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**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 last 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 presently known about the neural and psychological mechanisms of impulsivity and discuss the relevance and application of these new insights to various neuropsychiatric disorders.

**Introduction**

Impulsivity is a multifaceted trait present in humans and other mammalian species and is generally regarded as a predisposition for rapid 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’[1](#_ENREF_1).The concept of the impulsivity trait became more widely accepted by Mischel’s classic experiments[2](#_ENREF_2) on how pre-school children fail to resist the immediate temptation of eating marsh-mellows. The concept was further reinforced when this impulsive tendency was 40 years later shown to be predictive of adult achievement and brain function[3](#_ENREF_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, perhaps representing extremes of normal tendencies[4](#_ENREF_4). In this article we demonstrate the translational applicability of this research to such psychiatric disorders as drug addiction, gambling, attention-deficit hyperactivity disorder (ADHD), Parkinson’s disease and affective disorders.

**[H1] 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 enhanced motivation and reduced motivation (‘apathy’) and it can represent both a failure to process information sufficiently or to control response output. This heterogeneity is captured by the Barratt Impulsiveness Scale (BIS)[5](#_ENREF_5)(Box 1), a set of three sub-scales 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’ — associated with differences in motor inhibition — from ‘impulsive choice’ — associated with differences in the control of value- or reward-based responding. However, this apparently useful dichotomy 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 action *per se* (see below).

Mischel’s original test has been closely related to the paradigm of temporal discounting of reward[6](#_ENREF_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](#_ENREF_7), [8](#_ENREF_8). Temporal discounting tests and premature-response tests both assess ‘waiting’, which is also a component of reflective decision-making[9](#_ENREF_9), whether perceptual or value-based, whereby it is adaptive to process sufficient information to make a correct choice.

‘Stopping impulsivity’ can occur after a choice has been made, but not yet fully executed, as in the stop-signal reaction time task[10](#_ENREF_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 often associated with impulsivity (‘risky impulsivity’); this is captured by the so-called probability-discounting paradigm[11](#_ENREF_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 to pit the occasional possibility of punishment against larger reward. The tendency to engage in risky behaviour is often associated with ‘sensation seeking’, whereby individuals apparently seek certain types of experience (such as mountaineering) despite the associated risks.

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](#_ENREF_11), suggesting also that some of the neural mechanisms may well be relatively independent of one another.

**At the behavioral level, a theoretical framework of value-based decision-making may also be useful for understanding the various components of risk and time discounting**[**12**](#_ENREF_12). These considerations are crucial to understanding the aetiology, diagnosis, and treatment of different psychiatric disorders involving impulsive tendencies.

**[H1] Neural substrates of impulsivity**

Human studies, generally 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 and 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](#_ENREF_13). **Further convergence of findings in humans and experimental animals is anticipated by the refinement of circuit-based homologies in primates and rodents**[**14**](#_ENREF_14).

[H2] Nucleus accumbens and dorsal striatum

The nucleus accumbens (NAcb) — which receives dopamine (DA) input from the ventral tegmental area (VTA) — has been identified as a key structure for certain forms of impulsivity (see **Fig.2**) by three key pieces of evidence. First, manipulation of DA levels within the NAcb greatly affects the frequency of premature responses, for example, in the 5-choice serial reaction time task (5CSRTT)[15](#_ENREF_15). Second, increased impulsivity in rats is associated with lower D2/3R ligand binding (reflecting lower numbers of receptors) in the NAcb[16](#_ENREF_16). Third, excitotoxic damage to the NAcb core sub-region increases the tendency of rats to choose an immediate over a delayed food reward[17](#_ENREF_17), [18](#_ENREF_18).

***[H3] Premature responding versus temporal discounting***

The two distinct task-related expressions of impulsivity (that is, failure to suppress premature responses, and a failure to delay gratification) may however depend on subtly different mechanisms within the NAcb. Whereas the capacity to delay gratification is associated with decreased dopamine (DA) release in the NAcb core, impulsive premature responding was associated with decreased DA release in the coreand increased DA release in the shell sub-region[19](#_ENREF_19). The reduction in NAcb D2/3Rs that is associated with increased premature responding was apparently restricted to the shell sub-region[20](#_ENREF_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 nafodotride also suppresses impulsive responding[21](#_ENREF_21). Moreover, DA transporter (DAT) expression is reduced in the shell of prematurely responding rats[20](#_ENREF_20), presumably further enhancing synaptic DA levels in this region. Additionally, lesions of the shell block the premature responding induced by amphetamine, probably by disrupting the DA-release-promoting actions of this stimulant[22](#_ENREF_22). A plausible working hypothesis, therefore, is that premature responding results from excess DA levels in the shell region associated with reduced D2/3Rs and DAT there — either reflecting a reduction in inhibitory D2/3 autoreceptors, or an adaptive down-regulation owing to excess DA release. **Intriguingly, impulsivity expressed as impaired delayed gratification appears not to be mediated by the shell region, as permanent excitotoxic lesions of the NAcb shell generally do not affect this behaviour**[**18**](#_ENREF_18)**. Nevertheless, reversible lesions separately of the NAcb shell and core increased impulsive choice on a T-maze task**[**23**](#_ENREF_23)**. This discrepancy does require further experiments to resolve but in general it appears that premature responding and temporal discounting may be mediated primarily by distinct regions of the NAcb**.

