Fractionating impulsivity: neuropsychiatric implications

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Abstract | The ability to make decisions and act quickly without hesitation can be advantageous in many settings. However, when persistently expressed, impulsive decisions and actions are considered risky, maladaptive and symptomatic of such diverse brain disorders as attention-deficit hyperactivity disorder, drug addiction and affective disorders. Over the past decade, rapid progress has been made in the identification of discrete neural networks that underlie different forms of impulsivity — from impaired response inhibition and risky decision making to a profound intolerance of delayed rewards. Herein, we review what is currently known about the neural and psychological mechanisms of impulsivity, and discuss the relevance and application of these new insights to various neuropsychiatric disorders.

Impulsivity is a multifaceted trait in humans and other mammalian species and is generally regarded as a predisposition for rapid, but often premature, actions without appropriate foresight. Historically, impulsivity has long been an important psychiatric concept; Freud, Kraepelin and Bleuler all referred to 'impulse control' disorders: the 'development of apparently purposeless acts predominating over volitional ones' (REF. 1). The concept of the impulsivity trait became more widely accepted after Mischel's classic experiments[2] on how pre-school children between 4 and 6 years of age fail to resist the immediate temptation of eating marshmallows. The concept was further reinforced when this impulsive tendency was 40 years later shown to be predictive of adult achievement and brain function[3]. Recent progress in the neuroscientific approach to impulsivity has enabled a further dissection of component behavioural functions according to their underlying neural substrates.

The construct of impulsivity is highly compatible with new concepts of psychiatric classification that seek to define symptoms in terms of dimensions that extend across categorical disorders and that may represent extremes of normal tendencies[4]. In this Review, we demonstrate the translational applicability of this research to such psychiatric disorders as drug addiction, gambling, attention-deficit hyperactivity disorder (ADHD), Parkinson disease and affective disorders.

The multidimensional nature of impulsivity

Considerable research indicates that impulsivity is a non-unitary trait mediated by distinct psychological and neural mechanisms. Impulsive behaviour can be related to both increased motivation and reduced motivation ('apathy'), and it can represent either a failure to process information sufficiently or to control response output. This heterogeneity is captured by the Barratt Impulsiveness Scale (BIS)[5] (BOX 1), a set of three subscales of self-report questions, the wide use of which initially accelerated the field. Experimental attempts to capture the components of impulsivity are also illustrated in BOX 1 and FIG. 1. One attempt at taxonomy has been to distinguish 'impulsive action' — which is associated with differences in motor inhibition — from 'impulsive choice' — which is associated with differences in the control of value- or reward-based responding. This dichotomy seems useful but is in fact problematic; for example, some measures of impulsive action may segregate more reliably in neural and functional terms with measures of choice rather than with measures of action per se (see below).

Mischel's original test has been closely related to the paradigm of temporal discounting of reward[6], whereby impulsivity is associated with choosing a small, immediate reward over a large, delayed one. An alternative method for assessing impulsivity depends on self-restraint being exerted to prevent an inappropriate, premature response — responding before reward is actually due. For example, this can be measured when the subject — rodent or human — must wait before emitting the correct response to a visual cue[7,8]. Temporal discounting tests and premature-response tests assess 'waiting', which is also a component of reflective decision making[9] (whether perceptual or value-based), whereby it is adaptive to process sufficient information to make a correct choice.

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doi:10.1038/nrn.2017.8
Published online 17 Feb 2017

Box 1 | **Assessing impulsivity**

Impulsivity is widely assessed in humans using self-report questionnaires. These are often structured according to different subtypes of impulsivity but are subjective and typically correlate poorly with objective laboratory-based measures. Most objective methods to assess impulsivity are available in humans and experimental animals.

Questionnaire-based methods

The most commonly used questionnaire for assessing impulsivity is the Barratt Impulsiveness Scale[5]. Subjects are asked to read a list of statements relevant to attention, motor and planning impulsivity and to circle the most appropriate answer from: 'rarely/never'; 'occasionally'; 'often'; or 'almost always/always'. For example, participants select the most appropriate response to sentences aimed at probing their attention: "I 'squirm' at plays and lectures"; "I don't pay attention"; or "I often have extraneous thoughts when thinking". Motor impulsivity may be assessed using responses to the following sentences: "I do things without thinking"; "I act on impulse"; "I make up my mind quickly"; or "I am happy-go-lucky". In addition, participants' tendency to plan ahead can be assessed using their responses to the following sentences: "I plan tasks carefully"; "I am self-controlled"; "I save regularly"; or "I am more interested in the present than in the future".

Objective measures of impulsivity

Decisional impulsivity

There are three types of decisional impulsivity that can be objectively measured: temporal discounting, probabilistic discounting and reflection impulsivity.

- Temporal discounting is the preference for small, immediate rewards versus larger but delayed rewards. An impulsive choice in a temporal discounting task is reflected as a preference for smaller, more-immediate outcomes and follows a delay-dependent hyperbolic function[6]
- Probabilistic discounting describes the risk-based aspects of impulsive decision making. Impulsivity on a probabilistic discounting task is inferred by the greater preference of subjects for smaller, more likely rewards than for larger, less likely rewards
- Reflection impulsivity is the tendency to make rapid decisions without adequate accumulation and consideration of the available evidence[9,123,124]

Motoric forms of impulsivity

Motor impulsivity can be broadly dissected into different aspects by the stop-signal reaction time (SSRT) task and tests of premature responding. SSRT procedures measure the ability to stop a response after it has been initiated[10]. Tasks that assess premature responding measure the ability to resist responding before a defined waiting interval has elapsed. Premature responding is typically measured in rodents using variants of the 5-choice serial reaction time task[7], go/no-go tasks and differential reinforcement of low rates of responding (DRL) schedules. In humans, it is measured using the 4-choice serial reaction time task[98].

'Stopping impulsivity' is the tendency to stop an already chosen and initiated, but not fully executed, response — as in the stop-signal reaction time (SSRT) task[10]. This ability to stop a response after it has been initiated is valuable and adaptive when action outstrips thought.

Finally, the importance of value and uncertainty of the outcome of responding produces risky behaviour that is often associated with impulsivity ('risky impulsivity'); this is captured by the so-called probability discounting paradigm[11], in which risky options (for example, 50% chance of a large reward versus 100% chance of a smaller reward) are preferred. Of course, the risk could also be an occasional possibility of punishment pitted against a larger reward. The tendency to engage in risky behaviour is often associated with sensation seeking.

Although some of these components of impulsivity are related in various ways, suggesting overlapping mechanisms, it is often the case that they fail to inter-correlate very well or even dissociate in certain situations[11], suggesting also that some of the underlying neural mechanisms may be relatively independent of one another.

At the behavioural level, a theoretical framework of value-based decision making may also be useful for understanding the various components of risk and time discounting[12]. These considerations are crucial to understanding the aetiology, diagnosis and treatment of different psychiatric disorders that involve impulsive tendencies.

Differential reinforcement of low rates of responding (DRL) schedules
Schedules of reinforcement of instrumental behaviour in which the animal must wait for a given time after the last reinforcer before making an instrumental response.

Sensation seeking
A type of behaviour in which individuals apparently seek certain types of experience (such as mountaineering) despite the associated risks.

Neural substrates of impulsivity

Human studies (generally those including functional neuroimaging) and behavioural experiments in animal models have helped to determine the neural substrates of impulsivity. Recently, these two approaches have begun to converge to provide viable candidate neural networks for mediating impulsive behaviour. Both approaches suggest that striatal interactions with the prefrontal cortex (PFC) and the hippocampus are central to impulsivity, with neuromodulation by the ascending monoamine systems, as well as an increasing number of other chemical influences, also being important[13]. Further convergence of findings in humans and experimental animals is anticipated by the refinement of circuit-based homologies in non-human primates and rodents[14].

