

## REVIEW

# DOPAMINE, SEROTONIN AND IMPULSIVITY

J. W. DALLEY<sup>a,b,\*</sup> AND J. P. ROISER<sup>c</sup>

<sup>a</sup> Behavioural and Clinical Neuroscience Institute and Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK

<sup>b</sup> Department of Psychiatry, University of Cambridge, Cambridge CB2 2QQ, UK

<sup>c</sup> UCL Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR, UK

**Abstract**—Impulsive people have a strong urge to act without thinking. It is sometimes regarded as a positive trait but rash impulsiveness is also widely present in clinical disorders such as attention deficit hyperactivity disorder (ADHD), drug dependence, mania, and antisocial behaviour. Contemporary research has begun to make major inroads into unravelling the brain mechanisms underlying impulsive behaviour with a prominent focus on the limbic cortico-striatal systems. With this progress has come the understanding that impulsivity is a multi-faceted behavioural trait involving neurally and psychologically diverse elements. We discuss the significance of this heterogeneity for clinical disorders expressing impulsive behaviour and the pivotal contribution made by the brain dopamine and serotonin systems in the aetiology and treatment of behavioural syndromes expressing impulsive symptoms. © 2012 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** delay discounting, stop signal reaction time, 5-choice serial reaction time task, prefrontal cortex, orbitofrontal cortex, nucleus accumbens.

\*Correspondence to: J. W. Dalley, Behavioural and Clinical Neuroscience Institute and Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK. Tel: +44 01223 765 291; fax: +44 01223 333 564.

E-mail address: [jwd20@cam.ac.uk](mailto:jwd20@cam.ac.uk) (J. W. Dalley).

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; BD, bipolar disorder; BIS, Barratt Impulsiveness Scale; BPD, borderline personality disorder; 5-CSRTT, 5-choice serial reaction time task; DA, dopamine; 5,7-DHT, 5,7-dihydroxytryptamine; DOI, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan; DRL, differential reinforcement of low rates of responding; 5-HTT, 5-HT transporter; 5-HTTLPR, 5-HT transporter gene; HVA, homovanillic acid; MDMA, 3,4-methylenedioxymethamphetamine; NAcb, nucleus accumbens; PD, Parkinson's disease; PET, positron emission tomography; SNc, substantia nigra compacta; SNP, single nucleotide polymorphism; SSRT, stop-signal reaction time; TPH2, tryptophan hydroxylase-2; UPPS, Urgency, Premeditation, Perseverance and Sensation Seeking; VTA, ventral tegmental area.

## Contents

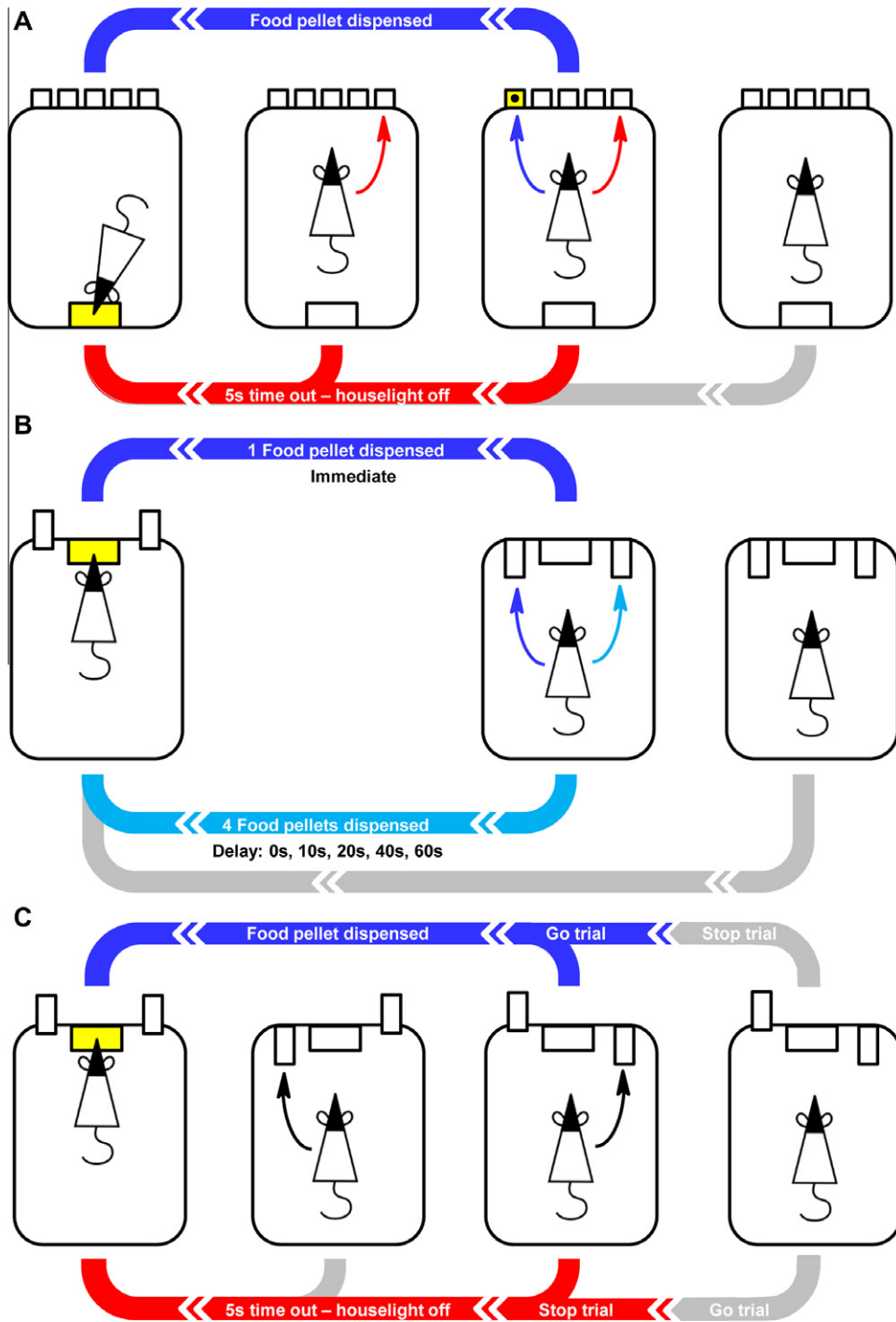
Introduction	42
The measurement of impulsivity: animals	44
The measurement of impulsivity: humans	44
Dopamine and serotonin influences on impulsivity in animals	45
The dopamine systems	45
The serotonin systems	47
Dopamine and serotonin influences on impulsivity in humans	48
The dopamine systems	49
The serotonin systems	50
Conclusions	51
Financial disclosure	52
Acknowledgements	52
References	52

