Current Topics in Behavioral Neurosciences 47

Harriet de Wit
J. David Jentsch *Editors*

Recent Advances in Research on Impulsivity and Impulsive Behaviors

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Preface

The concept of impulsivity, and its role in both normal and pathological behavior, has become a major topic of research over the past 30 years. According to PubMed, the number of publications on impulsivity and inhibitory control has increased from about 700 in 1990 to well over 4000 in 2019. We have made major advances in our understanding of the behavioral processes that comprise what we refer to as "impulsive" behavior, as well as its neural and genetic underpinnings. Impulsive behaviors are involved in almost every psychiatric disorder, most notably in drug use disorders, externalizing behaviors, and childhood disruptive behavior disorders. This volume brings together recent findings from several of these areas, written by experts in the respective fields. We bring together a number of sometimes disparate topics, including empirical studies with laboratory animals, healthy volunteers and patients, and address theoretical analyses as well as practical considerations.

The first section addresses what is known about the neurobiological basis of impulsive behaviors. Pattij and Vanderschuren first introduce the different types of impulsive behavior, and some of the challenges in harmonizing studies with humans and nonhuman species, and then review the evidence for the involvement of dopamine and norepinephrine, as well as some novel targets including opioid receptors and ErbB signaling pathways. Although early studies focused on serotonin as a key neurotransmitter in impulsive behaviors, this review demonstrates that impulsive behaviors are controlled by a broader array of neurotransmitter systems. Groman similarly reviews the procedures typically used to study impulsive behavior, and then examines these procedures from the lens of reinforcement learning, and temporal difference signals. She examines the evidence for the respective roles of several neurotransmitter systems in reinforcement learning and risky decision-making, arguing that these comprise the basic components of impulsive behavior. London examines what is known about the neural processes involved in impulsive decision-making from the point of view of human imaging studies such as PET and fMRI, in both healthy adults and in patients. Specifically, she points to the importance of striatal D2-type dopamine receptors and corticostriatal connectivity in cognitive control, impulsivity, and response inhibition. Such information is critical to develop possible therapeutic targets for disruptive

impulsive behaviors. Weafer reviews the recent evidence of sex differences in brain engagement during inhibitory control. Inhibitory control is one form of impulsive behavior, and there is evidence that there are sex differences in the neural correlates of successful and unsuccessful inhibitions. The author notes that there is a lack of comprehensive data on sex differences and the role of circulating hormones in the neural processes underlying inhibition.

The next section of the book examines more closely some of the behavioral manifestations of impulsive behavior. Barr and Dick focus on the role of impulsive choice and impulsive action in externalizing behaviors, using data from human genetic studies. They summarize the evidence for the heritability of externalizing behaviors, and how these behaviors change over developmental stages and in interactions with the environment. They also summarize recent whole genome studies with phenotypes related to impulsivity, showing that these behaviors have clear genetic underpinnings. Levitt et al focus on one form of impulsive behavior, namely delay discounting. They review the evidence for the importance of delay discounting in addiction, attention deficit/hyperactivity disorder, and obesity, and discuss both environmental and genetic factors that influence these behaviors. Bickel et al provide a unique perspective on delay discounting, with their Reinforcer Pathology Theory. This theory describes the interaction among strong preferences for immediate rewards, insensitivity to negative consequences, and over-valuation of specific commodities that offer brief, intense reinforcement. This theoretical framework provides novel avenues for modulating the valuation of reinforcers (e.g., working memory training, TMS).

The final series of chapters addresses topics of direct clinical relevance. Liu et al discuss developmental trajectories of impulsive behaviors across the lifespan, with a particular focus on middle to older adulthood. Impulsive behaviors are common among adolescents and young adults, but a small but significant subset of adults continues to exhibit these behaviors, with negative consequences including substance abuse. The authors note that these behaviors are often accompanied by emotional states such as negative urgency, pointing to the important link between affect and cognition. Swann et al discuss the role of impulsivity in suicidal behaviors, noting important links between negative affective states or depressive symptoms and impulsive action and impulsive choice. They also review some of the neurochemical mechanisms believed to be involved. Herman and Duka examine the role of impulsive behavior in the context of alcohol use disorders, with careful consideration of the different forms of impulsive behavior that affect drug use. They also review some of the literature on the neural correlates of impulsive behaviors.

Collectively, the chapters that constitute this volume highlight a number of current issues in the study of impulsivity and impulsive behaviors, address some of the relevant challenges and controversies and outline relevant future directions for related research.

