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Review

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Neural circuitry and mechanisms of waiting impulsivity: relevance to addiction

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Impatience—the failure to wait or tolerate delayed rewards (e.g. food, drug and monetary incentives)—is a common behavioural tendency in humans. However, when rigidly and rapidly expressed with limited regard for future, often negative consequences, impatient or impulsive actions underlie and confer susceptibility for such diverse brain disorders as drug addiction, attention-deficit hyperactivity disorder (ADHD) and major depressive disorder. Consequently, 'waiting' impulsivity has emerged as a candidate endophenotype to inform translational research on underlying neurobiological mechanisms and biomarker discovery for many of the so-called impulse-control disorders. Indeed, as reviewed in this article, this research enterprise has revealed a number of unexpected targets and mechanisms for intervention. However, in the context of drug addiction, impulsive decisions that maximize short-term gains (e.g. acute drug consumption) over longer-term punishment (e.g. unemployment, homelessness, personal harm) defines one aspect of impulsivity, which may or may not be related to rapid, unrestrained actions over shorter timescales. We discuss the relevance of this distinction in impulsivity subtypes for drug addiction with reference to translational research in humans and other animals.

This article is part of the theme issue 'Risk taking and impulsive behaviour: fundamental discoveries, theoretical perspectives and clinical implications'.

1. Introduction

As an assumed dimensional construct or endophenotype, research interest in 'waiting' impulsivity has increased in recent years to help inform clinical diagnoses and novel brain mechanisms for intervention [1]. Thus, individuals diagnosed with attention-deficit hyperactivity disorder (ADHD) are intolerant of delayed rewards relative to unaffected controls [2,3], a characteristic also observed in addicted individuals across several classes of abused drugs [4–6]. Aversion to delayed rewards, as a presumed consequence of chronic drug exposure, also predicts increased vulnerability and responding for cocaine, nicotine and alcohol in rodents [7–10], and for nicotine in humans [11]. Thus, a consensus has emerged that the innate or acquired bias for immediate incentives is a powerful underlying drive for the development and maintenance of addiction and related disorders [12–14]. Given the alarming rise in cocaine-related deaths in the UK published recently by the Office for National Statistics (432 deaths in England and Wales in 2017 compared with 112 in 2011), there has never been a more pressing need to understand the cause of addiction. In this article, we review what is presently known about 'waiting' impulsivity, some of the controversies in the field, and opportunities for developing new therapies.

With its evident complexity and multifactorial nature, the term *impulsivity* has just about outlasted its usefulness as a unitary psychological and behavioural construct. Nevertheless, the term survives because people intuitively understand what it means to be impulsive—to act rashly without adequate foresight. Yet

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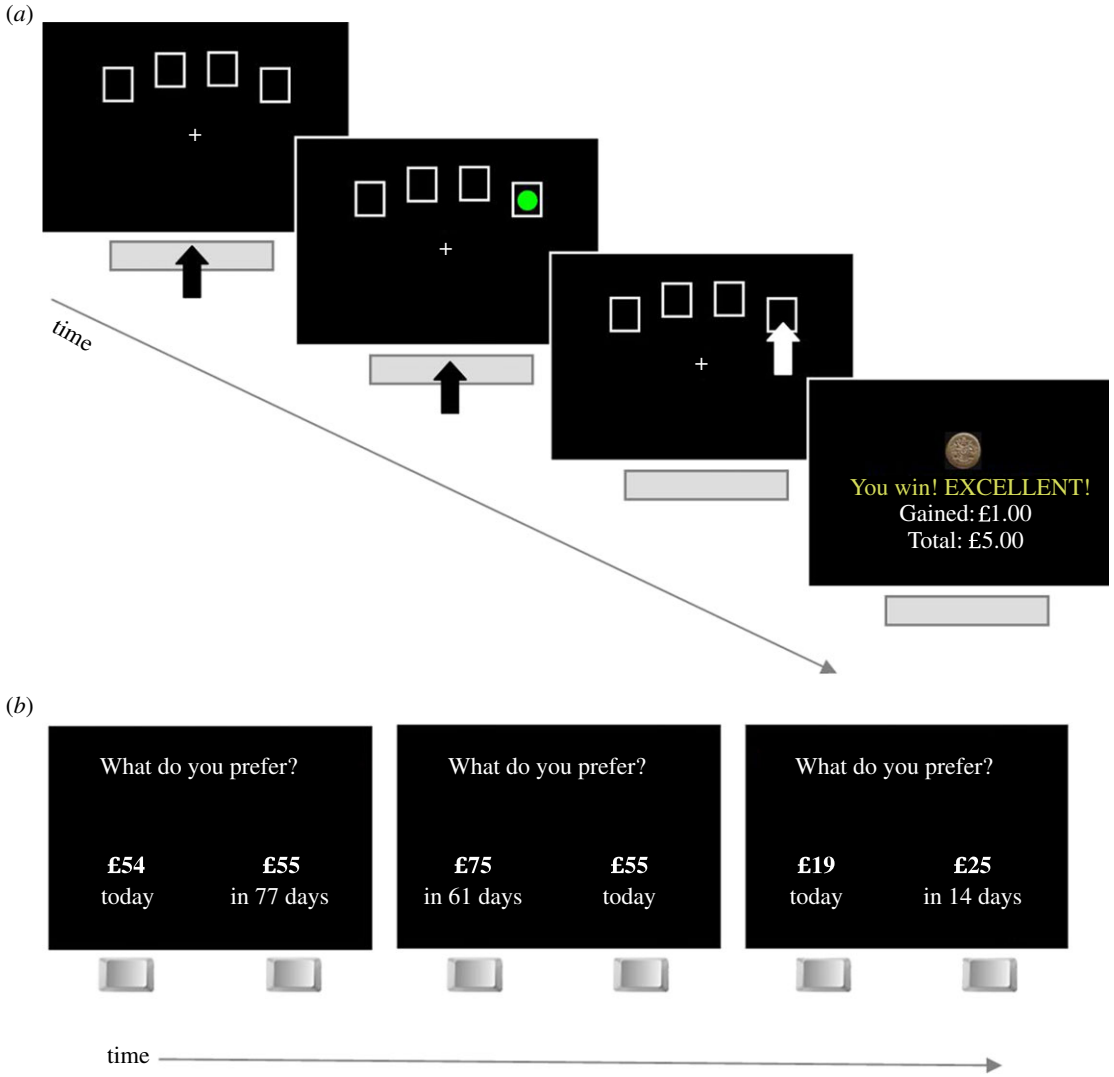

