Neurochemical substrates linked to impulsive and compulsive phenotypes in addiction: A preclinical perspective

Jolyon A. Jones¹ | Katharina Zuhlsdorff¹ | Jeffrey W. Dalley¹,²

¹Department of Psychology, University of Cambridge, Cambridge, UK
²Department of Psychiatry, Herschel Smith Building for Brain and Mind Sciences, Cambridge, UK

Correspondence
Jeffrey W. Dalley, Department of Psychology, University of Cambridge, Downing St, Cambridge CB2 3EB, UK.
Email: jwd20@cam.ac.uk

Funding Information
Medical Research Council (MRC), Grant/Award Number: MR/N02530X/1; Institute for Neuroscience at Cambridge University; GlaxoSmithKline; Boehringer Ingelheim Pharma GmbH

Abstract
Drug compulsion manifests in some but not all individuals and implicates multifaceted processes including failures in top-down cognitive control as drivers for the hazardous pursuit of drug use in some individuals. As a closely related construct, impulsivity encompasses rash or risky behaviour without foresight and underlies most forms of drug taking behaviour, including drug use during adverse emotional states (i.e., negative urgency). While impulsive behavioural dimensions emerge from drug-induced brain plasticity, burgeoning evidence suggests that impulsivity also predates the emergence of compulsive drug use. Although the neural substrates underlying the apparently causal relationship between trait impulsivity and drug compulsion are poorly understood, significant advances have come from the interrogation of defined limbic cortico-striatal circuits involved in motivated behaviour and response inhibition, together with chemical neuromodulatory influences from the ascending neurotransmitter systems. We review what is presently known about the neurochemical mediation of impulsivity, in its various forms, and ask whether commonalities exist in the neurochemistry of compulsive drug-motivated behaviours that might explain individual risk for addiction.

KEYWORDS
dopamine, GABA, glutamate, neuromodulation, noradrenaline, prefrontal cortex, serotonin, striatum

This Review article is part of the special issue “Neurochemistry of Reward-Seeking”
Severe substance use disorder (SUD), herein referred to as addiction, is a brain disorder characterised by compulsive drug seeking and intake despite harmful consequences. Given the worldwide increase in drug consumption (UNODC, 2020) and the opioid epidemic in many countries (CDC, 2020), the establishment of new treatments has never been more urgent. Clinically, the compulsive quality of drug-seeking behaviour features prominently in the revised Diagnostic and Statistical Manual of Mental Disorders, specifically the repeated use of drugs even when it endangers the life of the user. This defining disregard for personal safety and wellbeing corresponds with increasingly risky behaviour that exemplifies addiction. Accommodating this contemporary view of addiction, experimental studies in animals have evolved from the study of drug reinforcement processes to procedures that operationalise addiction in terms of drug-seeking persistence in the face of punishment ( représentation as if you were reading it naturally.
(Soubrié, 1986) was a breakthrough that catalysed efforts to refine the neurochemistry of impulsivity. Subsequently, reports emerged that forebrain 5-HT depletion in rats selectively increased premature responding on the 5-CSRTT (Harrison et al., 1999; Winstanley, Theobald, Dalley, et al., 2004) and impulsivity in the DDT (Mobini et al., 2000), thus affecting both action and choice impulsivity, respectively. Additionally, optogenetic stimulation of 5-HT neurons in the dorsal raphé nucleus (DRN) reduced impulsivity on a DDT—in other words, mice shifted their preference away from small, immediate rewards (Miyazaki et al., 2014). These findings are consistent with a role of 5-HT neurons in behavioural restraint for delayed rewards. The same group later proposed that serotonergic afferents in the OFC, rather than the nucleus accumbens (NAcb), mediated the effect of DRN stimulation, which transferred to the medial prefrontal cortex (mPFC) when the timing of rewards was uncertain (Miyazaki et al., 2020). Thus, 5-HT neurons appear to promote patience for delayed rewards via signalling to the mPFC and OFC. The striatal locus of this effect is unresolved but may involve the dorsal striatum and interactions with dopamine (DA) in this region. This is supported by the finding that selective DA depletion in the rat dorsal striatum increased impulsive choice for low magnitude intracranial self-stimulation (Tedford et al., 2015).

It is noteworthy that 5-HT dysfunction was one of the first neurochemical phenotypes identified in rats screened for impulsivity in the 5-CSRTT. However, against expectations, levels of 5-HT in the mPFC, assessed using in vivo microdialysis, correlated positively with impulsivity (Dalley et al., 2002), a finding consistent with increased cortical 5-HT utilization post-mortem in rats screened for impulsivity on this task (Puumala & Sirviö, 1998) but contrary to other impulsivity phenotypes linked to low 5-HT function at this time. However, a striking positive relationship between an analogous form of impulsivity in rats was related to the ratio of 5-HT₂A to 5-HT₂C receptors in the mPFC, suggesting that 5-HT receptor subtypes play distinct roles in the modulation of motor impulsivity (Anastasio et al., 2015). Supporting this idea, 5-HT₂C receptor knockdown increased waiting impulsivity and upregulated 5-HT₂A receptor expression, indicating an opponent relationship between 5-HT₂C and 5-HT₂A receptor subtypes (Anastasio et al., 2015), conceivably co-expressed within the same population of PFC neurons (Nocjar et al., 2015). Serotonergic receptor interactions extend to the dorsomedial striatum where activation and antagonism of 5-HT₂C and 5-HT₂A receptors, respectively, decreased premature and perseverative (a form of compulsivity) responses in the 5-CSRTT following local N-methyl-D-aspartate (NMDA) receptor antagonism in the mPFC (Agnoi & Carli, 2012). Contrary to these findings, interventions in rodents affecting 5-HT neuronal transmission such as gene knockdown, 5-HT depletion and selective 5-HT reuptake inhibition do not affect impulsivity assessed using the SSRTT (Hausknecht et al., 2006; Bari et al., 2009; Eagle et al., 2008; Eagle et al., 2009). Such dissociations point to a selective involvement of 5-HT in specific aspects of impulsivity. The implications of these findings for drug compulsion are discussed in later sections.

2.2 | Noradrenaline and dopamine

The catecholamines DA and noradrenaline (NA) lie at the centre of many impulsive behaviours. The clearest evidence comes from administering amphetamine and other stimulant drugs, generally improving stopping impulsivity in the rodent SSRTT (Eagle et al., 2007; Feola et al., 2000) and decreasing choice impulsivity in delay-discounting procedures (Floresco et al., 2008; van Gaalen et al., 2006). Stopping efficiency appears to have its origins within PFC circuitry and NA transmission (Bari et al., 2011) and via opponent interactions between D1 and D2 receptors in the dorsomedial striatum (Eagle et al., 2011). Delay-discounting impulsivity implicates reduced DA release in the mPFC, NAcbC, NAcbS (Diergaarde et al., 2008) and altered DA receptor signalling in prefrontal regions such as the mPFC, where D1/D5 receptor stimulation increased choice for delayed rewards (Loos et al., 2010). This form of impulsivity also inversely relates to D2 receptor availability in the NAcbC, assessed using positron emission tomography (PET) and autoradiography (Barlow et al., 2018). However, stimulant effects on delay discounting depend critically on the functional integrity of the 5-HT systems (Winstanley et al., 2003), a salutary lesson that interactions between the amine transmitters often underlie impulsivity phenotypes (Dalley & Roiser, 2012).

