The neuropharmacology of impulsive behaviour

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Impulsivity is a heterogenous phenomenon encompassing several behavioural phenomena that can be dissociated neuroanatomically as well as pharmacologically. Impulsivity is pathological in several psychiatric disorders including attention-deficit/hyperactivity disorder (ADHD), drug addiction and personality disorders. Pharmacological agents alleviating impulsivity therefore might substantially aid the treatment of these disorders. The availability of preclinical models that measure various forms of impulsivity has greatly increased our understanding of its neuropharmacological substrates. Historically, deficits in central serotonin neurotransmission are thought to underlie impulsivity. Accumulating evidence also points towards an important role of brain dopamine and noradrenaline systems in impulsive behaviour, consistent with the therapeutic efficacy of amphetamine, methylphenidate and atomoxetine in ADHD. However, recent findings also implicate glutamate and cannabinoid neurotransmission in impulsivity. In this review, we will discuss some of the recent developments in the neuropharmacological manipulation of impulsive behaviour.

Introduction

Impulsivity or diminished inhibition of behaviour might have evolved to allow individuals to adapt successfully to uncertainty, complexity and rapidly changing environments. Acting without forethought is considered one of the main behavioural expressions and most common definition of impulsivity. However, a growing body of data has indicated that impulsivity is heterogeneous: it consists of several distinct behavioural phenomena that are dissociable at the neuroanatomical as well as neuropharmacological levels [1]. The behavioural expressions of impulsivity range from disturbed inhibition of behaviour and lack of reflection on the consequences of one’s behaviour to the inability to postpone reward, that is, delay aversion. Thus, impulsivity includes categories of behaviours that result from difficulties in the ability to inhibit actions, often referred to as impulsive action, and behaviours that reflect impulsive decision making, for example, intolerance to delay of gratification or delay aversion, which is exemplified by increased preference for immediate reward over more beneficial but delayed reward [2].

Various preclinical models, most of them translated from human neuropsychological tasks, exist that have greatly contributed to our understanding of the neural correlates of impulsivity in rodents. A commonly used behavioural paradigm that reliably measures aspects of the inhibition of actions, or impulsive action, in rodents is the 5-choice serial reaction time task (5CSRTT). The 5CSRTT was originally developed to measure visuospatial attention [3]. In this paradigm, rats have to attend to an array with five apertures, each one fitted with a stimulus light and they have to make a response into a briefly illuminated aperture to receive a small food reward. These visual stimuli are presented to the rats on a trial-by-trial basis and the rats do not know the next location of the visual stimulus. Successful performance in this paradigm therefore requires attentional processing. Over the course of extensive training in this paradigm, rats learn that they have to inhibit making a response until a next visual stimulus is presented to them. The number of responses before the onset of the visual stimulus (or premature responses) is generally regarded to be a measure of impulsivity, because low levels of premature responses require the ability to inhibit actions, whereas high levels might reflect disturbances in the inhibition of behaviour [3]. Preclinical models that are used to tax impulsive decision making often measure delay aversion. Typically in these delayed reinforcement tasks [4], rats are faced with a choice between two response options. One option is associated with small and immediate food reward, whereas the second option results in larger but delayed food reward. Clearly, the second response option is more beneficial, but the subjective value of the large food reward declines with increasing delay to its delivery. Individuals that are more impulsive in these paradigms are generally more delay averse and will tend to choose the response option associated with small reward at shorter delays.

As can be seen from the studies discussed in this review, most of the work on impulsive behaviour has been done using the 5CSRTT or delayed reinforcement procedures that measure very distinct behavioural forms of impulsivity. Quite clearly, these studies have been invaluable for our understanding the neural and pharmacological basis of impulsivity, but it should be borne in mind that impulsive behaviour entails more than is measured in these procedures. As such, the emerging interest in impulsive action assessed using other paradigms, such as the stop signal
Impulsivity in psychiatric disorders

Impulsivity is not defined in a separate diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) [6], but is a key characteristic of several psychiatric disorders. Treating impulsivity therefore might represent a novel intervention strategy. Here, we will only briefly address this because in depth discussion on this topic has been provided elsewhere [7].