***[H3] Core versus shell***

Notwithstanding, it seems that the NAcb core also contributes importantly to premature responding on the 5CSRTT, albeit in an ‘opposite’ way to the shell; lesions of the core exacerbate the impulsivity produced by amphetamine. Moreover, opposite to its effects in the core, when administered to the shell, nafodotride enhances premature responding[21](#_ENREF_21). Consistent with a functional opposition between the shell and the core, deep brain stimulation (DBS) targeting the shell, but not the core, increases premature responding, presumably through anti-dromic stimulation of VTA projections[24](#_ENREF_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 NAcb)[25](#_ENREF_25). These animals also exhibit decreased grey matter density in the core sub-region[26](#_ENREF_26), decreased expression of GABA decarboxylase (GAD)[26](#_ENREF_26) (which presumably impairs GABA-ergic transmission in medium spiny cells of the core), and reduced expression of other synaptic proteins there, such as spinophilin[26](#_ENREF_26). Premature responding can also be promoted in normal rats by infusions of anti-sense to GAD in the core region[26](#_ENREF_26). Thus, premature responding may be linked to a dysregulation of DA in the shell sub-region, leading to output that is inadequately gated by the core sub-region and expressed through the spiralling output pathways of the striatum[27](#_ENREF_27). A particularly important structure for mediating premature responding is the subthalamic nucleus (STN), which receives projections from the striatal indirect pathway[28](#_ENREF_28). In humans, low D2/3R binding in the midbrain predicts BIS scores of impulsivity; low numbers of D2/3R here would also lead to elevated DA release by terminals in the ventral striatum[29](#_ENREF_29).

***[H3] ‘Waiting’ impulsivity***

The original finding[17](#_ENREF_17) that delayed discounting is impaired by lesions of the core region of the NAcb is thus consistent with evidence that rats that are impulsive on the 5CSRTT are also intolerant of delayed rewards[30](#_ENREF_30), potentially due to the overlapping involvement of the core sub-region in both tasks[13](#_ENREF_13). The NAcb also has important roles in processing primary and conditioned reward[18](#_ENREF_18), but further analyses suggest that the effects lesions to the NAcb core on discounting cannot simply have been due to failures to discriminate reward magnitude[17](#_ENREF_17), [18](#_ENREF_18).

The role of NAcb DRs 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](#_ENREF_31), an effect that is not only sensitive to DR blockade but is also 5-HT-dependent[32](#_ENREF_32). **Confirming a role of 5-HT in waiting impulsivity, optogenetic activation of 5-HT neurons in the dorsal raphé nucleus decreased impulsivity in a delayed reward task**[**33**](#_ENREF_33). **However, one complication of tasks of this nature is the difficulty of interpreting how the 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 is more likely to enhance large later choice; however, if it is unsignalled, the animal is more likely to opt for the small, sooner reward[32](#_ENREF_32). A recent study in rats showed that DA depletion from the dorsolateral striatum also produced steep delayed discounting of brain stimulation reward[34](#_ENREF_34). Thus, it seems that separate measures of ‘waiting impulsivity’ respond differentially to manipulation of striatal DA. Moreover, lesions of the STN actually promote choice of the large, delayed reward[35](#_ENREF_35) — that is, it reduces ‘impulsive choice’ — opposite to the effects on ‘impulsive action’ in the 5CSRTT[28](#_ENREF_28) or the stop-signal reaction time task[36](#_ENREF_36).

***[H3] Delayed discounting versus probabilistic discounting***

Another relevant comparison is between delayed discounting and probabilistic discounting. Excitotoxic lesions of the NAcb core also impair probabilistic discounting, by reducing aversion to the risky choice[37](#_ENREF_37). Silencing the NAcb with acute infusions of GABA agonists has broadly similar effects, although there are distinct contributions of the shell and core sub-regions[38](#_ENREF_38). Similarly, NAcb D1R blockade also reduces risky choice, whereas a D1R agonist appears to promote risky choices. D3R antagonism had effects almost opposite to those of D1R antagonism, possibly reflecting the presynaptic role of D3Rs. Surprisingly, D2 receptor agents in that study had no obvious effects[39](#_ENREF_39), unlike findings for ‘waiting impulsivity’, although there is clear overlap in the neural substrates for both types of impulsivity. By contrast, other findings support a role for D2R in affecting risky choice. The propensity of rats to be ‘risk averse’ (or ‘wager insensitive’) 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 NAcb, as measured by microPET[40](#_ENREF_40). Systemic and intra-NAcb core administration of the D2R agonist pramipexole enhanced risky behaviour in rats when expected values of reward were held constant[41](#_ENREF_41). Through optical recording of D2R-expressing cells of the NAcb, the same study discovered that these optical responses represented a naturally occurring correlate of risk preference, which signalled unfavorable recent outcomes, which presumably were then able to influence subsequent decisions. Moreover, simulation of this phasic signal, through spatially- and temporally-precise optogenetic excitation of D2R-expressing NAcb cells, converted risk-preferring rats to risk-averse[41](#_ENREF_41). Presumably, this suggests that whereas the D2R agonist normally eliminates the unfavorable recent outcome event by inhibiting D2R-expressing NAcb neurons, excitation of the same neuron by another input or transmitter besides DA is sufficient to produce risk aversion.

