for stopping an already triggered motor response	Right inferior frontal gyrus and subcortical (including subthalamic) connections	Norepinephrine	Reduced by methylphenidate and atomoxetine
Disadvantageous decision-making	Difficulty weighing options and taking appropriate risks based on available information	Decision-making or gambling tasks, eg, Cambridge Gambling Task, CANTAB, Iowa Gambling Task	OFC and subcortical connections	Cortex: serotonin Subcortical circuitry: serotonin/ dopamine	Reduced by methylphenidate
Choice impulsivity	Excessive discounting of delayed reinforcement	Delay-discounting task (DDT)	VMPFC, OFC Valuation: Substantia nigra, ventral striatum and VMPFC Cognitive control: Anterior cingulate cortex and VMPFC Imagery/prospection: Medial temporal lobe and white matter connections	VMPFC: serotonin OFC: dopamine	Increased by D1 dopamine receptor antagonist and alpha2 adrenergic receptor agonist Reduced by methylphenidate. for experimental rewards (but not for hypothetical rewards)
Reflection impulsivity	Reduced tendency to collect salient information from the environment before decision-making	Information-sampling tasks, eg, Cambridge Information Sampling Task (IST)	Not known	Serotonin	Increased by 5-HT2R antagonist; Reduced by 5-HT2R agonist

OFC = orbitofrontal cortex; VMPFC = ventromedial prefrontal cortex; CANTAB = Cambridge Neuropsychological Test Automated Battery.

motor responses to "go" cues (eg, directional arrows), but attempt to suppress responses when a stop signal occurs some period of time after presentation of the go cue. The chief distinction is that GNG involves stopping responses before they have been initiated, while SSRT involves termination at a later stage of the motor response. For the latter type of task, the period between the "go" and "stop" signal is varied using a tracking algorithm over the course of the task for each participant depending on performance. This enables calculation of the stop-signal reaction time, which is a measure of the internal time required to stop the already-triggered motor command.

Multiple tiers of evidence from functional magnetic resonance imaging (fMRI) findings, individuals with focal frontal lobe lesions, and animal research have demonstrated that response inhibition is sub-served by a neural network that encompasses the right inferior frontal gyrus (RIFG) and sub-cortical (including sub-thalamic) connections.[32,35] Pharmacological manipulations in rats and in humans suggest that inhibitory control, as operationalized by the SSRT, falls under the neuromodulatory influence of the noradrenaline/ norepinephrine system.[36–38] In contrast, serotonin appears not to be centrally involved in this particular measure of impulsivity.[35,39]

Impaired response inhibition has been reported across many impulsive–compulsive disorders to different degrees. Motor impulsivity in the context of ADHD is perhaps the best-studied construct. Meta-analysis has indicated that people with ADHD, which may be considered the archetypal impulsive disorder, manifest impaired response inhibition with a medium–large effect size (Cohen's D = 0.64–0.89).[40,41] This paradigm is useful in understanding treatment mechanisms for the disorder. Medications with demonstrable efficacy in treating the core impulsive symptoms of ADHD, such as methylphenidate (stimulant) and atomoxetine (selective noradrenaline reuptake inhibitor, SNRI), have been shown to improve response inhibition in ADHD patients following acute administration.[35,42,43]

In a study in healthy volunteers that combined pharmacological manipulation with functional MRI (pharmaco-fMRI), it was found that single-dose atomoxetine augmented right frontal brain activation during inhibitory control on the SSRT task, and that the extent of augmentation correlated with greater drug plasma levels.[44] Using a flanker GNG task and a higher atomoxetine dose in pharmaco-fMRI, more failed inhibitions were observed in healthy volunteers after medication (single dose), along with drug-dependent increases in error-signaling in bilateral inferior frontal

cortices and the pre-supplementary motor area (pre-SMA).[45] More recent work has sought to explore the effects of methylphenidate and atomoxetine on inhibitory control during pharmaco-fMRI in ADHD itself. Cubillo *et al* found that both medications (single-doses) normalized left prefrontal cortex under-activation (observed versus controls), while similar right-sided effects were more pronounced for methylphenidate.[46] Collectively, these data suggest that people with ADHD show motor impulsivity coupled with fronto-striatal dysfunction, both of which can be normalized, to some degree, with ADHD medication. However, considerably more work is needed to elucidate the precise mechanisms (eg, specific receptor subtypes involved), reasons for different responses across individuals, and brain effects with longer-term dosing.

Neurocognitive studies of response inhibition as measured by the SSRT and GNG tasks have also been performed in predominantly "compulsive" disorders such as OCD. Such investigations have frequently reported abnormalities in motor inhibition in OCD[47] and possibly also in BDD.[48] Impaired response inhibition is shared by unaffected, first-degree relatives of OCD subjects.[49] In addition, the degree of impairment is significantly associated with reduced gray matter volume in the OFC and RIFG and increased gray matter volume in cingulate, parietal, and striatal regions.[50] Thus, structural variation in large-scale brain systems related to motor inhibitory control may mediate a component of the genetic risk for OCD and arguably represents a neurocognitive endophenotype of OCD-related response inhibition difficulties. Relative to comparison subjects, patients with OCD and their siblings additionally showed greater activation in the left pre-SMA during successful inhibition using the SSRT task,[51] as well as a state-dependent deficit in recruiting RIFG and right inferior parietal cortex, which may contribute to the inhibition deficit. Pre-SMA hyperactivity may therefore constitute another neurocognitive endophenotype of OCD that is possibly related to inefficient neural processing within the pre-SMA itself.

Impaired response inhibition on the SSRT task has been reported in other impulsive or compulsive disorders, including trichotillomania,[3] repetitive skin picking,[52] and pathological gambling.[53] However the neural basis of these deficits has yet to be clearly elicited in the majority of disorders. The SSRT deficit appears to be particularly pronounced in trichotillomania, with impairments similar to those seen in adults with ADHD when not taking their usual stimulant medication. In contrast, individuals with OCD show significantly less stop-signal impairment in direct comparison with those with trichotillomania.[3] It is, however, important to note that heterogeneity in the expression of SSRT deficits exists in these disorders, and some studies have not replicated the findings.[54] One possible explanation under active consideration is the existence of distinct subtypes of these disorders, each with a different neurocognitive profile.[55,56] Understanding cognitive heterogeneity in these disorders, for motor impulsivity, but also for all cognitive functions considered in this article, could be important in terms of enabling treatments that are tailored to individual patients.

Disadvantageous decision-making

Decision-making is typically quantified using gambling tasks such as the Cambridge Gamble Task (CGT), and the extent to which this represents a distinct domain of impulsivity has been debated.[57] The CGT fractionates different components of decision-making. As operationalized by this paradigm, impulsive decision-making is defined as (i) gambling an excessive proportion of one's points, (ii) disproportionately choosing the "risky" decision option (the option less likely to yield a win), or (iii) disproportionately "crashing out" and losing all one's points (going bankrupt). The Iowa Gambling Task (IGT), another decision making task, has yielded inconsistent results,[58,59] which could be a result of its potential sensitivity to additional cognitive processes such as reversal learning.[60] In comparison with the IGT, the CGT quantifies decision-making under risk with explicit probabilities rather than ambiguity, and also more specifically examines decision-making as opposed to other confounding cognitive domains (since it minimizes demands for learning, working memory, and cognitive flexibility).[59,61] Decision-making on the CGT and related tasks is mediated through orbitofrontal and related cortical circuitry under probable serotonergic modulation,[62] and subcortical circuitry under joint dopaminergic, noradrenergic, and serotonergic control.[63,64]

Although OCD has been conceptualized as "a disorder of decision-making,"[65] findings with the CGT and related tests have generally indicated intact decision-making in patients with OCD versus controls.[58,66] This finding is perhaps surprising given that the OFC is heavily implicated in the pathophysiology of the disorder. To some extent, an underlying decision-making deficit could have been masked by SSRIs, which many participants were taking in the above CGT studies, since there is reason to expect that these medications affect decision-making function. This issue is being explored further in medication-free OCD individuals. CGT decision-making was found to be intact in trichotillomania,[65] while children with ADHD showed impulsive decision-making on the aspects of tasks that were normalized by methylphenidate treatment.[67]

Pathological gambling is another condition in which logically one would expect decision-making impairments to manifest, since the core features are highly suggestive

of underlying difficulties in weighing options and taking appropriate risks based on the available environmental information. Consistent with this proposition, studies have identified disadvantageous decision-making not only in people with pathological gambling, but also in "at risk" individuals who currently do not meet clinical criteria.[60,68] Pathological gambling shows high comorbid expression with substance-use disorders and has been proposed as a useful model of "behavioral addiction" to explore the neurobiology underlying "addiction" without the potential confounding effects of repeated substance misuse on brain function. Supporting this proposition, disadvantageous decision-making occurs both in pathological gambling and in substance-use disorders (see below; Substance Addiction, Behavioral Addiction). Impaired CGT decision-making has also been found in people at elevated risk of suicidality.[37,69]

If we draw together findings related to disadvantageous decision-making, the emerging picture is of relatively spared decision-making in OCD and related grooming disorders (eg, trichotillomania), but of pronounced decision-making deficits in behavioral addiction (eg, pathological gambling) and substance addictions. These decision-making tendencies may predispose not only to these disorders but also to suicidality in some cases, with important clinical implications.

Choice impulsivity

Choice impulsivity (or "impulsive choice") refers to the excessive discounting of delayed reinforcement.[70] While a measure of choice impulsivity is theoretically obtainable from some decision-making tasks, more usually it is obtained in studies via a stand-alone temporal discounting task that is specifically designed for this purpose. Participants are trained to select between small rewards that are given immediately and larger rewards that are given after a relative delay. The temporal discounting function quantifies the effect of delay on preference: the greater the discounting parameter, the greater the choice impulsivity.[71] In rats undertaking a delay-discounting task (DDT), real-time increases in serotonin efflux were observed in the medial prefrontal cortices while increases in 3,4-di-hydroxy-phenylocetic acid (DOPAC, a dopamine metabolite) were observed in the OFC, suggesting a double dissociation between serotonergic and dopaminergic modulation of impulsive decision-making within distinct areas of frontal cortex.[72] Translational research indicates that pro-dopamine/noradrenaline stimulant medications generally reduce choice impulsivity, albeit not consistently.[73,74] There is also evidence from rats that D1 dopamine receptor antagonism increases choice impulsivity, as does alpha-2 adrenergic receptor agonism,[75] whereas changes in serotonin neurotransmission exert a complex influence on choice impulsivity, probably depending on the receptor type stimulated.[73,76] Moreover, recent studies in rats have also implicated glutamatergic[77–79] and cannabinoid[80,81] signaling in choice impulsivity.[82] It has been suggested that temporal discounting involves 3 distinct sets of neural regions: those involved in valuation (substantia nigra, ventral striatum, and VMPFC), cognitive control (anterior cingulate cortices and VMPFC), and imagery/prospection (medial temporal lobe).[83] White matter tract connections between these implicated neural nodes are also likely to be important, since it has been shown that reduced white matter integrity within fronto-striatal tracts is associated with higher choice impulsivity in healthy volunteers.[84]

To the knowledge of the authors, delay discounting (choice impulsivity) has not yet been studied in OCD, trichotillomania, or pathological skin picking. Exaggerated choice impulsivity has been reported in several ADHD studies.[85–88] Methylphenidate reduces discounting of rewards in children with ADHD,[89] but intriguingly, only for those rewards that are experiential (real money) rather than hypothetical. Increased impulsive choice has also consistently been observed in substance-addicted individuals, including those addicted to opiates, alcohol, tobacco, and psychostimulants.[90–92] These changes have been observed when money, substances, health, or freedom are used as rewards.[93–96] Interestingly, these increased discounting rates are absent or less prominent in former addicts,[92,94] suggesting that increased discounting is either a consequence of prolonged substance abuse or a predictor of unsuccessful abstinence. There is evidence from animal studies to support both explanations (see below).