Impulsivity is most prominent in attention-deficit/hyperactivity disorder (ADHD), a debilitating childhood condition, characterized by both difficulties in inhibiting actions and delay aversion [8]. In addition, impulsivity also plays a crucial role in drug addiction, and disturbances in inhibition of behaviour that result from prolonged drug intake have been proposed to maintain compulsive drug abuse [9]. In itself, drug addiction can also be seen as a form of delay aversion because addicts prefer the immediate ‘small’ reward of a drug high over the delayed long-term benefits of a drug-free lifestyle. Moreover, the notion that drug addiction and impulsivity are strongly interrelated has been supported by recent empirical evidence. Several studies demonstrate that elevated impulsivity might predispose individuals to initiate or maintain drug seeking and taking in both humans [10,11] and laboratory animals [12–14]. Finally, pathological impulsivity is observed in certain personality disorders and mania, although the role of impulsivity in the etiology of these disorders is scantly understood as yet.

Recent advances in genetics have allowed the detection of polymorphisms (i.e. variants) of several genes that might lead to quantitative or qualitative differences in resultant protein products. Polymorphisms of genes that have been linked to ADHD and addiction in humans include those that encode for the dopamine transporter, dopamine D2, D4 and D5 receptors, the serotonin transporter and serotonin 1B receptors [15,16]. Besides these polymorphisms that have been linked to ADHD and addiction in humans, our current understanding of underlying changes in brain neurotransmitter systems in humans is limited. To our knowledge, the most solid evidence in this regard comes from imaging studies that demonstrate diminished availability of dopamine D2 receptors in the striatum of human addicts [17]. Together, the advances in genetics and imaging techniques in humans together with growing knowledge from preclinical approaches could drive the development of novel pharmacotherapies for ADHD and addiction.

Neuroanatomical circuitry of impulsivity

The neuroanatomical circuitry involved in impulsivity has been well mapped in rodents. Consistent with human imaging and brain damage data [18], prefrontal cortical, striatal and limbic brain regions have been found to play an important role in impulsivity in rodents (Figure 1). In

![Figure 1](image-url). Schematic overview of the neuroanatomical regions in the brain involved in impulsive action, that is, inhibitory control processes and delay aversion. Lesion studies that employ different preclinical models of impulsivity have demonstrated that there is considerable overlap in brain areas, including cortical and limbic regions, that modulate impulsive action and delay aversion in rodents. Red indicates that lesions of these regions increase impulsive action or delay aversion. Green indicates beneficial effects of lesions on impulsivity and in particular more self-controlled choice. Blue indicates that lesions of these brain regions did not affect impulsive action nor delay aversion; dark grey/black areas indicate ventricles in the brain, and light grey areas indicate fibre tracts in the brain. Note that some brain regions dissociate between varieties of impulsivity both in terms of involvement as well as the direction of lesion effects. For example, the infralimbic cortex appears primarily involved in impulsive action, whereas limbic regions such as the basolateral amygdala and hippocampus primarily modulate delay aversion processes, although their role in impulsive action has not been established. Moreover, lesions of the subthalamic nucleus have opposing behavioural effects on impulsivity. To a lesser extent this also holds true for the orbitofrontal cortex, although inconsistent findings have been obtained with respect to delay aversion. Abbreviations: ACC, anterior cingulate cortex; BLA, basolateral amygdala; HAB, habenula; HPC, hippocampus; IL, infralimbic cortex; MS, medial striatum; NAC, nucleus accumbens core region; NAS, nucleus accumbens shell region; OFC, orbitofrontal cortex; PL, prelimbic cortex; STN, subthalamic nucleus.
particular, the prefrontal cortex in conjunction with one of its primary subcortical output structures, that is, the nucleus accumbens, mediates the structuring of behaviour appropriate to the situation. Because recent reviews have provided in depth discussion of experimental evidence obtained in rodents [2,4], we will only briefly discuss some novel findings that have further extended our understanding of the neural basis of impulsivity. For instance, functional differences have recently been reported between subregions of the nucleus accumbens in modulating impulsivity. In particular, this work stresses involvement of the core and not shell portion of the nucleus accumbens in delay aversion as well as impulsive action [19]. Recent findings have implicated the orbitofrontal cortex in impulsive action [20], whereas, to date, damage to this brain area was mainly found to produce or alter delay aversion [21–24] and not impulsive action [25]. In addition, a role for limbic regions such as the habenula and hippocampus in impulsive action [26] and delay aversion [27], respectively, has now been more firmly established, consistent with earlier data [28]. The precise mechanisms by which these limbic structures affect impulsivity are not completely understood, although both regions project to striatal brain areas including the nucleus accumbens.