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Abstract Neuropharmacological interventions in preclinical translational models of impulsivity have tremendously contributed to a better understanding of the neurochemistry and neural basis of impulsive behaviour. In this regard, much progress has been made over the last years, also due to the introduction of novel techniques in behavioural neuroscience such as optogenetics and chemogenetics. In this chapter, we will provide an update of how the behavioural pharmacology field has progressed and built upon existing data since an earlier review we wrote in 2008. To this aim, we will first give a brief background on preclinical translational models of impulsivity. Next, recent interesting evidence of monoaminergic modulation of impulsivity will be highlighted with a focus on the neurotransmitters dopamine and noradrenaline. Finally, we will close the chapter by discussing some novel directions and drug leads in the neuropharmacological modulation of impulsivity.

Keywords Behavioural neuroscience · Dopamine · Noradrenaline · Pharmacology · Translational models

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A little over a decade ago, we wrote a review on impulsivity on the occasion of the celebration of 100 years of pharmacology research in the Netherlands. This review addressed the neuropharmacology of impulsivity, focusing on the collective work from preclinical translational models of impulsivity (Pattij and Vanderschuren 2008). At that time, the study of the neural basis of impulsivity relied on behavioural pharmacological intervention techniques in preclinical translational animal models. Other often-used intervention techniques back then – and still today – consisted of, for instance, performing selective (neurochemical) lesions/disconnections of brain regions, conducting targeted gene deletions (primarily in murine models) and measuring mRNA/protein/neurotransmitter levels in selected brain regions.

Since then, the introduction of novel genetic techniques such as optogenetics and chemogenetics has created unique opportunities to manipulate brain function in a cell-type-specific, circuit-specific and bidirectional manner (see for recent reviews on these techniques: Rajasethupathy et al. 2016; Roth 2016). These novel techniques have revolutionized behavioural neuroscience, which is also contributing to our understanding of the neurobiology of impulsivity (see for recent review: Carr et al. 2018). However, whereas optogenetic and chemogenetic approaches have provided detailed fundamental knowledge of the neural underpinnings of cognition – in a projection and/or cell-type-specific way – from a clinical perspective, there are many hurdles to be overcome before these novel techniques can be implemented for therapeutic purposes on a large scale. As such, behavioural pharmacological systems approaches are closer to clinical implementation and still provide valuable insights into the neurochemical basis of impulsivity, despite some of the obvious disadvantages such as off-target tissue or off-target receptor effects of drugs (Berger and Iyengar 2011) and blood-brain barrier limitations (Patel and Patel 2017). In this chapter, we will give an update of how the behavioural pharmacology field has progressed and built upon existing data since our 2008 review. We will focus on two neuromodulator systems widely implicated in impulsivity – i.e. dopamine and noradrenaline – as well as novel targets that have emerged from the field.

1 Preclinical Translational Models of Impulsivity

Most of our understanding of the neural basis and neurochemistry of impulsivity is derived from rodent experiments. The majority of this work has been carried out using rats as model species, yet since the availability of genetically engineered mouse models (Capecchi 2005), mice also have been used to study the neurobiology of impulsivity.

To this aim, various operant tasks have been developed over the last 40 or so years. Some of these tasks have been directly adopted from human neuropsychological tasks measuring aspects of impulsivity, such as the 5-choice serial reaction time task (5-CSRTT; Carli et al. 1983), the stop-signal task (Feola et al. 2000), Go/No-Go tasks (Terman and Terman 1973) and various temporal and delay discounting tasks (Evenden and Ryan 1996; Mazur 1987; Richards et al. 1997). Other tasks used were originally developed for other purposes, such as differential-

reinforcement-of-low-rate (DRL) schedules of reinforcement, which detect effects of antidepressant drugs (McGuire and Seiden 1980) and at the same time capture aspects of impulsive behaviour. There are many excellent reviews that describe these rodent translational models of impulsivity in detail (see e.g. Eagle and Baunez 2010; Robbins 2002; Winstanley 2011; Yates 2018); we will briefly describe the main principles of the most often-used impulsivity tasks here.

Given the multidimensional nature of the impulsivity construct (Evenden 1999; Dalley and Robbins 2017), these translational models should be distinguished based on the aspects of impulsivity they measure. Typically, a distinction is made between impulsive action and impulsive choice (although one can also distinguish models of 'stopping' and 'waiting'). On the one hand therefore, models are used that measure impulsivity related to the ability to inhibit prematurely expressed behavioural responses or the ability to cancel and disengage from ongoing behaviour. Examples of models measuring these aspects of impulsivity in rodents are the 5-CSRTT, DRL schedules of reinforcement, Go/No-Go tasks and the stop-signal task. Typically, increased impulsivity in such models is exemplified by either high levels of prematurely expressed responses or the inability to inhibit ongoing behaviour. In this chapter, we will refer to impulsive action as an umbrella term when addressing data from these models. On the other hand, delay discounting tasks in which animals have control over delays, c.q. adjusting-delay/adjusting-amount procedures, or do not have control over delays, measure the preference for delayed larger reinforcement over immediate small reinforcement. Such tasks typically generate delay discounting curves, whereby steeper discounting, i.e. a larger preference for immediate small reinforcement, reflects more impulsive choice.