Reflection impulsivity

Reflection impulsivity refers to a reduced tendency toward collecting salient information from the external environment before making a decision.[97] People who are "reflectively impulsive" tend to make choices rapidly rather than wait for more information germane to that decision to become available as time progresses. Reflection impulsivity is typically measured using information-sampling tasks such as the Cambridge Information Sampling Task (IST).[98] Research in rats found that reflection impulsivity was increased and reduced respectively by 5-HT2 receptor antagonism and agonism.[99] In healthy human volunteers, transient reduction of brain serotonin using the tryptophan depletion technique selectively disinhibited the suppressive effects of small losses of information sampling behavior on the IST, such that subjects collected more information despite their being a cost to this.[100] The neural substrates that mediate reflection impulsivity have yet to be delineated.

TABLE 2. Subdividing compulsivity: abbreviated summary of neurocognitive domains, tasks, and neural and neurochemical correlates

Neurocognitive domain	Definition	Task	Neural system	Neurochemistry
Contingency-related cognitive flexibility	Impaired adaptation of behavior after negative feedback	Probabilistic reversal-learning tasks	OFC, parietal cortex, and subcortical connections	Serotonin
Task/attentional set-shifting	Impaired switching of attention between stimuli	Extra-dimensional attentional set-shifting (CANTAB)	Ventrolateral PFC and subcortical connections[263]	Dopamine
Attentional bias/ disengagement	Impaired shifting of mental sets away from disorder-relevant stimuli	Attentional bias/disengagement tasks, eg, Dot-Probe, Stroop, Affective Go/No-Go (CANTAB)	Frontal and subcortical regions	Emotion-dependent attentional bias/disengagement: serotonin[264]
Habit learning	Lack of sensitivity to goals or outcomes of actions	Habit formation tasks testing appetitive or avoidance habit-learning	Fronto-striatal circuits Habit activity involves connections between premotor cortex and posterior putamen Goal-directed activity involves connections between VMPFC and caudate	Dopamine

OFC = orbitofrontal cortex; PFC = prefrontal cortex; VMPFC = ventromedial prefrontal cortex; CANTAB = Cambridge Neuropsychological Test Automated Battery.

Elevated reflection impulsivity has been found in people with substance dependence, and also in those who previously used illicit substances.[97,101] People with problem gambling (a clinical disorder that does not fulfill full criteria for pathological gambling, or putative prodromal form) showed increased reflection impulsivity compared to controls, as did alcohol-dependent individuals.[60]

There has been limited research using reflection impulsivity tasks in impulsive-compulsive disorders otherwise. Reflection impulsivity did not differ significantly between children with ADHD and healthy matched controls, nor was it affected by single-dose methylphenidate.[102] Reflection impulsivity was also found to be intact in OCD and trichotillomania,[65] and in pathological skin picking.[103]

Compulsivity: Neurocognitive Components and Role in Impulsive and Compulsive Disorders

Compulsivity is, perhaps, less well-defined or well-investigated than impulsivity. Compulsive behavior is likely to result from alteration within a wide range of neural processes, including attention, perception, and coordination of motor or cognitive responses. Convergent evidence from translational studies of mental disorders characterized by high levels of behavioral compulsivity, such as OCD, implicates "behavioral disinhibition," resulting from failures in "top-down" cortical control of fronto-striatal circuits, or alternatively from over-activity within striatal habit circuitry, as key neurocognitive mechanisms that underpin the repetitive performance of compulsive acts.[104] The diminished ability or tendency to restrain prepotent motor responses, as exhibited in studies of OCD patients using the SSRT task[3] (see above), raises the intriguing possibility that behavioral mechanisms that are usually considered to contribute toward impulsive behavior additionally contribute to disorders characterized by high levels of compulsivity and/or the tendencies to perform compulsive acts.

To date, neurocognitive measures of compulsivity have typically assessed the repetitive component of the construct with respect to the ability to flexibly (i) adapt behavior after negative feedback (eg, probabilistic reversal learning tasks) or (ii) switch attention between stimuli [eg, intra-dimensional/extra-dimensional (ID/ED) set-shifting task]. The diminished ability or willingness to disengage from repetitive acts or obsessive thoughts could be described as a persistence of a behavioral or mental set, or a diminished ability or willingness to shift sets. Perseveration of actions and thoughts could be conceptualized as reflecting cognitive inflexibility and representing a key neurocognitive process in compulsivity. Additionally, tasks that assess (iii) attentional bias or (iv) the formation of automatic stimulus-response behaviors (ie, habits) may contribute to compulsivity and so warrant consideration. See Table 2.

Contingency-related cognitive flexibility

Exerting flexibility in learning and unlearning behavior, based on (probabilistic) contingencies ("probabilistic reversal-learning"), may be particularly relevant to the development of compulsive tendencies. Contingency-related flexibility is dependent on serotoninergic systems[35,105] and has been linked to OFC function. OFC function contributes to the ability to use outcome expectancies in adapting future behavior,[106,107] as does thalamic and striatal function.[108–110] Perseverating on a behavior that was once rewarded, but is later associated with negative consequences, may reflect a lack of

flexibility in learning and result in rigid, maladaptive, or compulsive behavior. As such, (probabilistic) reversal-learning paradigms and tasks employing stimulus-response contingencies paired with changes in reward and loss schedules are relevant to investigate in relation to compulsivity.

Across species, reversal learning is impaired by lesions to the OFC but not the DLPFC.[111,112] Reduced activation of the OFC, lateral PFC, and parietal cortex is observed during reversal learning not only in patients with OCD but also in their unaffected, never-treated relatives.[113,114] Reversal-learning–related hypofunction, therefore, appears to be a candidate endophenotype for compulsivity that exists in people at increased genetic risk of OCD, even in the absence of chronic treatment or symptom confounders.

Task/attentional set-shifting

Task-shifting (also referred to as set-shifting or attention-switching) can be subdivided into rule-shifting and perception-shifting: whereas rule-shifting requires a change of goal-related information (a change of the task that should be performed), perception-shifting refers to reorienting of attention to different characteristics of the same stimuli.[115] A "set" usually refers to the characteristic that is relevant in a given trial (for example "color" when the task is to define the color of a stimulus, and the appropriate stimulus-response mapping). Set-switching and task-switching are sometimes used interchangeably. Rule-switching is associated with a greater engagement of the DLPFC, whereas perception-shifting is associated with a greater recruitment of the parietal cortex.[116]

The ID/ED shift task examines different components of attentional flexibility, including reversal learning, set formation and inhibition, and shifting of attention between stimulus dimensions (ED shifting).[117] Studies have demonstrated that ED shifting is impaired in OCD but not in trichotillomania,[3,118] and additionally in the unaffected first-degree relatives of OCD subjects,[48] which implicates this aspect of cognitive inflexibility as an additional candidate endophenotype for OCD-related compulsivity. Moreover, ED shift impairment has been identified in patients with obsessive-compulsive spectrum disorders including obsessive-compulsive personality disorder,[119] schizo-OCD,[120] and possibly BDD.[47]

Attentional bias/disengagement

Another concept that may contribute to compulsive symptoms within disorders such as OCD and BDD involves attentional bias, ie, the degree to which an individual attends or avoids attending disorder-relevant stimuli. Attentional bias involves preferential attention toward disorder-relevant stimuli, and is evident in anxiety, mood, and addictive disorders.[121,122] Attentional disengagement refers to the ability to disengage and shift attention away from disorder-relevant stimuli (eg, from disorder-relevant stimuli, relative to non-disorder–relevant stimuli).

Attentional disengagement difficulties may contribute to compulsive symptoms by inducing rigidity in the presence of disorder-relevant stimuli. Several neurocognitive studies have investigated the interfering effect of disorder-relevant material on task performance in OCD. For example, the presentation of OCD-related stimuli versus non-OCD–related stimuli results in increased difficulty in switching away from such stimuli in a stop-change paradigm in individuals with OCD.[123] The evidence concerning attentional bias toward OCD-related stimuli has been rather more varied and inconsistent,[124–127] which has been taken as evidence to distinguish OCD from other anxiety disorders. It remains possible that a bias may only be present in patients with specific symptoms and not others.[128] Patients with BDD may show a variety of disorder-relevant perceptual biases,[129] including a tendency to poorly recognize fearful expressions on the Facial Expression of Emotion: Stimuli and Test,[130,131] which implicates an influence of attentional bias on neurocognitive processing in this disorder as well.[47] Brain imaging studies in OCD suggest exaggerated symptom-specific frontal and subcortical activations to disorder-relevant stimuli in OCD patients,[132,133] which may reflect a sustained effort to suppress strong responses to OCD triggers.[131]

Habit learning

Repetitive performance of behaviors without apparent adaptive function may be characterized by not only a diminished ability to inhibit action, but also a lack of sensitivity to goals. In OCD, for example, many patients are fully aware that compulsive responses may have little to no relation to desirable outcomes, yet despite this knowledge, they continue to perform them. According to associative learning theories of instrumental behavior,[134,135] actions can be supported by 2 systems: a goal-directed system and a habitual system. When the goal-directed system functions, actions are performed to obtain desired goals or to avoid undesired events. After multiple repetitions, the habitual system begins to render behavior automatic,[136–138] allowing simple acts to be conducted without much effort. An imbalance between these systems is thought to contribute to OCD, whereby compulsivity is hypothesized to arise from a shift from goal-directed action to habit, rendering behavior insensitive to its outcome. In this way, habit

formation may be a process that captures the ego-dystonic aspect of compulsivity, while also appealing to the previously described deficits in response inhibition observed in OCD.