The mesolimbic DA system further modulates premature responding in the 5-CSRTT, with DA depletion in the NAcb greatly reducing this form of impulsivity (Cole & Robbins, 1989). Infusions of a D1 receptor antagonist decreased premature responses whether given in the NAcbS or NAcbC (Pattij et al., 2007) implying behavioural activation to depend on D1 receptors in these regions. Following systemic amphetamine administration or disinhibiting lesions of the PFC, NAcbC infusions of D2 antagonists attenuate premature responding (Pattij et al., 2007; Pezze et al., 2009). Opposing these effects, blocking D2-like receptors in the NAcbS increased premature responding (Besson et al., 2010), consistent with trait impulsivity correlating with low D2 receptor binding in this region (Jupp et al., 2013). These findings imply that inhibitory presynaptic D2 receptors may be selectively downregulated in the NAcbS of trait impulsive rats, in turn leading to increased synaptic DA release. Evidence that intra-NAcbS administration of the selective NA reuptake inhibitor, atomoxetine, reduces premature responding (Economou et al., 2012) lends further support to interactive relationships between the amine neurotransmitters.

2.3 | Glutamate

As the backbone of the impulsivity networks, glutamate has been widely researched in recent years (Carli & Invernizzi, 2014; Ucha et al., 2019; Weidacker et al., 2020; Yates & Bardo, 2017), with glutamatergic and gamma-aminobutyric acid (GABA)-ergic interactions within and between the PFC/OFC and basal ganglia mediating different aspects of inhibitory control. To illustrate this point, rat PFC neurons encode waiting intervals by ramping activity upwardly
or downwardly to the expected timing of rewards (Donnelly et al., 2015) and target the dorsomedial striatum to mediate proactive inhibitory control (Terra et al., 2020), perhaps by shifting the balance between the direct (Go) and indirect (No-Go) striatal pathways (Dunovan et al., 2015). The PFC, especially the more ventral infralimbic cortex, plays an important role in the regulation of waiting impulsivity. Thus, locally administered NMDA receptor antagonists in this subregion (Benn & Robinson, 2014; Murphy et al., 2005) weakened impulse control and increased premature responding in the 5-CSRTT. Further implicating PFC glutamatergic dysfunction in impulse control, an altered subunit composition of NMDA receptors was recently identified in trait impulsive rats. Rats deemed high-impulsive on a simple serial reaction time task, showed low expression of GluN1 and GluN2A but increased expression of GluN2B and phosphorylated GluN2B compared with low-impulsive rats (Davis-Reyes et al., 2019). Such findings reinforce translational interest in the GluN2B subunit as a target to treat impulsive and compulsive disorders (Higgins et al., 2016).

In humans, glutamate levels in the ACC, assessed using magnetic resonance spectroscopy (MRS), correlated positively with impulsive symptoms in subjects with attention-deficit hyperactivity disorder (ADHD) (Bauer et al., 2018; Ende et al. 2016). Similar findings were found in relation to SUD using the Barratt Impulsiveness Scale (Li et al., 2020), which collectively highlight an involvement of glutamate signalling in prefrontal cortical regions in impulsive behaviour.

### 2.4 GABA

GABA-ergic neurons in cortical microcircuits contribute to a variety of cognitive control processes, including working memory (Auger & Floresco, 2015), attention (Auger & Floresco, 2017; Paine et al., 2015) and cognitive flexibility (Page et al., 2018; Reichel et al., 2015). In rodents, an MRS-GABA study revealed decreased GABA levels in the ventral striatum of high-impulsive rats in the 5-CSRTT (Sawiak et al., 2016). Grey matter density in the core subregion of the NAc was also decreased in these animals and was accompanied by reduced expression of glutamate decarboxylase, the rate-limiting enzyme responsible for GABA synthesis and synaptic proteins, such as spinophilin (Caprioli et al., 2014). Validating these findings, fast-spiking GABA-ergic neurons in the NAc, was recently shown to restrain behaviour and lessen the likelihood of impulsive responses (Pisansky et al., 2019). In the lateral OFC, but not the medial OFC, lower gene expression of the α1 GABA<sub>A</sub> receptor subunit correlated with impulsive action but not impulsive choice in rats (Ucha et al., 2019). In humans, reduced MRS-GABA levels in the PFC correlated with risky and impulsive decision making (Boy et al., 2011; Weidacker et al., 2020), with Barratt Impulsiveness Scale impulsivity scores correlating negatively with MRS GABA levels in the PFC and ACC (Ende et al. 2016; Li et al., 2020). Finally, reductions in GABA levels in the inferior frontal gyrus were found to underlie SSRT impulsivity (Murley et al., 2020), suggesting that multiple subtypes of impulsivity implicate diminished GABA-ergic function in several cortico-striatal regions.

The above synopsis, summarised in Table 1, highlights distinct nodes within the stopping and waiting impulsivity networks that depend on separate and interacting contributions from the ascending monoaminergic systems and amino-acid neurotransmitters. We recognise that our analysis is far from complete and omits, for example, neuropeptides (Alcaraz-Iborra & Cubero, 2015), endocannabinoids (Ucha et al., 2019) and the cholinergic systems (Mamiya et al., 2020), but nevertheless enables the greatest volume of literature on impulsive and compulsive behaviours to be integrated. We next discuss the neurochemistry of drug compulsion as a prelude to identifying neurochemical substrates and mechanisms that overlap with impulsivity.

### 3 NEUROCHEMICAL MARKERS OF DRUG COMPULSION

The transition to compulsion is hypothesised to result from impaired inhibitory response control and a progressive shift in the locus of behavioural control from ventral limbic regions of the striatum (i.e., the NAc) to more dorsal associative and sensorimotor areas of the striatum (Everitt & Robbins, 2016; Jentsch & Taylor, 1999; Kalivas & Volkow, 2005; Lüscher et al., 2020; Porrino et al., 2004). Although experimental approaches in rodents can never fully recapitulate the complex personal and environmental reasons why humans abuse drugs, behavioural paradigms have been developed in rodents to investigate tractable components of addiction that contribute to compulsive drug seeking. Thus, contemporary procedures to assess ‘addiction-like’ or compulsive behaviour in rodents de-emphasise the reinforcing effects of drugs that determine individual variation in the acquisition, escalation and reinstatement of drug responses and instead probe the persistence of drug-seeking and drug-taking in the face of punishment or aversive consequences (Lüscher et al., 2020). Compulsive drug-taking is assessed by response-contingent self-administration despite concurrent punishment (e.g., a mild footshock or adding an unpleasant tastant like quinine to an alcohol solution) and forms one component of the three-criteria model of stimulant addiction (Deroche-Gamonet et al., 2004).