## INTRODUCTION

In the broadest terms, impulsivity describes poor self-control, characterised by making decisions quickly, without forethought or regard for potential consequences (Durana and Barnes, 1993; Evenden, 1999a; Moeller et al., 2001; Winstanley et al., 2006a; Dalley et al., 2011). The importance of impulsivity in decision-making, child development and neuropsychiatric disorders has long been recognised (Hollander and Cohen, 1996).

In the past several decades, the notion that impulsivity may play a central role in the pathogenesis of neuropsychiatric disorders has become increasingly popular. Impulsivity has been proposed to contribute to a wide range of psychopathology, including: bipolar disorder (BD) (Swann, 2009); attention deficit hyperactivity disorder (ADHD) (Winstanley et al., 2006a); borderline personality disorder (BPD) (Bornovalova et al., 2005); alcohol and substance dependence (Ersche et al., 2010); pathological behaviours triggered by Parkinson's disease (PD) medication (Housden et al., 2010); as well as suicidality, a feature of several different disorders (Dougherty et al., 2004; Klonsky and May, 2010). However, the precise definition of the term "impulsivity", and how it is defined operationally, varies greatly across studies; as a result drawing clear conclusions on the influence of monoamine transmission in impulsivity is extremely challenging.

In this article we begin by outlining what is meant by the term impulsivity, in particular how it is measured in the laboratory, and how its conceptualisation has changed over time from a unitary description to a multi-factorial construct comprising several aspects of behaviour that



**Fig. 1.** Schematic representation of (A) 5-choice serial reaction time task, (B) delay discounting task and (C) stop-signal task. Each figure shows a representation, from above, of the 5-choice task (A) or operant-conditioning chamber (B, C). Blue arrows indicate correct responses and outcomes, red arrows indicate incorrect responses and outcomes and grey arrows indicate the outcome following a non-response. The 5-CSRTT requires subjects to restrain from responding while waiting for a cue predictive of reward. Trials are initiated by subjects entering a food magazine (leftmost panel). After a 5 s interval has elapsed, a brief light stimulus is presented on a random basis in one of five open apertures. A nose-poke response made *before* the onset the stimulus is classified as ‘impulsive’ or premature and results in a 5 s timeout period (2nd panel from left). A response in the illuminated aperture is deemed ‘correct’ and results in the delivery of a single reward pellet in the food magazine (3rd panel from left). Responses in a non-illuminated aperture or a failure to respond within a 5 s response window are classed as ‘incorrect’ and ‘omission’ trials and initiate a 5 s timeout period. In the delay discounting task (B), subjects make a choice between responding on a lever for an immediate, but low magnitude reward (left lever), or on a lever for a larger but delayed reward (right lever). Impulsivity is assessed by preference for the immediate low magnitude reward. In the stop-signal task (C), rats begin each trial with a nose poke in the central food magazine. The response phase of the trial begins with a left lever press. Following this, a rapid response on the right lever is classified ‘correct’ on Go trials, but classified as ‘incorrect’ on stop-signal trials (20% of trials in which a brief tone is played before the right lever press is completed). Conversely, inhibition of right lever press is classified as ‘correct’ on stop-signal trials but ‘incorrect’ on go trials.

are not necessarily related. We then review data from experiments performed in both animals and humans that support a role for the monoamine neurotransmitters dopamine (DA) and serotonin (5-HT) in influencing certain aspects of impulsivity. We end by discussing whether impulsivity remains a useful term, other than in the broadest terms, and make some recommendations for future research.