The hypothesis that habits may substantially contribute to OCD developed from the observation that the fronto-striatal circuits that are affected in OCD also mediate the formation of normal habits in healthy individuals and rodents.[139] Since then, several studies have tested this possibility and revealed a consistent pattern of dysfunction in OCD. The first such study examined the formation of appetitive habits, and observed that OCD patients show impairment in goal-directed learning, leading them to respond excessively to stimuli that are no longer associated with valuable outcomes.[140] A subsequent study replicated this effect using a different paradigm, and found that economic decision-making that relies on action–outcome simulation is impaired in OCD patients.[141] Another study tested whether OCD patients form habits in avoidance more readily than healthy control subjects. The authors found that this was the case and presented preliminary evidence to support the interesting possibility that rather than being driven by fear, the development of avoidance habits might actually induce irrational harm-related beliefs (obsessions) in some patients with OCD.[142]

Although a direct neuroimaging investigation of excessive habit formation in OCD is still wanting, basic research in healthy individuals and experimental animals has implicated the fronto-striatal circuits in the balance between goal-directed action and habit.[113,143] In a diffusion tensor imaging study, habitual action toward no-longer-rewarding outcomes was predicted according to the estimated white matter tract strength in the premotor cortex seeded from the posterior putamen (as well as by gray matter density in the posterior putamen determined with voxel-based morphometry). In contrast, flexible, goal-directed action was predicted by estimated tract strength in the ventromedial prefrontal cortex seeded from the caudate.[144] While the role of dopamine in human action control remains poorly understood, reducing dopamine function using acute dietary phenylalanine and tyrosine depletion has been shown to shift the balance of responding toward habitual control in females.[145]

Interestingly, habit formation is also thought to play a major role in drug addiction, as initially impulsive drug-seeking becomes compulsive with continued use.[8] An important avenue for future research will be to delineate the behavioral and neurobiological overlap between disruption in the habit system in disorders of appetitive compulsion such as drug addiction and disorders where avoidance compulsions are characteristic of the psychiatric phenotype, such as OCD.

How Far Do Impulsive and Compulsive Mechanisms Contribute to Disorders of Substance or Behavioral Addictions?

Substance addiction

Substance addiction may be defined as a chronic relapsing disorder characterized by diminished control over substance intake.[146] Almost by definition, the phenotype of substance addiction contains elements of impulsive and compulsive behavior. That is, the diminished ability or willingness to shift thoughts and behavior away from substance use and control urges to consume the substance, and the preference for the immediate reward (or, in some circumstances, reduction of distress) associated with substance intake over the, arguably larger, but delayed benefits associated with a non-addicted lifestyle, indicate that compulsive and impulsive traits, respectively, are inherent components of addiction.[8,9,91,133,147–153] Indeed, there is a wealth of evidence that shows impulse-control deficits and compulsive behaviors in humans with substance addictions. This has been demonstrated using tasks for impulsive action, such as GNG and SSRT tasks, impulsive choice in DDTs, and reflection impulsivity tasks, as well as self-report measures of impulsivity. Moreover, tasks that assess cognitive flexibility, such as set-shifting paradigms and probabilistic reversal-learning tasks, have also demonstrated impairments in individuals with substance addictions.[146,147,149,152] This begs the question of whether impulsive and compulsive behaviors represent vulnerability factors for addiction or are the consequence of prolonged excessive substance intake.

One way to address this issue is to perform prospective studies, or to compare addicted individuals with their non-addicted siblings. Importantly, studies in animals have provided evidence to indicate that there is a bidirectional relationship between impulsivity and addiction. Thus, high impulsivity on the 5-choice serial reaction time task (5-CSRTT; a rodent analogue of the continuous performance task) predicts sensitivity to the reinforcing properties of cocaine and nicotine, the progression to cocaine addiction–like behavior, and sensitivity to relapse after abstinence.[154–157] Furthermore, high levels of impulsive choice in a DDT are associated with increased alcohol and cocaine self-administration, and higher persistence of nicotine- and cocaine-seeking,[155,158–160], but interestingly impulsive response on these scales was not a good predictor of increased heroin self-administration.[161,162] Conversely, several studies have shown that a period of drug self-administration enhances impulsive behavior in the 5-CSRTT or DDT.[154,157,160,163–166] Interestingly, the increases in impulsivity in the DDT after heroin self-administration seem to be transient,[161] which is

consistent with studies in humans that show ameliorations in delay discounting in abstinent or former addicts.[92,94] The reduced impulsive choice in abstinent addicts could mean that increased discounting is the result of prolonged substance abuse, or that lower discounting rates represent a predictor for successful abstinence.[167] This latter suggestion is supported by the findings in animal studies that increased impulsivity in the DDT predicts slower extinction of self-administration and greater cue-induced reinstatement of extinguished responding.[155,157] Together, these studies provide evidence for the notion that impulse-control deficits are a risk factor for addiction, although this seems to depend on the type of impulsivity and substance used. In addition, substance abuse itself may enhance impulsivity, especially impulsive choice.

Recent studies in humans have also shed light on the validity of impulsivity as a vulnerability marker for addiction. Siblings of psychostimulant-addicted individuals were found to display higher levels of impulsivity in the SSRT[168,169] and higher self-reported impulsivity than controls (albeit lower than their addicted siblings).[168,170] These data suggest that motor impulsivity is a vulnerability factor for psychostimulant addiction, leading to the intriguing question as to what protects the impulsive, but non-addicted, individuals from substance-abuse problems. An important clue to this question is provided by studies that have shown increased sensation-seeking characteristics in recreational psychostimulant users as well as those with stimulant addiction, but not in their non-addicted siblings.[169,171] Together, these studies suggest that the combination of increased impulsivity and increased sensation-seeking, but not just 1 of these 2 characteristics, confers a greatly enhanced risk for psychostimulant addiction. Prospective studies have also provided evidence for impulsive behavior as a possible risk factor for addiction. Impulsive choice in a DDT was found to predict smoking,[172] and lower SSRT performance predicted alcohol- and drug-related problems in adolescents.[173] However, another study found SSRT performance not to predict the progression to heavy alcohol drinking in college students (in which performance on the Iowa Gambling Task did have predictive value[174]).

Regarding compulsivity, attentional set-shifting (in a rodent analogue of the Wisconsin Card Sort Test) has been shown to be impaired in rats with a history of methamphetamine self-administration,[175] and cocaine self-administration in rats and primates leads to reversal-learning deficits.[176,177] Importantly, compulsive aspects of addiction have been found to occur in animals after prolonged substance self-administration.[178,179] That is, after prolonged cocaine and alcohol intake, rodents have been shown to display insensitivity to punishment and persistent substance-seeking.[153,180–186] Recent studies have suggested altered functioning in the prelimbic PFC, nucleus accumbens core, and dorsolateral striatum as well as reduced forebrain serotonin (in particular through 5-HT2C receptors) as underlying mechanisms of compulsive substance-seeking in rodents.[181,187–191]

Whether compulsivity is a cause or consequence of addictive behavior has not been investigated in great detail. The animal studies cited above suggest that compulsivity results from substance abuse, contributing to the development of addictive behavior, particularly in vulnerable individuals, such as those with impulse-control deficits.[192,193] However, reduced cognitive flexibility has also been shown to predict addictive behavior to some degree in prospective and sibling studies.[168,172] In a resting-state fMRI study that directly compared OCD and stimulant-dependent individuals, reduced functional connectivity between the OFC and dorsal medial premotor cortex was observed in both patient groups, compared with healthy controls, and the degree of "OFC disconnection" correlated with ratings of clinical compulsivity,[194] which implicates functional OFC-disconnection as a possible endophenotype for compulsivity across diagnostic categories.

In summary, there is evidence to support the idea that impulse-control deficits represent a risk factor for substance addiction, and, conversely, that substance abuse induces or exacerbates impulsivity. Prolonged excessive substance use may lead to compulsive behavior, particularly in impulsive individuals.[153,169,191] Whether compulsive traits also comprise a vulnerability factor for addiction remains to be thoroughly investigated. Importantly, studies into the relationship between impulsive and compulsive behavior on the one hand, and substance addiction on the other, need to consider the heterogeneities of the impulsivity and compulsivity constructs as well as the substances abused. There is likely to be specificity regarding the subtype of impulsivity/compulsivity that is related to addiction to certain substances.[147,153,160,161]

Behavioral addiction

Arguably the best-studied behavioral addiction is pathological gambling, a condition that was recently reclassified as an addiction and renamed as "gambling disorder" in DSM-5.[7,195] Several theoretical models have been proposed to explain addictions and addiction vulnerability (eg, reward deficiency, impaired response inhibition and salience allocation, allostasis, misdirected motivations[196]), and most of these have applicability to gambling and substance-use disorders. Several studies have investigated reward processing in pathological gambling and have identified similarities with substance-use disorders. For example, using the monetary incentive delay task,

individuals with pathological gambling were found to demonstrate relatively reduced ventral striatal activation in anticipation of monetary rewards,[197,198]–a finding similar to that observed in people with alcohol dependence.[199] As in alcohol dependence, an inverse relationship between ventral striatal activation during reward anticipation and self-reported impulsivity was observed in both the pathological-gambling and alcohol-dependent groups,[196,200] which suggests that this feature of blunted ventral striatal activation across behavioral- and substance-addiction groups relates similarly to impulsivity. These findings resonate with those from neurocognitive assessments of people with gambling and alcohol-use problems in which both groups demonstrated greater impulsivity, but the alcohol-dependent group additionally showed impairments on executive functioning that are thought to involve greater involvement of the DLPFC.[201]

Preliminary findings suggest that these patterns might extend to other behavioral addictions. For example, binge-eating disorder, in part because of its association with poor impulse control, has been proposed to represent the eating disorder with the most similarities to addictions.[202] Obese individuals with binge-eating disorder, as compared to a body mass index–matched group without binge-eating disorder, show relatively diminished activation of the ventral striatum during reward anticipation,[203] which is a finding similar to those with alcohol dependence and pathological gambling.[196–198] Furthermore, preliminary data suggest that among individuals with binge-eating disorder, the degree of activation of the ventral striatum relates importantly to clinically relevant measures such as treatment outcome.[204] These findings highlight the importance of identifying clinically relevant subgroups of people with obesity and suggest the clinical relevance of impulsivity.[205–207] The extent to which these findings might extend to other behavioral addictions warrants direct examination.

Although dopamine function has been linked to reward processing in the striatum,[208] differences have been observed in striatal dopamine function in behavioral and substance addictions. For example, diminished D2-like dopamine receptor availability in the striatum has been reported in stimulant dependence and obesity, which provides support for a relationship between the disorders.[209] However, several studies indicate a lack of differences in D2-like dopamine receptor availability in the striatum between individuals with pathological gambling and those without, although dopamine has been preliminarily associated with risk-taking and mood-related impulsivity in pathological gambling.[210] Furthermore, among individuals with Parkinson's disease, those with pathological gambling showed differences in ventral but not dorsal striatal availability of D2-like dopamine receptors, as well as differences in ventral striatal displacement of [C11]raclopride during performance of a decision-making ("gambling") task, which suggests greater dopamine release in the group with pathological gambling.[209] These findings are similar to those in which individuals with dopamine dysregulation syndrome (taking more dopamine replacement therapy medications than prescribed, as if "addicted" to the medication) showed differences in ventral but not dorsal striatal D2-like dopamine receptor availability following levo-dopa administration.[211] Thus, there seem to be both similarities and differences in the relationships between striatal dopamine function and behavioral and drug addictions.