Nucleus accumbens and dorsal striatum

The nucleus accumbens (NAc) — which receives dopamine (DA) input from the ventral tegmental area — has been identified as a key structure for certain forms of impulsivity (FIG. 2) by three key pieces of evidence. First, depletion of DA within the NAc greatly affects the

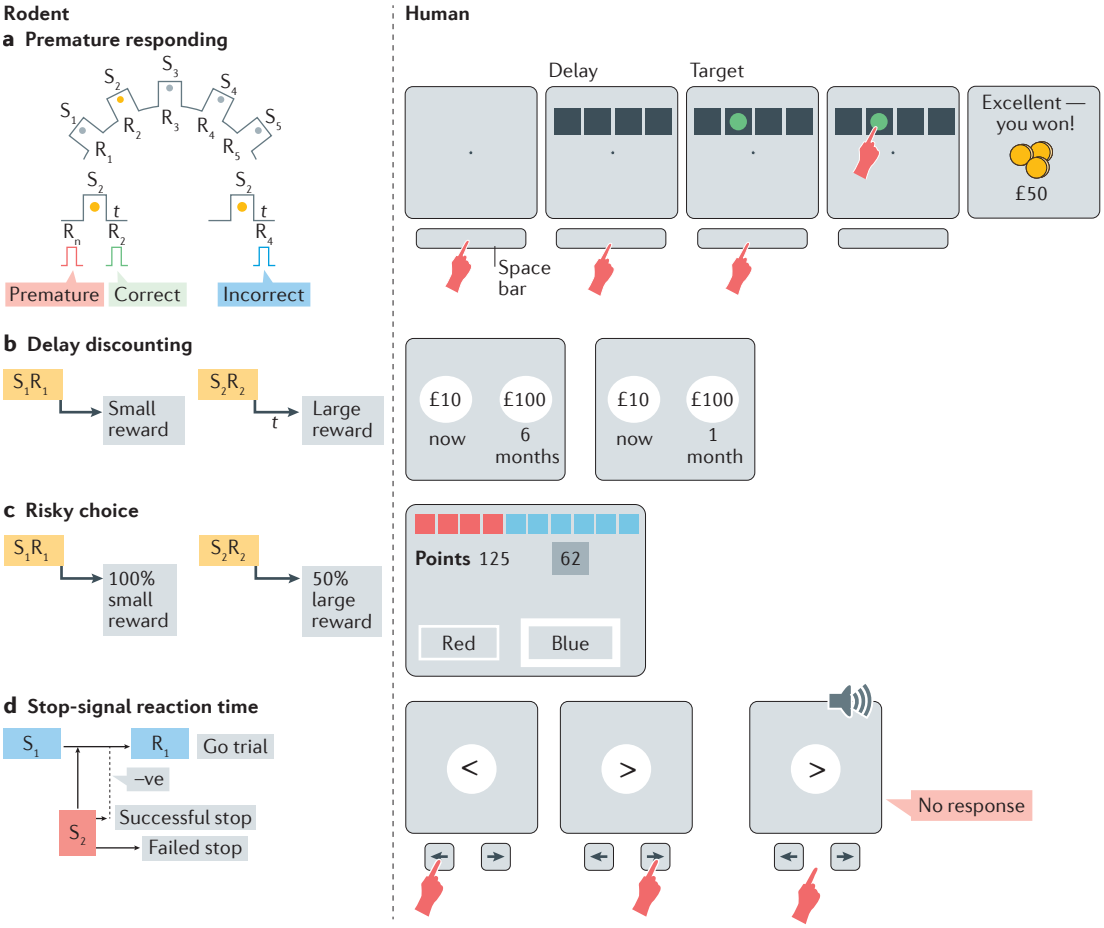

Figure 1 | **Translatable experimental paradigms to assess impulsivity in rodents and humans. a** | The main measure of impulsivity on the 5-choice serial reaction time task is premature responses. Rodents are trained to detect brief flashes of light to earn food from one of five apertures. Hence, when stimulus hole S_2 is illuminated, a response there (R_2) is correct, whereas a response in an alternative aperture (such as R_4) is punished by reward omission. However, the rodent has to wait for the visual targets to be presented before responding, and premature responses in any aperture (that is, R_n) are also punished. In the human (4-choice serial reaction time) version[70] (right panel), the subject places their finger on a space bar before releasing it to touch the visual target on a touch-sensitive screen. Premature releases of the button (as well as premature touching of the screen) can be measured as aspects of impulsive responding. **b** | In delay discounting, only two stimuli (S_1 and S_2) are used. Responding on one (for example, R_1) produces an immediate but small food reward (for example, one pellet), whereas responding on the other (R_2) produces a large food reward (for example, four pellets) but delayed by *t* seconds. Hyperbolic discounting of reward occurs as the rat discounts the value of the large reward according to the time it has to wait for it. In the human version (right panel), the choice is often presented in a verbal manner and over longer, hypothetical delays. **c** | In risky choice procedures (which assess probabilistic discounting), again only two stimuli are used (S_1 and S_2). Responding on one (for example, R_1) produces an immediate and consistent small food reward (such as one pellet) on every R_1 (that is, 100% of the time), whereas responding on the other (R_2) produces a large food reward (for example, two pellets) but only 50% of the time. Thus, expected overall rewards are equivalent in this case but R_2 is a 'riskier' response. The less likely R_2 is to be rewarded, the more likely the subject will choose R_1. There are many human versions of this type of task (which effectively amounts to gambling). The right panel depicts a screenshot from the Cambridge Gamble Task[152], in which the odds for reward choosing between red and blue are depicted explicitly on the screen in a row of red and blue boxes. Following the initial selection of a red or a blue box, the subject can 'bet' a proportion of their points on whether their selection is correct, earning an equivalent number if correct and losing them if not. The aim of the task is to accrue as many points as possible. **d** | The stop-signal reaction time task measures the time it takes to cancel or inhibit an already initiated response[153]. Thus, following S_1, a subject typically rapidly responds R_1, but, if a stop-signal (S_2) is presented any time after R_1 initiation on a proportion of trials, then R_1 has to be aborted for a successful stop. If it is not, and R_1 proceeds to completion ahead of inhibition (which is represented as '–ve'), then the trial fails. By measuring the time it takes to successfully stop 50% of the time (and taking into account the delay of S_2 presentation after R_1 is initiated), a stop-signal reaction time can be computed. This task has been implemented in rodents in various ways, sometimes by the rapid completion of a two-response sequence, cancelling the second response on stop (S_2) trials. The human version (right panel) may use visual cues (for example, directional arrows) for S_1, with S_2 being an auditory 'beep'. In other words, the subjects usually respond as quickly as possible to the right or the left as indicated by the arrow, but must stop the response if a beep sounds a short time after the arrow has appeared. In some versions, they inhibit all responses; in others, they perform an alternative. Adapted with permission from REF. 70 and from REF. 152, Macmillan Publishers Limited.

5-choice serial reaction time task
(5CSRTT). A behavioural test of sustained attention; animals must detect brief signals that predict food rewards. Importantly, animals are punished for responding prematurely.

Nafadotride
A relatively selective dopamine D3 receptor antagonist.

Dopamine transporter
(DAT). A transmembrane protein that pumps dopamine from the synapse into the neuron. Some drugs (for example, cocaine, methylphenidate and amphetamine) increase synaptic dopamine levels by blocking DAT.