Taken together, considerable overlap exists in the neural pathways that mediate impulsive action and delay aversion. However, some brain areas do dissociate between different forms of impulsivity, which supports the notion that the different behavioural phenomena of impulsivity rely on separate neural pathways.

Neuropharmacology of impulsivity

Serotonin

Altered functioning of the serotonin (5-hydroxytryptamine, 5-HT) system has long been implicated in impulsivity. In particular, decreased 5-HT transmission has been hypothesized to correlate with diminished inhibitory control and elevated aggression [29]. In this view, 5-HT would act as a ‘brake’ to inhibit behaviour. However, the role of the 5-HT system in impulsivity has turned out to be markedly more complicated. In fact, the mechanisms by which the 5-HT system modulates impulsivity are incompletely understood, partly owing to the complex nature of this system that contains at least fourteen different receptor subtypes each belonging to one of seven receptor families (5-HT1–7) [30].

A substantial body of evidence has supported this 5-HT hypothesis by demonstrating that lowered 5-HT signaling, for instance by depletions, impairs impulsive action [31–33]. Conversely, enhanced 5-HT transmission, as recently demonstrated in transgenic rats that lack 5-HT transporters, has been found to reduce premature responding in the 5CSRTT [34]. Nonetheless, some studies have challenged the 5-HT hypothesis and, for instance, showed that ‘increased’ 5-HT release within the medial prefrontal cortex correlated with elevated impulsive action in the 5CSRTT [35]. The role of 5-HT in delay aversion remains less clear. Data obtained from depletion studies are inconclusive [4]. In a study that directly addressed this issue, 5-HT depletions were only found to impair impulsive action and not delay aversion [32] in accordance with clinical data [36]. These observations might indicate differential 5-HT involvement in impulsive action versus delay aversion. However, performance in a delayed reinforcement procedure has recently been reported to correlate with increased 5-HT efflux in the medial prefrontal cortex [37].

In recent years, the 5-HT1 (particularly 5-HT1A/B/D) and 5HT2 (5-HT2A/B/C) receptor families have been reasonably well studied in relation to impulsivity (see Table 1). Most drugs that act on 5-HT1A receptors increase impulsivity. This might be explained by the fact that these receptors can be located presynaptically on 5-HT neurons, where their activation inhibits the release of 5-HT. Thus, treatment with 5-HT1A agonists would result in decreased 5-HT efflux [38]. Despite the observations that polymorphisms of the 5-HT1B receptor have been associated with ADHD [15], selective 5-HT1B receptor agonists and antagonists have been ineffective in altering impulsivity [39]. Antagonists of the 5-HT2A receptor appear promising drugs to alleviate impulsivity because most of these compounds have been shown to reduce impulsivity in the 5CSRTT [33,40–44]. Complex opposing interactions of 5-HT2A with other 5-HT receptor subtypes such as the 5-HT1A and 5HT2C receptor could account for these effects [45].

In conclusion, 5-HT is clearly involved in impulsivity, but the exact mechanisms remain unclear. This could be because of the complexity of the 5-HT system itself, the lack of availability of selective ligands for 5-HT receptor subtypes and the interactions with other neurotransmitters, including dopamine, noradrenaline and glutamate [41,46–48].