In the three-criteria model, both drug delivery and foot-shocks are delivered concurrently on an FR-5 schedule of reinforcement, with an additional foot-shock delivered during the response preceding drug delivery (i.e., FR-4). In a series of studies, the three-criteria model has been used to assess interindividual differences in clinically translatable behavioural endophenotypes in rodents and has demonstrated striking cross-species convergence. For example, high levels of trait impulsivity predict compulsive cocaine taking in rodents (Belin et al., 2008) and is also a vulnerability marker for human substance dependence (Verdejo-Garcia et al., 2008; Verdejo-Garcia & Albein-Urrios, 2021). However, in the three-criteria model, punishment is immediate and explicitly linked to the drug-taking response. In humans, this may not always be the case, where drug-taking...
| Task | Manipulation | Mechanism of action | Route or site of administration | Effect | Reference |
|------|-------------|---------------------|-------------------------------|--------|-----------|
| DA   | 6-hydroxydopamine | Selective neurotoxin | NAcb | ↓ premature responses | Cole and Robbins (1989) |
| 5-CSRTT | SCH 23390 | Selective D1R antagonist | NAcb | ↓ premature responses | Pattij et al. (2007) |
| 5-CSRTT | Sulpiride administration after mPFC lesion | Selective D2/3R antagonist | NAcbC | ↓ increase in premature responses caused by lesion | Pezze et al. (2009) |
| 5-CSRTT | Nafadotride | D3R antagonist | NAcbS NAcbC | ↑ premature responses (HI) ↓ premature responses (HI) | Besson et al. (2010) |
| SSRTT | Amphetamine | DA/NA reuptake inhibitor | I.P | ↓ SSRT (HI) | Feola et al. (2000) |
| SSRTT | Methylphenidate | DA/NA reuptake inhibitor | I.P | ↓ SSRT (HI) ↑ SSRT (LI) | Eagle et al. (2007) |
| SSRTT | SCH 23390 Sulpiride | Selective D1R antagonist; selective D2/3R antagonist | DMS | ↓ SSRT ↑ SSRT | Eagle et al. (2011) |
| DDT  | 6-hydroxydopamine | Selective neurotoxin | DMS | ↑ delay aversion | Tedford et al. (2015) |
| DDT  | Ibotenic acid | Neurotoxin | STN | ↓ delay aversion | Winstanley et al. (2005) |
| 5-HT  | Flupenthixol | D1R/D2R antagonist | I.P | ↑ delay aversion | Floresco et al. (2008) |
| 5-CSRTT | 5,7-dihydroxytryptamine | Selective neurotoxin | ICV | ↑ premature responses | Winstanley, Theobald, Dalley, et al. (2004) |
| 5-CSRTT | 5,7-dihydroxytryptamine | Selective neurotoxin | ICV | ↑ premature responses | Harrison et al. (1997) |
| 5-CSRTT | M100907 | 5-HT2AR antagonist | DS | ↑ premature responses | Agnoli and Carli (2012) |
| 5-CSRTT | Lorocserin SB-242084 | 5-HT2cR agonist, 5-HT2cR antagonist | S.C | ↓ premature responses ↑ premature responses | Higgins et al. (2020) |
| 1-CSRTT | 5-HT2CR knockdown | — | mPFC | ↑ premature responses | Anastasio et al. (2015) |
| DDT  | 5,7-dihydroxytryptamine | Selective neurotoxin | Dorsal and median raphe nuclei | ↑ delay aversion | Mobini et al. (2000) |
| DDT  | Optogenetic stimulation | — | Dorsal raphe nucleus | ↓ delay aversion | Miyazaki et al. (2014) |
| NA   | Atomoxetine | Selective NA reuptake inhibitor | NAcbS | ↓ premature responses | Economidou et al. (2012) |
| 5-CSRTT | Atomoxetine | Selective NA reuptake inhibitor | I.P | ↓ premature responses | Robinson et al. (2008) |
| 5-CSRTT | Prazosin | α1-adrenoceptor antagonist | S.C | ↑ premature responses | Koskinen et al. (2003) |
| DDT  | Atomoxetine | Selective NA reuptake inhibitor | I.P | ↓ delay aversion | Robinson et al. (2008) |
| DDT  | Phenylephrine | α1-adrenoceptor agonist | I.P | ↑ delay aversion | van Gaalen et al. (2006) |
| SSRTT | Atomoxetine | Selective NA reuptake inhibitor | I.P | ↓ SSRT | Robinson, Dalley, et al. (2008), Robinson, Eagle, et al. (2008) |
| SSRTT | Atipamezole | α2-adrenoceptor antagonist | I.P | ↓ SSRT | Bari and Robbins (2013) |

(Continues)
TABLE 1 (Continued)

| Task          | Manipulation | Mechanism of action | Route or site of administration | Effect        | Reference                  |
|---------------|--------------|---------------------|---------------------------------|---------------|----------------------------|
| SSRTT         | Atomoxetine | Selective NA reuptake inhibitor | dPL, OFC | ↓ SSRT | Bari et al. (2011) |
| SSRTT         | Guanfacine  | α2-adrenoceptor agonist | dPL | ↑ SSRT | Bari et al. (2011) |
| GLUT 5-CSRTT  | (R)-CPP     | NMDAR antagonist | IL | ↑ premature responses | Murphy et al. (2005) |
| 5-CSRTT       | MK801        | Non-competitive NMDAR antagonist | IL | ↑ premature responses | Benn and Robinson (2014) |
| GABA 5-CSRTT  | Muscimol     | GABA_A receptor | IL | ↑ premature responses | Murphy et al. (2012) |
| SSRTT         | Muscimol     | GABA_A receptor | dPL, ACC | ↓ SSRT | Bari et al. (2011) |

Abbreviations: ↑, increased; ↓, decreased; 1-CSRTT, 1-choice serial reaction time task; 5-CSRTT, 5-choice serial reaction time task; ACC, anterior cingulate cortex; D1R, dopamine D1 receptor; D2/3R, dopamine D2/3 receptor; DA, dopamine; DDT, delay-discounting task; DMS, dorsomedial striatum; dPL, dorsal prelimbic cortex; DS, dorsal striatum; GABA, γ-amino butyric acid; GABA_A, γ-amino butyric acid A receptor; Glut, glutamate; HI, high impulsive; I.P, intraperitoneal; ICV, intracerebroventricular; IL, infralimbic cortex; LI, low impulsive; mPFC, medial prefrontal cortex; NA, noradrenaline; NAcb, nucleus accumbens; NAcbC, nucleus accumbens core; NAcbS, nucleus accumbens shell; NMDAR, N-methyl-D-aspartic acid receptor; OFC, orbitofrontal cortex; S.C, subcutaneous. (R)-CPP, 3-(R)-2-carboxypiperazin-4-yl-propyl-1-phosphonic acid; SSRT, stop-signal reaction time; SSRTT, stop-signal reaction time task; STN, subthalamic nucleus.

responses can be associated with delayed and often probabilistic detrimental consequences. In addition, the three criteria model primarily models compulsive drug-taking and does not assess drug-seeking behaviour under the threat of punishment.

Conversely, well-established cue-controlled cocaine seeking and compulsive drug-seeking responses can be measured using second-order schedules of reinforcement paired with or without contingent foot-shocks, respectively. In such procedures, drug delivery occurs after a certain time has elapsed—the fixed interval (e.g., 15 min), with drug-seeking responses maintained by classically conditioned stimuli previously paired with a drug reinforcer. One advantage of the second-order schedule is that it can be used to probe drug-seeking behaviour in the absence of direct drug effects. Thus, an important distinction between instrumental responding during the first drug-free interval and subsequent intervals is made, the former behaviour being directly under control of the conditioned reinforcing properties of the drug-conditioned stimulus, the latter behaviour influenced also by the rate-altering effects of the drug.

So-called heterogeneous seeking-taking chain schedules index compulsive drug-seeking by requiring animals to press a ‘seeking’ lever, to gain access to a drug ‘taking’ lever, responding on which results in drug delivery. Under this schedule, compulsive drug-seeking is assessed with the introduction of an unpredictable, mild foot-shock that occurs 50% of the time after the completion of the seeking lever response (Pelloux et al., 2012). The unpredictable nature of punishment under these conditions may more closely relate to the uncertainty of adverse consequences during drug procurement in humans. Alternatively, threat of punishment and anticipation of aversive consequences has been used in conjunction with the seeking-taking chain schedule as an alternative to contingent foot-shock punishment delivered immediately after the instrumental seeking response (Vanderschuren & Everitt, 2005). After limited drug taking experience, presentation of a tone previously paired with foot-shock suppressed cocaine seeking, an effect not observed after prolonged self-administration (i.e., after an extended history of self-administration cocaine seeking was no longer suppressed by the presentation of the aversive conditioned stimulus) (Vanderschuren & Everitt, 2005).