Figure 1. Measurement of waiting impulsivity endophenotypes in humans. (*a*) The Four-Choice Serial Reaction Time Task (4CSRTT) is a direct translation of the rodent Five-Choice Serial Reaction Time Task (5CSRTT), which measures the ability to monitor and restrain responding in the face of unpredictable visual targets. The task is administered on a touch-sensitive computer. To initiate a trial, participants are instructed to press and hold down with their index finger the space bar on the computer key board, which results in four white squares appearing on the black computer screen. Following a pre-set cue-trial interval, the target stimulus (a green circle) appears briefly in one of the four squares. Participants are instructed to immediately release the space bar with the same finger and touch the screen in the square where the target had appeared. Correct responses are reinforced by a hypothetical monetary reward. Missed or delayed responses are punished by the deduction of money for that trial. Premature responses, where participants responded prior to the onset of the visual target, however, were not punished. (*b*) The Monetary Choice Questionnaire qualifies the decline of the value of a monetary reward with increasing delay of its delivery. It consists of a fixed set of 27 choices between a smaller immediate and postponed monetary rewards. The key outcome measure *k* reflects the degree to which the value of the reward is affected by delay (i.e. higher *k* values indicate steeper discounting of delayed rewards).

even at this most straightforward level of description, two processes can be identified: (1) motor inhibition to suppress inappropriate, often anticipatory actions; (2) forward looking decisional mechanisms to weigh up and reflect on the cost of rash behaviour. Both processes are linked by temporal judgements to optimize performance but clearly on very different timescales or temporal horizons. Thus, motor inhibition depends on moment-to-moment self-restraint whereas foresight requires subjective decisions over much longer time frames—primarily to reflect on the consequences of prior impulsive acts. In the latter case, such decisions are affected by the inherent tendency of individuals to discount or devalue future outcomes—be they rewarding or punishing—according to delay-dependent hyperbolic or exponential discounting functions [15,16]. Objectively, this aspect of decision-making can be assessed using intertemporal choice tasks (or delay discounting tasks) where subjects choose between a small immediate reward and a larger but delayed reward (figure 1). With increasing delay, preference switches away from the larger outcome to the smaller immediate outcome. Such tendencies can be contrasted against other forms of impulsivity measured for example by the stop-signal reaction time task [17] and self-report inventories such as the Barrett Impulsiveness Scale [18]. There are, however, poor correlations between objective assessments of impulsivity using experimental tasks and subjective reports of impulsivity, as measured by questionnaires, suggesting that they might assess different components of impulsivity [19,20].

2. Waiting impulsivity: behavioural assessment and brain networks

The measurement of waiting impulsivity broadly requires humans and other animals to resist from responding until signalled to do so by explicit cues—a capacity also assessed