Amphetamine
A psychomotor stimulant drug (a catecholaminergic indirect agonist) that increases activity and arousal. It is used as an effective, although perhaps paradoxical, treatment for attention-deficit hyperactivity disorder.

Autoreceptors
Receptors found in the presynaptic neuronal membrane, at both the neuronal bodies and the terminals. Their activity negatively regulates neurotransmitter release.

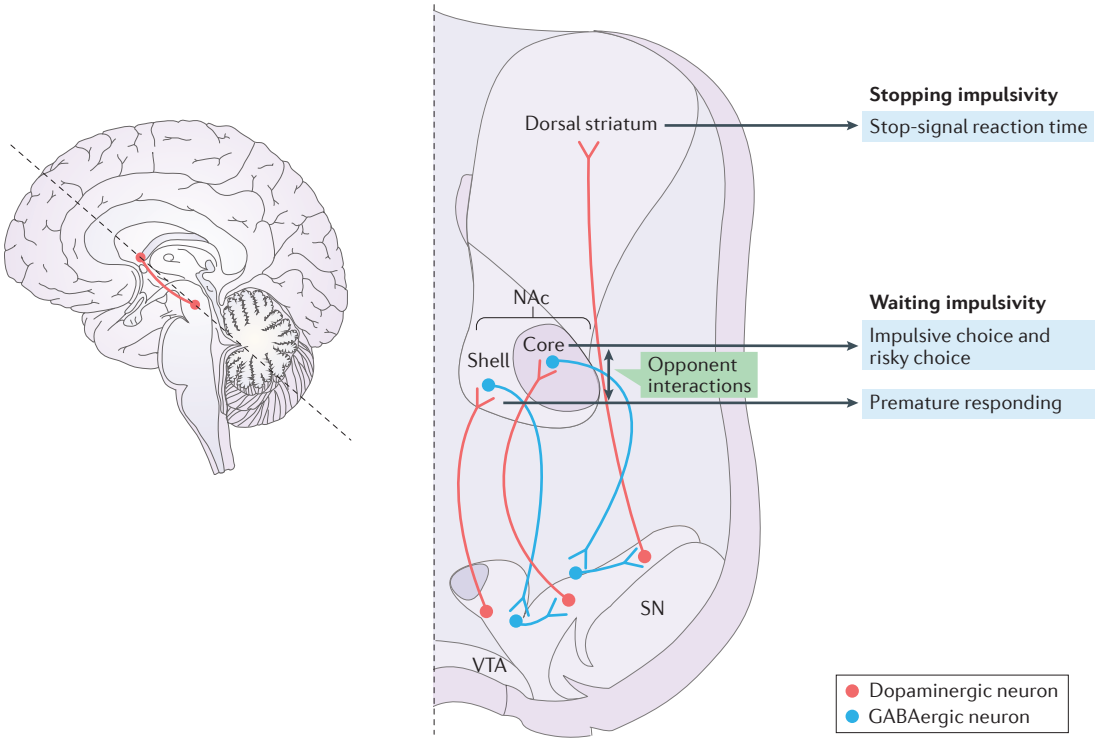

Figure 2 | **Distinct loci of 'stopping' and 'waiting' impulsivity in the dorsal and ventral striatum.** Stopping impulsivity is regulated by dorsostriatal-dependent mechanisms and is widely assessed as the ability of subjects to stop a response after it has been initiated. Tasks that assess waiting impulsivity measure the ability of subjects to withhold from responding until sufficient information has been gathered or until they are signalled to do so by explicit cues, often involving a choice between alternative outcomes (as in delay discounting and probability discounting tests), or after a waiting interval has elapsed (as measured by premature or anticipatory responding tasks). Waiting impulsivity is mainly regulated by convergent mechanisms within the ventral striatum, specifically by the core and shell subregions of the nucleus accumbens (NAc). Trait-like impulsivity on the rodent 5-choice serial reaction time task is associated with reduced dopamine D2 receptor availability in the NAc shell[20,154] and diminished concentration of glutamic acid decarboxylase — the rate-limiting enzyme responsible for GABA synthesis — in the NAc core[26]. Dopaminergic inputs to the dorsal and ventral striatum arise from the substantia nigra (SN) and ventral tegmental area (VTA), respectively, with dopamine cell bodies in these regions innervated by inhibitory GABAergic neurons, which form striatonigrostriatal loops that, through the SN, connect the NAc shell with the dorsal striatum[27]. This spiralling circuitry between ascending dopaminergic and descending GABAergic neurons may be responsible for the reported opponent interactions between the NAc core and NAc shell in waiting impulsivity[24]. Adapted with permission from REF. 155, Macmillan Publishers Limited.

frequency of premature responses in, for example, the 5-choice serial reaction time task (5CSRTT)[15]. Second, increased impulsivity in rats is associated with lower DA D2 and D3 receptor (D2/3R) ligand binding (reflecting lower numbers of receptors) in the NAc[16]. Third, excitotoxic damage to the NAc core subregion increases the tendency of rats to choose an immediate over a delayed food reward[17,18]. Here, we provide an overview of the role of the NAc in different forms of impulsivity.

Premature responding versus temporal discounting. The two distinct task-related expressions of impulsivity described to be affected by changes to the NAc (that is, failure to suppress premature responses, and failure to delay gratification) may depend on subtly different mechanisms within this structure. Whereas the capacity to delay gratification is associated with decreased DA release in the NAc core, impulsive premature responding is associated with decreased DA release in the core and increased DA release in the shell subregion[19].

The reduction in NAc D2/3Rs that is associated with increased premature responding was apparently restricted to the shell subregion[20], suggesting that it may be secondary to increased DA release in this region. This biochemical evidence is supported by findings that the D2/3R antagonist nafadotride also suppresses impulsive responding[21]. Moreover, dopamine transporter (DAT) expression is reduced in the shell of prematurely responding rats[20], presumably further increasing synaptic DA levels in this region. In addition, lesions of the shell block the premature responding that is induced by amphetamine, probably by disrupting the DA-release-promoting actions of this stimulant[22]. A plausible working hypothesis, therefore, is that premature responding results from excess DA levels in the shell region of the NAc. Increased DA release may thus be mediated by reduced DAT expression (leading to reduced DA clearance) and a compensatory downregulation of inhibitory D2/3 autoreceptors.

Intriguingly, impulsivity expressed as impaired delayed gratification seems not to be mediated by the shell region, as permanent excitotoxic lesions of the NAc shell generally do not affect this behaviour[18]. Nevertheless, reversible lesions of the NAc shell or the core increased impulsive choice on a T-maze task[23]. Further experiments are required to resolve this discrepancy, but, in general, it seems that premature responding and temporal discounting may be mediated primarily by distinct regions of the NAc.

Nucleus accumbens core versus shell in premature responding. The NAc core also seems to contribute importantly to premature responding on the 5CSRTT, albeit it in an 'opposite' way to the shell; lesions of the core exacerbate the impulsivity that is produced by amphetamine. Moreover, opposite to its effects in the core, when administered to the shell, nafadotride enhances premature responding[21]. Consistent with a functional opposition between the shell and the core, deep brain stimulation targeting the shell, but not the core, increases premature responding, presumably through antidromic stimulation of ventral tegmental area projections[24]. This opponent hypothesis is further supported by recent MRI evidence that trait-impulsive rats show decreased GABA levels in the ventral striatum (which includes the NAc)[25]. The core subregion of these animals also exhibits decreased grey-matter density, decreased GABA decarboxylase (GAD) expression (which presumably impairs GABAergic transmission in medium spiny cells of the core) and reduced expression of other synaptic proteins, such as spinophilin[26].