In terms of validity of aforementioned translational models for the impulsivity construct in humans, it would go beyond the scope of this chapter to give a full account of the different validity criteria. Several reviews have eloquently and elaborately discussed the validity and utility of these models (Dalley and Robbins 2017; Eagle and Baunez 2010; Winstanley 2011). Nonetheless, there are some common characteristics of rodent models that differ from human impulsivity tasks that are noteworthy for the reader who is not fully familiar with the rodent literature. For example, the vast majority of rodent impulsivity models use positive reinforcement to train task contingencies and maintain task performance (although some studies require decisions between rewards and punishments; see Simon et al. 2009 and Verharen et al. 2019), for instance, by using highly palatable food pellets or small amounts of condensed milk. This differs from studies in humans, in which the typical reward is often (hypothetical) money, and involves both gains and losses. Monetary losses are difficult to implement in an animal experiment. Also, animals are usually mildly food-deprived to enhance motivation and task engagement; this can impact the interpretation of pharmacological effects. A second important difference between laboratory tests of impulsivity in rodents vs humans is the length of training. In humans, subjects are typically given brief instructions, and a few practice trials before testing. In rodents, prolonged periods of daily training are required before animals achieve stable responding in the tasks. As a result, different memory systems (short-term/explicit in humans, long-term/implicit in animals) may be engaged, which should be taken into account when interpreting data on a systems

neuroscience level. In addition, impulsivity experiments in animals are usually long-lasting and labour-intensive; it is not uncommon that a single experiment can take up to 6 months or longer before completion. To circumvent this, a novel direction is the development of automated home-cage-based approaches of measuring cognition and impulsivity, which (1) allows animals to voluntarily engage in the tasks; (2) tremendously speeds up training time; and (3) reduces possible experimenter-induced interference. Although only a few studies have been published using such an approach to measure impulsivity (Bruinsma et al. 2019; Carr et al. 2018; Koot et al. 2009; Remmelink et al. 2017; Rivalan et al. 2017), the approach is starting to gain interest from the field. This, also since new computational approaches such as, for instance, machine-learning algorithms to analyse video-tracks of behaviour are rapidly developing (Kabra et al. 2013; Kwok 2019; Lorbach et al. 2018) and would allow for integrative analyses of home-cage behaviour with cognitive performance following, for instance, pharmacological manipulations.

2 Monoaminergic Modulation of Impulsivity

Traditionally, most behavioural pharmacological interventions in animal models of impulsivity have focused on the monoamine neurotransmitters dopamine, noradrenaline and serotonin. This fits well with the mechanisms of action of ADHD pharmacotherapies such as amphetamine, atomoxetine and methylphenidate, which generally increase efflux of dopamine, noradrenaline and to a lesser extent serotonin and histamine (for review, see Heal et al. 2009). Since our 2008 review, many studies have further elaborated on the role of dopamine, noradrenaline and serotonin in impulsivity (for recent reviews see Bacqué-Cazenave et al. 2020; Dalley and Robbins 2017; Winstanley 2011). In this chapter we will highlight recent interesting observations, with a focus on dopamine and noradrenaline, since over the last decade, most behavioural pharmacological work has investigated these neurotransmitters (see for overview, Table 1).

2.1 Dopamine

Recent studies have further pinpointed involvement of dopamine D2-like receptors in impulsive action in the 5-CSRTT, building on earlier work showing the importance of dopamine D2/D3 receptors in the ventral striatum in impulsivity (Dalley et al. 2007; Pattij et al. 2007). As such, it was shown that increased impulsive action due to medial prefrontal cortex damage can be reduced by treatment with the selective dopamine D2/D3 receptor antagonist sulpiride into the ventral striatum (Pezze et al. 2009). Subregional ventral striatal dopamine involvement in impulsivity has been demonstrated in several other studies. For instance, the preferential dopamine D3 receptor antagonist nafadotride was found to increase impulsive action in

Table 1 Pharmacological modulation of dopamine and noradrenaline receptor subtypes in impulsivity