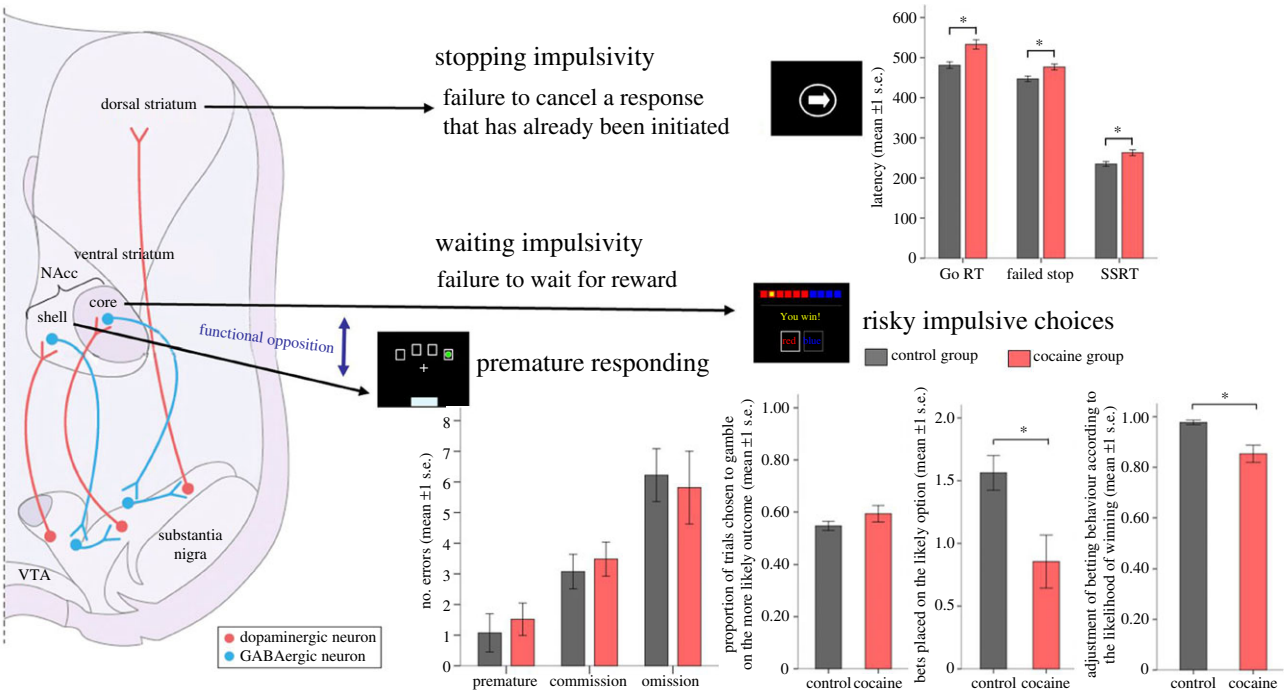

Figure 2. Dissociation between the neural substrates underpinning waiting and stopping impulsivity (adapted from Clark *et al.* [21] with permission). Stopping impulsivity, which requires the cancellation of an ongoing motor response, frequently measured using the stop-signal task, is dependent on dorsostriatal mechanisms. By contrast, waiting impulsivity describes a failure to inhibit the initiation of an inappropriate response that is based on incorrect predictions of time or probability. Waiting impulsivity relies on the functional integrity of the ventral striatum. Data collected from 28 healthy control participants and 28 matched cocaine-addicted patients show prolonged response latencies for both going and stopping in the cocaine group. On the 4CSRTT, cocaine-addicted individuals exhibit a tendency to respond more prematurely or incorrectly (commission errors) relative to their healthy peers. In a decision-making context, using the Cambridge Gamble Task (www.cambridgecognition.com) cocaine-addicted individuals make disadvantageous choices as they are less likely to play safe (select the most likely option), but are not more prone to gamble more on the risky options. NAcc, nucleus accumbens; VTA, ventral tegmental area.

by tests of *reflection* impulsivity in humans where evidence to respond gradually accumulates over time [21]. In rodents, the ability to wait is assessed classically by schedules of differential reinforcement of low rates of responding (DRL), in which the animal should allow a specified time to elapse between successive responses to obtain a reward, and the analogous 5-choice serial reaction time task (5CSRTT) where animals learn to refrain from responding for several seconds prior to the onset of a visual cue [22]. A failure to suppress responding is signalled with a timeout and loss of reward and is registered as a premature response. Waiting impulsivity can also be assessed in humans by two analogues of the rodent 5CSRTT—the 4-choice serial reaction time task [23] and the Sussex5CSRTT [24] (figure 1). As pointed out above, intertemporal choice tasks measure a different aspect of waiting with an initial choice offered between two alternate outcomes—one a small instant reward, the other a larger but delayed reward. Obscuring cross-species translation, however, choice procedures in experimental animals normally use shorter delays than humans and food rather than monetary incentives [20].

Turning next to the neural substrates and mechanisms of waiting impulsivity, it is helpful to revisit the early theorizing of Soubrié [25] who argued that serotonergic transmission in the brain facilitates tolerance for delayed rewards, especially in settings where acting and restraint are in competition (e.g. go/no-go discrimination tasks and conflict procedures). Indeed restraint linked to punishment-induced suppression of behaviour was known several years earlier to depend on brain serotonin (5-HT) [26] such that experimental interventions that reduced 5-HT levels in the brain led to disinhibited behaviour and a shift toward responding for immediate rewards [25]. Thus, reducing brain 5-HT increased the probability of behaviours that were normally suppressed by punishment. In the intervening years, this theory has been consistently reinforced—e.g. by findings that central 5-HT depletion effected either by a selective neurotoxin in rodents [27] or dietary tryptophan depletion in humans [28] increased premature responding in the 5CSRTT and human 4CSRTT. Serotonergic neurons in the dorsal raphe nucleus (DRN) also increased their firing on a task that required rats to wait for delayed rewards and remarkably stopped firing just before waiting ceased [29]. Moreover, optogenetic activation of DRN neurons facilitated patient waiting [30,31], an effect hypothesized to strengthen the confidence of reward delivery in the face of sensory evidence [32]. Obviously, there is no way of knowing whether these reported changes in tonic DRN activity in rats would translate to humans, especially monetary delay discounting tasks involving hypothetical trade-offs (e.g. £10 now or £100 in six months) but we can at least begin to consider the broader neural circuitry that 5-HT and other neurotransmitters modulate and how imbalances in waiting impulsivity might contribute to addiction.