***[H3] Stopping impulsivity***

Despite this evidence, the NAcb does not seem to mediate all forms of impulsivity. Notably, in rodents, excitotoxic lesions of the NAcb core have no effects on the SSRT task, which measures stopping impulsivity[42](#_ENREF_42). By contrast, excitotoxic lesions of the dorsomedial striatum slow SSRT and impair performance, an effect also found with a D2R antagonist infused into the dorsal, but not the ventral striatum[42](#_ENREF_42), [43](#_ENREF_43). Infusion of a D1R antagonist into the dorsal striatum surprisingly had the opposite effect — speeding of SSRT — perhaps reflecting possible opponent functions of the striatal direct and indirect output pathways[43](#_ENREF_43). A human PET study using the DA ligands [11C]NNC-112 and [18F]fallypride examined individual differences in D1Rs and D2Rs, respectively, in relation to SSRT performance[44](#_ENREF_44). It confirmed that binding potentials in the dorsal and not the ventral striatum are associated with significant differences in SSRT performance, although in both cases, reduced response inhibition was negatively correlated with D2R binding[44](#_ENREF_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 DAergic 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 versus those for inhibitory control to cancel a response that has already been initiated, consistent with different roles of the ventral versus the dorsal striatum in controlling response sequences.

[H2] 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 neocortex, including the prefrontal cortex, and ‘bottom-up’ modulation from monoamine systems besides DA. To some extent, the ‘top-down’ mechanisms arise from the topographical projections of cortical-striatal pathways (**see Fig.3**).

***[H3] Impulsivity networks in rodents***

Virtually all of the afferent structures of the NAcb 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](#_ENREF_45) (all three of which project primarily to the shell region) and also the cingulate cortex[50](#_ENREF_50), [51](#_ENREF_51), which projects mainly to the NAcb core, and the dorsal striatum, in mediating premature responding in the 5-choice task.

The basolateral amygdala and the hippocampus, as well as the lateral orbitofrontal cortex and medial orbitofrontal cortex (mOFC) — but not the medial PFC[17](#_ENREF_17) — exert significant modulatory effects for delayed discounting[52-60](#_ENREF_52). The role of the OFC is especially highlighted by studies that have identified single units that show increased activity with time-discounted rewards after a short delay, and less activity after a long delay, independent of the absolute size of the reward[61](#_ENREF_61).

Risk-based impulsivity appears to recruit neural circuits distinct from other forms of impulsivity. Thus lesions of the ventral hippocampus have no effects on probabilistic discounting[54](#_ENREF_54), whereas the mOFC has been shown to have a special role in this aspect of impulsivity. Reversible inactivation of the mOFC with baclofen and muscimol infusions increased risky choice in rats[62](#_ENREF_62), and failed to affect discounting of delayed reward, again indicating some dissociation in controlling mechanisms, as well as highlighting the role of the mOFC in processing reward uncertainty[62](#_ENREF_62). By contrast, inactivation of 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](#_ENREF_63). The amygdala is also implicated in risky choice, via its connectivity with the NAcb[64](#_ENREF_64), as well as the lateral habenula, where inactivation essentially randomized choice preference in the risk task[65](#_ENREF_65). It will be important in future studies to compare effects of manipulations in several key structures and networks in several parallel forms of impulsivity. **Increasingly, optogenetic and chemogenetic approaches have been used to interrogate circuit-based mechanisms in impulsivity**. **Thus, optogenetic silencing of glutamatergic neurons in ventral PFC increased premature responding in the 5CSRTT whereas the same intervention in the dorsal PFC reduced attentional accuracy**[**66**](#_ENREF_66)**. Impaired attention and processing speed was also observed following chemogenetic inactivation of neurons in the anterior cingulate cortex**[**67**](#_ENREF_67)**, equivalent to the dorsal PFC, and consistent with the effects of excitotoxic lesions of this region**[**68**](#_ENREF_68)**. Rather surprisingly, however, chemogenetic activation of the mesolimbic DA system had no significant effect on premature responding in the 5CSRTT**[**69**](#_ENREF_69)**. This null result may potentially be explained by a net cancellation of opponent DAergic mechanisms in the NAcb core and shell, as discussed above. However, further experiments are needed to investigate this hypothesis.**

***[H3] 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 recent introduction of the human 4-choice serial reaction time task (4CSRTT[70](#_ENREF_70)) has been used in conjunction with structural imaging and resting-state functional imaging. In humans, increased premature responding in the 4CSRTT task is linked with reduced resting-state functional connectivity, specifically of the right ventral striatum with the bilateral subgenual cingulate and bilaterally with the STN[71](#_ENREF_71). These findings thus provide translational support for convergent circuitry in humans and rodents. Moreover, these findings suggest a separation between the effects of the 4CSRTT and motor response inhibition, as assessed the SSRT task, which instead implicates reduced connectivity between hyper-direct projections of the right pre-supplementary motor area (SMA) and left STN, and decreased connectivity between the dorsal caudate and STN[71](#_ENREF_71) — consistent with rodent data[36](#_ENREF_36).