### The measurement of impulsivity: animals

In experimental animals, different aspects of impulsivity can be measured using computerised behavioural paradigms that are often based on equivalent tasks in humans (see Fig. 1). Traditionally, these are divided into paradigms that assess different aspects of response inhibition involving actions that are premature, mistimed or difficult to suppress, and paradigms that assess actions that fail to take into account other possible options or outcomes, and hence may be sub-optimal. In the latter case 'impulsive choice' is generally assessed by delay discounting tasks, in which subjects are trained to choose between small immediate rewards and larger but delayed rewards (Cardinal et al., 2001; Pothuizen et al., 2005). Impulsive subjects show delay aversion and a high preference for small immediate rewards. In the case of 'impulsive response' paradigms, subjects are trained to suppress a response made pre-potent by its association with reward. Prototypical paradigms in this category include the stop-signal reaction time task (SSRT: Eagle et al., 2008); the 5-choice serial reaction time task (5-CSRTT: Robbins, 2002); the go/no-go task (Harrison et al., 1999); and delayed response tasks such as differential reinforcement of low rates of responding (DRL: Evenden, 1999a). Note that these distinct forms of impulsivity are not dissimilar to the constructs of 'restraint' and 'cancellation', respectively, derived from the human literature and defined by the inability of an individual to withhold a strong behavioural tendency or to cancel an on-going action (Schachar et al., 2007).

The measurement of impulsive choice, which captures elements of waiting impulsivity (or delay aversion), can be empirically derived by the so-called indifference point whereby small immediate and large delayed rewards are chosen with equal frequency (Ainslie, 1975; Mazur and Coe, 1987). In a variant of this procedure the dimension of waiting is replaced by that of reinforcer uncertainty (e.g. St Onge and Floresco, 2010). Thus, in a procedurally similar manner to temporal discounting tasks, subjects trained on probabilistic discrimination tasks must choose between two response options; one delivering a smaller reward with high (often 100%) probability, the other delivering a larger reward with varying probabilities over blocks of trials (Zeeb et al., 2009). Both forms of impulsive discounting behaviour potentially involve overlapping decision processes about the relative value of delayed or uncertain rewards (Dalley et al., 2011).

Impulsive response is typically assessed in experimental animals by measuring the reaction time to stop a response that has already been initiated. This form of response inhibition is normally measured using the SSRT where subjects must restrain from responding on a small

proportion of trials when a stop-signal is presented (Eagle et al., 2008). The response to be inhibited is made pre-potent by its high frequency and fast execution and is strongly influenced by the delay between the initiation of the response and onset of the stop-signal; stopping being more difficult when the stop-signal is delayed than when it occurs immediately. As there is no clearly observable behavioural endpoint for a successful stop response, the SSRT is typically estimated within the theoretical framework of the 'race' model, which assumes that 'go' and 'stop' processes proceed independently from one another (Logan, 1994). Not dissimilar to the SSRT, the go/no-go task assesses the ability of subjects to withhold a pre-potent response on a small subset of discrete 'no-go' trials, which are signalled by a discriminative sensory cue (Harrison et al., 1999).

In both the go/no-go and SSRT paradigms an explicit signal is used to indicate a subset of trials requiring inhibition; the absence of a response on such trials is reinforced. However, in other motor inhibition tasks such as the 5-CSRTT (see Fig. 1A), there are no trials with an explicit signal to inhibit responding, nor any feedback that a trial has been successfully inhibited. The basic configuration of the 5-CSRTT is analogous to the continuous performance test in humans, a neuropsychological procedure used to assess sustained and selective attention and requires subjects (usually mice or rats) to detect the spatial location of brief visual stimuli presented in one of five recesses in an operant chamber (Robbins, 2002). Impulsivity is measured on this task by the number of premature or anticipatory responses made before the onset of the target stimulus and increases when the pre-stimulus interval is lengthened. It is related to impulsivity on DRL schedules, in which subjects are trained to withhold responding until a set delay has elapsed (Evenden, 1999a).

### The measurement of impulsivity: humans

In humans, impulsivity is most commonly measured using self-report questionnaires, including the Barratt Impulsiveness Scale (BIS), the Urgency, Premeditation, Perseverance and Sensation Seeking (UPPS) Impulsive Behaviour Scale, the Impulsiveness Venturesomeness and Empathy Questionnaire; and the Lifetime History of Impulsive Behaviours (Eysenck and Eysenck, 1991; Patton et al., 1995; Whiteside and Lynam, 2001; Schmidt et al., 2004). These questionnaires recognise the multifactorial nature of impulsivity; for example, the BIS-11 is split into three subscales, attentional, motor and non-planning impulsiveness, which arise from factor analysis (Patton et al., 1995). Nonetheless, scores on factors within each test are commonly correlated, to some extent supporting the notion of impulsivity as a unitary phenomenon.

Numerous behavioural tests of impulsivity in humans have also been proposed, in some cases mirroring those developed in experimental animals. Assessments include (among others): temporal discounting; stop-signal reaction time (Logan, 1994); information sampling tests (Kagan et al., 1964; Clark et al., 2006); the tendency to make commission errors (false alarms) or premature responses on a go/no-go or continuous performance test, sometimes expressed in the "criterion" (beta) statistic

arising from signal detection theory (Stanislaw and Todorov, 1999); and gambling or risk-taking tests (Bechara et al., 1994; Rogers et al., 1999). That quite different cognitive constructs are entailed in each of these tests suggests from the outset that quite different features of behaviour are being assessed. Temporal-discounting measures tolerance to delays for financial rewards, though typically over hypothetical timescales of days and weeks, as opposed to real timescales of seconds in studies in experimental animals. Similar to the test in rodents described above, SSRT indexes how quickly an individual is able to stop a movement once it has already been initiated. Criterion statistics assess an individual's general tendency to make a response, independent of the ability to discriminate between targets and distracters, mirroring the measurement of the ability to withhold a prepotent response on equivalent tests in animals. Performance on decision-making tests can indicate sensitivity to probability, or to financial gains and losses, similar to recently-developed tests in animals (Zeeb et al., 2009). Information sampling tests assess the degree of certainty required before a choice is made; to our knowledge no comparable tasks to these yet exist in the animal literature.