Convergent findings in humans and rodent models have shed light on the neural circuitry of waiting impulsivity, which implicate a separation of motor restraint and temporal discounting subtypes (figure 2). In particular, it appears these two subtypes map to distinct topographically organized limbic cortico-basal-ganglia pathways [20]. Thus, lesion studies in rodents and functional imaging studies in humans implicate the nucleus accumbens core (NAC), basolateral amygdala (BLA), hippocampus, insula, lateral prefrontal cortex (PFC), posterior cingulate cortex, parietal cortex, and medial and lateral orbitofrontal cortex (OFC) in delay discounting impulsivity

[33–38]. However, it remains unclear how time-discounted rewards of differing magnitudes are encoded—for example, through delay-dependent single unit activity in the OFC [39], neural coding of the subjective value of delayed rewards within the ventral striatum, PFC and posterior cingulate cortex [36], and/or dual coding of delay and reward magnitude [35]. However, at the very least, the NAC is a necessary forebrain structure involved in processing behavioural output for immediate versus delayed rewards [33,40] and dopamine (DA) neuronal activity has been shown to scale with reward magnitude and delay [41] implicating DA neurotransmission in the NAC as a key substrate underlying aspects of waiting impulsivity.

Premature responding, by contrast, seems to depend on slightly different pathways within the ventral striatum with a greater involvement of the more medial nucleus accumbens shell (NAS). Thus, lesions of afferent structures to this region—the infralimbic cortex [42], insula cortex [43] and ventral hippocampus [44]—all increase premature responding in the 5CSRTT. Further, rats expressing trait-like impulsivity in this task have reduced DA D2 receptor (D2R) availability in the NAS (see below). Yet the NAC *also* seems to contribute to premature responding but intriguingly in an apparently opposite way to the NAS [10,45,46] (figure 2). Importantly, neither the NAS nor NAC are functionally separated but connected by spiralling medial to lateral connectivity between midbrain DA neurons and different functional domains of the striatum [47]. Speculatively, this intricate connectivity may provide a substrate for the integration of different 'temporal horizons' with respect to premature responding and delay discounting. Thus, afferent inputs to the NAS may provide *temporal* context (ventral hippocampus), *interoceptive* context (insula) and '*top-down*' inhibitory control (infralimbic cortex) over relatively short timescales. This integration would presumably complement the subjective evaluation of delayed rewards by the NAC discussed above. The serial transfer and integration of output from the NAS to the NAC and in turn the dorsal striatum also perhaps explains the critical involvement of the subthalamic nucleus (STN) in premature responding [48], a structure in receipt of input from the indirect striatal pathway [49] and whose neurons display pacemaker-like activity during the controlled execution of learnt behavioural sequences [50]. Notably, increased premature responding in the human 4CSRTT was recently linked to reduced connectivity of the STN with the subgenual cingulate cortex and ventral striatum [51].

Taken together, the above described circuits are also compatible with NOW versus LATER brain circuits described by Volkow & Balar [12] —with LATER circuitry recruiting striatal and PFC regions to sustain effort via tonic DA activity and NOW circuitry dependent on phasic DA activity and modulation by the insula and hippocampus. According to Goto & Grace [52], the switch to LATER circuits would hypothetically depend on D2R activation while the switch to NOW circuits would require D1R activation [52]. Therefore, speculatively, shortened temporal horizons in drug-addicted individuals may be driven in part by a pre-existing or drug-induced down-regulation in D2Rs (see below).

3. Neurotransmitter substrates of waiting impulsivity

Research on the neurochemical modulation of waiting impulsivity has tended to cycle from one neurotransmitter to another over the decades with 5-HT the main early focus of interest, especially *low* 5-HT phenotypes associated with suicide and unprovoked aggression and violent acts [53]. As discussed above, depletion of brain 5-HT profoundly increases premature responding in the rodent 5CSRTT [27] and human 4CSRTT [28] (figure 1*a*) and many studies over the years report significant effects of various 5-HT compounds on measures of waiting [54,55], though the reported effects were often complex and it soon became apparent that tonic 5-HT release and turnover were in fact *increased* in the PFC of rats showing high levels of premature responding [56,57]. Furthermore, although 5-HT neurons in the DRN showed increased activity to later rewards [29], profound 5-HT depletion in rats had surprisingly little effect on intertemporal choice [58]. Clearly, therefore, the jury is out until circuit-specific interventions are more widely adopted to interrogate brain impulsivity networks, including chemogenetic targeting of DRN neurons and DREADD-associated metabolic mapping or DREAMM [59].