Advances in Understanding the Genetics of Impulsive and Compulsive Behaviors and Disorders

Intensive efforts have been made to characterize the cerebral circuits that underpin cognitive traits and to define their genetic vulnerability, which would potentially lead to new effective treatments in psychiatry.[212] The impulsivity trait is one of the most frequently studied traits in this regard. Impulsivity is at least moderately heritable in children[213] and in adults,[214,215] with a strong genetic continuity from mid- to late adolescence.[212] A 45% heritability of self-rated impulsivity in adults is compatible with the 3 twin studies that have been performed on the topic.[216–218] Compulsivity has been infrequently studied; to date the "compulsive" dimensions of OCD or obsessive-compulsive personality show little evidence of significant heritability.[219]

No genome-wide association study (GWAS) has yet been performed on impulsivity. Candidate genes, or testing the "usual suspects" (ie, mainly the genes coding for serotonin[220] or dopamine[221] receptors and/or transporters), have been analyzed. The *DRD2* A1-allele was associated with impulsive behaviors using a response inhibition test[222] and a DDT.[223] The A1 allele of the *DRD2* gene may therefore relate to (1) heightened reinforcement sensitivity, (2) greater need for practice to overcome inherent reinforcement-related learning deficits (associated with fewer dopamine receptors in key brain reinforcement sites), or (3) reduced inhibitory control.[224] Interestingly, some dopamine genes were associated with impulsivity and one or more addictive disorders, including *DRD4*, *DAT*, *MAOA*, and *COMT*,[225] which showed that a bridge between quantitative impulsivity and qualitative psychiatric disorders can be proposed.[226] In a large study that was conducted in adolescents, allelic variation in rs36024, a single nucleotide polymorphism that is involved in encoding the norepinephrine transporter (NET), was

significantly associated with extent of activation in the right frontal inhibitory network during successful response inhibition.[227] These findings accord well with the previously described pharmacological data, which linked norepinephrine with response inhibition and right frontal activation.[35,42,43]

Some of these genes had independent replication(s), and some even led to positive meta-analyses, but the effect size was limited (eg, the Taq1 A1 allele of the *DRD2* gene increased the risk of impulsive traits or disorders by only 30%[220]). The genes involved might therefore (1) have a role on specific characteristics of impulsivity, (2) may need to interact with environmental factors that are present only in subgroups of subjects to be deleterious (gene-by-environment interactions), (3) or may be numerous, with each mutation having an important impact but on a limited number of patients. Favoring this last hypothesis, 2 genes that may have a particularly strong relationship with impulsivity (*MAO-A* and *5-HT2B* genes) share different characteristics.[228,229] The genetic polymorphisms detected in these 2 studies concern rare and severe mutations (stop codons), involve dopamine and/or serotonin, and were revealed in very small samples of patients with high impulsivity associated with criminal offenses.

Does the Presence of Impulsivity or Compulsivity Have Prognostic Implications for Treatment Response?

As indicated above, there is a growing body of literature that implicates neurocognitive impulsivity (assessed as poor response inhibition, steep temporal discounting, and possibly disadvantageous decision-making) in multiple neuropsychiatric disorders. Parallel to this, the clinical implications of increased impulsivity for treatment response or treatment drop-out have been studied in prospective studies. In addictive disorders, there is evidence that higher levels of impulsivity, specifically in the areas of reward-related and motor impulsivity, but also attentional-bias,[230–233] result in earlier treatment drop-out, a higher likelihood of relapse into addictive behaviors/disorders, and/or exacerbation of substance-use–related problems. (For examples of motor impulsivity and reward-related impulsivity in substance-use disorders, see Nigg *et al*,[173] Schmitz *et al*,[234] Bowden-Jones *et al*,[235] Passetti *et al*,[236] and Krishnan-Sarin *et al*[237]; for examples in problem/pathological gambling, see Goudriaan *et al*,[238] Alvarez-Moya *et al*,[239] Blanco *et al*,[240] and Grant *et al*.[241])

Interestingly, the treatment setting may affect the influence that impulsivity has on treatment outcome: in a study that compared inpatient and outpatient treatment, impulsivity only influenced treatment outcome in the outpatient treatment setting.[242] This suggests that having a protective environment surrounding impulsive patients (ie, in a residential treatment setting) may restrict the negative influence of impulsivity on treatment outcome. With regard to other disorders, such as OCD, there is mixed evidence with regard to the prognostic role of neurocognitive functions for treatment response. A study of 138 OCD patients indicated that most neurocognitive measures did not predict treatment response to cognitive behavioral treatment with or without additional pharmacotherapy, although trends were found for several measures relating to cognitive flexibility such as performance on an alternation test and perseveration errors on the Wisconsin Card Sort Test (WCST).[243] A study of 63 pediatric OCD patients indicates that, on a broader level, diminished memory and executive functions may have a negative effect on treatment response to cognitive behavioral therapy and/or sertraline in children with OCD.[244] Of interest, in a study that included tests on impulsivity (Stroop) and mental flexibility (perseverations on a verbal learning test), lower perseveration was associated with better response to cognitive behavioral therapy (CBT), but with worse response to fluoxetine, which implies that this form of mental flexibility may be a neurocognitive predictor of divergent outcome directions for CBT versus fluoxetine. Given the small sample size (a total of 38 patients across 2 treatment conditions), this finding needs to be replicated in further studies, although a neuroimaging study (see below) from the same research group indicates that responsivity to CBT versus fluoxetine is predicted by differential structural brain characteristics as well.[245]

Neuroimaging data indicate that an important relationship exists between the neurocircuitry that underlies both reward impulsivity and attentional bias (cue reactivity) and treatment outcome in substance-use disorders. One of the first such studies investigating methamphetamine patients found that diminished frontal and cingulate cortex activity during a decision-making task was associated with a higher rate of relapse.[246] In an fMRI Stroop study, DLPFC activation was inversely associated with treatment retention, and VMPFC, striatal, and cingulate activation was positively associated with cocaine abstinence in cocaine-dependent subjects.[18] An independent component analysis of the fMRI Stroop data from the same cocaine-dependent subjects identified 5 functionally integrated activations linked to Stroop performance, with the 2 circuits involving predominantly striatal and ventral PFC regions associated with cocaine abstinence measures.[247] Preliminary findings in individuals with pathological gambling also link activations of these brain regions (VMPFC, ventral striatum) to treatment outcome.[248] Among treatment-seeking adolescent smokers who received behavioral therapies for smoking cessation,

fMRI Stroop measures related to within-treatment urine cotinine (nicotine metabolite) levels, with greater activation in the inferior frontal gyrus, insula, thalamus, and anterior cingulate, were associated with greater reductions in cotinine levels during treatment.[249] A study in smokers indicated that both behavioral responses (attentional bias to smoking-related words in a Stroop task) and decreased functional MRI connectivity between the anterior insula and dorsal anterior cingulate cortex were associated with relapse.[250] Neural responses in a gambling task indicate that reward impulsivity also relates to escalation of cannabis use.[251]

In OCD, several small treatment studies have focused on the unraveling of the neurophysiological mechanisms of treatment response. For instance, a study in 10 OCD patients showed an increase in N-acetyl-aspartyl-glutamate in the pregenual anterior cingulate cortex (ACC) and a decrease in glutamate plus glutamine (Glx) in the anterior middle cingulate cortex after CBT.[252] Structurally, smaller gray matter putamen in OCD, normalized in response to fluoxetine treatment compared to CBT treatment,[253] and smaller lateral OFC was associated with responsivity to fluoxetine, whereas larger right medial prefrontal cortex was associated with better response to CBT.[244] Functionally, higher insular responses in high-conflict trials in a Flanker task, diminished in response to CBT treatment in pediatric OCD patients,[254] and in another fMRI study, increased caudate activity on a cognitive flexibility task[255] was present in treated OCD patients. Positron emission tomography (PET) studies showed increased glucose metabolism in the caudate[256] and decreased thalamic glucose metabolism in combination with increased right ACC metabolism[257] to be associated with treatment response in OCD.

In addiction research, studies focusing on the neurophysiological mechanisms of treatment response are in their infancy.[258] Currently, only 3 neuroimaging studies[259–261] have focused on the neurobiological mechanisms of treatment in addiction, and only 1 of these studies included addictive behavior as an outcome measure.[261] In this study, lower baseline dopamine (DA) transmission was associated with worse treatment outcome, but the studied form of treatment–contingency management within a community reinforcement approach–did not change DA transmission in the responders.[261] In the 2 other studies that investigated neurophysiological mechanisms of action in substance dependence, one of the studies examined the effect of cue exposure training (CET) on changes in functional brain activations to alcohol cues.[258] CET was associated with diminished cue reactivity in frontostriatal brain circuitry, but no clinical outcomes were reported. In the other study, DeVito *et al*[260] investigated improvement on an (fMRI) Stroop task in 12 participants with an substance use disorder (SUD) by comparing treatment-as-usual to computer-assisted CBT combined with treatment as usual. The CBT-combined treatment resulted in better Stroop performance and lower frontal, ACC, and thalamic brain activation patterns in combination with decreased subthalamic nucleus (STN) activation compared to the healthy controls. Clearly, the topic of measuring neurophysiological mechanisms of behavior change in addictive disorders is in need of larger studies that include outcome measures relating to the relevant addictive disorder, in order to investigate how impulsivity and compulsivity interact and which role they play in the treatment effects of addiction.

In summary, there is evidence from neurocognitive and neuroimaging studies that specific aspects of impulsivity may contribute importantly to relapse in addictive disorders. In contrast, only a few studies have investigated the role of compulsivity for the course of neuropsychiatric disorders characterized by impulsive–compulsive characteristics, although existing data support roles for both impulsivity and compulsivity in treatment outcome (eg, see Alvarez-Moya *et al*[239] and Blanco *et al*[240]). For disorders that are more strongly associated with compulsivity, such as OCD, the few studies on the prognostic role of neurocognitive compulsivity in this disorder show mixed results. Neuroimaging studies that have investigated the neurophysiological mechanisms of both cognitive behavioral therapy and pharmacotherapy in OCD indicate that treatment effects are associated with metabolic and functional changes in the fronto-striatal brain circuitry. However, not all research results are consistently found across studies, and most of these studies were done in small (pilot) studies, which indicates the need for larger studies before translation of neurophysiological treatment mechanisms into treatment allocation in OCD can be made. Therefore, there is a clear need for studies on the prognostic value of compulsivity in addictive disorders, for studies on the prognostic value of both impulsivity and compulsivity for neuropsychiatric disorders like OCD, and for large-scale studies investigating the neurophysiological mechanisms of treatment response in addictive disorders and in OCD.

Next Steps for Research

Despite significant progress in our understanding of the constructs of impulsivity and compulsivity, their underlying psychobiology, and their contributions to various psychiatric disorders, much remains to be learned. Here we highlight a number of questions that seem particularly tractable using basic and clinical science methods.

First, there is a need to further clarify the operationalization of compulsivity and impulsivity. We have noted that a range of neuropsychological mechanisms

contribute to both impulsive and compulsive responses. Nonetheless, as many of the relevant studies comprise work on patients with putative impulsive and compulsive psychiatric disorders, it is difficult to draw generalized conclusions about the relationship between transdiagnostic behaviors and underlying mechanisms. There is a literature on clinician-rated and self-reported impulsive and compulsive symptomatology, some of which is based on dimensional self-reported measures of behavioral tendencies, and some of which is based on categorical psychiatric disorders. Further work is needed, in order to provide validated clinical measures that can be used transdiagnostically.