How do such behavioural measures relate to questionnaire-based indices of impulsivity, and do they themselves represent the same underlying cognitive construct? Reynolds et al. (2006) performed the most comprehensive investigation of this important question to date, taking questionnaire measures of impulsivity along with performance on tests of SSRT, go/no-go, delay discounting and risk-taking in around 100 healthy volunteers. Despite high correlations between different questionnaire measures of impulsivity, the authors reported only one statistically significant correlation between questionnaire and behavioural measures, which was below  $r = 0.3$ . Factor analysis of the behavioural measures revealed two independent latent variables: one corresponded to the "impulsive response" measures (stop signal; go/no-go); the other corresponded to the "impulsive choice" measures (delay discounting; risk taking). This pattern might not be surprising, since the respective tests loading onto each factor shared a response format (reaction times versus choices versus questionnaire), which would be predicted to reduce shared variance between the different measurement types. Nonetheless, the correlations identified were sufficiently low for the authors of this study to conclude that a unitary construct of "impulsivity" does not exist, and that "impulsive choice" and "impulsive response" behavioural measures tap into different cognitive processes.

Other studies using comparable designs have similarly failed to find any great degree of correspondence between questionnaire and behavioural measures of impulsivity (Swann et al., 2002; Lane et al., 2003; Zermatten et al., 2005; Dom et al., 2007). Some positive relationships have been reported (Moeller et al., 2002; Meda et al., 2009), especially in one study with a very large sample that included several personality questionnaires as well as a temporal-discounting questionnaire (Kirby and Finch, 2010), though even in this latter study the loading of the temporal discount  $k$  parameter was

weak. In general, the correlation coefficients linking behavioural and questionnaire measures of impulsivity rarely exceed  $r = 0.4$ , though this might be expected given the different sources of error potentially contributing to the different measurement formats. Hence, it might not be surprising that only the largest studies are able to identify statistically significant relationships between questionnaire and behavioural measures of impulsivity. However, it should be noted that studies investigating this issue using a different strategy, dividing subjects into groups according to whether they scored "high" or "low" on impulsivity questionnaires (or simply by using a median split analysis), have tended to find significant effects more consistently. For example, "high" impulsive subjects have been reported to perform worse on tests of decision-making (Crean et al., 2000; Franken et al., 2008) and to have longer SSRTs (Logan et al., 1997). Importantly, many of the above studies did not take a measurement of intelligence quotient, a potentially important confounding variable.

To summarise, impulsivity appears to be a multifactorial construct; questionnaire measurements conducted in humans may not reflect behavioural measurements in either humans or experimental animals (see Evenden, 1999b). As outlined in the rest of the review, these apparent dissociations in the measurement of impulsivity are supported by different neurochemical influences on different impulsivity subtypes.