Dopamine

An important role for dopamine in impulsive behaviour has been inferred from the therapeutic efficacy of psychostimulant drugs, such as amphetamine and methylphenidate, in the treatment of ADHD (see Table 1). However, psychostimulant drugs do not reduce all forms of impulsivity. In fact, amphetamine has quite consistently been found to enhance impulsive action in the 5CSRTT [3], and this effect is dependent on increases in dopamine neurotransmission. Thus, the dopamine reuptake inhibitor GBR12909 (see Chemical names) increased impulsive action in the 5CSRTT, and the effect of amphetamine was inhibited by the dopamine D2 receptor antagonist eticlopride [49]. Conversely, treatment with low doses of the dopamine receptor agonist apomorphine or the dopamine D2 receptor agonist quinpirole that reduce dopamine neurotransmission by stimulating presynaptic D2 autoreceptors, or treatment with dopamine receptor antagonists reduced impulsive action in the 5CSRTT [26,49–51]. Both dopamine D1 receptors and D2 receptors might mediate this latter effect. The effect of amphetamine on impulsive action in the 5CSRTT is exerted through the nucleus accumbens, because 6-hydroxydopamine lesions of the nucleus accumbens prevent the effect of amphetamine [3], and treatment with eticlopride into the accumbens (its core region in particular) blocked the effect of amphetamine in the 5CSRTT [52]. Furthermore, infusions of the dopamine D1 receptor agonist SKF38393 into the nucleus accumbens enhanced impulsive action in the 5CSRTT [53].
Treatment with psychostimulant drugs has been shown to improve performance in the stop signal task in rats and humans [54–56]. Psychostimulants are particularly effective in alleviating impulsive action in the stop signal task in individuals with relatively poor baseline performance [56,57]. Interestingly, the effect of methylphenidate in the stop signal task was not blocked by the dopamine receptor antagonist α-flupenthixol, which suggests a non-dopamine (most likely noradrenaline, see below) mechanism of action.

Dopamine neurotransmission plays an important role in delay aversion. In most studies, treatment with amphetamine, methylphenidate and cocaine has been found to reduce delay aversion in humans and rodents [58–64]. These effects depend on dopamine neurotransmission, because GBR 12909 reduces delay aversion, and dopamine

<table>
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<th>Agonist</th>
<th>Antagonist</th>
<th>Region</th>
<th>Impulsive action</th>
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Glutamate

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Noradrenaline

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*Red up arrows indicate that ligands increase impulsive action or delay aversion. Green down arrows indicate beneficial effects of ligands on impulsivity, and blue equals signs indicate no behavioural effects of these ligands on impulsivity.

*Abbreviations: DLS, dorsolateral striatum; mPFC, medial prefrontal cortex; Noradrenaline, NA; NAC, nucleus accumbens.

*Effects of local infusion of ligands into specific brain regions; see Figure 1 for overview involvement of various brain regions in impulsivity.

*Buspirone also has affinity for other receptors, for example, dopamine D2 receptors; moreover, in this study the acute deleterious effects differed from the chronic beneficial effects of buspirone on delay aversion.
receptor antagonists increase it [61,64,65]. Moreover, the dopamine depletion of the nucleus accumbens [48]. Rather, amine on delay aversion was not altered in animals with a on impulsive action in the 5CSRTT, the effect of amphet-
amphetamine activity, perhaps within the orbitofrontal cortex, accumbens enhances impulsive action, increasing dopamine neurotransmission in the orbitofrontal cortex might play an important modulatory role in delay aversion [21,48].

Together, the role of dopamine neurotransmission in impulsivity is quite well established. Interestingly, whereas increasing dopamine activity in the nucleus accumbens enhances impulsive action, increasing dopamine activity, perhaps within the orbitofrontal cortex, decreases delay aversion. The role of dopamine in impulsivity is therefore an excellent example of its heterogeneous nature: it has bidirectional effects on two distinct forms of impulsivity, through an action in different brain areas.