Compulsive alcohol intake is often assessed by the addition of the bitter taste of quinine to an oral alcohol solution, rendering the solution less palatable (for review see Hopf & Lesscher, 2014). Several aspects of the human disorder are captured within the quinine model. For example, alcohol-dependent individuals will consume toxic products that contain alcohol (e.g., Eau de Cologne and antiseptics) (Leon et al., 2007), clearly demonstrating alcohol use in the face of negative consequences. This has obvious parallels with quinine adulteration and highlights the face validity of the paradigm in simulating alcohol abuse in humans. Similar to compulsive cocaine use, rats become averse-resistant to quinine after extended access to alcohol (Hopf et al., 2010), a phenotype that persists for many months (Wolffgramm & Heyne, 1991). Approximately 15% of animals with extensive alcohol self-administration exposure (~10 weeks) continue to administer alcohol when offered an alternative sugar reward. This subpopulation of rats then go on to display several addiction-like behaviours and continue to self-administer alcohol in (a) the face of foot-shock punishment and (b) the adulteration of alcohol with quinine (Augier et al., 2018). This report, and others (Seif et al., 2013), suggests that resistance to multiple forms of punishment may be subserved by overlapping neural mechanisms and co-occur within an individual. Thus, Seif et al. showed that compulsive alcohol taking as measured by both quinine adulteration and foot-shock punishment is mediated by PFC to NAcBc circuitry (Seif et al., 2013). Indeed, preclinical circuit-mapping studies have shown impaired fronto-striatal connectivity in compulsive drug-seeking rats (Chen et al., 2013). Moreover, translationally relevant imaging
techniques have highlighted overlapping cross-species neural circuits linked to compulsive drug use (Hu et al., 2015, 2019).

Finally, for the purposes of this review, schedule-induced polydipsia (SIP) assesses the compulsive consumption of freely available water when food reward is unpredictable. Adjunctive drinking behaviour under SIP captures several hallmark features of compulsive disorders, specifically the tendency of some animals to develop drinking that is excessive, repetitive and maladaptive. Although the link between compulsive drinking and psychostimulant use has yet to be fully explored, enhanced self-administration of amphetamine is related to enhanced levels of SIP (Piazza et al., 1993) and several behavioural traits confer risk for both SIP and stimulant use. For example, rats screened for high impulsivity in the 5-CSRTT, which subsequently develop compulsive cocaine self-administration (Belin et al., 2008), develop high levels of drinking when trained on a SIP task (Belin-Rauscent et al., 2016; Higgins et al., 2020). In the sections that follow, we survey the evidence linking each of the major neurotransmitter systems with compulsive drug-seeking and drug-taking (for a summary see Table 2).

3.1 | 5-HT

The 5-HT systems have long been implicated in reward and punishment (Patkina & Lapin, 1976; Soubrie et al., 1981) with median and dorsal raphe 5-HT neurons contributing, respectively, to conditioned fear and behavioural control under punishment (Avanzi et al., 2003; Thiébot et al., 1983). Adaptations in the 5-HT systems are also widely implicated in addiction to a variety of abused drugs (for review see Müller & Homberg, 2015). In the context of compulsive rats identified as compulsive drug seekers on a seeking-taking task showed reduced 5-HT turnover (5-HT/5-HIAA ratio) in the PFC, striatum and amygdala and decreased DA turnover in the dorsal striatum, compared with non-compulsive rats (Pelloux et al., 2012). Roughly 20% of rats developed compulsive cocaine seeking, a proportion comparable to the probability of humans giving way to compulsive drinking and decreasing premature responding (Higgins et al., 2020). High drinking in the SIP procedure was also associated with reduced 5-HTT2A receptor binding in the PFC, and DOI, a 5-HTT2A/C receptor agonist decreased water consumption when infused directly into this region (Mora et al., 2018), an effect found earlier to be mediated by 5-HTT2A receptors (Navarro et al., 2015). Taken together, these findings reveal a bidirectional role of 5-HT in compulsive cocaine seeking and imply specific key roles of 5-HTT2A and 5-HTT2C receptors.

3.2 | Dopamine

The ascending DA systems contribute in multifaceted ways to reward and addiction by supporting the initiation and reinforcing effects of drugs, associative learning processes and vulnerability mechanisms (Berridge & Robinson, 2016; Hyman, 2005; Koob & Volkow, 2016; Lüscher et al., 2020; Nader et al., 2002). Spiralling pathways between midbrain DA neurons and striatal subregions (Haber et al., 2000; Ikemoto, 2007) are hypothesised to underlie the shift in behavioural control over drug seeking (Everitt et al., 2008) with established seeking responses eventually transferring to the dorsal striatum and a habit-based system (Belin et al., 2013). Disconnecting intrastriatal connectivity through specific lesions of the NAcB as well as dorsolateral striatal infusions of the DA receptor antagonist α-flupenthixol decreased cocaine seeking in rats extensively trained under a second order schedule of reinforcement (Belin & Everitt, 2008). This observed shift in behavioural control by DA reflects well-established cue-controlled cocaine-seeking, reflecting the habitual quality of drug-seeking behaviour but not necessarily compulsion per se. Nonetheless, consistent with this shift, earlier seminal studies remarkably demonstrated that neurochemical and metabolic markers in the dorsal striatum were affected by chronic, but not acute, cocaine self-administration in non-human primates (Letchworth et al., 2001; Porrino et al., 2004). Moreover, phasic DA release decreased in the ventromedial striatum (VMS) and increased in the dorsolateral striatum after several weeks of cocaine exposure (Willuhn et al., 2012), while DA release in the dorsal striatum, but not the ventral striatum, was evoked by response-contingent, drug-associated stimuli, during well-established cocaine seeking (Ito et al., 2002).

After extended training, compulsive alcohol seeking in a punished seeking-taking task was recently shown to depend on the DA-rich anterior dorsolateral striatum (Giuliano et al., 2019). Animals showing increased reliance on anterior dorsolateral striatum dopaminergic mechanisms were subsequently more likely to develop compulsive alcohol seeking. As well as the dorsal striatum, D1 receptors in the NAcB and NAcBc play a critical role in drug-seeking after punishment. Infusions of the D1-R antagonist SCH 23390 in both the NAcB and NAcBc decreased the renewal of alcohol seeking after
| Task | Manipulation | Mechanism of action | Route or site of administration | Effect | Reference |
|------|-------------|---------------------|---------------------------------|--------|-----------|
| DA Cocaine SA—SOR | Intrastriatal disconnection α-flupenthixol | D1R/D2R antagonist | NAcB +DLS DLS | ↓ cocaine-seeking ↓ cocaine-seeking | Belin and Everitt (2008) |
| Alcohol SA—STCS | α-flupenthixol | D1R/D2R antagonist | aDLS | ↓ alcohol-seeking | Giuliano et al. (2019)* |
| Alcohol SA—punishment-induced abstinence | SCH 23390 | Selective D1R antagonist | S.C NAcB NAcB | ↓ alcohol-seeking ↓ alcohol-seeking ↓ alcohol-seeking | Marchant and Kaganovsky (2015)* |
| Cocaine SA—conflict based relapse model | Flupenthixol Amphetamine | D1R/D2R antagonist; DA/NA reuptake inhibitor | NAcB NAcB | ↓ cue-evoked reinstatement ↑ cue-evoked reinstatement | Saunders et al. (2013) |
| Cocaine SA—SOR | SB-277011-A | Selective D3R antagonist | Systemic | ↓ cocaine-seeking | Di Ciano et al. (2003) |
| Cocaine SA—SOR | α-flupenthixol | D1R/D2R antagonist | DS | ↓ cocaine-seeking | Vanderschuren et al. (2005) |
| 5-HT Cocaine SA—STCS | mCPP SB-242084 Citalopram 5,7-DHT | Partial 5-HT2CR agonist; selective 5-HT2CR antagonist; SSRI; selective serotonin neurotoxin | I.P | ↓ cycles-completed ↑ cycles-completed ↓ cycles-completed ↑ cycles-completed | Pelloux et al. (2012)* |
| Cocaine SA | 5-HT2CR knockdown | — | mPFC | ↑ cocaine cue reactivity after forced abstinence | Anastasio et al. (2014) |
| SIP | Lorcaserin CP-8091010 SB-242084 | 5-HT2CR agonist; selective 5-HT2CR agonist; selective 5-HT2CR antagonist | S.C | ↓ water intake ↓ water intake ↑ water intake (LD) | Higgins et al. (2020) |
| SIP | DOI | 5-HT2A/C receptor agonist | mPFC | ↓ water intake (HD) | Mora et al. (2018) |
| SIP | Citalopram DOI SB-242084 | SSR1; 5-HT2A/C receptor agonist | I.P | ↓ water intake (HD) | Navarro et al. (2015) |
| NA Cocaine SA—saline, cocaine or foot-shock-induced reinstatement | Clonidine Lofexidine Guanabenz | α2-adrenoceptor agonists | I.P | ↓ fs-induced reinstatement ↓ fs-induced reinstatement ↓ fs-induced reinstatement | Erb et al. (2000) |
| Cocaine SA—cue- and cocaine-induced reinstatement | Clonidine UK-14,304 Guanfacine Moxonidine | II / α2-adrenoceptor agonist; II / α2-adrenoceptor agonist; α2-adrenoceptor agonist; α2-adrenoceptor agonist | I.P | ↓ cue-induced reinstatement ↓ cue-induced reinstatement ↓ cue-induced reinstatement ↓ cue-induced reinstatement | Smith and Aston-Jones (2011) |