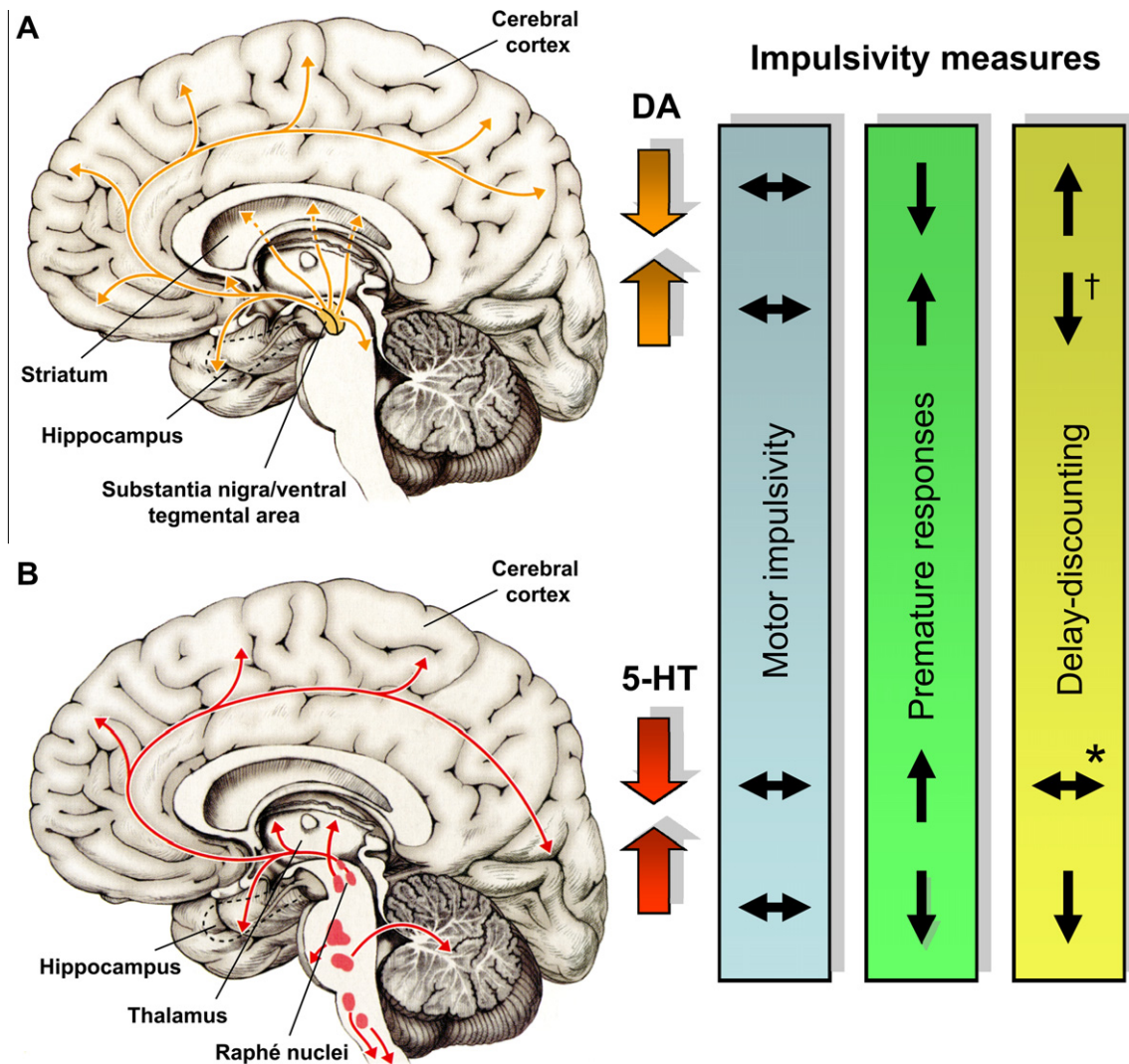
## DOPAMINE AND SEROTONIN INFLUENCES ON IMPULSIVITY IN ANIMALS

Research on the neurochemical basis of impulsivity in experimental animals began in earnest with the seminal work of Soubrié (1986). After integrating the literature on the effects of drugs on the brain serotonergic systems Soubrié concluded that 5-HT has a special role in modulating the expression of punished behaviour. Drugs which decreased 5-HT function such as anxiolytics, for example, were found to reinstate behaviour in rats that previously was suppressed by a mild electric shock (Tye et al., 1977). However, rather than suggesting a common underlying effect on anxiety, Soubrié postulated that 5-HT plays a specific role in mediating behavioural inhibition, specifically in situations of conflict between a rewarded "go" response and a punished "no-go" response. Over the last 25 years considerable progress has been made in defining the role of 5-HT in different forms of impulsivity and there is growing recognition that such behaviour is additionally and critically regulated by the neurotransmitter DA.

### The dopamine systems

DA inputs to the forebrain originate from cell bodies located in the substantia nigra zona compacta and ventral tegmental area (see Fig. 2A) giving rise to the nigrostriatal, mesolimbic and mesocortical systems (Dahlstrom et al., 1964). Based on the clinical efficacy of stimulant drugs that boost brain DA function it is axiomatic to postulate that DA plays a significant role in the aetiology and





**Fig. 2.** Distribution of dopamine (A) and serotonin (B) neurotransmitters in the human brain. Diagrams show the distribution of cell bodies in the ventral tegmental area/substantia nigra (DA) and raphe nuclei (5-HT) together with their ascending projections (arrows) to structures in diencephalon and telencephalon. The main effects of depleting or boosting DA (orange arrows) and 5-HT (red arrows) neurotransmission in the brain on motor impulsivity (e.g. SSRT), premature responses (e.g. 5-choice serial reaction time task) and delay discounting are summarised in the panels on the right, which are based on a consensus of pre-clinical and clinical experimental psychopharmacology studies. Upward and downward arrows denote increased and decreased impulsivity, respectively. Horizontal bidirectional arrows indicate no effect of the manipulation unless otherwise specified. Note that complexities exist in the effects of DA and 5-HT receptor agonists and antagonists on each form of impulsivity that depend in some cases on baseline variation in impulsive behaviour (see text for more details). <sup>†</sup>L-DOPA increases delay discounting impulsivity in humans whilst amphetamine and other stimulants increase impulsivity when delays to reinforcement are unsignalled. <sup>\*</sup>5-HT depletion increases delay discounting in humans but this effect is controversial in animals. Figure adapted from Fig. 4.3 and Fig. 4.5; *Biological Psychology: An Introduction to Behavioural, Cognitive, and Clinical Neuroscience*, Fifth Edition (Eds. S. Marc Breedlove, Mark R. Rosenzweig and Neil V. Watson), Sinauer Associates, Inc.

treatment of impulsivity symptoms in ADHD (Solanto et al., 2001; Kollins and March, 2007; Swanson and Volkow, 2009). Research in animals supports this view. In the SSRT, the stimulant drugs d-amphetamine and methylphenidate improve stopping performance but only in rats that perform sluggishly at baseline (Feola et al., 2000; Eagle and Robbins, 2003; Eagle et al., 2007). The same stimulant drugs also generally reduce impulsivity on delay discounting procedures (Richards et al., 1999; Wade et al., 2000; Isles et al., 2003; Winstanley et al., 2003; van Gaalen et al., 2006; Adriani et al., 2007; Floresco et al., 2008) although there have been notable conflicting results as well (e.g. Helms et al., 2006; Stanis

et al., 2008; Slezak and Anderson, 2009; Wooters and Bardo, 2011) and there is evidence questioning the special role of DA in this process. For example, the ability of amphetamine to reduce impulsivity on the delay-discounting procedure is lost in rats depleted of brain 5-HT (Winstanley et al., 2003; Helms et al., 2006). Such interactions between the DA and 5-HT systems are a recurring theme in the expression of impulsive behaviour (Winstanley et al., 2005; Oades, 2007). Moreover, the effects of stimulants on delay discounting impulsivity have been shown to depend upon whether delayed rewards are signalled or not. Thus, amphetamine decreases impulsivity when delays are signalled (i.e. promotes

choice for delayed rewards) but increases impulsivity when delays are unsignalled (Cardinal et al., 2000). This effect is hypothesised to reflect the potentiating effects of stimulants on cues predicting delayed reinforcement (Cardinal et al., 2000) and may explain some of the discrepancies in the literature on this topic.