Receptor	Agonist	Antagonist	Region	Impulsive action	Impulsive choice	References
Dopamine						
D2		Sulpiride	NA	↓		Pezze et al. (2009)
D2/D3	Quinpirole		NAC	↑		Moreno et al. (2013)
			NAS	=		
D3		Nafadotride	NAC	↓		Besson et al. (2010)
			NAS	↑		
Noradrenaline						
Transporter		Atomoxetine		=		Baarendse and Vanderschuren (2012) and Sun et al. (2012)
				↓		Bari et al. (2009), Benn and Robinson (2017), Blondeau and Dellu-Hagedorn (2007), Broos et al. (2012), Liu et al. (2015), Navarra et al. (2008), Paine et al. (2007), Paterson et al. (2011), Robinson et al. (2008), Sasamori et al. (2019), Sun et al. (2012) and Tsutsui-Kimura et al. (2009)
		Atomoxetine			↓	Bizot et al. (2011) and Robinson et al. (2008)
		Atomoxetine			↑	Broos et al. (2012)
		Desipramine		↓		Pattij et al. (2012)
					↓	Bizot et al. (2011)
		Nortriptyline		↓		Roychowdhury et al. (2012)
Alpha-1		Prazosin		=		Mahoney et al. (2016) and Roychowdhury et al. (2012)
			OFC	=		Adams et al. (2017)
	Phenylephrine			(↓)		Pattij et al. (2012)
					=	Van Gaalen et al. (2006b)
			OFC/ mPFC		=	Pardey et al. (2013)
Alpha-2	Clonidine			(↓)		Pattij et al. (2012)

(continued)

Table 1 (continued)

Receptor	Agonist	Antagonist	Region	Impulsive action	Impulsive choice	References
	Guanfacine			(↓)		Terry et al. (2014)
				=		Mahoney et al. (2016)
			OFC/ mPFC		=	Pardey et al. (2013)
		Yohimbine		↑		Adams et al. (2017), Broos et al. (2017), Funk et al. (2019), Mahoney et al. (2016), Sun et al. (2010) and Schippers et al. (2016)
					↓	Schippers et al. (2016)
			OFC	↓		Adams et al. (2017)
Beta-1/ beta-2	Isoprenaline			(↓)		Pattij et al. (2012)
		Propranolol		=		Mahoney et al. (2016), Milstein et al. (2010) and Roychowdhury et al. (2012)
			OFC	=		Adams et al. (2017)
Beta-1	Dobutamine			(↓)		Pattij et al. (2012)
Beta-2	Clenbuterol			↓		Pattij et al. (2012)

Upward arrows indicate that ligands increase impulsive action or impulsive choice Downward arrows indicate beneficial effects of ligands on impulsivity, and equals signs indicate no behavioural effects of these ligands on impulsivity. Parentheses indicate that the effects were likely secondary to other (motor) effects *mPFC* medial prefrontal cortex, *NA* nucleus accumbens, *NAC* nucleus accumbens core region, *NAS* nucleus accumbens shell region, *OFC* orbitofrontal cortex

the 5-CSRTT when infused into the nucleus accumbens shell region and to decrease impulsive action when infused into the nucleus accumbens core region (Besson et al. 2010). In addition, microinfusion of the dopamine D2/D3 receptor agonist quinpirole into the nucleus accumbens core, but not shell, was also found to increase impulsive action as well as locomotor activity (Moreno et al. 2013). The fact that in this latter study, nafadotride treatment blocked the effects of quinpirole on locomotor activity, but not impulsive action, suggests a dopamine D2 receptor-mediated mechanism in impulsive action. Intriguingly, these pharmacological modulations of impulsivity were only found in animals with high baseline levels of impulsive action, indicating altered dopamine functioning in trait impulsive individuals. This latter notion is supported by abundant neurochemical and pharmacological data in trait impulsive rats. As briefly highlighted above, microPET (positron emission tomography) approaches in highly impulsive rats in the 5-CSRTT have demonstrated reduced binding of the dopamine D2/D3 receptor antagonist ^{18}F-fallypride in the ventral striatum (Dalley et al. 2007), a finding which was later found to be more pronounced in the left hemisphere (Caprioli et al. 2013). Autoradiographic work has further strengthened these PET findings, demonstrating reduced dopamine D2/D3 receptor and dopamine transporter binding in the nucleus accumbens shell, as well as reduced dopamine D1 receptor binding in the nucleus accumbens core in trait impulsive rats as assessed in the 5-CSRTT (Jupp et al. 2013). Other approaches, such as ex vivo neurochemistry, showed differential dopamine release from the nucleus accumbens core and shell region in rats characterized for high impulsive action. Whereas in high trait impulsive rats (tested in the 5-CSRTT) electrically stimulated dopamine release was found to be increased in the nucleus accumbens shell region, dopamine release from the nucleus accumbens core region was found to be decreased (Diergaarde et al. 2008). In addition, high trait impulsive action in a DRL task was associated with increased dopamine D1 receptor gene expression in the nucleus accumbens shell and decreased dopamine D2 receptor gene expression in the nucleus accumbens core (Simon et al. 2013).