Premature responding can also be promoted in non-impulsive rats by infusions of antisense RNA to *Gad* in the core region[26]. Thus, premature responding may be linked to a dysregulation of DA in the shell subregion, leading to an output that is inadequately gated by the core subregion and expressed through the spiralling output pathways of the striatum[27]. A particularly important structure for mediating premature responding is the subthalamic nucleus (STN), which receives projections from the striatal indirect pathway[28]. In humans, low D2/3R binding in the midbrain predicts BIS scores of impulsivity; low numbers of D2/3Rs here are associated with elevated DA release in the striatum[29].

The original finding[17] that delay discounting is impaired by lesions of the core region of the NAc is thus consistent with evidence that rats that are impulsive on the 5CSRTT are also intolerant of delayed rewards[30], potentially owing to the overlapping involvement of the core subregion in both of these tasks[13]. The NAc also has important roles in processing primary and conditioned reward[18], but further analyses suggest that the effects of lesions to the NAc core on discounting cannot simply have been due to failures to discriminate reward magnitude[17,18].

'Waiting' impulsivity. The role of NAc DRs in delay discounting impulsivity does not seem to have been investigated, although systemically administered DR antagonists tend to enhance discounting, and systemic amphetamine, an indirect DA agonist, often increases preference for the large delayed reward[31], an effect that is not only sensitive to DR blockade but is also serotonin (5-HT) dependent[32]. Confirming a role of 5-HT in reducing waiting impulsivity, optogenetic activation of 5-HT neurons in the dorsal raphe nucleus decreased the tendency of mice to opt for the sooner, smaller reward in a delayed-reward task[33].

One complication of tasks that test waiting impulsivity is the difficulty of interpreting how a rodent perceives the large, later-reward contingency — for example, whether it is actually associated with the choice. If the large, later reward is signalled by a visual conditioned reinforcer, systemic amphetamine makes the animal more likely to take the large, later choice; however, if it is not signalled, the animal is more likely to opt for the small, sooner reward[32].

A recent study in rats showed that depletion of DA in the dorsolateral striatum also produced steep delay discounting of brain stimulation reward[34]. Moreover, lesions of the STN actually promote choice of the large, delayed reward[35] — that is, it reduces 'impulsive choice' — but decrease 'impulsive action' in the 5CSRTT[28] and in the SSRT task[36]. Thus, it seems that separate measures of waiting impulsivity respond differentially to manipulation of striatal DA and of the indirect (STN-dependent) pathway.

Delay discounting versus probabilistic discounting. Another relevant comparison is between delay discounting and probabilistic discounting. Excitotoxic lesions of the NAc core impair probabilistic discounting by reducing aversion to the risky choice[37]. Silencing the NAc with acute infusions of GABA agonists has broadly similar effects[38]. Similarly, NAc D1R blockade reduces risky choice, whereas a D1R agonist seems to promote risky choices[39]. D3R antagonism had effects almost opposite to those of D1R antagonism, possibly reflecting the role of presynaptic D3Rs in the negative regulation of DA release. Surprisingly, in the same study, neither D2R agonists nor D2R antagonists had obvious effects on risky choice[39], unlike findings for waiting impulsivity, although there is clear overlap in the neural substrates for both types of impulsivity. By contrast, other findings do support a role for D2R activation in affecting risky choice. The propensity of rats to be 'risk averse' when given a choice between an uncertain, large reward and a certain, smaller reward was reduced after D2/3R blockade and correlated with D2/3R binding in the NAc, as measured by micropositron emission tomography (microPET)[40]. By contrast, systemic and intra-NAc core administration of the D2R agonist pramipexole increased risky behaviour in rats[41]. Through optical recording of D2R-expressing cells of the NAc, the same study discovered that the activity of these cells signalled unfavourable recent outcomes and thus represented a naturally occurring correlate of risk preference that presumably was then able to influence subsequent decisions. Moreover, simulation of this phasic signal, through spatially and temporally precise optogenetic excitation of D2R-expressing NAc cells, rendered risk-preferring rats more risk averse[41]. Presumably, this

Antidromic
Referring to conduction of an action potential in the opposite direction; that is, away from the axon terminal to the cell body.

Striatal indirect pathway
A striatal output pathway in which striatal medium spiny neurons project via inhibitory neurons, first to the globus pallidus externa and thence to the subthalamic nucleus, which disinhibits the substantia nigra pars reticulata–globus pallidus interna.

Striatal direct pathway
A striatal output pathway in which inhibitory neurons directly project onto the cells of the substantia nigra pars reticulata–globus pallidus interna.

suggests that, whereas the D2R agonist normally eliminates the unfavourable recent outcome event by inhibiting D2R-expressing NAc neurons, excitation of the same neuron by another input or transmitter besides DA is sufficient to produce risk aversion.

Stopping impulsivity. Despite the evidence discussed above implicating the NAc in delay discounting, premature responding, waiting impulsivity and probabilistic discounting, the NAc does not seem to mediate all forms of impulsivity. Notably, in rodents, excitotoxic lesions of the NAc core had no effects on the SSRT task, which measures stopping impulsivity[42]. By contrast, excitotoxic lesions of the dorsomedial striatum slowed SSRT and impaired performance on this task — indicating a reduction in stopping impulsivity — an effect that is also induced by a D2R antagonist infused into the dorsal, but not the ventral, striatum[42,43]. Infusion of a D1R antagonist into the dorsal striatum surprisingly had the opposite effect — a speeding of SSRT — perhaps reflecting possible opponent functions of the striatal direct pathway and indirect pathway[43].

A human PET study using the DA ligands [^{11}C]NNC-112 and [^{18}F]fallypride examined individual differences in D1Rs and D2Rs, respectively, in relation to SSRT performance[44]. It confirmed that binding potentials in the dorsal, but not the ventral, striatum are associated with significant differences in SSRT performance, although in both the dorsal and the ventral striatum reduced response inhibition was negatively correlated with D2R binding[44]. Consequently, although there is considerable evidence that in the SSRT task striatal output pathways mediate a 'race' between a 'go' process and a 'stop' process, the relative roles of dopaminergic modulation of the direct and indirect striatal pathways remain to be defined. Nonetheless, these investigations of SSRT suggest a dissociation between mechanisms of inhibitory control while waiting for a reward and mechanisms for inhibitory control while cancelling a response that has already been initiated, consistent with different roles of the ventral and the dorsal striatum in controlling response sequences.