Contrasting with the findings above, when the delay to reward is fixed and constant, as is generally the case in the 5-CSRTT, stimulant drugs invariably *increase* impulsivity (Cole and Robbins, 1987; van Gaalen et al., 2006; Blondeau and Dellu-Hagedorn, 2007). This effect can be reversed in a less common variant of the 5-CSRTT when premature responses are recorded but not punished (Bizarro et al., 2004) as well as in animals showing high baseline levels of premature responses (Puumala et al., 1996). Arguably this pattern of effects is consistent with the rate dependency model used to explain the baseline dependent effects of stimulant drugs in children with ADHD (Robbins and Sahakian, 1979). But in the case of methylphenidate the observed bimodal effects on impulsivity may additionally be generated by differential effects on noradrenaline and DA availability in the nucleus accumbens. Low doses of this compound, which affect locus coeruleus noradrenergic activity (Devilbiss and Berridge, 2006), decrease impulsivity on the 5-CSRTT (Pattij et al., 2007), similar to selective noradrenaline reuptake inhibitors (Robinson et al., 2008b; Pattij et al., 2012). However, higher doses increase both DA and noradrenaline (Kuczenski and Segal, 1997; Gerasimov et al., 2000) with increases in DA release thought most likely to underscore the increase in impulsivity (Cole and Robbins, 1989; van Gaalen et al., 2006).

While the evidence reviewed above questions a singular involvement of DA in impulsivity it is abundantly clear that specific DA receptors play an important modulatory role in the expression of such behaviour. For example, the D<sub>2/3</sub> antagonist eticlopride when infused in the nucleus accumbens core completely blocked the impulsive behaviour induced by amphetamine on the 5-CSRTT (Pattij et al., 2007). A similar striking result was obtained in rats made impulsive by selective lesions of the PFC (Pezze et al., 2009). Such findings match recent findings from Besson et al. (2010) showing impulsivity to be alleviated by core infusions of the D<sub>2/3</sub> antagonist nafadotride but *exacerbated* by infusions of the same compound in the adjacent shell sub-region. However, some key challenges lie ahead in understanding the significance of these results. First, it is unclear exactly what role D<sub>2</sub> and D<sub>3</sub> receptors play as most drugs tested have high affinity for both receptors. Second, identifying the synaptic location of the critical DA receptor (i.e. pre- or post-synaptic) is virtually impossible *in vivo* and would require transgenic approaches not yet available in rats (e.g. Bello et al., 2011). Third, the pharmacological findings discussed above need to be integrated with our earlier discovery that D<sub>2/3</sub> receptors are significantly *reduced* in number in the ventral striatum (collectively the core and shell of the nucleus accumbens) of trait impulsive rats (Dalley et al., 2007).

Resolving these questions has implications for impulsive behaviour assessed on delay discounting procedures and the SSRT, which is also regulated by DA receptors.

Just as amphetamine decreases impulsive decision-making on delay discounting tasks (see above), systemic administration of D<sub>1</sub> and D<sub>2</sub> receptor antagonists increase delay discounting impulsivity (i.e. choices of sooner, smaller rewards: Wade et al., 2000; van Gaalen et al., 2006; Floresco et al., 2008). This effect may be mediated by blockade of D<sub>1</sub> receptors in medial prefrontal cortex (Loos et al., 2010) and by D<sub>1</sub> and D<sub>2</sub> receptors in the orbitofrontal cortex (Zeeb et al., 2010). Interestingly, the effects of D<sub>1</sub> and D<sub>2</sub> receptor antagonists on impulsivity were only observed when an explicit cue to the larger delayed reward was presented (Cardinal et al., 2000; Zeeb et al., 2010). Through conditioning such cues evidently engage DA signalling in orbitofrontal cortex and increase preference of subjects' for larger delayed rewards (i.e. they reduce impulsivity). In the absence of such cues, choice may be governed preferentially by D<sub>1</sub> receptors in medial prefrontal cortex instead. Such findings resonate with the demonstration that increasing DA transmission at D<sub>1</sub> and D<sub>2</sub> receptors favours choice towards larger, probabilistic rewards, whereas D<sub>3</sub> receptor activation has the opposite effect (St Onge and Floresco, 2009). Intriguingly, DA may act via D<sub>2</sub>-like receptors to encourage risky decisions during so-called near-miss events when rewards are tantalizingly close (Winstanley et al., 2011).