(Continues)
| Task | Manipulation | Mechanism of action | Route or site of administration | Effect | Reference |
|------|--------------|---------------------|---------------------------------|--------|-----------|
| Cocaine SA—cue-induced reinstatement after forced abstinence | Prazosin Terazosin Phenylephrine RX281001 | Selective α<sub>1</sub>-adrenoceptor antagonist; selective α<sub>2</sub>-adrenoceptor antagonist; selective α<sub>1</sub>-adrenoceptor agonist; selective α<sub>2</sub>-adrenoceptor agonist | VTA | ↓ cue-induced reinstatement ↓ cue-induced reinstatement ↑ cue-induced reinstatement ↑ cue-induced reinstatement | Solecki et al. (2018) |
| | | | | | |
| CPP, extinction, drug-induced and stress-induced reinstatement | Yohimbine BRL 44408 | α<sub>2</sub>-adrenoceptor antagonists | I.P | ↑ time in cocaine compartment ↑ time in cocaine compartment | Mantsch et al. (2010) |
| Cocaine SA—ShA and LgA | Prazosin | α<sub>1</sub>-adrenoceptor antagonist | I.P | ↓ breakpoint (LgA) | Wee et al. (2008) |
| Heroin SA—ShA and LgA | Prazosin | α<sub>1</sub>-adrenoceptor antagonist | I.P | ↓ heroin intake (LgA) | Greenwell et al. (2009) |
| Cocaine SA—STCS | Atomoxetine | Selective NA reuptake inhibitor | I.P | ↓ relapse to cocaine seeking after punishment induced reinstatement | Economidiou et al. (2009)<sup>a</sup> |
| SIP | Atomoxetine | Selective NA reuptake inhibitor | I.P | ↓ water intake | Ansquer et al. (2014) |
| GLUT | Cocaine SA—extinction-reinstatement | AMPA Cis-ACDA | AMPAR agonist; NMDAR agonist | NAcb ↑ reinstatement ↑ reinstatement | Cornish et al. (1999) |
| | | | | | |
| | Heroin SA—extinction-reinstatement | CNQX | AMPA/Kainate receptor antagonist | NAcbC ↓ reinstatement | LaLumiere and Kalivas (2008) |
| | | | | | |
| | Cocaine SA—SOR | LY293558 | AMPA/Kainate receptor antagonist | NAcbC ↓ cocaine-seeking | Di Ciano and Everitt (2001) |
| | | | | | |
| | Cocaine SA—SOR | LY293558 | AMPA/Kainate receptor antagonist | DS ↓ cocaine-seeking | Vanderschuren et al. (2005) |
| | | | | | |
| | Cocaine SA—SOR | N-acetylcysteine | Synaptic glutamate release inhibitor | I.P ↓ cocaine-seeking | Murray et al. (2012) |
| SIP | Memantine Lamotrigine | NMDAR antagonist; sodium channel blocker | I.P ↓ water intake (HD) ↓ water intake (HD) | | Prados-Pardo et al. (2019) |
| GABA | Alcohol SA—multiple models | GAT-3 transporter knockdown — Amygdala | ↑ alcohol choice | Augier et al. (2018)<sup>a</sup> |
| | Cocaine SA—STCS | Muscimol Baclofen | GABA<sub>R</sub> agonist; GABA<sub>B</sub>R agonist | CeA ↑ cocaine SA ↑ cocaine SA | Sun and Yuill (2020)<sup>a</sup> |
| | Cocaine/Heroin SA—SOR | Baclofen | GABA<sub>B</sub>R agonist | I.P ↓ cocaine-seeking ↓ heroin-seeking | Di Ciano and Everitt (2003) |
| | Alcohol SA—extinction-reinstatement | Baclofen | GABA<sub>B</sub>R agonist | I.P ↓ reinstatement | Maccioni et al. (2008) |

<sup>a</sup> Continued
### TABLE 2 (Continued)

| Task | Manipulation | Mechanism of action | Route or site of administration | Effect | Reference |
|------|--------------|---------------------|---------------------------------|--------|-----------|
| Chronic alcohol choice—extinction-reinstatement and Cocaine SA—extinction-reinstatement | Baclofen | GABA_B agonist; GABA_B positive allosteric modulator | I.P | ↓ reinstatement (alcohol) | Vengeliene et al. (2018) |
| SIP | PTZ | GABA_B antagonist | Systemic | ↓ water intake | López-Grancha et al. (2008) |

Abbreviations: (R)-CPP, 3-[(R)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid; ↑, increased; ↓, decreased; 5,7-DHT, 5,7-dihydroxytryptamine; aDLS, anterior dorsolateral striatum; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CeA, central amygdala; cis-ACDA, 1-aminoacyclobutane-cis-1,3-dicarboxylic acid; CMPP, 2-[1-[2-(4-Chlorophenyl)-5-methylpyrazol[1,5-a]pyrimidin-7-yl]-2-piperidinyl]ethanol; CNQX, cyanoquinoline (6-cyano-7-nitroquinoxaline-2,3-dione); CPP, conditioned place preference; D3R, dopamine D3 receptor; DA, dopamine; DLS, dorsolateral striatum; DOI, 2,5-dimethoxy-4-iodoamphetamine; DS, dorsal striatum; fs, foot-shock; GABA, γ-aminobutyric acid; GABA_A, γ-aminobutyric acid A receptor; GABA_BR, γ-aminobutyric acid B receptor; GABA_AR, γ-aminobutyric acid A receptor; GAT-3, GABA transporter; Glut, glutamate; HD, high drinker; I.M, intramuscular; I.P, intraperitoneal; ICV, intracerebroventricular; LD, low drinker; LGa, long-access; mPFC, medial prefrontal cortex; NA, noradrenaline; NAcb, nucleus accumbens; NAcbC, nucleus accumbens core; NAcbS, nucleus accumbens shell; NMDAR, N-methyl-D-aspartic acid receptor; PTZ, pentylenetetrazol; Sc, subcutaneous; SA, self-administration; SHA, short-access; SIP, schedule-induced polydipsia; SOR, second order schedule of reinforcement; SSRI, selective serotonin reuptake inhibitor; STCS, seeking-taking chain schedule; VTA, ventral tegmental area.

References represent studies where compulsivity has been assessed with drug-seeking or drug-taking evaluated in the face of punishment or threat of punishment.