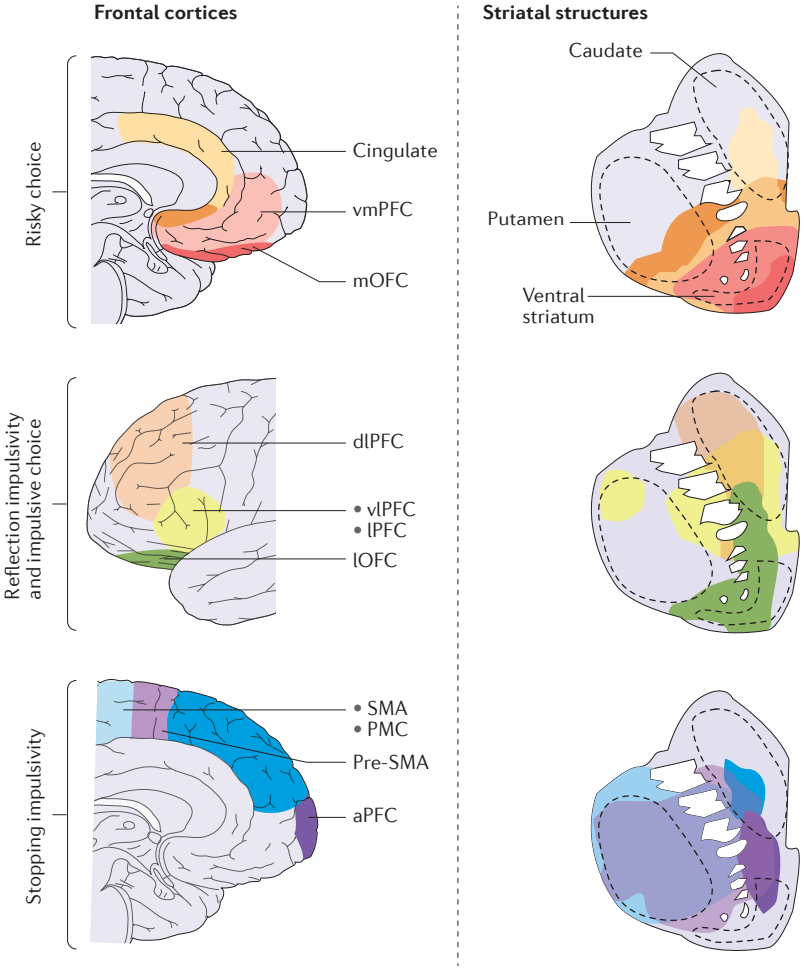

Figure 3 | **Topographical organization of the corticostriatal circuitry and associated impulsivity constructs in humans.** Risky choice, impulsive choice and stopping impulsivity are mediated by distinct cortical loci and striatal territories. Frontal and striatal areas sharing the same colouring show functional connectivity. The neural substrates of reflection impulsivity are less well understood but may involve structural abnormalities in the dorsolateral prefrontal cortex (dlPFC) and inferior parietal cortex[156]. aPFC, anterior PFC; lOFC, lateral orbitofrontal cortex; lPFC, lateral PFC; mOFC, medial OFC; PMC, premotor cortex; pre-SMA, pre-supplementary motor area; vlPFC, ventrolateral PFC; vmPFC, ventromedial PFC. Adapted with permission from REF. 157, Springer.

Neural networks of impulsivity

Although the striatum is an important neural focus of impulsive behaviour, it operates within a complex network comprising not only the basal ganglia themselves but also 'top-down' influences from limbic structures and the neocortex, including the PFC, and 'bottom-up' modulation from monoamine systems including, but limited to, the dopaminergic system. To some extent, the top-down mechanisms arise from the topographical projections of corticostriatal pathways (FIG. 3).

Impulsivity networks in rodents. Almost all of the afferent structures of the NAc have been shown to be relevant for its role in impulsive behaviour. Lesion, infusion and electrophysiological studies in freely moving animals have implicated the infralimbic cortex, insula and ventral hippocampus[45–49] (all of which project primarily to the shell subregion), as well as the cingulate cortex[50,51] (which projects mainly to the NAc core) and the dorsal striatum, in mediating premature responding in the 5SCRTT.

The basolateral amygdala and the hippocampus, as well as the lateral orbitofrontal cortex (lateral OFC) and medial OFC (mOFC) — but not the medial PFC[17] — have considerable modulatory effects on delay discounting[52–60]. The role of the OFC is especially highlighted by studies that have identified single units that show increased activity in response to rewards after a short delay compared with that in response to rewards after a long delay, independent of the absolute size of the reward[61].

Risk-based impulsivity seems to recruit neural circuits that are distinct from those that are involved in other forms of impulsivity. For example, whereas probabilistic discounting is not affected by lesions of the

ventral hippocampus (which is involved in premature responding in the 5CSRTT)[54], it does involve the mOFC. Reversible inactivation of the mOFC with baclofen or muscimol infusions increased risky choice in rats[62], without affecting discounting of delayed reward, again indicating some dissociation in controlling mechanisms, and highlighting the role of the mOFC in processing reward uncertainty[62]. By contrast, inactivation of the prelimbic cortex increased risky choice in rats when reward probabilities were initially high and decreased over the session, but had the opposite effect when the reward probabilities began low and subsequently increased[63].

The amygdala is also implicated in risky choice, via its connectivity with the NAc[64]. In addition, inactivation of the lateral habenula essentially randomized choice preference in a risk-based task[65]. It will be important in future studies to compare the effects of manipulations in different key structures and networks in several parallel forms of impulsivity. Optogenetic and chemogenetic approaches have been increasingly used to interrogate circuit-based mechanisms in impulsivity. Optogenetic silencing of glutamatergic neurons in the ventral PFC increased premature responding in the 5CSRTT, whereas the same intervention in the dorsal PFC reduced attentional accuracy in this task[66]. Consistent with the impairing effects of excitotoxic lesions of the anterior cingulate cortex on visual attention[67], impaired attention and processing speed was also observed after chemogenetic inactivation of neurons in the anterior cingulate cortex[68]. Rather surprisingly, however, chemogenetic activation of the mesolimbic DA system had no effect on premature responding in the 5CSRTT[69]. This null result may potentially be explained by a net cancellation of opponent dopaminergic mechanisms in the NAc core and shell, as discussed above; however, further experiments are needed to investigate this hypothesis.

Impulsivity networks in humans. Human brain imaging studies are especially useful for defining functional neural networks, although the capacity for convergence with the basic neuroscience findings clearly depends on the extent to which the various paradigms for defining impulsivity can be generalized across species. The recently introduced human 4CSRTT[70] has been used in conjunction with structural imaging and resting-state functional imaging. In humans, increased premature responding in the 4CSRTT is linked with reduced resting-state functional connectivity, specifically that of the right ventral striatum with the bilateral subgenual cingulate and bilaterally with the STN[71]. These findings thus provide translational support for convergent circuitry in humans and rodents. Moreover, these findings suggest a separation between the functional connectivity patterns that are associated with good performance in the 4CSRTT and those associated with motor response inhibition (as assessed by the SSRT task), which instead involves reduced connectivity of the hyperdirect pathway projections of the right pre-supplementary motor area (pre-SMA) to the left STN, and decreased connectivity between the dorsal caudate and the STN[71] — consistent with rodent data[36].

Hyperdirect pathway
Direct excitatory projections from several cortical areas, including the motor cortex, premotor cortex, supplementary motor area, anterior cingulate and dorsolateral prefrontal cortex, to the subthalamic nucleus, by-passing the striatum.

The neural circuits mediating performance on the SSRT task (and the partly overlapping go/no-go paradigm) have been highly specified in humans, and include elements of the anterior cingulate cortex, right inferior (lateral) frontal cortex, premotor and pre-supplementary cortex, striatum and STN[72]. In patients with frontal brain damage, the volume of grey matter lost in the right inferior frontal sulcus correlated most highly with prolongation of the SSRT measure (and not at all with the go reaction time)[73]. A subsequent functional MRI (fMRI) study also highlighted an association of the right inferior frontal cortex with premotor, striatal and STN circuitry during this task[74]. More recently, an fMRI study of 2,000 adolescents performing the SSRT task enabled a factor analysis of the structures that are activated during successful and failed stopping responses[75]. This revealed seven independent networks implicated in successful stopping: the bilateral putamen, caudate, pallidum and thalamus; the right inferior frontal gyrus, right insula and right anterior cingulate; the bilateral substantia nigra and STN; the bilateral superior and middle orbital gyri; the bilateral pre-SMA and precentral gyrus; the bilateral inferior and superior parietal lobes; and the bilateral medial orbital gyri. The network activated during failed stop trials involved similar regions except the pre-SMA node, suggesting that this region is important for the inhibitory process.