DA is implicated in the modulation of SSRT from the efficacy of psychostimulants in ADHD (Tannock et al., 1989; Feola et al., 2000). Even so, when given systemically, neither D<sub>1</sub> nor D<sub>2</sub> receptor antagonists appear to affect SSRT in rats (Eagle et al., 2007). At first glance such findings may seem surprising but an increasingly prominent role for noradrenaline in response inhibition has been established (Chamberlain et al., 2006; Eagle et al., 2008), and this effect is thought to have its origins within prefrontal cortical circuitry (Bari et al., 2011). At the level of the dorsomedial striatum (homologous to the caudate in humans), D<sub>1</sub> and D<sub>2</sub> receptors *are* reported to modulate SSRT but in an opposing manner (Eagle et al., 2011), thereby implicating competing interactions between the direct (D<sub>1</sub> receptor modulated striatonigral neurons) and indirect (D<sub>2</sub> receptor striatopallidal neurons) pathways in response inhibition.

### The serotonin systems

The primary ascending serotonergic neurons originate from the median and dorsal raphe nuclei (see Fig. 2B) (Dahlstroem and Fuxe, 1964; Azmitia and Segal, 1978) and make extensive connections with a number of structures involved in the regulation of impulse control, principally the ventral tegmental area (VTA), substantia nigra (SNc), nucleus accumbens (NAcb), hippocampus, amygdala, and prefrontal cortex (Dalley et al., 2011; Hayes and Greenshaw, 2011). At the synaptic level 5-HT regulates the activity of many neurotransmitters including DA-containing neurons in the VTA and SNc (McMahon et al., 2001; Fink and Gothert, 2007; Bubar et al., 2011) and interactions between 5-HT and DA reportedly contribute to the expression of certain categories of impulsivity (Winstanley et al., 2006a) and may even have a bearing on the aetiology of ADHD (Oades, 2002, 2007).

Early studies in rats assessed the effects on impulsivity of globally depleting 5-HT in the brain with the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) infused directly into the cerebro-ventricular system. Depletion of 5-HT was accompanied by a selective increase in premature responding on the 5-CSRTT (Harrison et al., 1997) and impaired behavioural restraint on a go/no-go task (Harrison et al., 1999). Consistent with these findings, rats administered the 5-HT depleting stimulant, parachloroamphetamine, showed impairments on a go/no-go task (Masaki et al., 2006) and global 5,7-DHT lesions increased impulsivity on a variant of the 5-CSRTT (Winstanley et al., 2004). Thus, manipulations that reduce 5-HT function impair the capacity of subjects to inhibit the initiation of a pre-potent response, a tendency that is exaggerated when subjects must avoid responding on explicit no-go trials.

However, the modulation of impulsivity by 5-HT appears to be heterogeneous and selective for 'action restraint' rather than delay discounting impulsivity or SSRT (Eagle et al., 2008). Thus, 5-HT depletion studies in rats have failed to provide convincing evidence that 5-HT contributes to the sensitivity of subjects to delayed (Winstanley et al., 2003, 2004) or probabilistic (Mobini et al., 2000b) rewards, but the impact of 5-HT loss on temporal discounting is controversial with some earlier studies reporting increased impulsivity in rats following selective 5-HT depletion (Wogar et al., 1993; Bizot et al., 1999; Mobini et al., 2000a). The reasons for this divergence of results are unclear but are probably related to differences in experimental procedures (see Winstanley et al., 2006a for further discussion of this issue). A much clearer set of findings has been reported in relation to the SSRT where neither 5-HT depletion (Eagle et al., 2009) nor selective serotonin reuptake inhibitors (Bari et al., 2009) had any major effect on SSRT, similar to results found in humans (see below and Clark et al., 2005). This suggests that 5-HT is critical for some forms of behavioural inhibition but not others.

Further insights have come from the effects of selective 5-HT agonists and antagonists, which exert both inhibitory and excitatory effects on impulsivity in rats. The 5-HT<sub>2A/2C</sub> agonist ( $\pm$ )-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan (DOI) administered systemically increases impulsivity on both reaction time and delay discounting tasks, an effect blocked by 5-HT<sub>2A</sub> antagonists (Evenden and Ryan, 1999; Koskinen et al., 2000; Blokland et al., 2005; Hadamitzky et al., 2009). The selective 5-HT<sub>2C</sub> antagonist SB242084 produced qualitatively similar effects to DOI on the 5-CSRTT following both systemic (Winstanley et al., 2004; Fletcher et al., 2007) and intra-NAcb (Robinson et al., 2008a) administration while the 5-HT<sub>2A/2C</sub> antagonist SER082 had no effect on 5-CSRTT impulsivity but decreased impulsive responding on the delay discounting task (Talpos et al., 2006). In a related study the selective 5-HT<sub>2A</sub> antagonist M100907 dose-dependently reduced impulsivity on the 5-CSRTT (Winstanley et al., 2004; Fletcher et al., 2007). The main brain site of this effect is probably the NAcb (Robinson et al., 2008a) but 5-HT<sub>2A</sub> receptor antagonism in the prefrontal cortex has also been shown to block impulsiveness

evoked on the 5-CSRTT by NMDA receptor antagonism in the PFC (Carli et al., 2006). The opponent nature of the serotonergic modulation of impulsivity is further exemplified by the effects of 5-HT<sub>1A</sub> agonist 8-OH-DPAT which decreased impulsivity on a choice reaction time task (Blokland et al., 2005) but increased delay discounting impulsivity. In the case of the selective 5-HT reuptake inhibitors, however, the main effects are to reduce impulsivity on *both* the 5-CSRTT and the delay discounting task (Wolff and Leander, 2002; Baarendse and Vanderschuren, 2012; Dalley et al., unpublished observations).