Over the last two decades, the field gradually shifted to the catecholamines DA and noradrenaline (NA), inspired by the theoretical impetus of Jentsch & Taylor [60] who hypothesized a key role of fronto-striatal circuits and DA in particular as drivers for impulsivity in addiction. Work in non-human primates established the dynamic regulation of D2Rs and importance of social context for cocaine reinforcement [61], consistent with neuroimaging studies in drug-addicted individuals where unequivocal reductions in striatal D2Rs had been reported [62,63]. We extended this work in rodents by showing that trait-like premature responding in the 5CSRTT predicted compulsive cocaine self-administration (reviewed in [43]) and pre-existing low D2R availability in the ventral striatum [64], which we subsequently localized to the NAS [65] and determined was modulated in a baseline-dependent manner by stimulant drugs [66,67]. We also demonstrated that atomoxetine, a selective NA re-uptake inhibitor, reduced premature responding when given locally in the NAS [68], presumably by counteracting the effects of DA in this region. When administered locally in the PFC, atomoxetine improved inhibition on the stop-signal reaction time task [69], indicating that stopping and waiting forms of impulsivity are differentially modulated by cortical and subcortical NA-ergic mechanisms. Other neurotransmitter systems have also been extensively investigated in delay discounting and 5CSRTT impulsivity, including ionotropic and metabotropic glutamate receptors [70–72] and endocannabinoids [55,73].

Although low D2R availability is an apparent risk marker or endophenotype for addiction, it is unclear whether the reduction in D2R binding reflects a predominately pre-synaptic population expressed on DA neurons or a post-synaptic population expressed on GABA-ergic medium spiny neurons and/or glutamatergic afferents in the ventral striatum. In humans, the trait of impulsivity is associated with reduced somatodendritic D2Rs in the midbrain leading to exaggerated DA release in the striatum [74]. A recent study in rats used an adeno-associated viral vector and short hairpin RNAs to selectively silence D2Rs in the ventral tegmental area (VTA), a procedure sparing post-synaptic D2Rs in the striatum, PFC and other terminal structures [75]. Consistent with a presynaptic locus, the authors found that selective knockdown of D2Rs in the VTA shifted the preference of rats toward immediate, small-magnitude rewards (i.e. they were more impulsive/less patient). Recently, we localized the modulatory effect of D2Rs on choice impulsivity to the NAC [76].

However, notwithstanding abundant evidence implicating D2Rs in waiting impulsivity, rats screened for impulsivity in the 5CSRTT also show decreased γ-amino-butyric acid (GABA) levels in the ventral striatum [77] and decreased grey-matter density and GABA decarboxylase expression in the NAC, alongside reduced dendritic spine markers in the region [78]. GABA-ergic abnormalities in the NAC may explain why these animals are also impulsive on a delay discounting task [79]. Based on these findings, we assessed the relationship between single unit neural activity in the nucleus accumbens and premature responding [80]. More than 50% of neurons in the nucleus accumbens increased or decreased activity during the delay period leading up to a response in the 5CSRTT. Remarkably, this delay-dependent ramping activity increased at the same rate and reached the same maximum (or minimum) just before a response was made—regardless of whether the response was correct, incorrect or premature. However, on premature trials, the ramping activity simply started earlier than other trials. Parallels of ramping activity during waiting delays have also been observed in humans. For example, in an impulsive choice task, local field potentials across multiple frequencies in the STN increased in power during the deliberation period leading up to a decision [81].

4. Studies in humans

(a) Impulsivity and addiction vulnerability

It is without a doubt that preclinical research has provided important insight into the drivers of the different facets of impulsive behaviour and advanced addiction research in humans. Impulsive personality traits have been widely regarded as both a determinant and a consequence of stimulant drug addiction [14], which has been supported by experimental approaches in animals [64,82]. For example, Belin and colleagues [83] differentiated two personality traits in rats, sensation-seeking and impulsivity, and showed that these traits were associated with differential risks for initiating and developing compulsive cocaine self-administration, respectively [83]. In human research, these two traits are often conflated because they both involve risky behaviours, yet they are distinct: impulsive actions may be risky because of a failure to inhibit premature responses, whereas sensation-seekers take risks deliberately because of a need for excitement and sensations. Numerous studies have shown that people with addiction, and specifically stimulant drug addiction, report significantly higher levels of both impulsivity and sensation-seeking [84,85]. There is growing evidence suggesting that impulsivity but not sensation-seeking is a predisposing trait. Sensation-seeking is highly expressed in both individuals who are addicted to stimulant drugs and those who only use stimulant drugs recreationally who have neither a family history nor a personal history of addiction [74]. As sensation-seeking traits are not increased in unaffected first-degree relatives of stimulant-addicted individuals, this trait does not seem to predispose one to developing addiction, but rather to initiating drug use in the first place. What differentiates the two drug user groups are the levels of impulsivity and compulsivity, two traits that are underpinned by failures of inhibitory control, with stimulant-addicted individuals showing higher levels of impulsivity and compulsivity than recreational users [84]. Clearly, these data mirror the results from studies in rodents, supporting the view that impulsivity is a predictive endophenotype for addiction. Nevertheless, more studies using an endophenotype approach will be needed to replicate these findings and to establish solid evidence for objective risk markers for the development of the disorder.