Regarding impulsive choice, we found that electrically stimulated dopamine release from both the nucleus accumbens core and shell region as well as the medial prefrontal cortex was decreased in high impulsive rats in a delay discounting task (Diergaarde et al. 2008). Moreover, we and others found that high impulsive choice also correlated with increased dopamine D1 receptor and dopamine D5 receptor gene expression (Loos et al. 2010) and lower dopamine D2 gene expression (Simon et al. 2013) in the medial prefrontal cortex. Recent PET approaches in rats using ^{18}F-fallypride also hinted towards functional changes in dopamine function in trait impulsive choice rats (Barlow et al. 2018), albeit that these changes were less pronounced compared to the findings in trait impulsive action rats (Caprioli et al. 2013; Dalley et al. 2007). Collectively, these data suggest differential involvement of dopamine in corticostriatal circuits in impulsive action and impulsive choice, substantiating earlier pharmacological work (see e.g. Cole and Robbins 1987; Winstanley et al. 2005; Van Gaalen et al. 2006a, b).

Importantly, whereas the preclinical literature on dopamine modulation of impulsivity is extensive, the cumulative work from this field strongly converges with

clinical observations. In this regard, recent human PET studies have reported that trait impulsivity is associated with enhanced amphetamine-evoked dopamine release in the striatum and lower dopamine D2/D3 receptor availability in the midbrain (Buckholtz et al. 2010), as well as altered availability of dopamine transporters in the striatum (Smith et al. 2019).

Taken together, accumulating evidence from both preclinical and clinical work strongly implicates dopamine D2-like receptors in the nucleus accumbens in impulsivity. The distinction between ventral striatal subregions (i.e. nucleus accumbens core and shell), subtypes of dopamine D2-like receptors (most prominently, the dopamine D2 and D3 receptors, whereas the involvement of the dopamine D4 receptor in impulsivity awaits thorough investigation) and impulsive choice vs impulsive action is expected to provide a fine-grained picture of how dopaminergic neurotransmission modulates impulse control. In this regard, involvement of dopamine D1-like receptor signaling and structures beside the ventral striatum (e.g. dorsal striatum and prefrontal cortical regions) in impulsive behaviour should not be overlooked.

2.2 Noradrenaline

Since our 2008 review, many new studies have been published investigating noradrenergic modulation of impulsivity. At the time of our review, the noradrenaline reuptake inhibitor atomoxetine had just entered the market as a newly approved drug for the treatment of ADHD symptoms. Importantly, since then the field has progressed, and many studies have demonstrated beneficial effects of various noradrenaline reuptake inhibitors, including atomoxetine, desipramine and milnacipran on impulsive action and/or impulsive choice in preclinical translational impulsivity models (see e.g. Bari et al. 2009; Bizot et al. 2011; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Broos et al. 2012; Liu et al. 2015; Navarra et al. 2008; Paine et al. 2007; Paterson et al. 2011; Pattij et al. 2012; Robinson et al. 2008; Roychowdhury et al. 2012; Sasamori et al. 2019; Sun et al. 2012; Tsutsui-Kimura et al. 2009). Nonetheless, not always beneficial effects of noradrenaline reuptake inhibitors have been reported on impulsivity, or alternatively, such effects were associated with simultaneous task slowing effects (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Paine et al. 2007; Sun et al. 2012). Altogether, the work with noradrenaline reuptake inhibitors suggests an important role for noradrenaline signaling in impulsivity and indicates that high noradrenaline activity is associated with lower impulsive action and/or impulsive choice. In terms of region-specific involvement of noradrenaline signaling in impulsivity, microinfusions of atomoxetine into the ventral striatum, in particular in the nucleus accumbens core, but not prefrontal cortex were found to mimic the effects of systemic atomoxetine (Economidou et al. 2012). This suggests a stronger involvement of subcortical over cortical noradrenaline in impulsivity. A subsequent elegant study (Benn and Robinson 2017) provided further evidence for this, using a saporin-

conjugated dopamine beta-hydroxylase neurotoxin to selectively induce noradrenergic lesions in the prefrontal cortex or ventral striatum. This work revealed that the integrity of noradrenaline transmission in the ventral striatum is required for the impulsivity-reducing effects of atomoxetine, whereas noradrenergic modulation in the prefrontal cortex is required for top-down control over amphetamine-induced impulsivity (Benn and Robinson 2017).

A subsequent question that then arises is which specific adrenoceptors play a role in impulsivity. In this regard, most recent work has focused on alpha2-adrenoceptors, and few studies have indicated a role for beta-adrenoceptors. Regarding alpha2-adrenoceptors in the brain, these receptors function both as (presynaptic) autoreceptors on noradrenergic cell bodies in the locus coeruleus and on noradrenergic nerve terminals in projection regions and as postsynaptic receptors in target regions such as the prefrontal cortex (for review, see Berridge and Waterhouse 2003). Activation of presynaptic alpha2-adrenoceptors decreases the activity of the noradrenaline system, an effect that is different from activation of postsynaptic alpha2-adrenoceptors. Whereas in vitro or ex vivo assays reveal that alpha2-adrenoceptor ligands might have different affinities for presynaptic or postsynaptic receptors (Molinoff 1984), it is important to keep in mind that it is difficult to truly distinguish presynaptic from postsynaptic effects in systemic behavioural pharmacological studies. Intracranial microinfusions with alpha2-adrenoceptor ligands in selected brain regions, as mentioned above for atomoxetine (Economidou et al. 2012), would be required for to disentangle pre- vs postsynaptic effects of alpha2-adrenoceptor ligands.