Second, while many of the advances in this area have relied on translational approaches, much further application of both basic and clinical neuroscience methods is needed. At an imaging level, new tools are available for addressing the mechanisms of impulsivity and compulsivity and for comparing and contrasting impulsive and compulsive disorders; these include functional and structural connectivity methods, along with novel developments in radioligands that are designed to quantify receptor binding for specific neurotransmitter receptors and transporters.[262] At a molecular level, there is again a need to apply recently developed methodologies to understand the precise basis of impulsivity and compulsivity, and to determine relationships between mental disorders; these include genetic sequencing methods, advances in epigenetics, and methods in proteomics and metabolomics. Much of the focus in this area has been on monoamine neurotransmitters; this needs to extend to include work on other neurotransmitter systems, molecules involved in neuroplasticity, and other relevant molecular systems.

Third, much clinical work in this area has focused on cross-sectional studies. There is a real need for longitudinal work, ranging from work to examine the prevalence and course of impulsive and compulsive disorders in the community, to work to examine the way in which impulsive and compulsive symptoms evolve over time in the community. Such work may well benefit from integration with basic and clinical neuroscience methods, so that we understand, for example, changes in neurocircuitry and molecular signatures over time, and their correlations with neuropsychological features and clinical symptoms over time. Work focused on proximal mechanisms (eg, understanding the precise genes and environments that predispose one to compulsive and impulsive responses) should be supplemented by work that addresses distal/evolutionary mechanisms (and so provides insight into the possible adaptive value of such responses).

The recent technological advances in imaging, genetics, and other domains thus offer a unique opportunity to investigate and better understand core components of disorders characterized by impulsivity and compulsivity. Improved understanding has a significant likelihood of being translated into improved and possibly personalized approaches toward prevention, treatment, and policy for a range of currently costly psychiatric disorders.

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REFERENCES:

1. Chamberlain SR, Sahakian BJ. The neuropsychiatry of impulsivity. *Curr Opin Psychiatry*. 2007; **20**(3): 255–261.
2. Potenza MN. To do or not to do? The complexities of addiction, motivation, self-control, and impulsivity. *Am J Psychiatry*. 2007; **164**(1): 4–6.
3. Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am J Psychiatry*. 2006; **163**(7): 1282–1284.
4. Hollander E, Cohen LJ. *Impulsivity and Compulsivity*. Washington, DC: American Psychiatric Press; 1996.
5. World Health Organization. *International Classification of Diseases*, 10th ed. (ICD-10). Geneva: World Health Organization; 1992.
6. Stein DJ, Hollander E. Obsessive-compulsive spectrum disorders. *J Clin Psychiatry*. 1995; **56**(6): 265–266.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013.
8. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci*. 2005; **8**(11): 1481–1489.
9. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn Sci*. 2012; **16**(1): 81–91.
10. Brewer JA, Potenza MN. The neurobiology and genetics of impulse control disorders: relationships to drug addictions. *Biochem Pharmacol*. 2008; **75**(1): 63–75.
11. Hollander E, Kim S, Khanna S, Pallanti S. Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. *CNS Spectr*. 2007; **12**(2 Suppl 3): 5–13.
12. Bienvenu OJ, Samuels JF, Wuyek LA, *et al*. Is obsessive-compulsive disorder an anxiety disorder, and what, if any, are spectrum conditions? A family study perspective. *Psychol Med*. 2012; **42**(1): 1–13.
13. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev*. 2005; **29**(3): 399–419.
14. Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. *J Clin Psychiatry*. 2006; **67**(3): 407–414.
15. Van Ameringen M, Mancini C, Patterson B, Bennett M, Oakman J. A randomized placebo controlled trial of olanzapine in trichotillomania. *Eur Neuropsychopharmacol*. 2006; **16**(suppl 4): S452.
16. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2009; **66**(7): 756–763.
17. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: Pharmacological treatment of tic disorders–efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev*. 2012; **37**(6): 1162–1171.
18. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry*. 2008; **64**(11): 998–1004.
19. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; **160**(4): 636–645.
20. Chamberlain SR, Menzies L. Endophenotypes of obsessive-compulsive disorder: rationale, evidence and future potential. *Expert Rev Neurother*. 2009; **9**(8): 1133–1146.
21. Kashyap H, Fontenelle LF, Miguel EC, *et al*. Impulsive compulsivity' in obsessive-compulsive disorder: a phenotypic marker of patients with poor clinical outcome. *J Psychiatr Res*. 2012; **46**(9): 1146–1152.
22. National Institute of Mental Health. Research domain criteria (RDoC). National Institute of Mental Health Web site. http://www.nimh.nih.gov/research-funding/rdoc/index.shtml. Accessed January 1, 2014.
23. Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. 2007; **362**(1481): 917–932.
24. van den Heuvel OA, Veltman DJ, Groenewegen HJ, *et al*. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2005; **62**(3): 301–309.
25. Page LA, Rubia K, Deeley Q, *et al*. A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res*. 2009; **174**(3): 202–209.
26. Gu BM, Park JY, Kang DH, *et al*. Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain*. 2008; **131**(Pt 1): 155–164.
27. Chamberlain SR, Menzies L, Hampshire A, *et al*. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008; **321**(5887): 421–422.
28. Hollander E, Wong CM. Obsessive-compulsive spectrum disorders. *J Clin Psychiatry*. 1995; **56**(4): 3–6; discussion 53–55.
29. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011; **12**(11): 652–669.
30. Luigjes J, Mantione M, van den Brink W, *et al*. Deep brain stimulation increases impulsivity in two patients with obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2011; **26**(6): 338–340.

31. Fineberg NA, Robbins TW, Bullmore E, *et al*. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology*. 2010; **35**(3): 591–604.
32. Potenza MN, de Wit H. Control yourself: alcohol and impulsivity. *Alcohol Clin Exp Res*. 2010; **34**(8): 1303–1305.
33. Aron AR, Poldrack RA. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005; **57**(11): 1285–1292.
34. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform*. 1984; **10**(2): 276–291.
35. Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 2003; **20**(1): 351–358.
36. Chamberlain SR, Muller U, Blackwell AD, *et al*. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science*. 2006; **311**(5762): 861–863.
37. Chamberlain SR, Del Campo N, Dowson J, *et al*. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry*. 2007; **62**(9): 977–984.
38. Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: therapeutic implications. *J Psychopharmacol*. 2013; **27**(8): 694–718.
39. Clarke HF, Walker SC, Crofts HS, *et al*. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *J Neurosci*. 2005; **25**(2): 532–538.
40. Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK. Executive functioning in adult ADHD: a meta-analytic review. *Psychol Med*. 2005; **35**(8): 1097–1108.
41. Chamberlain SR, Robbins TW, Winder-Rhodes S, *et al*. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry*. 2010; **69**(12): 1192–1203.
42. Aron AR, Dowson JH, Sahakian BJ, Robbins TW. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2003; **54**(12): 1465–1468.
43. Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK. Does methylphenidate improve inhibition and other cognitive abilities in adults with childhood-onset ADHD? *J Clin Exp Neuropsychol*. 2005; **27**(3): 278–298.
44. Chamberlain SR, Hampshire A, Muller U, *et al*. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. *Biol Psychiatry*. 2009; **65**(7): 550–555.
45. Graf H, Abler B, Freudenmann R, *et al*. Neural correlates of error monitoring modulated by atomoxetine in healthy volunteers. *Biol Psychiatry*. 2011; **69**(9): 890–897.
46. Cubillo A, Smith AB, Barrett N, *et al*. Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys. *Cereb Cortex*. 2014; **24**(1): 174–185.
47. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev*. 2005; **29**(3): 399–419.
48. Jefferies K, Laws K, Fineberg NA. Cognitive and perceptual processing in body dysmorphic disorder. *Eur Neuropsychopharmacol*. 2010; **20**(3): s309.
49. Chamberlain SR, Fineberg NA, Menzies LA, *et al*. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2007; **164**(2): 335–338.
50. Menzies L, Achard S, Chamberlain SR, *et al*. Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain*. 2007; **130**(12): 3223–3236.
51. de Wit SJ, de Vries FE, van der Werf YD, *et al*. Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. *Am J Psychiatry*. 2012; **169**(10): 1100–1108.
52. Odlaug BL, Chamberlain SR, Grant JE. Motor inhibition and cognitive flexibility in pathologic skin picking. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010; **34**(1): 208–211.
53. Verbruggen F, Adams RC, Van't Wout F, Stevens T, McLaren IP, Chambers CD. Are the effects of response inhibition on gambling long-lasting? *PLOS-one*. 2013; **8**(7): e70155. doi 10.1371/journal.pone.0070155 (in press).
54. Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Impulsivity and response inhibition in alcohol dependence and problem gambling. *Psychopharmacology (Berl)*. 2009; **207**(1): 163–172.
55. Grant JE, Odlaug BL, Chamberlain SR. A cognitive comparison of pathological skin picking and trichotillomania. *J Psychiatr Res*. 2011; **45**(12): 1634–1638.
56. Odlaug BL, Chamberlain SR, Harvanko AM, Grant JE. Age at onset in trichotillomania: clinical variables and neurocognitive performance. *Prim Care Companion CNS Disord*. 2012; **14**(4).
57. 9th Annual Scientific Meeting of the International Society for Research on Impulsivity. May 15, 2013; San Francisco, CA. http://www.impulsivity.org/pdf/Meeting%20Program%202013.pdf.
58. Cavedini P, Riboldi G, D'Annucci A, *et al*. Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes. *Neuropsychologia*. 2002; **40**: 205–211.
59. Nielen MM, Veltman DJ, de Jong R, Mulder G, den Boer JA. Decision making performance in obsessive compulsive disorder. *J Affect Disord*. 2002; **69**(1–3): 257–260.
60. Fellows LK, Farah MJ. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cereb Cortex*. 2005; **15**(1): 58–63.
61. Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Problem gamblers share deficits in impulsive decision-making with alcohol-dependent individuals. *Addiction*. 2009; **104**(6): 1006–1015.
62. Rogers RD, Everitt BJ, Baldacchino A, *et al*. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology*. 1999; **20**(4): 322–339.
63. Zeeb FD, Robbins TW, Winstanley CA. Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology*. 2009; **34**(10): 2329–2343.
64. Baarendse PJJ, Winstanley CA, Vanderschuren LJMJ. Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task. *Psychopharmacology (Berl)*. 2013; **225**(3): 719–731.
65. Sachdev PS, Malhi GS. Obsessive-compulsive behaviour: a disorder of decision-making. *Aust N Z J Psychiatry*. 2005; **39**(9): 757–763.
66. Chamberlain SR, Fineberg NA, Blackwell AD, *et al*. A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. *Neuropsychologia*. 2007; **45**(4): 654–662.
67. DeVito EE, Blackwell AD, Kent L, *et al*. The effects of methylphenidate on decision making in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2008; **64**(7): 636–639.
68. Odlaug BL, Chamberlain SR, Kim SW, Schreiber LR, Grant JE. A neurocognitive comparison of cognitive flexibility and response inhibition in gamblers with varying degrees of clinical severity. *Psychol Med*. 2011; **41**(10): 2111–2119.