The stop-signal task (and the partly overlapping Go/No-Go paradigm) has perhaps been associated with the most highly specified neural network in humans, including elements of the anterior cingulate, right inferior frontal cortex, premotor and pre-supplementary cortex, striatum and STN[72](#_ENREF_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](#_ENREF_73). A subsequent fMRI study also highlighted an association of the right inferior frontal cortex with premotor, striatal and STN circuitry[74](#_ENREF_74). More recently, an fMRI study of 2000 adolescents using the SSRT task enabled a factor analysis of the structures activated during successful and failed stopping responses[75](#_ENREF_75). This revealed 7 independent circuits implicated in successful stopping: (1) bilateral putamen, caudate, pallidum and thalamus; (2) right inferior frontal gyrus, right insula and right anterior cingulate; (3) bilateral substantia nigra and STN; (4) bilateral superior and middle orbital gyri); (5) bilateral pre-SMA/precentral gyrus; (6) bilateral inferior and superior parietal lobes, and (7) bilateral medial orbital gyri. The ‘stop-fail’ circuit involved similar circuits except the pre-supplementary motor cortical node, suggesting that this region plays an important role in the inhibitory process.

Aron *et al.*[76](#_ENREF_76) originally 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-analysis of many functional imaging studies. Cai *et al.*[77](#_ENREF_77) reviewed 70 fMRI studies and came to the following conclusions: two adjacent clusters of activation in the right insula and inferior frontal cortex exhibited distinct functional characteristics. Specifically, whereas the insula cluster was more closely coupled to the anterior cingulate and showed greater activation on unsuccessful SSRT trials, the inferior frontal cluster was functionally connected to the parietal and dorsomedial PFC activations, had relatively greater activation on successful 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 rather than in monitoring outcomes of the task. However, there seems to be little doubt that the inferior lateral PFC has functions besides inhibition or braking; thus, a repeated response – rather than a stop response or attentional shift – may also activate the right inferior frontal cortex[78](#_ENREF_78). However, this activation may be relatively weaker than in other regions connected to the inferior frontal cortex, such as parietal cortex. Overall, there seems to be good evidence linking this inferior frontal network to inhibitory response task performance. This may therefore have relevance for a number of neuropsychiatric disorders and task-related pharmacological modulation. It was reported recently that the inferior frontal gyrus modulates the preSMA – STN excitatory circuit, leading to enhanced inhibition from the STN to the motor cortex. Notably, the connection strength between the preSMA and STN, and strength of modulation by the inferior frontal gyrus, predicted individual variation in SSRT performance[79](#_ENREF_79).

The involvement of prefrontal structures in SSRT performance raises the intriguing issue of homology in relating the findings to rodent studies. Indeed, the cortical sites in the rat most affecting SSRT seem to be in the lateral OFC and the anterior cingulate[36](#_ENREF_36) — the former possibly corresponding to the lateral inferior PFC site in humans, and contrasting with the infralimbic prefrontal involvement in premature responding on the 5CSRT task in rodents[45](#_ENREF_45). Further analysis of the network nature of the response control exerted in the SSRT task may benefit from the suggested distinction between proactive versus reactive modes of performance[80](#_ENREF_80). The proactive mode involves preparation for inhibition and has been linked to fronto-striatal functioning, whereas reactive inhibition to the stop signal may implicate the so-called ‘hyperdirect’ cortical pathway to the STN[80](#_ENREF_80).

Consistent with the evidence from basic neuroscience, human imaging studies of (often hypothetical) delayed discounting for secondary (points or money) and primary rewards, implicate the ventral striatum, OFC, lateral PFC, insula, amygdala, posterior cingulate, and parietal cortex[81](#_ENREF_81),[82](#_ENREF_82). For the latter, the so-called beta system activates the ventral striatum (including the NAcb) and medial PFC and is linked with preference for immediate rewards, whereas delta regions (dorsolateral, ventrolateral PFC and parietal cortices) also activate 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 lateral PFC–parietal circuit and reward magnitude by the ventral striatum–mPFC[83](#_ENREF_83). However, magnitude and delay were also integrated in certain regions such the right inferior lateral PFC[12](#_ENREF_12), [83](#_ENREF_83). Moreover, more impulsive individuals exhibited diminished neural activation in the ventral striatum related to the magnitude of future rewards with more pronounced deactivations in the lateral PFC to delayed rewards[83](#_ENREF_83). Other evidence suggests that the ventral aspect of the anterior striatum processes immediate choices while delayed choices preferentially involve the dorsal posterior striatum[84](#_ENREF_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) with ambiguity (uncertainty with unknown probabilities)[85](#_ENREF_85). The former was associated with posterior parietal cortex activation while the latter associated more strongly with lateral PFC activation. Notably, activation of the lateral PFC in response to ambiguous decisions was greater in subjects deemed low-impulsive on the BIS[85](#_ENREF_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 (see Box 3).