Interestingly, in recent years several studies with the alpha2-adrenoceptor antagonist yohimbine have been conducted, showing that this drug increases impulsive action (Adams et al. 2017; Broos et al. 2017; Funk et al. 2019; Mahoney et al. 2016; Sun et al. 2010; Schippers et al. 2016) and reduces impulsive choice in a delay discounting task (Schippers et al. 2016). Moreover, yohimbine was found to attenuate the beneficial effects of the noradrenaline reuptake inhibitor nortriptyline on impulsive action, without having effects by itself (Roychowdhury et al. 2012). This latter observation links activation of postsynaptic alpha2-adrenoceptors to noradrenaline's effects on impulsivity. With regard to its neural site of action, recent work has also shown that microinfusion with yohimbine, but not an alpha-1 or beta-adrenoceptor antagonist, into the orbitofrontal cortex reduces impulsive action (Adams et al. 2017). Whether the effects of yohimbine on impulsivity are purely explained by its actions on noradrenaline transmission is open for further investigation. It would fit with the idea that increased noradrenaline transmission is associated with decreased impulsivity, yet yohimbine also has affinity for several serotonin receptor subtypes as well as the dopamine D2 receptor (Millan et al. 2000), the latter of which has been strongly implicated in impulsivity as discussed earlier in this chapter. Importantly, recent behavioural pharmacological studies have demonstrated that the effects of yohimbine on impulse action are not mediated via interactions with alpha-1 adrenoceptors, corticotropin-releasing factor 1 receptors, dopamine D1/D5 receptors, glucocorticoid receptors and mu-opioid receptors (Mahoney et al. 2016). However, blockade of kappa-opioid receptors attenuated the effects of yohimbine on

impulsive action (Funk et al. 2019), suggesting that yohimbine stimulates release of dynorphin which in turn modulates impulsivity. Taken together, the effects of yohimbine on impulsivity most likely result from a complex interplay between the noradrenergic signaling (most prominently, alpha2-adrenoceptors) and other neurotransmitter systems. Conversely, cocaine-induced increments in impulsive action have also been shown to be attenuated by simultaneous treatment with the alpha2-adrenoceptor agonist guanfacine (Terry et al. 2014), and, more recently, the beneficial effects of atomoxetine on impulsive action were blocked by microinfusions of a dopamine D1/D5 receptor antagonist into the medial prefrontal cortex (Sasamori et al. 2019), further underlining the complex interplay between different neurotransmitter systems in the modulation of impulsivity.

Only a few studies in the last decade have investigated involvement of alpha-1 or beta-adrenoceptors in impulsivity. First, pharmacological challenges with direct alpha-1 or alpha2-adrenoceptor agonists, such as phenylephrine, clonidine and guanfacine, have been shown to be without effect in several studies (Pardey et al. 2013; Van Gaalen et al. 2006b), whereby apparently beneficial effects on impulsivity of these ligands were likely secondary to motor effects (Pattij et al. 2012; Terry et al. 2014). Other studies have reported that treatment with beta-adrenoceptor antagonists such as propranolol was ineffective in modulating impulsive action and impulsive choice (Adams et al. 2017; Mahoney et al. 2016; Milstein et al. 2010; Roychowdhury et al. 2012). This suggests that tonic activation of beta-adrenoceptors is not involved in modulating impulsivity. In contrast, the impulsivity-reducing effects of methylphenidate and nortriptyline could be blocked by propranolol (Milstein et al. 2010; Roychowdhury et al. 2012), suggesting that phasic activation of beta-adrenoceptors does play a role in impulsivity. In support of this, treatment with the selective beta2-adrenoceptor agonist clenbuterol (but not the selective beta1-adrenoceptor agonist dobutamine) was found to reduce impulsive action (Pattij et al. 2012). In the brain, beta2-adrenoceptors are widely expressed in cortical areas, including the prefrontal cortex (Nicholas et al. 1996; Liu et al. 2014), and as such, clenbuterol might shape top-down cortical control (Luo and Zhou 2018).

In sum, studies on the noradrenergic modulation of impulsive behaviour have for the most part focused on alpha2-adrenoceptors. As this noradrenergic receptor subtype can function both as an autoreceptor and as a heteroreceptor, it is important to disentangle whether alpha2-adrenoceptor influence on impulse control is the result of stimulation or inhibition of noradrenergic signaling, the evidence so far pointing towards the former possibility. Future work should be aimed at the identification of the neural sites of action by which alpha2-adrenoceptors regulate impulse control, while the involvement of other adrenoceptor types – which has thus far been much less investigated – should also be assessed in more detail.