Aron *et al.*[76] reviewed evidence for a dedicated 'stopping' circuit and responded to various critiques of this evidence. One issue has been how specific the hypothesized stopping circuits are for response inhibition, as opposed to other component processes contributing to SSRT performance, such as sustained attention. This issue has prompted much theoretical and empirical analysis involving human electrophysiological investigations, as well as meta-analyses of many functional imaging studies. Cai *et al.*[77] reviewed 70 fMRI studies and concluded that two adjacent clusters of activation in the right insula and right inferior lateral frontal cortex exhibit distinct functional characteristics. Specifically, whereas the insula cluster was more closely coupled with the anterior cingulate and showed greater activation on unsuccessful SSRT trials, the inferior frontal cluster was functionally connected to the parietal cortex and dorsomedial PFC, had relatively greater activation on successful trials than on unsuccessful trials and showed a close relationship to individual differences in SSRT performance. This perhaps implies a more important role for the inferior frontal cluster in response inhibition than in monitoring outcomes of the task but does not exclude the possibility that this structure has other functions such as executive attention or overall motor control[78] and operates as a node in other neural networks. This strategic importance in executive functioning, including inhibitory control, has relevance for several neuropsychiatric disorders and the pharmacological treatment of their behavioural and cognitive impairments. The inferior frontal gyrus was recently reported to modulate the pre-SMA–STN excitatory circuit, leading to enhanced inhibition from the STN to the motor cortex. Notably, the strength of the connection between the pre-SMA and

Beta system
A set of brain regions, including the nucleus accumbens and medial prefrontal cortex, that are postulated to process immediate rewards and hypothetically interact functionally with the so-called delta system.

Delta system
A set of brain regions, including the dorsolateral and ventrolateral prefrontal cortex and parietal cortex, that are thought to discount rewards over longer time periods and to determine behaviour by interactions with the so-called beta system.

the STN and the strength of the modulation of this pathway by the inferior frontal gyrus predicted individual variation in SSRT performance[79].

The involvement of prefrontal structures in SSRT performance raises the intriguing issue of homology when relating these findings to rodent studies. Indeed, in rats, the cortical sites that most affect SSRTs seem to be in the lateral OFC and anterior cingulate[36] (the former possibly corresponding to the lateral inferior PFC site in humans), contrasting with the infralimbic prefrontal involvement in premature responding on the 5CSRTT in rodents[45]. Further analysis of the network nature of the response control that is exerted in the SSRT task may benefit from the suggested distinction between proactive and reactive modes of performance[80]. The proactive mode involves preparation for inhibition and has been linked to frontostriatal functioning, whereas reactive inhibition to the stop signal involves the hyperdirect cortical pathway to the STN[80].

Consistent with the evidence from basic neuroscience, human imaging studies implicate the ventral striatum, OFC, lateral PFC, insula, amygdala, posterior cingulate and parietal cortex in (often hypothetical) delay discounting for primary or conditioned rewards (for example, points or money)[81,82]. The so-called beta system — which includes the ventral striatum (including the NAc) and medial PFC — is associated with a preference for immediate rewards, whereas the delta system — which includes the dorsolateral PFC, ventrolateral PFC and parietal cortices — is activated during decisions involving delayed reward. The beta system is postulated to overestimate immediate rewards, whereas the delta system is thought to discount rewards over a constant rate with time. Alternatively, it has been proposed that delays may be encoded by the lateral PFC–parietal circuit, and reward magnitude by the ventral striatum–medial PFC[83]. However, these variables of reward magnitude and delay also have to be brought together for decisional computations, and there is evidence that this integration occurs in regions such as the right inferior lateral PFC[12,83]. More-impulsive individuals exhibited less neural activation related to the magnitude of future rewards in the ventral striatum and showed more-pronounced deactivations in the lateral PFC in response to delayed rewards[83]. Other evidence suggests that the ventral aspect of the anterior striatum processes choice for immediate rewards, whereas the dorsal posterior striatum is preferentially activated when choosing delayed reward[84].

Neural studies of risky impulsive decision making in humans have been led by the seminal dissection of neural mechanisms underlying preference for risk (that is, uncertainty with known probabilities of outcomes) versus preference for ambiguity (uncertainty with unknown probabilities of outcomes)[85]. The former was associated with posterior parietal cortex activation, whereas the latter was associated more strongly with lateral PFC activation. Notably, responses of the lateral PFC to ambiguous decisions were greater in participants deemed 'low-impulsive' on the BIS[85]. These findings accord with the widely acknowledged involvement of the lateral PFC in several measures of impulsivity and are relevant to the neural basis of temptation and willpower (BOX 2).

Neurochemical substrates

The neural networks underlying impulsivity are modulated by bottom-up signals such as those from the ascending monoamine projections, which include not only the mesolimbic DA pathways but also the ascending noradrenergic systems from the locus coeruleus and other brainstem structures and the 5-HTergic systems from the dorsal and median raphe nuclei[13,86].

Dopamine and noradrenaline

An overarching consideration when describing the neurochemical basis of impulsivity is the profound effects of psychomotor stimulant drugs such as methylphenidate (Ritalin; a DA- and noradrenaline-reuptake inhibitor) and amphetamine (an indirect DA agonist) on impulsivity, as indicated clinically by their use in treatment of ADHD. Given the aforementioned implication of DA in impulsivity and the fact that these drugs also affect noradrenaline and 5-HT signalling[87], it is still unclear precisely which actions are most relevant to the therapeutic effects of these drugs. Recently, it was shown that methylphenidate dose-dependently reduced premature responding and normalized the density of D2/3Rs in high-impulsive, low-striatal-D2R rats but increased premature responding in normally non-impulsive rats[88]. However, the behavioural effects in individual animals were not necessarily predicted by effects on D2R, and other possible mechanisms may be implicated. Foremost among these may be noradrenergic mechanisms; in line with this, the selective noradrenaline reuptake inhibitor atomoxetine has striking anti-impulsivity effects in all major impulsivity tests in rodents (including premature responding tests, delay discounting tasks and SSRT task)[89]. Furthermore, microinfusions of methylphenidate into the NAc core but not into the NAc shell increased premature responding, whereas infusions of atomoxetine into the shell but not into the core reduced premature responding[90].

This locus of action for atomoxetine in the premature responding task seems to contrast with that in the SSRT task, in which the drug is most effective in speeding

Box 2 | **Willpower**

Willpower is the capacity of individuals to repel short-term temptations in order to safeguard longer-term goals. The consistent involvement of the lateral prefrontal cortex (PFC) in paradigms measuring impulsivity evokes the concept of 'willpower'; failures of willpower through immaturity, ageing, fatigue or brain disease result in impulsive behaviour. There is an alternative mechanism for combating impulsivity, termed pre-commitment, in which there is a voluntary denial of access to temptation. A study directly comparing delay discounting with and without pre-commitment showed that discounting with pre-commitment recruited PFC mechanisms in the frontopolar cortex in addition to those willpower-associated regions that are usually activated in the standard delay discounting situation (without pre-commitment), such as the dorsolateral PFC, inferior lateral PFC and posterior parietal cortex[125]. Impulsive participants who stood to benefit more from pre-commitment — that is, those who were more likely to succumb to temptation when attempting to exert willpower — showed stronger connectivity between frontopolar and willpower regions during pre-commitment than did their less-impulsive peers. This increased connectivity was accompanied by activation of the ventromedial PFC during pre-commitment, suggesting calculation of the values of alternative courses of action[125].