**[H1] Neurochemical substrates**

The neural networks underlying impulsivity are modulated by ‘bottom-up’ mechanisms such as the ascending monoamine projections, including not only the mesolimbic DA pathways, but also the ascending noradrenergic (NA) systems from the locus coeruleus and other brainstem structures, and the serotonergic (5‑HTergic) systems from the dorsal and median raphé nuclei[13](#_ENREF_13), [86](#_ENREF_86).

[H2] Dopamine and noradrenaline

An over-arching consideration when describing the neurochemical basis of impulsivity is the profound effects of psychomotor stimulant drugs such as methylphenidate (Ritalin; a DA- and NA-reuptake inhibitor) and amphetamine (an indirect DA agonist) on impulsivity, as indicated clinically by their use in treatment of ADHD. Despite the aforementioned implication of DA in impulsivity, given the effects of these drugs on NA and 5-HT[87](#_ENREF_87), it is still unclear precisely which actions are most relevant to their therapeutic effects. Recently, it was shown that methylphenidate dose-dependently reduced premature responding in high-impulsive rats, but increased premature responding in normal rats — effects that were paralleled by opposite effects on low and high D2R binding potentials throughout the striatum[88](#_ENREF_88). That is, methylphenidate specifically normalized the behaviour and DR density of high impulsive, low-striatal-D2R rats, but induced a high-impulsivity phenotype in normally non-impulsive rats. However, the effects on behaviour were not necessarily predicted by effects on D2R in individual animals, and other possible mechanisms may be implicated. Foremost amongst these may be NAergic mechanisms; in line with this, the selective NA re-uptake inhibitor atomoxetine has striking anti-impulsivity effects in all major impulsivity tests in rodents (premature responding, delayed discounting and SSRT)[89](#_ENREF_89). Furthermore, microinfusions of methylphenidate in the NAcb core but not the shell increased premature responding, while infusions of atomoxetine into the shell but not the core reduced premature responding[90](#_ENREF_90).

This locus of action for atomoxetine in the premature responding task seemingly contrasts with that for the SSRT task, where the drug is most effective in speeding SSRT when infused into those cortical regions that seem to control inhibitory performance (anterior cingulate and lateral OFC)[91](#_ENREF_91). Additional pharmacological manipulation suggests that these effects are related more to NAergic actions of atomoxetine in the cortex[92](#_ENREF_92). The beneficial effects of atomoxetine (as well as methylphenidate[93](#_ENREF_93)) on SSRT performance in healthy humans, as well as in patients with ADHD[94](#_ENREF_94) and Parkinson’s disease[95](#_ENREF_95), similarly depend on its ability to specifically enhance connectivity between the inferior frontal cortex and anterior cingulate, as indicated in fMRI studies[96](#_ENREF_96).

[H2] Serotonin

5-HT has long been implicated in behavioural inhibition, and hence in impulsivity. However, different forms of impulsivity appear to respond differentially to treatments affecting central 5-HT levels. Depletion of forebrain 5-HT greatly increases impulsive responding in the rodent 5CSRTT[97](#_ENREF_97) and also in the human 4CSRTT[98](#_ENREF_98) (via acute dietary tryptophan depletion), hence indicating considerable cross-species transferability. Premature responding in rats is reduced by 5-HT2A receptor antagonism in either the medial PFC or the NAcb[99](#_ENREF_99), [100](#_ENREF_100), whereas intra-NAcb 5-HT2C receptor antagonism had the opposite effect[100](#_ENREF_100). These treatments exerted qualitatively similar effects on premature responding in 5-HT-depleted rats[101](#_ENREF_101).

The role of 5-HT in delayed and probabilistic discounting is more complicated, with some findings indicating greater impulsive choice after 5-HT depletion[13](#_ENREF_13). 5‑HT neurons in the rat dorsal raphé show increased activity during delays to reward[102](#_ENREF_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 procedures but remarkably had much less effect in the SSRT paradigm[103](#_ENREF_103). Acute treatment with the selective 5-HT-re-uptake inhibitor citalopram also had no significant effects on SSRT in rat or human volunteer variants of the task[104](#_ENREF_104), [105](#_ENREF_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 Parkinson’s disease, citalopram — like atomoxetine[96](#_ENREF_96) — has been shown to enhance inferior frontal activation and improve SSRT performance[106](#_ENREF_106).