Impulsivity is a multifaceted psychological construct, which spans several domains, many of which are not captured by questionnaire measures. There is accumulating evidence showing that addiction to drugs, and specifically addiction to stimulant drugs, is associated with aspects of *waiting impulsivity* as reflected by impulsive choices [23], premature responding [23], delay discounting [86], delay aversion [87,88], lack of consideration when making decisions [21], difficulties adjusting to changing response criteria [89] and difficulties in managing time [90]. Clearly, impulsivity occurs in a variety of forms, which are not *per se* pathological. In fact, impulsivity covers the entire spectrum from normal to maladaptive behaviour. In the light of such widespread dysfunction in regulatory control in drug addiction, it is not difficult to apprehend how disruptive life is not only for individuals affected by the disorder but also for their families and friends. With impulsive choices of drug-taking being readily triggered by environmental cues, for example, by visiting certain places or simply hearing rumours of drugs being available, long-agreed important commitments towards work or family life are quickly overturned in favour of immediate drug use. In as much as impulsive behaviour does not take into consideration the potential consequences of these spontaneous actions, harm may only be averted in the short term by great efforts of friends and family, but the risk of adversity in the long term continuously increases. Crisis situations such as personal bankruptcy, unemployment, a relationship breakdown or the loss of custody for beloved children, which on their own anyone would find difficult to deal with, often co-occur in drug-addicted individuals, who find themselves unprepared for such outcomes and unable to cope. Moreover, their unpredictable behaviour and preoccupation with drugs are likely to fuel disappointment and frustration in people who have been supporting them, and that support may start to wane as a result. In many cases, the drug-using community cannot compensate for the declining familial and social support over time, further exacerbating the downward spiral, and contributing to poverty as well as poor physical and mental health. Importantly, and characteristic of addiction, such devastating consequences do not lead to a reduction in drug use, but rather increase drug-taking either through deliberate attempts to cope with the situation and self-medicate with drugs of abuse or through habitual drug-taking patterns and compulsions. Consequently, this vicious circle does not simply stop following incarceration or enrolment into treatment. With impulsivity being a key component of addictive behaviour, attenuating impulsive actions through targeted interventions has been suggested as a way forward to alleviate symptoms of addiction [91]; however, so far promising effects have only been shown in addition to nicotine [92]. Figure 2 illustrates the profile of impulsive behaviour in cocaine-addicted individuals, as assessed by laboratory tasks. However, it remains unclear which of these different facets of impulsivity might predispose to addiction, and which are caused and/or worsened by continued use of stimulant drugs.

Addressing the question of causality through research in humans is challenging because controlled experiments to study the long-term effects of drugs are unethical in humans. An ethically acceptable way is to compare people with stimulant drug addiction syndromes with both their first-degree

relatives (e.g. biological siblings) and healthy unrelated control volunteers. By comparing the phenotypic profile of these groups, using cognitive measurements focused on abnormalities that are associated with addiction (e.g. high levels of different types of impulsivity), it should be possible to distinguish the neurocognitive endophenotypes shared between first-degree relatives that predispose individuals to developing addiction from the profile of abnormalities unique to the drug-addicted state, which are therefore presumably an effect rather than a cause of chronic stimulant drug addiction.

An endophenotype approach to investigating the role of impulsivity in stimulant drug addiction is particularly interesting because drug addiction is widely believed to derive from a combination of both genetic and environmental factors [93]. The contribution of genetic factors seems to vary with regard to the drug's addiction liability [94]. For cocaine, which has a high addiction liability, heritability has been estimated at 72% [94]. The relationship between addiction liability to a particular drug and the heritability of addiction to that drug suggests that individual variations in DA-related neural networks mediate a person's vulnerability to develop addiction to stimulant drugs following regular use. Converging lines of evidence show that alterations in the DA system and related fronto-striatal networks are associated with an increased risk for the development of stimulant drug addiction. These alterations involve high levels of impulsivity [85], reduced presynaptic DA release [95], reduced white matter integrity in the right inferior frontal gyrus [96] and volume enlargement of the putamen [96], all of which have been associated with a family history of substance dependence. Furthermore, low D2R density in the ventral striatum has also been linked with increased levels of impulsivity [64] and high sensitivity to stimulant reinforcement [97], rendering individuals vulnerable to the reinforcing effects of stimulant drugs. Animal models of addiction have also shown that both reduction in striatal D2R density [98,99] and volume enlargement of the putamen [100] do not necessarily predate drug-taking but can also be caused by chronic exposure to stimulant drugs. A family history of addiction may thus be a risk marker for developing addiction if the individual starts taking stimulant drugs. However, whether or not these findings may generalize to other drug classes or polydrug use warrants further investigation. Evidence from studies comparing brain function during reward anticipation in unrelated individuals with and without a family history of alcohol addiction has been inconclusive. For example, some studies report reduced activation in the ventral striatum during reward anticipation in individuals with familial risk [101], while others show increased activation in this region [102] or do not find group differences [103,104]. In light of the ethical limitation of studying the question of causality in humans, it is recommended that research tackling the question of causality include related individuals both with and without drug use as well as with and without a family history of addiction. However, as much as this would be theoretically desirable, it would involve substantial practical constraints of recruiting appropriate participant pairs. Translational research paradigms may thus offer an attractive alternative to investigate the causal trajectories across species.