**Noradrenaline**

Depletions of forebrain noradrenaline using 6-hydroxy-
dopamine lesions of the locus coeruleus, or selective nor-
adrenaline depletions of the prefrontal cortex did not alter impulsive action in the 5CSRTT [3,66], but treatment with the noradrenaline reuptake inhibitors desipramine and atomoxetine produced modest reductions in impulsive action in this task [49,67–69]. This effect might be mediated through α1 or α2 adrenoceptors, which have been shown to be involved in impulsive action in the 5CSRTT [46].

Noradrenaline neurotransmission plays an important role in impulsive action as investigated in the stop signal task, because the noradrenaline reuptake inhibitors desipramine and atomoxetine increased the ability to suppress an ongoing response in this task. Remarkably, this effect was found in both rodents [68] and humans [70,71]. These findings suggest that the effects of amphetamine and methylphenidate in the stop signal task are mediated by increased noradrenaline neurotransmission.

There is also some evidence to support a role for nor-adrenaline neurotransmission in delay aversion. Thus, whereas the noradrenaline reuptake blocker desipramine had inconsistent, delay- and dose-dependent effects on delay aversion [64,68], the more selective noradrenaline reuptake inhibitor atomoxetine reduced delay aversion [68]. This latter effect seems consistent with the observation that the α2 adrenoceptor agonist clonidine, which decreases noradrenaline release by stimulating presynaptic α2 autoreceptors, increased delay aversion [64], which suggests that enhancing noradrenaline activity could decrease delay aversion. By contrast, because cloni-dine can also stimulate postsynaptic α2 adrenoceptors, these data might also indicate that the role of noradrenaline neurotransmission in delay aversion relies on a complex interplay between various adrenoceptors, and that perhaps noradrenaline tone needs to be within certain ranges to optimal performance in this task. α1 Adrenoceptors do not seem to be involved, because the α1 adrenoceptor agonist phenylephrine had no effect in this task [64].

Thus, enhancing noradrenaline signaling decreases impulsive action, in both 5CSRTT and stop signal tasks, as well as delay aversion. It should be noted, however, that the effects of noradrenaline reuptake inhibition in the stop signal task are strongest and most consistent between studies. In addition, the brain regions and receptors through which noradrenaline neurotransmission modulates impulsivity remain to be established. Nevertheless, targeting noradrenaline neurotransmission seems to be a promising avenue to treat impulsive behaviour.

**Glutamate**

Converging findings have implicated glutamate neuro-transmission in impulsivity. Systemic injections of non-selective NMDA receptor antagonists such as CPP, dizocilpine (MK801) and ketamine have been reported to increase impulsive action in the 5CSRTT [47,72] as well as delay aversion [65]. In addition, a novel selective NMDA 2B receptor subunit (NR2B) antagonist Ro 63–1908 also markedly increased impulsivity in the 5CSRTT [72], thereby emphasizing a specific role for these receptor subunits in impulsive action.

In addition to NMDA receptors, metabotropic gluta-mate receptors (mGlURs; in particular mGlUR1 and to a lesser extent mGlUR5) have been shown to modulate impulsivity. Interestingly, the mGlUR1 appears differen-tially involved in impulsive action and delay aversion based on data obtained with the selective mGlUR1 antagonist EMQMCM [73]. The role of mGlUR5 in impulsivity is less clear; the mGlUR5 receptor antagonist MPEP was found to increase impulsive action in the 5CSRTT, but
effective doses also caused sedative effects, which questions the selectivity of these findings [74]. In this study, the mGluR2 and mGluR3 receptor antagonist LY341495 did not change impulsivity in the 5CSRTT, which suggests limited involvement of these receptors.

In terms of neuroanatomical localization, altering glutamate transmission in the medial prefrontal cortex and especially its infralimbic region has been associated with impulsive action as demonstrated by CPP infusions into these regions [47,75,76] and thus parallel lesion studies (Figure 1).

Collectively, these findings indicate that impaired glutamate transmission might lead to impulsive symptoms and stress a particular role for the medial prefrontal cortex. NMDA receptors and mGlus might represent interesting novel targets for pharmacological interventions to alleviate impulsivity.