3 Novel Targets

It is beyond doubt that neurotransmitter systems other than the monoamine 'usual suspects' play a role in the control of impulsivity. For example, much progress has been made in understanding glutamatergic modulation of impulsive action and impulsive choice. Some interesting observations in this respect include the findings that the metabotropic glutamate receptor 5 (mGluR5) is differentially involved in impulsive action and impulsive choice, as positive allosteric modulation of this receptor reduces impulsive action but does not affect impulsive choice (Isherwood et al. 2015). Also, emphasizing the crosstalk between neurotransmitter systems in modulating impulsivity, it has recently been shown that glutamate-mediated increments in impulsive action could be blocked by treatment with the selective dopamine D2 receptor antagonist eticlopride (Isherwood et al. 2017). This observation reiterates the importance of dopamine D2 receptors as a central mechanism steering impulse control. Since work on the role of glutamate in the modulation of impulse control has been excellently reviewed recently (Carli and Invernizzi 2014; Yates 2018), we now continue with several examples of novel (non-glutamatergic, non-monoaminergic) directions and leads in the pharmacological regulation of impulse control.

First, from a clinical perspective, the opioid system has received a substantial amount of interest as a potential treatment target to ameliorate impulse control in disorders such as behavioural addictions, including pathological gambling, Parkinson's disease and personality disorders. This because in these disorders, the opioid receptor antagonist naltrexone was found to have beneficial therapeutic effects (see e.g. Anderson 2020; Chamberlain and Grant 2019; Goslar et al. 2019; Sgroi and Tonini 2018), which may be (in)directly related to positive effects on impulse control. Preclinical behavioural pharmacological work over the last decade has learned us more about opioid modulation of impulsive behaviour, in terms of subtypes of opioid receptors and brain regions involved. Most studies have demonstrated mu-opioid receptor involvement in impulsive action and impulsive choice, as both acute and subchronic treatments with the mu-opioid receptor agonist morphine were found to increase impulsivity in several translational tasks including the 5-CSRTT, a fixed interval response inhibition task, stop-signal tasks and delay discounting tasks (Harvey-Lewis et al. 2012; Harvey-Lewis and Franklin 2015; Maguire et al. 2016, 2018; Mahoney et al. 2013; Moazen et al. 2018; Pattij et al. 2009). Intracranial microinfusion studies with morphine and DAMGO, a more selective mu-opioid receptor agonist, have pinpointed the prefrontal cortex and nucleus accumbens shell region as candidate brain sites for mu-opioid modulation of impulsivity (Selleck et al. 2015; Wiskerke et al. 2011). In comparison to mu-opioid receptors, kappa-opioid and delta-opioid receptor modulation of impulsivity has been less well documented. Thus, in one study, treatment with a delta-opioid receptor agonist, but not morphine, was found to increase impulsive action in a response inhibition task (Befort et al. 2011). The null effects of morphine in this study seem at odds with the abundant evidence of treatment with this drug increasing

impulsivity. This discrepancy might be explained by methodological characteristics of the response inhibition task used that relied on variable intervals, whereas in a comparable response inhibition task with fixed intervals, morphine did increase impulsive action (Mahoney et al. 2013). Finally, kappa-opioid receptor modulation of impulsivity has also been demonstrated previously. In several studies, systemic injections with the kappa-opioid receptor agonists salvinorin A and U69,593 were found ineffective in affecting impulsive action in the 5-CSRTT (Paine et al. 2007; Nemeth et al. 2010). In contrast, a more recent study did find differential effects of intracerebroventricular administration of the kappa-opioid receptor agonist U50,488 on impulsive action and impulse choice. In a stop-signal task, treatment with U50,488 impaired response inhibition and increased impulsive action, whereas the agonist did not affect impulsive choice in a delay discounting task (Walker and Kissler 2013). Moreover, these effects of U50488 on impulsive action could be blocked by treatment with the noncompetitive kappa-opioid receptor antagonist nor-BNI. These observations are relevant in view of withdrawal-induced increases in dynorphin levels occurring in several substance use disorders, which contributes to the negative emotional symptoms and possibly impulsivity that may precipitate relapse (Zorrilla and Koob 2019). As discussed earlier, resonating well with this idea is the finding that the effects of yohimbine on impulsive action also could be attenuated by nor-BNI (Funk et al. 2019), also suggesting a role for increased dynorphin levels in impulsivity. Not only the interaction with the noradrenaline system is important in how kappa-opioid receptor activation modulates impulsivity. Recent evidence in mice convincingly demonstrates that the impulsivity-inducing effects of a kappa-opioid receptor agonist using a DRL schedule of reinforcement are mediated via dopamine neurons in the ventral tegmental area (Abraham et al. 2018), indicating a dopamine-dependent mechanism. Taken together, the data on delta- and kappa-opioid regulation of impulsive behaviour are equivocal and less clear-cut compared to our understanding of mu-opioid receptors therein. Further work with delta-opioid and kappa-opioid receptor ligands in various tasks is required to better understand the role of these receptors in impulsivity.