The high levels of impulsivity that are shared by stimulant-addicted individuals and their unaffected first-degree relatives can be measured not only by self-report [85] but also by objective markers of motor impulsivity such as prolonged stopping responses during stop-signal task performance [96]. In terms of cognitive impulsivity, as reflected by unplanned approaches on tasks of working memory, mental organization or attentional control, their performance was either not measurably impaired [105] or showed less efficiency when compared with peers without a family history of addiction [106]. Importantly, normal task performance does not necessarily imply normality, as neuroimaging evidence suggests that unaffected siblings might employ compensatory mechanisms to perform adequately [107].

The inability to wait for reward (waiting impulsivity) has also been associated with stimulant drug addiction. The Monetary Choice Questionnaire [108] (figure 1*b*) is one of the most widely used self-report measures of the extent to which the value of a monetary reward declines the longer the individual is waiting for it. Importantly, the preference for immediate outcomes at the expense of larger distant ones is not necessarily pathological, but rather constitutes part of normal personality characteristics [91]. Numerous studies have shown that the decline in the reward value is not only significantly steeper in addicted individuals compared with their non-drug-using peers [88], but the steepness of decline varies across different drug classes [87]. Choice preference has also been shown to persist during early abstinence [109], which is consistent with the notion of delay discounting being a heritable trait [110–112], which may be further exacerbated by chronic substance abuse [113]. However, whether or not delay discounting actually represents an endophenotype for addiction is still unclear. Endophenotypes, which have been defined as a quantitative trait that is an intermediate between the predisposing genes (genotype) and the clinical symptoms (phenotype), should meet the following criteria [114]: they should (1) be associated with the disorder; (2) be genetically determined; (3) manifest in periods of health as well as during acute illness; (4) co-segregate with the disorder within families and finally (5) be over-represented in non-affected family members as compared to the general population. This final criterion has, however, not been consistently met for delay discounting, as measured by self-report (Monetary Choice Questionnaire) [115] or by premature responding, as measured by behavioural paradigms such as the 4CSRTT [24]. Individuals with and without a family history of addiction cannot be differentiated by their responses on the questionnaire or the task. However, under the influence of alcohol, individuals with a family history of addiction have been shown to respond impatiently, making many more premature responses compared with their peers without familial risk. Presumably, vulnerability for addiction appears to mediate the effect of the drug on premature responding in this task, but delay discounting is not a defining feature of addiction vulnerability *per se*.

(b) Impulsivity and resilience to addiction

Stimulant drugs such as amphetamines and cocaine are widely used all over the world, but only one in six recreational stimulant drug users become addicted [116]. While most attention is focused on those individuals who develop addiction and the factors that precipitate its development, relatively little is known about those individuals who are using addictive drugs such as cocaine without ever making the transition to addiction. The most important and defining characteristic of this type of recreational drug use is the controlled and goal-directed manner in which they use the drug, and their ability

to sustain this control for prolonged periods of time. These recreational cocaine users, who tend to have no family history of addiction and to have not made severe adverse experiences during childhood, have also been found to differ on a number of other variables from addicted users [84]. Firstly, they usually started using simulant drugs during early adulthood (compared with addicted users, who often start during their teenage years) once they completed their basic education (secondary school). Through their occupations, they can often afford the use of cocaine as well as other expensive interests. Cocaine is for them just one of many pleasures in life that they would not be willing to sacrifice over others, which is why they reported using cocaine in a controlled manner, i.e. always in the company of others and never alone, never spending more on the drug than planned, not using it alongside other drugs, and keeping consumption of alcohol within the recommended limits. These so-called recreational cocaine users when tested showed normal levels of impulsivity, as assessed both by self-report (BIS-11) and behavioural paradigms such as the stop-signal reaction time or Stroop tasks [117,118]. Moreover, their brain morphology did not display the abnormalities typically associated with stimulant drug addiction. On the contrary, they showed increased grey-matter volume in the OFC, which declined in volume in addicted individuals as a function of the duration of stimulant drug use [84]. However, their brain activation during task performance indicated that they could possibly be recruiting a compensatory mechanism to buffer the effects of the drug in order to maintain normal levels of impulsivity.

It is important to clarify that not all recreational stimulant drug users are resilient to the effects of the drug. In fact, previous studies on regular non-dependent stimulant drug users did not show the aforementioned characteristics. Thus, these individuals exhibited similar cognitive and behavioural profiles as addicted cocaine users [119,120], which fuelled speculations that they could be on the trajectory to addiction. A subset of recreational stimulant users, who use prescription stimulant drugs on occasions to enhance cognitive function [121], show altered brain function during decision-making and interoceptive processing [122], which may also render them vulnerable to the transition to addiction. Presumably, the individual characteristics of users matter as much as the addictive liability of the drug.