More generally, DA mechanisms are implicated in a variety of compulsive, behavioral phenotypes from rigid, stereotyped movements of dorsal striatal origin (Amici & Koob, 1993) to compulsive checking by suppressing responses in the NaC decreases cue-evoked cocaine seeking. These studies highlight the important contribution of ventral and dorsal striatal DA in the NaC, decreased cue-evoked cocaine seeking, a hypnotic effect (Ozerdo, 2017). In one noteworthy study, D2 receptor availability correlated with behavioral sensitivity to positive, but not negative, feedback during learning. Parallel findings from the same group further showed that decreased dopamine levels predicted reversal performance. Thus, variance in behavioral inflexibility was largely accounted for by ex vivo D1 and D2 levels in the dorsal striatum and OFC, respectively (Groman et al., 2013).
self-administer cocaine under a seeking-taking chain schedule. After stable responding was acquired, seeking was paired with a mild foot-shock for several sessions. Following punishment, drug seeking was assessed after 1 week of withdrawal. It was found that atomoxetine, a selective NA reuptake inhibitor, that also increases DA release in cortical regions, attenuated the enhanced propensity to relapse after abstinence, an effect that was more pronounced in high-impulsive rats than low-impulsive rats (Economidou et al., 2014). Here, chronic administration of atomoxetine reduced premature responding in high impulsive rats, as well as compulsive addictive drinking (Anquer et al., 2014), although it should be noted that null effects of atomoxetine on SIP have also been reported (Higgins et al., 2020; Navarro et al., 2015). More recent studies confirm the anti-compulsivity actions of atomoxetine, for example, in compulsive marble burying (Grassi et al., 2016), a behaviour that depends on the functional integrity of the brain NA systems (Lustberg et al., 2020).

3.4 | Glutamate

The transition to addiction is hypothesised to involve a dysregulation of glutamate homeostasis and long-term changes in synaptic plasticity (van Huijstee & Mansvelder, 2015; Kalivas, 2009). Using the three-criteria model of addiction, Kasanetz et al. (2010) evaluated long-term depression (LTD) in the NAcB following short and long access exposure to cocaine self-administration. Short access cocaine led to a suppression in NMDA receptor-dependent LTD in all subjects. However, after prolonged access to cocaine, three criteria rats (rats showing three of the addiction-like behaviours, including compulsive cocaine intake in the face of punishment) showed persistently impaired LTD whereas LTD progressively recovered in zero criteria rats (rats showing no addiction-like behaviours). Utilising the same paradigm, three criteria rats showed impaired mGluR2/3-dependent LTD mechanisms in the dorsomedial PFC and reduced mGluR2/3 protein expression. Moreover, the α-amino-3-hydroxy-4-isoxazolepropionic acid (AMPA) to NMDA ratio, an index of synaptic strength, increased in the prelimbic cortex (PrL) of three criteria rats (Kasanetz et al., 2013). Extending these findings, Chen et al., (2013) used a seeking-taking chain task to demonstrate that compulsive cocaine seeking manifests from PrL hypoactivity (Chen et al., 2013). Thus, optogenetic stimulation and inhibition of the PrL bi-directionally modulated compulsive cocaine seeking, both suppressing and enhancing seeking behaviour, respectively. The causally responsible output structures mediating top-down inhibitory control by the PrL remain to be fully defined but may involve in part circuits to the dorsal periaqueductal grey in the brainstem (Siciliano et al., 2019) and NAcB5 (Piantadosi et al., 2020). More globally, deletion of the NMDAR subunit GluN2B in principal neurons of the cortex and hippocampus reduced punished suppression of reward seeking in mice (Radke et al., 2015). This report and others (Wang et al., 2010) highlight the important role of NMDAR subunit composition on glutamatergic signalling and reward seeking. In humans, perturbations in glutamate concentration are reported in the NAc (Engeli et al., 2020) and caudate putamen (Ersche et al., 2020) of substance dependent individuals.

Many studies have investigated the role of specific glutamate receptor subtypes in cue-induced reinstatement of drug seeking. For example, AMPA receptor blockade in the NAcB, but not the NAcB5, prevented reinstatement (Cornish et al., 1999). Furthermore, inactivation of the PFC → NAcB pathway via administration of baclofen and muscimol in the PrL cortex decreased glutamate output in the NAcB and decreased drug-seeking (LaLumiere & Kalivas, 2008). Glutamatergic mechanisms of drug-seeking have also been assessed using second order schedule of reinforcement. Thus, intra-NAcB but not intra-NAcB5 infusions of the selective AMPA/kainate receptor antagonist LY293558 dose-dependently decreased cocaine seeking in rats during the drug-free first interval and throughout the session. Infusion of the NMDA receptor antagonist AP-5 in the NAcB produced a limited effect and no effect in the NAcB (Di Ciano & Everitt, 2001). LY293558 (and the DA receptor antagonist sp-f flavlentrol) also decreased well-established cue-controlled cocaine seeking when infused in the dorsolateral striatum (Vanderschuren et al., 2005). Additionally, systemic administration of N-acetylcysteine, which reduces glutamate release, reduced cocaine seeking in the first drug-free interval of a second order schedule of reinforcement (Murray et al., 2012). In summary, several lines of enquiry converge on the importance of glutamatergic signalling in regulating drug-seeking behaviour. It is clear that this may be dependent on the specific location (ventral striatum versus PFC), as well as specific glutamatergic receptor subtypes.

Alcohol consumption has also been linked to glutamatergic neurotransmission. Selectively bred alcohol-prefering rats homozygous for the Grm2 stop codon, a phenotype that results in a severe loss of mGluR2 and impaired mGluR2 synaptic depression, showed increased alcohol intake (Zhou et al., 2013). In the SIP paradigm, rats showing compulsive addictive drinking had reduced levels of glutamate in the mPFC (Mora et al., 2018). Nevertheless, whereas N-acetylcysteine did not reduce water intake in high drinking animals, both the non-competitive NMDA receptor antagonist, memantine, and the glutamate/aspartate release-lowering drug, lamotrigine, did reduce SIP (Prados-Pardo et al., 2019).

In a longitudinal, pre-clinical imaging study using PET, Grom and colleagues assessed baseline levels of dopamine D2/3 and metabolotropic Glu5 (mGluR5) receptor availability in rats trained on a probabilistic reversal learning task before and after cocaine self-administration (Grom et al., 2020). Cocaine exposure significantly disrupted reversal learning performance, leading to a reduced sensitivity to, and integration of, negative feedback. These outcomes were associated with an increase in mGlu5 binding potential in the mPFC, suggesting that impaired mGlu5 signalling in this region may contribute to the formation of inflexible, perseverative-like responding (Grom et al., 2020).
Abnormalities in GABA signalling are seen across a wide range of neuropsychiatric disorders including obsessive compulsive disorder (Li et al., 2019), schizophrenia (de Jonge et al., 2017) and addiction (Tyacke et al., 2010). In a recent study to investigate GABA-ergic mechanisms in compulsive alcohol consumption, rats were given a choice between alcohol and a high incentive sweetened solution (Augier et al., 2018). A small subset of the rats (~15%) preferred alcohol and developed addiction-like behaviours, including (a) an increased motivation to work for alcohol, as indexed by increased breakpoints in a progressive ratio task, (b) increased alcohol intake when the alcohol solution was adulterated with quinine and (c) continued alcohol intake despite foot-shock punishment. Investigation of the molecular substrates revealed a significant decrease in the GABA transporter, GAT-3, in the amygdala of alcohol-choosing rats. This was associated with increased tonic inhibition in the central nucleus of the amygdala (CeA). Moreover, short hairpin RNA knockdown of GAT-3 in the high incentive preferring group increased choice behaviour for alcohol, demonstrating a causal role of GABA-ergic mechanisms in the CeA in the development of alcohol-choice behaviour. Activation of GABA receptors in the CeA has also been shown to influence cocaine seeking under punishment (Sun & Yuill, 2020). Thus, reversibly inactivating doses of GABA agonists in the CeA increased the number of punished seeking responses. These findings are consistent with reports demonstrating increased inhibitory GABAergic transmission in rats after chronic ethanol treatment (Roberto et al., 2004). Using slice electrophysiology and in vivo microdialysis, rats treated chronically with ethanol exhibited augmented inhibitory postsynaptic potentials, an index of increased basal GABA release, relative to control animals. Moreover, both at baseline and after chronic ethanol treatment, dialysate levels of GABA were higher in rats treated chronically with ethanol than ethanol-naive control rats (Roberto et al., 2004).