69. Passetti F, Clark L, Davis P, *et al*. Risky decision-making predicts short-term outcome of community but not residential treatment for opiate addiction: implications for case management. *Drug Alcohol Depend*. 2011; **118**(1): 12–18.
70. Evenden JL, Ryan CN. The pharmacology of impulsive behaviour in rats VI: the effects of ethanol and selective serotonergic drugs on response choice with varying delays of reinforcement. *Psychopharmacology (Berl)*. 1999; **146**(4): 413–421.
71. Cardinal RN. Neural systems implicated in delayed and probabilistic reinforcement. *Neural Netw*. 2006; **19**(8): 1277–1301.
72. Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb Cortex*. 2006; **16**(1): 106–114.
73. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. *Neuroscience*. 2012; **215**: 42–58.
74. Pattij T, Vanderschuren LJMJ. The neuropharmacology of impulsive behavior. *Trends Pharmacol Sci*. 2008; **29**(4): 192–199.
75. van Gaalen MM, van Koten R, Schoffelmeer AN, Vanderschuren LJ. Critical involvement of dopaminergic neurotransmission in impulsive decision making. *Biol Psychiatry*. 2006; **60**(1): 66–73.
76. Baarendse PJJ, Vanderschuren LJMJ. Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. *Psychopharmacology (Berl)*. 2012; **219**(2): 313–326.
77. Floresco SB, Tse MT, Ghods-Sharifi S. Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology*. 2008; **33**(8): 1966–1979.
78. Wischhof L, Hollensteiner KJ, Koch M. Impulsive behaviour in rats induced by intracortical DOI infusions is antagonized by co-administration of an mGlu2/3 receptor agonist. *Behav Pharmacol*. 2011; **22**(8): 805–813.
79. Cottone P, Iemolo A, Narayan AR, *et al*. The uncompetitive NMDA receptor antagonists ketamine and memantine preferentially increase the choice for a small, immediate reward in low-impulsive rats. *Psychopharmacology (Berl)*. 2013; **226**(1): 127–138.
80. Wiskerke J, Stoop N, Schetters D, Schoffelmeer ANM, Pattij T. Cannabinoid CB1 receptor activation mediates the opposing effects of amphetamine on impulsive action and impulsive choice. *PLoS One*. 2011; **6**(10): e25856.
81. Navarrete F, Pérez-Ortiz JM, Manzanares J. Cannabinoid CB_2 receptor-mediated regulation of impulsive-like behaviour in DBA/2 mice. *Br J Pharmacol*. 2012; **165**(1): 260–273.
82. Winstanley CA. The utility of rat models of impulsivity in developing pharmacotherapies for impulse control disorders. *Br J Pharmacol*. 2011; **164**: 1301–1321.
83. Peters J, Buchel C. The neural mechanisms of inter-temporal decision-making: understanding variability. *Trends Cogn Sci*. 2011; **15**(5): 227–239.
84. Peper JS, Mandl RC, Braams BR, *et al*. Delay discounting and frontostriatal fiber tracts: a combined DTI and MTR study on impulsive choices in healthy young adults. *Cereb Cortex*. 2012; **23**(7): 1695–1702.
85. Rapport MD, Tucker SB, DuPaul GJ, Merlo M, Stoner G. Hyperactivity and frustration: the influence of control over and size of rewards in delaying gratification. *J Abnorm Child Psychol*. 1986; **14**(2): 191–204.
86. Sonuga-Barke EJ, Taylor E, Heptinstall E. Hyperactivity and delay aversion–II. The effect of self versus externally imposed stimulus presentation periods on memory. *J Child Psychol Psychiatry*. 1992; **33**(2): 399–409.
87. Sonuga-Barke EJ, Taylor E, Sembi S, Smith J. Hyperactivity and delay aversion–I. *The effect of delay on choice. J Child Psychol Psychiatry*. 1992; **33**(2): 387–398.
88. Tripp G, Alsop B. Sensitivity to reward delay in children with attention deficit hyperactivity disorder (ADHD). *J Child Psychol Psychiatry*. 2001; **42**(5): 691–698.
89. Shields K, Hawk LW Jr, Reynolds B, *et al*. Effects of methylphenidate on discounting of delayed rewards in attention deficit/hyperactivity disorder. *Exp Clin Psychopharmacol*. 2009; **17**(5): 291–301.
90. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron*. 2011; **69**(4): 680–694.
91. De Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict Biol*. 2009; **14**(1): 22–31.
92. Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacology (Berl)*. 2008; **200**(1): 1–26.
93. Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology (Berl)*. 1999; **146**(4): 447–454.
94. Madden GJ, Petry NM, Badger GJ, Bickel WK. Impulsive and self-control choices in opioid-dependent patients and non-drug-using control participants: drug and monetary rewards. *Exp Clin Psychopharmacol*. 1997; **5**(3): 256–262.
95. Petry NM. Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology (Berl)*. 2001; **154**(3): 243–250.
96. Petry NM. Discounting of money, health, and freedom in substance abusers and controls. *Drug Alcohol Depend*. 2003; **71**(2): 133–141.
97. Kagan J. Reflection–impulsivity: the generality and dynamics of conceptual tempo. *J Abnorm Psychol*. 1966; **71**(1): 17–24.
98. Clark L, Robbins TW, Ersche KD, Sahakian BJ. Reflection impulsivity in current and former substance users. *Biol Psychiatry*. 2006; **60**(5): 515–522.
99. Evenden J. The pharmacology of impulsive behaviour in rats V: the effects of drugs on responding under a discrimination task using unreliable visual stimuli. *Psychopharmacology (Berl)*. 1999; **143**(2): 111–122.
100. Crockett MJ, Clark L, Smillie LD, Robbins TW. The effects of acute tryptophan depletion on costly information sampling: impulsivity or aversive processing? *Psychopharmacology (Berl)*. 2012; **219**(2): 587–597.
101. Clark L, Roiser JP, Robbins TW, Sahakian BJ. Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstasy users. *J Psychopharmacol*. 2009; **23**(1): 14–22.
102. DeVito EE, Blackwell AD, Clark L, *et al*. Methylphenidate improves response inhibition but not reflection-impulsivity in children with attention deficit hyperactivity disorder (ADHD). *Psychopharmacology (Berl)*. 2009; **202**(1-3): 531–539.
103. Snorrason I, Smari J, Olafsson RP. Motor inhibition, reflection impulsivity, and trait impulsivity in pathological skin picking. *Behav Ther*. 2011; **42**(3): 521–532.
104. Fineberg NA, Potenza MN, Chamberlain SR, *et al*. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology*. 2010; **35**(3): 591–604.
105. Clarke HF, Walker SC, Crofts HS, *et al*. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *J Neurosci*. 2005; **25**(2): 532–538.
106. Pickens CL, Saddoris MP, Setlow B, *et al*. Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. *J Neurosci*. 2003; **23**(25): 11078–11084.
107. Pickens CL, Saddoris MP, Gallagher M, Holland PC. Orbitofrontal lesions impair use of cue-outcome associations in a devaluation task. *Behav Neurosci*. 2005; **119**(1): 317–322.
108. Ghahremani DG, Monterosso J, Jentsch JD, Bilder RM, Poldrack RA. Neural components underlying behavioral flexibility in human reversal learning. *Cereb Cortex*. 2010; **20**(8): 1843–1852.

109. Schlund MW, Ortu D. Experience-dependent changes in human brain activation during contingency learning. *Neuroscience*. 2010; **165**(1): 151–158.
110. Wrase J, Kahnt T, Schlagenhauf F, *et al*. Different neural systems adjust motor behavior in response to reward and punishment. *Neuroimage*. 2007; **36**: 1253–1262.
111. Boulougouris V, Dalley JW, Robbins TW. Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. *Behav Brain Res*. 2007; **179**(2): 219–228.
112. Hornak J, O'Doherty J, Bramham J, *et al*. Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *J Cogn Neurosci*. 2004; **16**(3): 463–478.
113. Remijnse PL, Nielen MM, van Balkom AJ, *et al*. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2006; **63**: 1225–1236.
114. Figee M, Wielaard I, Mazaheri A, Denys D. Neurosurgical targets for compulsivity: what can we learn from acquired brain lesions? *Neurosci Biobehav Rev*. 2013; **37**(3): 328–339.
115. Monsell S. Task switching. *Trends Cogn Sci*. 2003; **7**(3): 134–140.
116. Ravizza SM, Carter CS. Shifting set about task switching: behavioral and neural evidence for distinct forms of cognitive flexibility. *Neuropsychologia*. 2008; **46**(12): 2924–2935.
117. Lawrence AD, Sahakian B, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends Cogn Sci*. 1998; **2**(10): 379–388.
118. Watkins LH, Sahakian BJ, Robertson MM, *et al*. Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychol Med*. 2005; **35**(4): 571–582.
119. Fineberg NA, Sharma P, Sivakumaran T, Sahakian B, Chamberlain SR. Does obsessive compulsive personality disorder belong within the obsessive-compulsive spectrum? *CNS Spectr*. 2007; **12**(6): 467–482.
120. Patel DD, Laws KR, Padhi A, *et al*. The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. *Psychol Med*. 2010; **40**(6): 921–933.
121. Browning M, Holmes EA, Harmer CJ. The modification of attentional bias to emotional information: a review of the techniques, mechanisms, and relevance to emotional disorders. *Cogn Affect Behav Neurosci*. 2010; **10**(1): 8–20.
122. Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend*. 2008; **97**(1–2): 1–20.
123. Morein-Zamir S, Fineberg NA, Robbins TW, Sahakian BJ. Inhibition of thoughts and actions in obsessive-compulsive disorder: extending the endophenotype? *Psychol Med*. 2010; **40**(2): 263–272.
124. Moritz S, Fischer B, Hottenrott B, *et al*. Words may not be enough! No increased emotional Stroop effect in obsessive-compulsive disorder. *Behav Res Ther*. 2008; **46**: 1101–1104.
125. Moritz S, Jacobsen D, Kloss M, *et al*. Examination of emotional Stroop interference in obsessive-compulsive disorder. *Behav Res Ther*. 2004; **42**: 671–682.
126. Harkness EL, Harris LM, Jones MK, Vaccaro L. No evidence of attentional bias in obsessive compulsive checking on the dot probe paradigm. *Behav Res Ther*. 2009; **47**: 437–443.
127. Kyrios M, Iob MA. Automatic and strategic processing in obsessive-compulsive disorder: attentional bias, cognitive avoidance or more complex phenomena? *J Anxiety Disord*. 1998; **12**: 271–292.
128. Sizino da Victoria M, Nascimento AL, Fontenelle LF. Symptom-specific attentional bias to threatening stimuli in obsessive-compulsive disorder. *Comprehensive Psychiatry*. 2012; **53**(6): 783–788.
129. Clerkin EM, Teachman BA. Perceptual and cognitive biases in individuals with body dysmorphic disorder symptoms. *Cognition and Emotion*. 2008; **22**(7): 1327–1339.
130. Young A, Perrett D, Calder A, Sprengelmeyer R, Ekman P. *Facial Expressions of Emotion–Stimuli and Tests (FEEST)*. Version 2.1. London: Adult Mental Health, InnouAct; 2002.
131. Jefferies K, Laws K, Fineberg NA. Superior face recognition in body dysmorphic disorder. *Journal of Obsessive-Compulsive and Related Disorders*. 2012; **1**(3): 175–179.
132. Simon D, Kaufmann C, Musch K, Kischkel E, Kathmann N. Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. *Psychophysiology*. 2010; **47**: 728–738.
133. van den Heuvel OA, Veltman DJ, Groenewegen HJ, *et al*. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Arch Gen Psychiatry*. 2005; **62**: 922–933.
134. de Wit S, Dickinson A. Associative theories of goal-directed behaviour: a case for animal-human translational models. *Psychol Res*. 2009; **73**: 463–476.
135. Dickinson A, Balleine B. Actions and responses: the dual psychology of behaviour. In: *Spatial Representation: Problems in Philosophy and Psychology*. New York, Oxford University Press, 1993: 277–293.
136. Adams C. Variations in the sensitivity of instrumental responding to reinforcer devaluation. *Q J Exp Psychol (Colchester)*. 1982; **34B**: 77–98.
137. Adams C, Dickinson A. Instrumental responding following reinforcer devaluation. *Q J Exp Psychol (Colchester)*. 1981; **33**: 109–121.
138. Thorndike A. *Animal Intelligence: Experimental Studies*. Mcmillan, New York, USA, 1911.
139. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron*. 2000; **28**: 343–347.
140. Gillan CM, Papmeyer M, Morein-Zamir S, *et al*. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry*. 2011; **168**: 718–726.
141. Gillan CM, Morein-Zamir S, Kaser M, et al. Counterfactual Processing of Economic Action-Outcome Alternatives in Obsessive-Compulsive Disorder: Further Evidence of Impaired Goal-Directed Behavior. *Biol Psychiatry*. In press. DOI: 10.1016/j.biopsych.2013.01.018.
142. Gillan CM, Morein-Zamir S, Urcelay GP, *et al*. Enhanced Avoidance Habits in Obsessive-Compulsive Disorder. *Biol Psychiatry*. In press. DOI: 10.1016/j.biopsych.2013.02.002.
143. Balleine BW, O'Doherty JP. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology*. 2010; **35**: 48–69.
144. de Wit S, Watson P, Harsay HA, *et al*. Corticostriatal connectivity underlies individual differences in the balance between habitual and goal-directed action control. *J Neurosci*. 2012; **32**(35): 12066–12075.
145. de Wit S, Standing HR, Devito EE, *et al*. Reliance on habits at the expense of goal-directed control following dopamine precursor depletion. *Psychopharmacology (Berl)*. 2012; **219**(2): 621–631.
146. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association, Fourth Edition; 2000.
147. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron*. 2011; **69**: 680–694.
148. Ersche KD, Sahakian BJ. The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychol Rev*. 2007; **17**: 317–336.
149. Garavan H, Stout JC. Neurocognitive insights into substance abuse. *Trends Cogn Sci*. 2005; **9**: 195–201.
150. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011; **12**: 652–669.

151. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)*. 1999; **146**(4): 373–390.
152. Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol*. 2001; **11**: 250–257.
153. Verdejo-García A, Lawrence AJ, Clark L. Impulsivity as a vulnerability marker for substance use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev*. 2008; **32**: 777–810.
154. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. *Science*. 2008; **320**: 1352–1355.
155. Dalley JW, Fryer TD, Brichard L, *et al*. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*. 2007; **315**: 1267–1270.
156. Diergaarde L, Pattij T, Poortvliet I, *et al*. Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. *Biol Psychiatry*. 2008; **63**: 301–308.
157. Economidou D, Pelloux Y, Robbins TW, Dalley JW, Everitt BJ. High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. *Biol Psychiatry*. 2009; **65**: 851–856.
158. Broos N, Diergaarde L, Schoffelmeer ANM, Pattij T, De Vries TJ. Trait impulsive choice predicts resistance to extinction and propensity to relapse to cocaine seeking: a bidirectional investigation. *Neuropsychopharmacology*. 2012; **37**: 1377–1386.
159. Perry JL, Larson EB, German JP, Madden GJ, Carroll ME. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology (Berl)*. 2005; **178**(2-3): 193–201.
160. Poulos CX, Le AD, Parker JL. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. *Behav Pharmacol*. 1995; **6**: 810–814.
161. McNamara R, Dalley JW, Robbins TW, Everitt BJ, Belin D. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. *Psychopharmacology (Berl)*. 2010; **212**(4): 453–464.
162. Schippers MC, Binnekade R, Schoffelmeer ANM, Pattij T, De Vries TJ. Unidirectional relationship between heroin self-administration and impulsive decision-making in rats. *Psychopharmacology (Berl)*. 2012; **219**(2): 443–452.
163. Dalley JW, Laane K, Theobald DE, *et al*. Enduring deficits in sustained visual attention during withdrawal of intravenous methylenedioxymethamphetamine self-administration in rats: results from a comparative study with d-amphetamine and methamphetamine. *Neuropsychopharmacology*. 2007; **32**: 1195–1206.
164. Gipson CD, Bardo MT. Extended access to amphetamine self-administration increases impulsive choice in a delay discounting task in rats. *Psychopharmacology (Berl)*. 2009; **207**(3): 391–400.
165. Mendez IA, Simon NW, Hart N, *et al*. Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. *Behav Neurosci*. 2010; **124**: 470–477.
166. Winstanley CA, Bachtell RK, Theobald DEH, *et al*. Increased impulsivity during withdrawal from cocaine self-administration: role for ΔFosB in the orbitofrontal cortex. *Cereb Cortex*. 2009; **19**: 435–444.
167. Yoon JH, Higgins ST, Heil SH, *et al*. Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women. *Exp Clin Psychopharmacol*. 2007; **15**: 176–186.
168. Ersche KD, Jones PS, Williams GB, *et al*. Abnormal brain structure implicated in stimulant drug addiction. *Science*. 2012; **335**: 601–604.
169. Ersche KD, Turton AJ, Chamberlain SR, *et al*. Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. *Am J Psychiatry*. 2012; **169**: 926–936.
170. Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW. Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biol Psychiatry*. 2010; **68**: 770–773.
171. Ersche KD, Jones PS, Williams GB, *et al*. Distinctive personality traits and neural correlates associated with stimulant drug use versus familial risk of stimulant dependence. *Biol Psychiatry*. 2013; **74**(2): 137–144.
172. Audrain-McGovern J, Rodriguez D, Epstein LH, *et al*. Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug Alcohol Depend*. 2009; **103**: 99–106.
173. Nigg JT, Wong MM, Martel MM, *et al*. Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2006; **45**: 468–475.
174. Goudriaan AE, Grekin ER, Sher KJ. Decision making and response inhibition as predictors of heavy alcohol use: a prospective study. *Alcohol Clin Exp Res*. 2011; **35**: 1050–1057.
175. Parsegian A, Glen WB Jr, Lavin A, See RE. Methamphetamine self-administration produces attentional set-shifting deficits and alters prefrontal cortical neurophysiology in rats. *Biol Psychiatry*. 2011; **69**: 253–259.
176. Calu DJ, Stalnaker TA, Franz TM, *et al*. Withdrawal from cocaine self-administration produces long-lasting deficits in orbitofrontal-dependent reversal learning in rats. *Learn Mem*. 2007; **14**: 325–328.
177. Porter JN, Olsen AS, Gurnsey K, *et al*. Chronic cocaine self-administration in rhesus monkeys: impact on associative learning, cognitive control, and working memory. *J Neurosci*. 2011; **31**: 4926–4934.
178. Lesscher HMB, Vanderschuren LJMJ. Compulsive drug use and its neural substrates. *Rev Neurosci*. 2012; **23**: 731–745.
179. Vanderschuren LJMJ, Ahmed SH. Animals studies of addictive behavior. *Cold Spring Harb Perspect Med*. 2013; **3**(4): a011932.
180. Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. *Science*. 2004; **305**: 1014–1017.
181. Hopf FW, Chang SJ, Sparta DR, Bowers MS, Bonci A. Motivation for alcohol becomes resistant to quinine adulteration after 3 to 4 months of intermittent alcohol self-administration. *Alcohol Clin Exp Res*. 2010; **34**: 1565–1573.
182. Jonkman S, Pelloux Y, Everitt BJ. Differential roles of the dorsolateral and midlateral striatum in punished cocaine seeking. *J Neurosci*. 2012; **32**: 4645–4650.
183. Lesscher HMB, Van Kerkhof LWM, Vanderschuren LJMJ. Inflexible and indifferent ethanol drinking in mice. *Alcohol Clin Exp Res*. 2010; **34**: 1219–1225.
184. Pelloux Y, Everitt BJ, Dickinson A. Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology (Berl)*. 2007; **194**(1): 127–137.
185. Vanderschuren LJMJ, Everitt BJ. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science*. 2004; **305**: 1017–1019.
186. Wolffgramm J. An ethopharmacological approach to the development of drug addiction. *Neurosci Biobehav Rev*. 1991; **15**(4): 515–519.
187. Bock R, Shin JH, Kaplan AR, *et al*. Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nat Neurosci*. 2013; **16**: 632–638.
188. Chen BT, Yau HJ, Hatch C, *et al*. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature*. 2013; **496**: 359–362.
189. Kasanetz F, Deroche-Gamonet V, Berson N, *et al*. Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science*. 2010; **328**: 1709–1712.