(c) Implications for treatment

Not only has impulsivity been associated with the transition from habitual to compulsive drug use, high levels have been shown to significantly hamper recovery from addiction in terms of treatment drop out [123,124] or increase the risk of relapse [125]. Impulsivity might therefore be a relevant factor to take into consideration for treatment, for example, by probing attentional control. One experimental study examined the effects of dopaminergic agents on the degree to which stimulant-addicted individuals are distracted by drug-related words [126]. Restoring midbrain DA transmission in stimulant-addicted individuals using DA agonists has been suggested as a treatment target to restore the downregulation of midbrain DA in this disorder, but clinical studies have not been conclusive [127]. Equally inconclusive were approaches for the use of DA receptor antagonists to block cue-induced DA release [128,129], which can induce craving and trigger relapse. This dilemma, namely whether treatment for stimulant addiction should stimulate the DA system or block DA receptor function, reflects the particular difficulties of treating this disorder. The aforementioned study, however, showed that the heterogeneity of participants' performance was partly explained by variations in participants' levels of compulsivity. While DA agonists abolished the attentional bias towards stimulant-related cues in individuals who used simulant drugs in a non-compulsive manner, they had the opposite effect in individuals who used stimulant drugs highly compulsively. This suggests some kind of switch in the underlying mechanism regulating attentional control, which the authors explain by the putative development of post-synaptic super-sensitivity in highly impulsive individuals [126]. Yet further research is warranted to further elucidate in finer detail the mechanisms underlying the transition from impulsive to compulsive stimulant drug use.

(d) Impulsivity versus compulsivity

Impulsivity has been shown to predict the development of compulsive drug-taking in experimental animals [83]. These two psychological constructs, impulsivity and compulsivity, are not only highly correlated in stimulant drug addiction, but also in a variety of other psychiatric disorders [130]. While impulsivity, as a personality trait, covers the spectrum from normal to maladaptive behaviour, the variation of compulsivity in the normal population is very low, and is expressed differently across different psychiatric disorders (e.g. checking behaviour in obsessive–compulsive disorder and compulsive drug use in substance use disorders). This may suggest that the effect of the drug influences the expression of compulsive behaviour. What could the mechanism be that renders impulsive individuals susceptible to using stimulant drugs in a compulsive manner?

One mechanism of emerging interest relates to the development of iron deficiency in the basal ganglia of chronic drug users. Iron is a coenzyme of DA synthesis [131] and involved in the storage of DA within the neuron [132], and therefore may influence DA-dependent functions and modulate the reinforcing effects of stimulant drugs. The iron content of DA neurons is relatively high because the synthesis of DA is strongly energy-dependent [133]. Within DA-ergic vesicles, iron and DA form stable complexes to protect the neuron from degradation by the enzyme monoamine oxidase. Iron deficiency has been shown to directly affect the neuron's iron-DA-binding capacity, rendering the neuron more prone to iron-related toxicity [132]. Consequently, iron deficiency is associated with increased extracellular DA levels in the striatum due to a decrease in DA re-uptake by transporters [134] and reduced DA-binding capacity within neurons [135]. Iron deficiency has also been shown to decrease D2R density in the striatum in animal models [136], a phenotype frequently reported in stimulant-addicted individuals [137]. This is interesting in light of the fact that iron regulation in stimulant-addicted individuals is significantly disrupted, as reflected by iron deficiency in the periphery and excessive iron accumulation in the brain [138]. Work in experimental animals has also shown that stimulant drugs cause a selected accumulation of iron in the globus pallidus, which together with the STN forms the 'indirect striatal pathway' implicated in regulatory control and compulsive behaviours [139]. Familial risk for developing compulsive stimulant drug use could be associated with a polymorphism in iron-regulatory genes, which in combination with chronic stimulant exposure, may lead to the low

density in D2Rs in addicted individuals [97] and the blunted pre-synaptic DA release in individuals at high risk for addiction [95]. Clearly, more work is needed to identify the underlying mechanisms of iron deficiency in stimulant users and, in particular, to back-translate findings in human stimulant users to experimental approaches in animals to assess addiction development in more detail, in order to provide the necessary knowledge to identify targets for more effective therapeutic and preventative strategies for stimulant drug addiction in the future.

5. Concluding remarks

Waiting impulsivity is an important dimensional trait that predisposes individuals to a variety of related disorders of incentive motivation. In this short review, we have argued in the context of drug addiction that processes underlying waiting operate on short- and long-term timescales and are mediated by distinct but nevertheless partially convergent pathways within the ventral striatum. Whereas moment-to-moment restraint of premature actions recruit a network encompassing the NAS, STN, ventral hippocampus, insula and PFC, longer-term decisions and patient choice require interactions between posterior (parietal, cingulate cortices) and anterior (lateral PFC, OFC) cortical regions and the NAC. Although the weight of evidence strongly implicates abnormalities in DA transmission in waiting impulsivity, other neurotransmitter systems are now attracting renewed interest including GABA and 5-HT. Indeed, as reviewed in this article, diminished serotonergic function—a phenotype linked to increased premature responding—is a consequence of protracted cocaine exposure [140] and may underlie the development of compulsive drug disorders [141,142].

It is now timely to strive for a deeper understanding of the brain mechanisms underlying waiting impulsivity and how these restraining processes are disrupted by drugs of abuse. Progress in this important research requires more examples of forward and back translation in humans and other animals.

Data accessibility. This article has no additional data.

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