GABA signalling has also been shown to play a role in well-established cue-controlled drug seeking. Using a second order schedule of reinforcement, Di Ciano and Everitt showed that administration of the GABA_A receptor agonist baclofen dose-dependently decreased cue-controlled cocaine and heroin seeking (Di Ciano & Everitt, 2003). Moreover, baclofen and muscimol administration in the ventral tegmental area dose-dependently decreased drug-free cocaine seeking during the first interval (Di Ciano & Everitt, 2004). Systemically administered baclofen also decreased cue-induced reinstatement of alcohol-seeking in Sardinian alcohol-prefering rats (Maccioni et al., 2008), an effect also generalising to the reinstatement of heroin-seeking (Spano et al., 2007).

Several studies have also evaluated the role of GABA signalling in SIP. Administration of the GABA_A receptor antagonist pentylene-tetrazol decreased drinking in both high- and low-drinkers (López-Grancha et al., 2008). However, the effects of the GABA_A agonist diazepam on SIP are more mixed and dependent on dose. In general, whereas low doses of diazepam increase compulsive adjunctive drinking (López-Grancha et al., 2008), higher doses reduce the temporal regulation of licking responses during intervals between food delivery (Pellon & Blackman, 1992). Although an emerging area of interest, one recent report indicates a potential role of GABA in the bed nucleus of the stria terminalis in modulating SIP (Angelis et al., 2019).

4 | SYNTHESIS AND THEORETICAL IMPLICATIONS

The now widely accepted multidimensionality of impulsivity challenges any straightforward relationship between impulsive and compulsive behavioural phenotypes in addiction. The broad construct of compulsivity also encompasses several psychological processes from rigid strategies or attentional set shifting, stereotypy, perseveration, resistance to extinction and the persistence of stimulus-response habits despite negative consequences (Robbins et al., 2012). Further challenges arise from the fact that impulsivity is often assessed in humans using subjective self-report measures, for example, the Barratt Impulsiveness Scale (Patton et al., 1995) or such factors as follows: (a) a lack of premeditation or the failure to plan carefully before acting; (b) sensation-seeking or the desire for intense, exciting experiences despite inherent risks; (c) a lack of perseverance during boring or demanding tasks; and (d) urgency or the propensity for rash or risky behaviour in positive or negative emotional settings (Whiteside & Lynam, 2001). Nevertheless, impulsivity and compulsivity both result from failures in response inhibition or top-down control and implicate aberrant reward processing and impaired insight into the consequences of inappropriately elicited actions (Dalley et al., 2011).

This review outlines the complexities of impulsive-compulsive phenotypes in addiction and highlights the shifting neural circuits underlying the transition to compulsive drug-seeking. The main neuromodulatory systems are all implicated in different aspects of impulsive-compulsive behaviours. However, DA and 5-HT dysfunction in striatal and cortical domains is a recurring theme, especially in trait impulsive subtypes, while enhanced noradrenergic neurotransmission in the brain reduces most forms of impulsive and compulsive behaviour. Overall, our analysis reveals partially overlapping neurochemical substrates of impulsivity and compulsivity, which may underlie the recognised causal influence of trait impulsivity on the emergence of compulsive drug-seeking (Everitt, 2014). Figure 1 provides an overview of the involvement of the main neurotransmitter systems in various forms of impulsivity and compulsivity. Overall, the evidence suggests that 5-HT similarly and bidirectionally modulates impulsive and compulsive phenotypes with reduced transmission associated with both increased impulsivity and compulsivity. The exception however is SSRT impulsivity which appears to be insensitive to alterations in 5-HT function. Enhancing NA function via selective reuptake inhibition decreases the main forms of impulsivity but to date there is a paucity of data on the effects of selective NA
depletion on impulsivity and compulsivity. Altered DA transmission generally has the opposite effects on impulsive-compulsive behaviours than 5-HT, presumably because these two monoamine systems are mutually regulated, often via antagonistic interactions (Howell & Cunningham, 2015). However, the effects of DA manipulations on impulsivity and compulsivity are more nuanced and task-dependent with the strongest alignment evident for premature responding in the 5-CSRTT and compulsive behaviour in the seeking-taking chain-schedule.

As highlighted in Figure 1, the most consistent overlap between impulsivity and compulsivity involves the 5-HT systems. Pelloux and colleagues showed that administration of the 5-HT2C receptor antagonist SB242084 increased drug seeking under punishment, while M100907, a 5-HT2A antagonist, decreased punished drug seeking (Pelloux et al., 2012). Consistent with these findings, knockdown of mPFC 5-HT2c receptor increased impulsivity in a 1-choice variant of the 5-CSRTT (Anastasio et al., 2015) while M100907 had the opposite effect (Fink et al., 2015). These findings lend support to the notion of overlapping 5-HT signalling across impulsive and compulsive phenotypes. The underlying mechanism is unclear but may relate to observations that 5-HT neurons innervating the OFC and mPFC mediate restraint for delayed and uncertain rewards (Miyazaki et al., 2020) while depletion of 5-HT from the OFC increases behavioural perseveration, a form of compulsive behaviour (Clarke et al., 2004). Evidence of diminished 5-HT levels in the PFC of stimulant-addicted individuals (Wilson et al., 1996), and following unlimited cocaine self-administration in rats (Parsons et al., 1995), links 5-HT dysfunction with impulsive-compulsive behavioural phenotypes. Also of relevance, 5-HT modulates sensitivity to negative and positive (reward) feedback (Bari et al., 2010), consistent with earlier theorising that tonic 5-HT activity signals average reward rate whereas phasic 5-HT codes prediction errors for future punishment (Daw et al., 2002). Thus, 5-HT plays a critical role in behavioural regulation and the processing of punishment signals. Through interactions with other neurotransmitters (e.g., DA), 5-HT dysfunction is a prime neurochemical substrate of impulsivity and compulsive drug-seeking.