To conclude this section, we would like to give two examples of novel leads for targeting impulsivity. Clearly, much more work is needed to firmly establish their involvement in impulsivity, yet they deepen our understanding of the neural underpinnings of impulsive behaviour and may provide new opportunities for therapeutic interventions.

The first example of such a novel target is the ErbB receptor which belongs to a family of tyrosine kinase receptors, which are widely studied in oncology. The neuregulin family includes the endogenous ligands for these receptors; within the central nervous system, these signaling pathways play an important role in neural development, neural circuit assembly, synaptic plasticity and neurotransmission (Mei and Nave 2014). There are at least four different ErbB kinase receptors, ErbB1, ErbB2, ErbB3 and ErbB4 (Birchmeier 2009), and particularly polymorphisms of the neuregulin-ErbB4 signaling pathway have been associated with neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder, bipolar disorders and schizophrenia (Mei and Nave 2014; Pan et al. 2011; Sonuga-Barke

et al. 2008). In support of a role for the neuregulin-ErbB signaling pathway in impulsivity, in the mPFC of mice a quantitative trait locus for impulsivity was identified containing the gene neuregulin 3. Further forward genetic approaches and viral overexpression of neuregulin 3 in the mPFC indicated a causal involvement of this gene in impulsivity as this manipulation selectively increased impulsive action in the 5-CSRTT (Loos et al. 2014). A follow-up study in rats strengthened this observation by demonstrating that pharmacological inhibition of the neuregulin-ErbB signaling pathway by microinfusion of an ErbB inhibitor into the mPFC reduced impulsive action without affecting other behaviours (Loos et al. 2016). Mechanistically, ErbB-mediated modulation of glutamate transmission in the mPFC could be a possible explanation for these effects. Thus, in the mPFC, ErbB activation has been shown to inhibit NMDA receptor signaling by promoting release of GABA from interneurons (Mei and Nave 2014), so that inhibition of ErbB likely has opposite effects to facilitate NMDA receptor-mediated function. Indeed, in support of this, positive allosteric mGluR5 modulation has been found to reduce impulsive action (Isherwood et al. 2015). Alternatively, it has been shown that disruption of neuregulin-ErbB signaling during development leads to elevated striatal dopamine levels (Golani et al. 2014), which could also explain why polymorphisms of these signaling pathways have been associated with neuropsychiatric disorders.

Another example of a recently identified molecule to be involved in impulsivity is *myo*-inositol, which is a membrane lipid and important precursor in the inositol 1,4,5-trisphosphate/calcium (InsP3/Ca2+) signaling pathway. This pathway controls many cellular processes and generates calcium signals required, e.g. contraction in muscle cells, formation of memory in neurons and insulin secretion from the pancreas (Berridge 2009). *Myo*-inositol is also a measurable metabolite in magnetic resonance spectroscopy, and using this approach in rats, it was found that trait high impulsive rats displayed lower *myo*-inositol content in the mPFC compared to low impulsive rats (Jupp et al. 2020). In the same study, ex vivo mass spectroscopy experiments also indicated lower *myo*-inositol levels in high impulsive rats, along with reductions in transcript levels of inositol monophosphatase 1 (IMPase1), a key protein involved in the synthesis of *myo*-inositol. Importantly, in a separate group of rats targeted knockdown of IMPase1 in the mPFC was then found to increase impulsive action, indicating causal involvement of this IMPase1-*myo*-inositol pathway in impulsivity. These data are also relevant from a clinical point of view, since magnetic resonance spectroscopy studies have also reported lower *myo*-inositol levels in the prefrontal cortex in neuropsychiatric disorders, including ADHD (Ferreira et al. 2009), schizophrenia (Das et al. 2018) and substance use disorder (Durazzo et al. 2016). The precise mechanism by which the IMPase1-*myo*-inositol pathway modulates impulsivity needs to be further investigated. Given the fact that the InsP3/Ca2+ pathway is also involved in insulin secretion (Berridge 2009), it is of interest that microinfusions of insulin into the nucleus accumbens were found to reduce impulsive action in the 5-choice serial reaction time task by modulating dopamine transporter function (Schoffelmeer et al. 2011). It is certainly worthwhile to pursue this area of research as it may result in novel targets for therapeutic interventions to ameliorate impulse control disorders.