**[H1] 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 addiction1.

[H2] 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**](#_ENREF_107)? This is a notoriously difficult issue to resolve experimentally, but in theory can be addressed by a combination of 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](#_ENREF_13), [16](#_ENREF_16), [19](#_ENREF_19), [108](#_ENREF_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](#_ENREF_13). A recent study showed that alcohol-dependent individuals and binge drinkers exhibited increased premature responding on the human 4CSRTT than controls. In heavy social drinker volunteers, the degree of alcoholic severity correlated negatively with connectivity between the bilateral STN and subgenual cingulate (as was anticipated from the rodent literature), suggestive of a possible endophenotype[71](#_ENREF_71).

Distinct aspects of impulsivity are related to stimulant drug abuse. Thus individuals who abuse stimulants exhibit increased premature responding (on the human 4CSRTT), steeper temporal discounting and risky choice as well as slowed SSRTs[71](#_ENREF_71). First-degree relatives of stimulant drug abusers who do not abuse drugs exhibit impairments in SSRT that almost as great as by their sibling drug abusers, associated with reduced white matter innervating the frontal lobes[109](#_ENREF_109). This is consistent with a weakening of top-down inhibitory control being an endophenotype conferring risk of stimulant drug abuse that cannot simply be the product of drug exposure. Presumably, unaffected siblings exhibit greater resilience to the temptations of drug abuse. Consistent with this, non-using first-degree relatives of drug users actually exhibit enhanced activity of the inferior frontal gyrus region during a Stop task, as compared with the diminished activity of this region in drug users[110](#_ENREF_110). Moreover, in the study of 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](#_ENREF_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 other factors[111](#_ENREF_111). **Another study of 1015 young adults showed that sensation seeking and reduced cortical thickness were localized to regions implicated in cognitive control, including anterior cingulate and middle frontal gyrus. These associations also related to self-reported motor impulsivity, replicated in an independent group (*n* = 219), and importantly correlated (but not caused by) heightened alcohol, tobacco, and caffeine use**[**112**](#_ENREF_112)**. Such findings raise the issue of whether impulsivity and sensation-seeking measures can distinguish between recreational versus compulsive drug use leading to DSM5 criteria for 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 it particularly interesting that such ‘recreational’ users do not in general exhibit strong evidence of impulsive behaviour or correlated brain changes, while nevertheless showing strong signs of sensation seeking — a trait not however strongly evident in non-using siblings of compulsive drug users[113](#_ENREF_113). Though possibly overlapping in part, impulsivity and sensation-seeking may not be as strongly related as sometimes assumed, although 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**](#_ENREF_114)**,** [**115**](#_ENREF_115)**. According to this hypothesis, the lack of top-down control over habits is a basis for compulsive behavior. Habitual control in humans can be captured to some extent by a bias towards ‘model free’ 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 model-based signatures were reduced in high-impulsive individuals**[**116**](#_ENREF_116).

[H2] ADHD

Impulsive behaviour, along with inattention, is also a characteristic symptom of ADHD. In the study of 2,000 adolescents described above[75](#_ENREF_75), those with subclinical symptoms of ADHD, as measured clinically 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, delayed discounting and SSRT, were not correlated in a large juvenile multi-centre sample of ADHD patients, but together they accounted for much of the variance discriminating children with ADHD and unaffected control participants[117](#_ENREF_117). This result is entirely consistent with the hypothesis advanced in this article that there are distinct forms of impulsivity, dependent on different fronto-striatal circuitries, and suggests a spectrum-like involvement of the fronto-striatal systems that underlie subtly distinct forms of ADHD symptoms.

[H2] 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 are theoretically distinct from impulsivity (involving respectively aberrant repetition of behaviour, enhanced irritability, and amotivational states), 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 clinically may be 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 linked to motor impulsivity on a go/no-task with overlapping activity in the bilateral insula cortex and left-lateralized thalamus, putamen and globus pallidus**[**118**](#_ENREF_118). **Age-related changes in insula cortical thickness have also been linked to self-rated impulsivity**[**119**](#_ENREF_119)**, consistent with a role of this region in emotional regulation**[**120**](#_ENREF_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, both1. The behaviour is thus impulsive in its initiation, but compulsive through failure to terminate the aberrant behaviour. In the case of gambling produced by D2R agonists in Parkinson’s disease[121](#_ENREF_121), we have already described above how D2/3Rs are implicated in the gating of risky responses. Additionally, distinct populations of striatal cells may mediate ‘Go’ and ‘No-Go’ responses, the latter modulated by D2Rs in the indirect striatal pathway[122](#_ENREF_122). This may explain how striatal networks tonically ‘overdosed’ by D2/3R agonists encourage compulsive, perseverative behaviour through excessive activity in the direct, D1R pathway[122](#_ENREF_122).

**[H1] 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 in order to illuminate commonalities and differences in their symptoms and underpinning neural origins.

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**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 (BIS)[5](#_ENREF_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”; “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”; “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”; “I am more interested in the present than 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 discountingis 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](#_ENREF_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 larger, less likely rewards.

- Reflection impulsivity is the tendency to make rapid decisions without adequate accumulation and consideration of the available evidence[123](#_ENREF_123).