SSRT when infused into those cortical regions that seem to control inhibitory performance (the anterior cingulate and lateral OFC)[91]. This conclusion is supported by pharmacological MRI[92]. The beneficial effects of atomoxetine (as well as methylphenidate[93]) on SSRT task performance in healthy humans, as well as in patients with ADHD[94] and Parkinson disease[95], similarly depend on its ability to specifically enhance connectivity between the inferior frontal cortex and anterior cingulate, as indicated in fMRI studies[96].

Serotonin

5-HT has long been implicated in behavioural inhibition, and hence in impulsivity. However, different forms of impulsivity seem to respond differentially to treatments affecting central 5-HT levels. Depletion of forebrain 5-HT greatly increases impulsive responding in the rodent 5CSRTT[97] and also in the human 4CSRTT[98] (via acute dietary tryptophan depletion), hence indicating considerable cross-species transferability. Premature responding in rats is reduced by 5-HT_{2A} receptor antagonism in either the medial PFC or the NAc[99,100], whereas intra-NAc 5-HT_{2C} receptor antagonism had the opposite effect[100]. These treatments exerted qualitatively similar effects on premature responding in 5-HT-depleted rats[101].

The role of 5-HT in delay discounting and probabilistic discounting is more complicated, with some findings indicating more-impulsive, rather than less-impulsive, choice after 5-HT depletion[13]. 5-HT neurons in the rat dorsal raphe show increased activity during delays to reward[102], indicating a possible role in reward anticipation, perhaps including the suppression of inappropriate responding. 5-HT depletion markedly impaired inhibitory control in go/no-go tasks but remarkably had much less effect in the SSRT task[103]. The selective 5-HT-reuptake inhibitor citalopram also had no substantial effects on SSRT in rat or human variants of the task[104,105]. This lack of effect of 5-HT manipulations in what is a classic version of an inhibitory response task is problematic for 5-HT theories of behavioural inhibition and may reflect a differential role of 5-HT modulation on selection versus execution of response sequences. However, in individuals with compromised 5-HT systems, as in those with Parkinson disease, citalopram — similar to atomoxetine[96] — enhances inferior frontal activation and improves SSRT performance[106].

Clinical syndromes of impulsivity

Impulsivity is an important dimension to consider in an entire set of impulse control disorders, ranging from substance abuse to compulsive gambling or eating, trichotillomania and Internet addiction[1].

Substance abuse

In the case of substance use disorders, a major question has been one of cause and effect: is the propensity to impulsive behaviour secondary to the neurotoxic effects of chronic drug exposure, or is it a predisposing trait[107]? This is a notoriously difficult issue to resolve experimentally but, in theory, can be addressed by longitudinal studies of human behavioural development or of endophenotypes, combined with animal models to probe for the two logical criteria for implicating causality: temporal precedence and intervention. Thus, several studies have now shown that rats with a propensity for impulsivity (as indicated by, for example, premature responding, steep discounting and risky behaviour) have a more pronounced drive to compulsive use of stimulant drugs, including not only cocaine but also nicotine[13,16,19,108], indicating that impulsivity may be a key factor that contributes to the development of addiction. This may not be the case for all drugs of abuse, although both opioid and alcohol addiction are associated with impulsive behaviour in humans[13]. A recent study showed that heavy alcohol use in humans is associated with increased premature responding on the 4CSRTT. Furthermore, in heavy social drinking volunteers, the severity of alcohol misuse correlated negatively with connectivity between the bilateral STN and the subgenual cingulate (as was anticipated from the rodent literature), suggestive of a possible endophenotype[71].

Distinct aspects of impulsivity are related to stimulant-drug abuse. Thus, individuals who abuse stimulants exhibit increased premature responding on the 4CSRTT, steeper temporal discounting, risky choice making and slowed SSRTs[71]. Stimulant-drug abusers' first-degree relatives who do not abuse drugs exhibit impairments in SSRT that are almost as great as those exhibited by their sibling drug abusers, and these impairments are associated with reduced white matter innervating the frontal lobes[109]. This similarity is consistent with the idea that a weakening of top-down inhibitory control is an endophenotype that confers risk of stimulant-drug abuse but is not simply a by-product of drug exposure. Presumably, the siblings who do not abuse drugs exhibit greater resilience to the temptations of drug abuse. Consistent with this idea, non-using first-degree relatives of drug users actually exhibit higher activity in the inferior frontal gyrus region during performance of a SSRT task than do drug users[110]. Moreover, in 2,000 healthy 14-year-old adolescents performing the SSRT task, activations in the OFC and inferior frontal and cingulate cortices were most predictive of their nascent abuse of alcohol, nicotine and illicit substances[75]. A major analysis of the influences on the development of alcohol use showed that impulsivity was indeed predictive, although only as one of many factors[111]. Another study of 1,015 young adults reported an association between sensation seeking and decreased cortical thickness of the anterior cingulate cortex and middle frontal gyrus[112]. This association extended to self-reported motor impulsivity on the BIS, which also correlated with, but was not caused by, use of alcohol, tobacco and/or caffeine. One issue raised by this study is therefore the exact relationship between impulsivity and sensation seeking and which of these traits best predicts compulsive substance use disorder.

Only a relatively small proportion (16%) of stimulant-drug users actually fulfil the *Diagnostic and Statistical Manual of Mental Disorders* criteria for substance use disorders and, interestingly, recreational users

Endophenotypes
A term from genetic epidemiology, implying, in psychiatry, an intermediate phenotype with a possible heritable basis, present not only in patients but also in their clinically non-affected first-degree relatives.

(who make up the residual 84%) do not generally exhibit strong evidence of impulsive behaviour or correlated brain changes, despite showing strong signs of sensation seeking — a trait not strongly evident in non-using siblings of compulsive drug users[113]. Thus, although they are possibly overlapping in part, impulsivity and sensation seeking may not be as strongly related as is sometimes assumed; nevertheless, their precise relationship requires further analysis.

High trait impulsivity in rats has been associated with compulsive drug seeking and a shift from goal-directed to habitual control over behaviour[114,115]. In this model, a lack of top-down inhibitory control over habits is hypothesized to be a basis for compulsive drug seeking behaviour. Habitual control in humans can be captured to some extent by a bias towards model-free learning algorithms in decision-making tasks. In support of the hypothesis described above, a recent fMRI study of 425 healthy volunteers confirmed that right lateral PFC signatures of model-based responses were reduced in high-impulsive individuals[116].

Attention-deficit hyperactivity disorder

Impulsive behaviour, along with inattention, is also a characteristic symptom of ADHD, and SSRT is generally lengthened in patients with ADHD[93]. In the study of 2,000 adolescents described above[75], participants with subclinical measures of ADHD-like behaviour, as measured by interviews and rating scales for the diagnosis of ADHD, had reduced activity on successful stop trials bilaterally in the inferior frontal cortex, as well as in the basal ganglia. A seminal study showed that the two common measures of impulsivity, delay discounting and SSRT, were not correlated in a large juvenile multicentre sample of patients with ADHD, but that together they accounted for much of the variance discriminating children with ADHD and unaffected control participants[117]. This result is entirely consistent with the hypothesis advanced in this Review that there are distinct forms of impulsivity that depend on different frontostriatal circuitries, and suggests a spectrum-like involvement of the frontostriatal systems that underlie subtly distinct forms of ADHD symptoms.