190. Kasanetz F, Lafourcade M, Deroche-Gamonet V, *et al*. Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Mol Psychiatry*. 2013; **18**(6): 729–737.
191. Pelloux Y, Dilleen R, Economidou D, Theobald D, Everitt BJ. Reduced forebrain serotonin transmission is causally involved in the development of compulsive cocaine seeking in rats. *Neuropsychopharmacology*. 2012; **37**(11): 2505–2514.
192. Everitt BJ, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci Biobehav Rev*. 2013; **37**(9 Pt A): 1946–1954.
193. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn Sci*. 2012; **16**: 81–91.
194. Meunier D, Ersche KD, Craig KJ, *et al*. Brain functional connectivity in stimulant drug dependence and obsessive-compulsive disorder. *Neuroimage*. 2012; **59**: 1461–1468.
195. Potenza MN. Neurobiology of gambling behaviors. *Curr Opin Neurobiol*. 2013; **23**(4): 660–667.
196. Potenza MN. Biological contributions to addictions in adolescents and adults: prevention, treatment and policy implications. *J Adolesc Health*. 2013; **52**: s22–s32.
197. Balodis IM, Kober H, Worhunsky PD, *et al*. Diminished fronto-striatal activity during processing of monetary rewards and losses in pathological gambling. *Biol Psychiatry*. 2012; **71**: 749–757.
198. Choi J-S, Shin Y-C, Jung WH, *et al*. Altered brain activity during reward anticipation in pathological gambling and obsessive-compulsive disorder. *PLoS One*. 2012; **7**(9): e45938.
199. Wrase J, Schlagenhauf F, Kienast T, *et al*. Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage*. 2007; **35**: 787–794.
200. Beck A, Schlagenhauf F, Wustenberg T, *et al*. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry*. 2009; **66**: 734–742.
201. Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Problem gamblers share deficits in impulsive decision-making with alcohol dependent individuals. *Addiction*. 2009; **104**: 1006–1015.
202. Gearhardt AN, White MA, Potenza MN. Binge eating disorder and food addiction. *Curr Drug Abuse Rev*. 2011; **4**(3): 201–207.
203. Balodis IM, Kober H, Worhunsky PD, *et al*. Monetary reward processing in obese individuals with and without binge eating disorder. *Biol Psychiatry*. 2013; **73**(9): 877–886.
204. Balodis IM, Grilo CM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, Potenza MN. A pilot study linking reduced fronto-striatal recruitment during reward processing to persistent bingeing following treatment for binge-eating disorder. *Int J Eat Disord*. In press. DOI: 10.1002/eat.22204.
205. Ziauddeen H, Farooqi IS, Fletcher PC. Obesity and the brain: how convincing is the addiction model? *Nat Rev Neurosci*. 2012; **13**: 279–286.
206. Avena NM, Gearhardt AN, Gold MS, Wang GJ, Potenza MN. Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data. *Nat Rev Neurosci*. 2012; **13**: 514.
207. Ziauddeen H, Farooqi IS, Fletcher PC. Food addiction: Is there a baby in the bathwater? *Nat Rev Neurosci*. 2012; **13**: 514.
208. Zald DH, Boileau I, El-Dearedy W, *et al*. Dopamine transmission in the human striatum during monetary reward tasks. *J Neurosci*. 2004; **24**(17): 4105–4112.
209. Frascella J, Potenza MN, Brown LL, Childress AR. Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint? *Ann N Y Acad Sci*. 2010; **1187**: 294–315.
210. Leeman RF, Potenza MN. A targetted review of the neurobiology and genetics of behavioural addictions; an emerging area of research. *Can J Psychiatry*. 2013; **58**(5): 260–273.
211. Evans AH, Pavese N, Lawrence AD, *et al*. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol*. 2006; **59**(5): 852–858.
212. Millan MJ, Agid Y, Brüne M, *et al*. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012; **11**(2): 141–168.
213. Niv S, Tuvblad C, Raine A, Wang P, Baker LA. Heritability and longitudinal stability of impulsivity in adolescence. *Behav Genet*. 2012; **42**(3): 378–392.
214. Coccaro EF, Bergeman CS, McClearn GE. Heritability of irritable impulsiveness: a study of twins reared together and apart. *Psychiatry Res*. 1993; **48**: 229–249.
215. Kendler KS, Aggen SH, Czajkowski N, *et al*. The structure of genetic and environmental risk factors for DSM-IV personality disorders. *Arch Gen Psychiatry*. 2008; **65**(12): 1438–1446.
216. Hur YM, Bouchard TJ Jr. The genetic correlation between impulsivity and sensation seeking traits. *Behav Genet*. 1997; **27**(5): 455–463.
217. Pedersen NL, Plomin R, McClearn GE, Friberg L. Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. *J Pers Soc Psychol*. 1988; **55**(6): 950–957.
218. Seroczynski AD, Bergeman CS, Coccaro EF. Etiology of the impulsivity/aggression relationship: genes or environment? *Psychiatry Res*. 1999; **86**(1): 41–57.
219. Livesley WJ, Jang KL, Vernon PA. Phenotypic and genetic structure of traits delineating personality disorder. *Arch Gen Psychiatry*. 1998; **55**(10): 941–948.
220. Stoltenberg SF, Christ CC, Highland KB. Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012; **39**(1): 182–191.
221. Gorwood P, Le Strat Y, Ramoz N, *et al*. Genetics of dopamine receptors and drug addiction. *Hum Genet*. 2012; **131**(6): 803–822.
222. White MJ, Morris CP, Lawford BR, Young RM. Behavioral phenotypes of impulsivity related to the ANKK1 gene are independent of an acute stressor. *Behav Brain Funct*. 2008; **4**: 54.
223. Eisenberg DT, Mackillop J, Modi M, *et al*. Examining impulsivity as an endophenotype using a behavioral approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behav Brain Funct*. 2007; **3**: 2.
224. Rodriguez-Jimenez R, Ãvila C, Ponce G, *et al*. The TaqIA polymorphism linked to the DRD2 gene is related to lower attention and less inhibitory control in alcoholic patients. *Eur Psychiatry*. 2006; **21**: 66–69.
225. Gorwood P, Le Strat Y, Ramoz N, *et al*. Genetics of dopamine receptors and drug addiction. *Hum Genet*. 2012; **131**(6): 803–822.
226. Robbins T, Gillan C, Smith D, de Wit S, Ersche K. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn Sci*. 1996; **16**(1): 81–91.
227. Whelan R, Conrod PJ, Poline JB, *et al*. IMAGEN Consortium. Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nat Neurosci*. 2012; **15**(6): 920–925.
228. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science*. 1993; **262**: 578–580.
229. Bevilacqua L, Doly S, Kaprio J, *et al*. A population-specific HTR2B stop codon predisposes to severe impulsivity. *Nature*. 2010; **468**(7327): 1061–1066.
230. Streeter CC, Terhune DB, Whitfield TH, *et al*. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology*. 2008; **33**: 827–836.
231. Marissen MA, Franken IH, Waters AJ, *et al*. Attentional bias predicts heroin relapse following treatment. *Addiction*. 2006; **101**: 1306–1312.

232. Cox WM, Hogan LM, Kristian MR, Race JH. Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug Alcohol Depend*. 2002; **68**: 237–243.
233. Waters AJ, Shiffman S, Sayette MA, *et al*. Attentional bias predicts outcome in smoking cessation. *Health Psychol*. 2003; **22**: 378–387.
234. Schmitz JM, Mooney ME, Green CE, *et al*. Baseline neurocognitive profiles differentiate abstainers and non-abstainers in a cocaine clinical trial. *J Addict Dis*. 2009; **28**: 250–257.
235. Bowden-Jones H, McPhillips M, Rogers R, Hutton S, Joyce E. Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *J Neuropsychiatry Clin Neurosci*. 2005; **17**: 417–420.
236. Passetti F, Clark L, Mehta MA, Joyce E, King M. Neuropsychological predictors of clinical outcome in opiate addiction. *Drug Alcohol Depend*. 2008; **94**: 82–91.
237. Krishnan-Sarin S, Reynolds B, Duhig AM, *et al*. Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. *Drug Alcohol Depend*. 2007; **88**: 79–82.
238. Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. The role of self-reported impulsivity and reward sensitivity versus neurocognitive measures of disinhibition and decision-making in the prediction of relapse in pathological gamblers. *Psychol Med*. 2008; **38**: 41–50.
239. Alvarez-Moya EM, Ochoa C, Jimenez-Murcia S, *et al*. Effect of executive functioning, decision-making and self-reported impulsivity on the treatment outcome of pathologic gambling. *J Psychiatry Neurosci*. 2011; **36**: 165–175.
240. Blanco C, Potenza MN, Kim SW, *et al*. A pilot study of impulsivity and compulsivity in pathological gambling. *Psychiatry Res*. 2009; **167**: 161–168.
241. Grant JE, Chamberlain SR, Odlaug BL, Potenza MN, Kim SW. Open-label memantine treatment of pathological gambling reduces gambling severity and cognitive inflexibility: a pilot study. *Psychopharmacology (Berl)*. 2010; **212**(4): 603–612.
242. Passetti F, Clark L, Davis P, *et al*. Risky decision-making predicts short-term outcome of community but not residential treatment for opiate addiction: implications for case management. *Drug Alcohol Depend*. 2011; **118**: 12–18.
243. Moritz S, Kloss M, Jacobsen D, *et al*. Neurocognitive impairment does not predict treatment outcome in obsessive-compulsive disorder. *Behav Res Ther*. 2005; **43**: 811–819.
244. Flessner CA, Allgair A, Garcia A, *et al*. The impact of neuropsychological functioning on treatment outcome in pediatric obsessive-compulsive disorder. *Depress Anxiety*. 2010; **27**: 365–371.
245. Hoexter MQ, Dougherty DD, Shavitt RG, *et al*. Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive–compulsive disorder. *Eur Neuropsychopharm*. 2013; **23**(7): 569–580.
246. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry*. 2005; **62**: 761–768.
247. Worhunsky PD, Stevens MC, Carroll KM, *et al*. Functional Brain Networks Associated with Cognitive Control, Cocaine Dependence and Treatment Outcome. *Psychol Addict Behav*. 2013; **27**(2): 477–488.
248. Potenza MN, Balodis IM, Franco CA, *et al*. Neurobiological considerations in understanding behavioral treatments for pathological gambling. *Psychol Addict Behav*. 2013; **27**(2): 380–392.
249. Krishnan-Sarin S, Balodis IM, Kober H, *et al*. A preliminary examination of the relationship between neural correlates of cognitive control and reduction in cigarette use among treatment-seeking adolescent smokers. *Psychol Addict Behav*. 2013; **27**(2): 526–532.
250. Janes AC, Pizzagalli DA, Richardt S, *et al*. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol Psychiatry*. 2010; **67**(8): 722–729.
251. Cousijn J, Wiers RW, Ridderinkhof KR, *et al*. Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. *Addict Biol*. 2013; **18**(6): 1013–1023.
252. O'Neill J, Gorbis E, Feusner JD, *et al*. Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive-compulsive disorder. *J Psychiatr Res*. 2013; **47**(4): 494–504.
253. Hoexter MQ, de Souza Duran FL, D'Alcante CC, *et al*. Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. *Neuropsychopharmacology*. 2012; **37**(3): 734–745.
254. Huyser C, Veltman DJ, Wolters LH, de Haan E, Boer F. Developmental aspects of error and high-conflict-related brain activity in pediatric obsessive-compulsive disorder: a fMRI study with a Flanker task before and after CBT. *J Child Psychol Psychiatry*. 2011; **52**(12): 1251–1260.
255. Freyer T, Klöppel S, Tüscher O, *et al*. Frontostriatal activation in patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. *Psychol Med*. 2011; **41**(1): 207–216.
256. Apostolova I, Block S, Buchert R, *et al*. Effects of behavioral therapy or pharmacotherapy on brain glucose metabolism in subjects with obsessive-compulsive disorder as assessed by brain FDG PET. *Psychiatry Res*. 2010; **184**(2): 105–116.
257. Saxena S, Gorbis E, O'Neill J, *et al*. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. *Mol Psychiatry*. 2009; **14**(2): 197–205.
258. Morgenstern J, Naqvi NH, Debellis R, Breiter HC. The contributions of cognitive neuroscience and neuroimaging to understanding mechanisms of behavior change in addiction. *Psychol Addict Behav*. 2013; **27**(2): 336–350.
259. Vollstädt-Klein S, Loeber S, Richter A, *et al*. Validating incentive salience with functional magnetic resonance imaging: association between mesolimbic cue reactivity and attentional bias in alcohol-dependent patients. *Addict Biol*. 2011; **17**(4): 807–816.
260. DeVito E, Worhunsky P, Carroll K, *et al*. A preliminary study of the neural effects of behavioral therapy for substance use disorders. *Drug Alcohol Depend*. 2012; **122**(3): 228–235.
261. Martinez D, Carpenter KM, Liu F, *et al*. Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. *Am J Psychiatry*. 2011; **168**(6): 634–641. Erratum in: *Am J Psychiatry*. 2011; 168(5): 553.
262. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2011; **69**(12): e145–e157.
263. Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacology (Berl)*. 1999; **146**(2): 162–174.
264. Harmer CJ. Serotonin and emotional processing: does it help explain antidepressant drug action? Neuropharmacology2008; **55**(6): 1023–1028.