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 ability to stop a response after it has been initiated[10](#_ENREF_10). Tasks that assess premature responding measure 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](#_ENREF_7), go/no-go tasks and differential rates of low reinforcement (DRL)[124](#_ENREF_124), and in humans using the 4-choice serial reaction time task[98](#_ENREF_98). DRL schedules are so arranged that a minimum amount of time must elapse between responses before a reward is delivered.

**Box 2: 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[125](#_ENREF_125). Some of the key genes implicated in impulsivity are provided in the table. Various impulsivity-related disorders – for example, drug addiction[126](#_ENREF_126) and ADHD[127](#_ENREF_127) – are heritable, with around one-half of the variance in impulsivity traits determined by genetic influences[128](#_ENREF_128). Variants in genes encoding DA and 5-HT receptors and the DA and the 5-HT transporters are widely associated with impulsivity-related disorders including addiction[129](#_ENREF_129), [130](#_ENREF_130), pathological gambling[131](#_ENREF_131), [132](#_ENREF_132), suicide[133](#_ENREF_133), [134](#_ENREF_134), and ADHD[135](#_ENREF_135), [136](#_ENREF_136). Notably, variation in the *5HT2B* gene has been associated with increased impulsivity in a group of violent offenders[137](#_ENREF_137).

**Box 3: Willpower**

Willpower is the capacity of individuals to repel short-term temptations in order to optimize longer-term goals. The consistent involvement of the lateral PFC in paradigms measuring impulsivity evokes the concept of ‘willpower’; failures of will-power 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 delayed discounting with and without pre-commitment showed that the former recruited additional PFC mechanisms in the frontopolar cortex to those ‘willpower’ regions usually found in the standard delay discounting situation, such as the dorsolateral PFC, inferior lateral PFC and posterior parietal cortex[138](#_ENREF_138). Impulsive participants who stood to benefit more from pre-commitment — that is, those more likely to succumb to temptation when attempting to exert willpower — showed stronger positive connectivity between frontopolar and ‘willpower’ regions during pre-commitment than did their less-impulsive peers. This increased connectivity was accompanied by activation of the vmPFC during precommitment, suggesting calculation of the values of alternative courses of action.

**Association of impulsivity subtypes with common gene variants in humans\***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Receptor or enzyme** | **Polymorphism** | **Participant group** | **Physiological consequences** | **Impulsivity subtype** | **Refs** |
| *DRD2* | D2 receptor | C957T T/T | HV | ↑striatal DA release | ↑ SSRT | [139](#_ENREF_139) |
|  |  | Taq1A allele | HV | ↓ D2 receptor density | ↔ BIS  ↑ DD | [140](#_ENREF_140), [141](#_ENREF_141) |
| *DRD3* | D3 receptor | BaLI | AD | ↑ DA binding affinity | ↑ BIS | [142](#_ENREF_142) |
| *DRD4* | D4 receptor | 48-bp VNTR | HV | ↓ D4R function | ↔ DD | [140](#_ENREF_140) |
| *SLC6A3* | Dopamine transporter 1 | 40-bp VNTR | HV | ↑ DAT activity | ↔ SSRT  ↔ BIS | [139](#_ENREF_139)  [143](#_ENREF_143) |
| ADHD | ↑ DAT activity | ↑ BIS ↑ DD | [144](#_ENREF_144) |
| *HTR1A* | 5-HT1A receptor | 1019 C/G | HV | 5-HT1A autoreceptor dysfunction | ↑ BIS  ↔ BIS | [145](#_ENREF_145)  [141](#_ENREF_141) |
| *HTR1B* | 5-HT1B receptor | 1997 A/G | HV | ↓ microRNA-mediated suppression of gene expression | ↓ BIS | [141](#_ENREF_141) |
| *HTR2A* | 5-HT2A receptor | T102C | AD | ↓ 5-HT2A receptors | ↑ SSRT ↔ BIS | [146](#_ENREF_146) |
|  |  |  | HV | ↓ 5-HT2A receptors | ↑ impulsivity CPT | [147](#_ENREF_147) |
| *HTR2B* | 5-HT2B receptor | Q20 stop codon | Violent offenders | ↓ 5-HT2B receptors | ↑ impulsive aggression | [137](#_ENREF_137) |
| *SLC6A4* | 5-HT transporter | 5HTTLPR s‑allele | ADHD | ↓ gene expression | ↑ DD | [148](#_ENREF_148) |
| *COMT* | Catechol-o-methyltransferase | Val-158-Met | HV | ↓enzyme activity | ↔ BIS  ↑ BIS ↔ SSRT | [141](#_ENREF_141)  [149](#_ENREF_149)  [139](#_ENREF_139) |
| MAOA | Monoamine oxidase A | 30-bp VNTR | HV | ↑ transcriptional activity | ↑BIS | [150](#_ENREF_150) |
| *TRH2* | Tryptophan hydroxylase 2 | rs1386483 | HV | ↓5-HT synthesis | ↑BIS | [151](#_ENREF_151) |

\*Table adapted from data reviewed in Jupp and Dalley 2016[125](#_ENREF_125). AD, alcohol dependence; ADHD, attention-deficit/hyperactivity disorder; BIS, Barratt Impulsivity Scale; CPT, continuous performance test; DAT, dopamine transporter; DD, delay-discounting; HV, healthy volunteers; SSRT, stop-signal reaction time; VNTR, variable number tandem repeat.