Cannabinoids

The cannabinoid system and particularly cannabinoid CB1 receptors have been implicated in higher cognitive functions including attention, behavioural flexibility, time estimation and working memory, based on emerging preclinical evidence [77]. In healthy volunteers, marijuana and delta^9-tetrahydrocannabinol, the principle active ingredient of marijuana, have been demonstrated to increase the occurrence of risk-taking behaviour in the laboratory [78] and induce impulsive action in a stop signal task, but not delay aversion [79,80], which suggests a role for the cannabinoid system in impulsivity. In support of these clinical findings, in a recent preclinical study the cannabinoid CB1 receptor agonist WIN552122 was found to modestly impair response inhibition in the stop signal task, whereas the cannabinoid CB1 receptor antagonist rimonabant reduced impulsive action in the 5CSRTT but did not change delay aversion [81]. In a task related to the 5CSRTT, rimonabant did not alter impulsive action. However, in this study, rats displayed low baseline impulsivity, possibly masking behavioural effects [82]. Thus, although cannabinoid agonists might modulate impulsive action, the aforementioned observations suggest a specific role for endocannabinoid signaling, possibly owing to their modulatory action on glutamate and dopamine signaling in the prefrontal cortex and striatum [83]. Considering the availability of rimonabant for clinical purposes, it might be worthwhile to study its effects on impulsivity in humans.

Concluding remarks

During the last decade, significant progress has been made in understanding the neural basis of impulsive behaviour. Thus, both pharmacological studies, as well as experiments that directly manipulate brain areas, have furthered our understanding of impulsivity. In addition, these studies have reinforced the notion that impulsivity is not a unitary phenomenon, but consists of a variety of behavioural expressions subserved by dissociable, if sometimes overlapping, neural substrates. However, there is still work to be done until a specific pharmacotherapy for impulsivity, or at least certain aspects thereof, can be expected.

With regard to the monoamine systems, the involvement of dopamine neurotransmission in impulsivity is now relatively well established. That is, increasing dopamine neurotransmission enhances one form of impulsive action, but reduces delay aversion. Interestingly, although not a lot of work has as yet been devoted to the involvement of noradrenaline neurotransmission, the recent finding that the noradrenaline reuptake inhibitor atomoxetine reduced impulsive behaviour in three rat models that assessed two forms of impulsive action as well as delay aversion [68], suggests that drugs targeted at this neurotransmitter system hold promise for the treatment of impulsivity. However, the exact receptor mechanisms through which these effects are exerted still need to be clarified. The involvement of 5-HT in impulsivity remains somewhat of an enigma, although the role of 5-HT_{2A} receptors in impulsivity seem quite clear. Work using more receptor-selective drugs will help to further elucidate the role of 5-HT neurotransmission. Recent work that addressed the involvement of glutamate and cannabinoids in impulsive behaviour has also yielded promising results.

We would like to conclude with two remarks. First, when studying the neuropharmacology of impulsivity, one should bear in mind that there are close interactions between the different neurotransmitter systems discussed here. Thus, although it is of course most informative to first study the different systems in isolation, interacting systems ultimately give rise to impulsive behaviour. In the context of impulsivity, it has for example been shown that the interactions between 5-HT and dopamine underlie the beneficial effect of amphetamine on delay aversion [48], and impulsive action in the 5CSRTT seems to be mediated by interacting 5-HT_{2A} receptors, α1 adrenoceptors and α2 adrenoceptors [46]. Interactions between other neurotransmitter systems still need to be explored but, given that impulsivity is modulated by a wide variety of neurotransmitters through an even larger number of receptors, it is quite likely that an optimal pharmacotherapy for impulsivity constitutes a drug targeting several receptors. Second, when considering alleviating impulsivity to treat a psychiatric disorder, one should be aware of which type of impulsive behaviour is manifest in that disorder. Thus, reducing impulsivity to treat psychiatric disorders will require fine-grained tailoring of pharmacotherapies, perhaps even on an individual basis.

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