FIGURE 1  Schematic sagittal sections showing the distribution of serotonin (5-HT), dopamine (DA) and noradrenaline (NA) pathways in the rat brain (far left images). Diagrams show the locations of cell bodies in the dorsal raphé nucleus (DRN), ventral tegmental area (VTA) and locus coeruleus (LC), together with their ascending projections to the forebrain. The main effects of globally increasing or decreasing 5-HT (yellow arrows) and DA (blue arrows) on different forms of impulsivity and compulsivity are summarised in the panels on the right. These manipulations typically involve selective neurochemical depletion (e.g., effected with ICV infusions of the 5-HT neurotoxin 5,7-DHT) or systemic pharmacological agents that directly or indirectly increase synaptic neurotransmission (e.g., stimulant drugs or selective reuptake inhibitors). As few or no studies have investigated the effects of reducing NA function on impulsive-compulsive behaviours, only the effects of increased NA neurotransmission are shown (orange arrows). Upward and downward arrows denote increased and decreased impulsivity and compulsivity, respectively. Horizontal bidirectional arrows indicate no clear effect of the manipulation. The red asterisk (*) indicates that studies have reported both a decrease and null effects on SIP. A dash (-) indicates that the effects are unknown. Abbreviations: 5-CSRTT, 5-choice serial reaction time task; DDT, delay-discounting task; SIP, schedule-induced polydipsia; SSRTT, stop-signal reaction time task.
Compulsivity can be operationally defined by the persistence of behaviour in the face of punishment. However, the relationship between impulsivity and compulsive drug-seeking/taking requires further discussion. Punishment is a multidimensional construct that may be experienced in different ways by people addicted to substances of abuse. For example, punishment may be experienced on different temporal scales with drug use associated with potentially immediate criminal and legal consequences versus longer-term financial loss, which often manifests long after drug use. In addition, substance-dependent individuals may compulsively seek drugs after experiencing aversive stimuli within the environment related to punishment, without actually experiencing direct punishment per se. Thus, negating signals of punishment may also capture one important dimension of compulsivity. In preclinical research studies, explicit punishment is presented in several ways. For example, mild electric foot-shock may be delivered (a) alongside a drug-taking response as in the three-criteria model of addiction-like behaviour (Belin et al., 2008; Deroche-Gamonet et al., 2004); (b) alongside a probabilistic drug seeking response, as in the seeking-taking chain task (Peloux et al., 2012) or (c) paired with a conditioned stimulus to suppress drug-seeking responses (Vanderschuren & Everitt, 2005). These procedures are based on the delivery of a foot-shock or the signalling of such with punishers delivered as a result of a particular instrumental response. Punishment is therefore immediately experienced, although it is important to note that punishment on the seeking-taking task is probabilistic in nature, and therefore, it is uncertain when the punishment will be delivered. Trait impulsivity in the 5-CSRTT predicts the persistence of cocaine-taking responses during the delivery of foot-shock (Belin et al., 2008) and also predicts higher levels of cocaine seeking after punishment induced abstinence in the seeking-taking chain task (Economidou et al., 2009). Thus, pre-existing impulsivity in the 5-CSRTT predicts compulsive responding for cocaine.

Punishment can also be modelled by the absence of an expected reward or combined with explicit punishment, for example, in such paradigms involving decision making tasks that also incorporate the risk (and delivery) of explicit punishment. For example, the risky decision-making task (RDT) combines a discounting procedure with an escalating risk of foot-shock punishment (Orsini et al., 2020; Orsini et al., 2019; Simon et al., 2009). This paradigm extends the traditional discounting paradigm (small rewards now versus larger rewards later) by the addition of a foot-shock delivered probabilistically in combination with the delivery of the large reward. Critically, the task models the discounting of delayed punishments and not delayed rewards as in the DDT. In humans, differences between discounting costs and rewards are also observed (Murphy et al., 2001), thus providing a translational impetus to dissociate the two experimentally in rodents, as in the RDT. At the behavioural level, it appears that this dissociation holds for rodents, with one report showing that discounting rewards on the DDT was unrelated to discounting risky choice on the RDT (Liley et al., 2019). One question, therefore, is how does increased levels of risky decision making, and insensitivity to delayed punishment on the RDT, relate to the self-administration of cocaine? To answer this question, Orsini and colleagues assessed performance on the RDT and then trained rats to self-administer cocaine on a short/long access paradigm (Orsini et al., 2020). Rats that showed a higher preference for the large, punished reward were more likely to escalate their cocaine intake; however, these effects were sex specific with the effect observed in females only. These results echo that observed for impulsive choice (Anker et al., 2009) and also converge with other reports demonstrating increased escalation of cocaine self-administration in rats who show deficits in the rat gambling task, an alternative measure of decision making with the risk of reward omission (Cocker et al., 2020).

Impulsive choice as measured through the delay discounting task is also linked to addiction-relevant behaviours. Thus, steeper discounting of delayed rewards, an index of increased impulsive choice, predicts increased acquisition (Perry et al., 2005) and escalation (Anker et al., 2009) of cocaine self-administration in rats. Rats with high trait levels of impulsive choice also show stronger resistance to extinction of cocaine seeking and higher rates of context-induced cocaine seeking (Broos et al., 2012). Taken together, these results suggest that both impulsive choice and impulsive action represent pre-existing vulnerability markers to the development of addiction-like behaviour. However, whereas impulsive choice may be important for the acquisition, initiation and escalation of cocaine self-administration, impulsive action is more strongly associated with compulsive cocaine-related behaviours. Molecular imaging techniques such as PET provide the unique opportunity to bridge the translational gap between rodents and humans to probe the underlying neurochemical substrates of addiction-like behaviour. In rats and humans, diminished D2/D3 receptor availability is related to increased impulsivity across multiple dimensions (Barlow et al., 2018; Buckholtz et al., 2010; Dalley et al., 2007). Further PET-derived markers include decreased glucose metabolism in the OFC and ACC of humans with SUD, assessed using [18F]-fluorodeoxyglucose (Volkow et al., 1993, 2001). Paralleling these findings, Cannella and colleagues showed that three criteria rats (rats displaying addiction-like behaviour) exhibit reduced frontal cortical glucose metabolism compared with zero criteria rats (rats displaying no addiction-like behaviour) and cocaine-naïve rats (Cannella et al., 2017). These reports and others (de Laat et al., 2018) reveal the translational utility of both longitudinal and cross-sectional PET studies to understand both vulnerability mechanisms and addiction-like behaviour, highlighting successful cross-species convergence.

As discussed throughout this review, 5-HT and DA have important and interacting roles in regulating impulsive action, impulsive choice and risky decision making (Basar et al., 2010; Winstanley et al., 2006; Yates, 2019). A potential locus for this interaction is via 5-HT neurons in the raphé nucleus which innervate the dopaminergic ventral tegmental area (Hervé et al., 1987) and substantia nigra (Clavier & Fibiger, 1977) and powerfully inhibit these regions and the terminal limbic cortico-striatal regions to which they project (Kapur & Remington, 1996). In a recent remarkable study, interactions between DA and 5-HT were investigated in seventeen non-dependent cocaine users using PET and [11C]-raclopride. 

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to image D2 receptors in the striatum (Cox et al., 2017). Acute dietary depletion of tryptophan to reduce brain 5-HT function led to greater reductions in [11C]-raclopride binding potential in response to a low intranasal dose of cocaine (an index of DA release) than when cocaine was administered alone. Augmented reductions in [11C]-raclopride binding potential were observed in dorsal regions of the anterior and posterior putamen, and bilateral caudate, and were associated with increased drug craving. These findings show that low 5-HT increases the subjective and DA releasing effects of cocaine in non-dependent drug users. Low 5-HT craving. These findings show that low 5-HT increases the subjective and DA releasing effects of cocaine in non-dependent drug users. Low 5-HT states, extending into the nigrostriatal DA system, may thus be further drivers for the development of compulsive drug-seeking in susceptible individuals, a possibility meriting further research.

In conclusion, we have discussed mainstream examples of neurochemical substrates underlying impulsive and compulsive behavioural phenotypes relevant to addiction. By continuing to research the neuromodulatory systems, a clearer understanding of the neurochemical substrates of impulsive-compulsive behaviours in addiction is expected, particularly the modulation of top-down cognitive control mechanisms by the major neurotransmitter systems.

ACKNOWLEDGEMENTS
J.A.J is supported by a Medical Research Council (MRC) Doctoral Training Programme scholarship. K.Z is supported by the Institute for Neuroscience at Cambridge University. J.W.D receives funding from GlaxoSmithKline and Boehringer Ingelheim Pharma GmbH and is a co-investigator on an MRC Programme Grant (MR/N02530X/1) with Barry J. Everitt, Trevor W. Robbins, David Belin and Amy L. Milton.

CONFLICT OF INTEREST
J.W.D. has received research grants from Boehringer Ingelheim Pharma GmbH and GlaxoSmithKline. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID
Jeffrey W. Dalley https://orcid.org/0000-0002-2282-3660

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How to cite this article: Jones JA, Zuhlsdorff K, Dalley JW. Neurochemical substrates linked to impulsive and compulsive phenotypes in addiction: A preclinical perspective. *J Neurochem*. 2021;157:1525–1546. [https://doi.org/10.1111/jnc.15380](https://doi.org/10.1111/jnc.15380)