**Figure 1. Translatable experimental paradigms to assess impulsivity in rodents and humans.** 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 5 apertures. Hence, when stimulus hole S2 is illuminated a response there (R2) is correct, whereas a response in an alternative aperture (e.g. R4) is punished. However, the rodent has to wait for the visual targets to be presented before responding and premature responses in any aperture (i.e. Rn) are also punished by reward omission. In the human (4-choice) version[70](#_ENREF_70), 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 the screen) can be measured as aspects of impulsive responding.

In delay discounting, two stimuli (S1, S2) only are used. Responding on one, e.g. R1 produces an immediate but small (e.g. 1 pellet) food reward. Responding on the other R2 produces a large (e.g. 4 pellets) food reward 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, the choice is often presented in a verbal manner and over longer, hypothetical delays.

In risky choice procedures (probabilistic discounting) again only two stimuli are used (S1 and S2). Responding on one, e.g. R1 produces an immediate and consistent small (e.g. 1 pellet) food reward, on every R1 (i.e. 100% of the time). Responding on the other R2 produces a large (e.g. 2 pellets) food reward but only 50% of the time. Thus, expected overall rewards are equivalent in this case but R2 is a ‘riskier’ response. The less likely R2 is to be rewarded the more likely the subject will choose R1. There are many human versions of this type of task which amounts to gambling. Depicted is a screen-shot from the Cambridge Gamble Task[152](#_ENREF_152), where the odds for reward choosing between red and blue are depicted graphically on the screen. Following the initial selection, the subject can ‘bet’ a proportion of their points on its correctness, earning an equivalent number if correct and losing them if not.

The stop-signal reaction time task measures the time it takes to cancel or inhibit an already initiated response[153](#_ENREF_153). Thus, following S1, a subject rapidly responds R1. If a stop-signal, S2 is presented any time after R1 initiation on a proportion of trials, then R1 has to be aborted for a successful stop. If it is not and R1 proceeds to completion ahead of inhibition, then the trial fails. By measuring the time it takes to successfully stop 50% of the time (and taking into account the delay of S2 presentation after R1 is initiated), a stop-signal reaction time can be computed. The task has been implemented in rodents in various ways, sometimes by the rapid completion of a 2 response sequence, cancelling the second response on stop (S2) trials. The human version may use visual cues (e.g. directional arrows) for S1 with S2 being an auditory ‘beep’.

**Figure 2.** **Distinct loci of ‘stopping’ and ‘waiting’ impulsivity in the dorsal and ventral striatum.** Stopping impulsivity is regulated by dorsal striatal-dependent mechanisms and is widely assessed by the capacity of subjects to stop a response after it has been initiated. Tasks that assess waiting impulsivity capture the capacity of subjects to withhold from responding until sufficient information has been gathered or signaled to do so by explicit cues, often involving a choice between alternative outcomes, as in delay and probability discounting procedures, or after a waiting interval has elapsed, as measured by premature or anticipatory responding. Waiting impulsivity is mainly regulated by convergent mechanisms within the ventral striatum, specifically by the core and shell sub-regions of the nucleus accumbens (NAcb). Trait-like impulsivity on the rodent 5CSRTT is associated with reduced D2R binding density in the NAcb shell[20](#_ENREF_20), [154](#_ENREF_154) and a diminished concentration of glutamic acid decarboxylase – the rate-limited enzyme responsible for GABA synthesis – in the NAcb core[26](#_ENREF_26). Dopamine inputs to the dorsal and ventral striatum arise from the substantia nigra and ventral tegmental area (VTA), respectively, with dopamine cell bodies in these regions innervated by inhibitory GABA-ergic neurons, which form striatonigrostriatal pathways that connect the NAcb shell with the dorsal striatum[27](#_ENREF_27). This spiraling circuitry between ascending dopaminergic and descending GABA-ergic neurons may be responsible for the reported opponent interactions between the NAcb core and shell in waiting impulsivity[24](#_ENREF_24).

**Figure 3. Topographical organization of corticostriatal circuitry and associated impulsivity constructs in humans.** Stopping impulsivity, risky decision-making and impulsive choice are mediated by distinct cortical loci and striatal territories. The neural substrates of reflection impulsivity are less well understood but may involve structural abnormalities in the dlPFC and inferior parietal cortex[155](#_ENREF_155). Abbreviations: dlPFC dorsolateral prefrontal cortex; vlPFC ventrolateral prefrontal cortex; lOFC lateral orbitofrontal cortex; vmPFC ventromedial prefrontal cortex; mOFC medial orbitofrontal cortex; SMA supplementary motor area; PMC premotor cortex; Pre-SMA pre-supplementary motor area; aPFC anterior prefrontal cortex.