Other behavioural disorders

Important considerations bear on the relationship of impulsive behaviour to other potentially important dimensions of behaviour, such as compulsive responding, aggression and apathy. Whereas each of these dimensions is theoretically distinct from impulsivity (involving aberrant repetition of behaviour, enhanced irritability and amotivational states, respectively), they are nevertheless often associated with impulsivity. Apathy could result in reduced reflection before sufficient evidence is obtained, for example in tests of reflection impulsivity. Alternatively, dysfunction of distinct PFC pathways might lead to impairments in top-down executive control that result in a failure to inhibit behaviour or a failure to identify goals or contingencies. The relationship of aggression to more-general forms of inhibitory control requires further investigation but may be clinically relevant to such widely distinct disorders such as suicide in depression or conduct disorder, which is associated with ADHD. Recent evidence suggests that reactive aggression to provocative social feedback is correlated with motor impulsivity on a go/no-go task, with overlapping activity in the bilateral insula cortex and left-lateralized thalamus, putamen and globus pallidus[118]. Age-related changes in insula cortical thickness have also been linked to self-rated impulsivity[119], consistent with a role of this region in emotional regulation[120].

It is also sometimes difficult, for example, to discern whether a particular behaviour such as gambling is impulsive, compulsive or, as is probably the case with gambling, both[1]. The behaviour is thus impulsive in its initiation but, with failure to terminate the aberrant behaviour, also compulsive. The involvement of D2/3Rs in the gating of risky responses (described above) is particularly relevant in the case of gambling produced by D2R agonists in some individuals with Parkinson disease[121]. In addition, distinct populations of striatal cells may mediate 'go' and 'no-go' responses, the latter modulated by D2Rs in the indirect striatal pathway[122]. This may explain how striatal networks that are tonically 'overdosed' by D2/3R agonists encourage compulsive, perseverative behaviour through a relative excess of activity in the direct D1R pathway[122].

Conclusions

The present synthesis highlights the considerable heterogeneity that exists in the underlying mechanisms and expression of impulsivity. In general, we advocate that disorders of impulse control may be better understood by including a range of translatable tests of impulsivity and other constructs such as compulsivity and apathy to illuminate commonalities and differences in their symptoms and underpinning neural origins.

This Review illustrates the likely future of a dimensional approach to psychiatry whereby initially a broad-based behavioural construct is linked to abnormalities at the macrocircuit level by methods such as MRI but then is shown through a bidirectional cross-species translational approach to comprise potentially separable, although often overlapping, mechanisms that underpin different forms of impulsive behaviour. Basic neuroscience research with animals, using a combination of increasingly sophisticated behavioural paradigms and neuroscience 'tools', is beginning to characterize the macrocircuits revealed in human studies at the molecular and cellular levels. Thus, new molecular targets, perhaps specific to certain circuits, will emerge and allow us to pinpoint novel therapeutic pharmacological approaches. Deep brain stimulation, for example, currently a candidate treatment for several impulsive–compulsive disorders, may become more refined using chemogenetic strategies. We also predict that these circuits may be common to several otherwise different psychiatric phenotypes, although they may (or may not) involve different molecular pathologies.

The other major areas to benefit from our approach are genetics and nature-versus-nurture investigations. The differentiation of impulsivity phenotypes that is

Goal-directed
Instrumental or purposeful, conscious and volitional, and in pursuit of defined outcomes.

Habitual
Elicited automatically by stimuli in the environment without reference to a goal or outcome.

Model-free learning algorithms
Algorithms for learning that reflect immediate reinforcement learning contingencies and therefore are associated with habitual behaviour.

Conduct disorder
A mental disorder of childhood or adolescence in which violent or disruptive anti-social behaviour is the main characteristic.

Box 3 | **Genetics of impulsivity**

The aetiological mechanisms of impulsivity are only partly understood but are known to involve genetic and environmental influences, including early experience and stress[126]. Some of the key genes that are implicated in impulsivity are provided in the table. Various impulsivity-related disorders — for example, drug addiction[127] and attention-deficit hyperactivity disorder (ADHD)[128] — are heritable, with around half of the variance in impulsivity traits determined by genetic influences[129]. Variants in genes encoding receptors and transporters for dopamine (DA) and serotonin (5-HT) are widely associated with impulsivity-related disorders such as addiction[130,131], pathological gambling[132,133], suicide[134,135] and ADHD[136,137]. Notably, variation in the *HTR2B* gene (which encodes 5-HT_{2B} receptor) has been associated with increased impulsivity in a group of violent offenders[138].

Gene	Receptor or enzyme	Genotype	Participant group	Physiological consequences	Impulsivity subtype	Refs
DRD2	D2R	C957T, homozygous	HV	↑ Striatal DA release	↑ SSRT	139
		Taq1A allele	HV	↓ D2R density	↑ DD	140
					↔ BIS	141
DRD3	D3R	Ball variant	AD	↑ DA binding affinity	↑ BIS	142
DRD4	D4R	48 bp VNTR	HV	↓ D4R function	↔ DD	140
SLC6A3	DAT	40 bp VNTR	HV	↑ DAT activity	↔ SSRT	139
					↔ BIS	143
			ADHD	↑ DAT activity	↑ BIS, ↑ DD	144
HTR1A	5-HT_{1A} receptor	C1019G	HV	5-HT_{1A} autoreceptor dysfunction	↑BIS	145
					↔BIS	141
HTR1B	5-HT_{1B} receptor	A1997G	HV	↓ Suppression of gene expression by microRNAs	↓ BIS	141
HTR2A	5-HT_{2A} receptor	T102C	AD	↓ 5-HT_{2A} receptors	↑SSRT, ↔ BIS	146
			HV	↓ 5-HT_{2A} receptors	↑ Impulsivity in CPT	147
HTR2B	5-HT_{2B} receptor	Q20 stop codon	Violent offenders	↓ 5-HT_{2B} receptors	↑ Impulsive aggression	138
SLC6A4	5-HT transporter	5-HTTLPR allele	ADHD	↓ Gene expression	↑ DD	148
COMT	Catechol-*O*-methyltransferase	V158M	HV	↓ Enzyme activity	↔ BIS	141
					↑ BIS	149
					↔ SSRT	139
MAOA	Monoamine oxidase A	30 bp VNTR	HV	↑ Transcriptional activity	↑ BIS	150
TRH2	Tryptophan hydroxylase 2	rs1386483	HV	↓ 5-HT synthesis	↑ BIS	151

Data in the table are reviewed in REF. 126. 5-HTTLPR, 5-HT-transporter-linked polymorphic region; AD, alcohol dependent; BIS, Barratt Impulsiveness Scale; CPT, continuous performance test; D2R, DA D2 receptor; DAT, DA transporter; DD, delay discounting; HV, healthy volunteers; *SLC6A3*, solute carrier family 6 member 3 (also known as *DAT1*); SSRT, stop-signal reaction time; VNTR, variable number tandem repeat.

implied by this Review highlights the likelihood that there are distinct genetic factors that will enrich the somewhat weakly developed genetic knowledge (BOX 3) that we have currently accrued, which is based mainly on the use of questionnaire methodology. This is clearly an area for future research, and the role of early experience in impulsivity is also ripe for analysis, especially alongside burgeoning fundamental studies of the developing brain. Impulsivity is therefore an excellent exemplar of how we may expect other neurobehavioural constructs that are important for neuropsychiatry and clinical neuroscience to evolve in the future.

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Acknowledgements
The authors acknowledge support from the Wellcome Trust (grant 104631/Z/14/Z), UK Medical Research Council (grants G0701500, G0802729 and G9536855) and the European Commission (IMAGEN LSHM-CT-2007-037286). The Cambridge University Behavioural and Clinical Neuroscience Institute is supported by a joint award from the Wellcome Trust (093875/Z/10/Z) and Medical Research Council (G1000183). The authors also thank L. Morris and V. Voon for the frontostriatal connectivity illustrations in figure 3.

Competing interests statement
The authors declare competing interests: see Web version for details.