Further converging evidence for an involvement of 5-HT in impulsivity was obtained through the direct measurement of 5-HT during performance of rats on a simplified variant of the 5-CSRTT which loads on response inhibition (Dalley et al., 2002) and a delay discounting task (Winstanley et al., 2006b). We found somewhat paradoxically that premature responses were positively correlated with tonic extracellular levels of 5-HT in the medial PFC, a result seemingly at odds with the effects of globally reducing or increasing 5-HT function described above but consistent with an earlier study showing up-regulated 5-HT function in the PFC of impulsive rats (Puumala and Sirvio, 1998). The basis of this paradox is unclear but suggests that sub-cortical sites may be responsible for the effects of global 5-HT depletion on impulsivity, possibly through interactions with the mesolimbic DA system (Robinson et al., 2008a). In a more recent study extracellular levels of 5-HT were measured in the PFC and orbitofrontal cortex of rats on a delay discounting task (Winstanley et al., 2006b). Although hampered by the poor temporal resolution of intracerebral microdialysis it was striking that 5-HT levels increased significantly in the medial PFC, but not the OFC during task performance. Arguably the 5-HT response in the medial PFC may be a neurochemical corollary of increased neuronal firing in the raphe nucleus reported recently in rats when rewards are delayed (Miyazaki et al., 2011). However this does not explain why rats with increased 5-HT tonus in the PFC are impulsive on tasks that load on 'waiting' (Dalley et al., 2002; Robinson et al., 2009) unless one assumes that phasic 5-HT signalling in the PFC is somehow compromised in these subjects. In any case the dissociation between medial and orbital frontal 5-HT release during delay discounting behaviour suggests prominent functional heterogeneity in the fronto-cortical 5-HT systems.

## DOPAMINE AND SEROTONIN INFLUENCES ON IMPULSIVITY IN HUMANS

While the range of experimental techniques and pharmacological interventions available to study the neurochemical basis of impulsivity in humans is considerably more limited than in experimental animals, neurochemical abnormalities in clinical syndromes associated with impulsivity provide importantly complementary insights into the understanding gained from the preclinical data discussed above. Although invasive techniques such as *in vivo* microdialysis and cyclic voltammetry to measure brain monoamine levels cannot be performed in humans for



ethical reasons, methods such as positron emission tomography (PET) have led to great insights into the neurochemistry of impulsivity, adding to data from experimental psychopharmacology studies and the measurement of monoamines or their metabolites in urine, plasma or CSF. Despite such experimental limitations, the picture emerging from studies of DA, 5-HT and impulsivity in humans are, on the whole, remarkably consistent with the animal literature in that different types of impulsivity appear to be modulated differentially by the different monoamines.

### The dopamine systems

Possibly the most dramatic clinical evidence for an influence of DA transmission on impulsivity in humans is the pronounced behavioural change observed in a small proportion (~10%) of patients with PD following the administration of DA replacement therapies such as levodopa and agonists at the D<sub>2</sub> and D<sub>3</sub> receptors: examples include pramipexole, ropinirole and bromocriptine. In these vulnerable patients a number of behavioural syndromes have been identified, some, but not all of which meet criteria for Impulse Control Disorders, including: compulsive gambling and shopping; hypersexuality; and binge eating (O'Sullivan et al., 2009).

Somewhat surprisingly, on behavioural tests of reward processing (Housden et al., 2010; Rossi et al., 2010; Voon et al., 2010a), PD patients who develop these behaviours do not behave differently to matched healthy volunteers. By contrast, on tests of delay discounting there is good evidence of impatience to delayed rewards (i.e. increased delay discounting) in these PD patients, at least in the "on" medication state (Housden et al., 2010; Voon et al., 2010b). Hence, these data suggest that D<sub>2</sub>/D<sub>3</sub> receptor signalling contributes to at least some aspects of impulsivity, consistent with a report that levodopa increased in delay discounting in healthy volunteers, an effect evident in every participant (Pine et al., 2010). However, in another study the D<sub>2</sub>/D<sub>3</sub> agonist pramipexole was reported to have no impact on delay discounting, at least at low-to-moderate doses (Hamidovic et al., 2008), and others reported no effects of L-dopa on SSRT performance (Overtoom et al., 2003; Obeso et al., 2011).

A role for disrupted DA transmission in some clinical aspects of impulsivity is also supported by studies of ADHD, though the dominant explanatory framework differs from that outlined above. Since stimulant medications, such as methylphenidate and amphetamine, induce increases in synaptic DA (Kuczenski and Segal, 1997), an influential model holds that impulsivity in these individuals is related to lower pre-treatment DA transmission, at least in the striatum. Consistent with this notion, individuals with ADHD have reduced CSF levels of the DA metabolite homovanillic acid (HVA: Shaywitz et al., 1977), and reduced urinary excretion (Hanna et al., 1996); paradoxically, however, higher HVA has been associated with better response to medication in ADHD (Castellanos et al., 1996).

PET studies of drug-naïve ADHD patients have also been used to examine this hypothesis, though conflicting findings have been reported. In one study, greater

methylphenidate-induced DA release, measured using raclopride displacement, was reported in medication-naïve ADHD patients relative to healthy volunteers (Rosa-Neto et al., 2005). In the same sample, there was a positive relationship between methylphenidate-induced DA release and commission errors at baseline (Rosa Neto et al., 2002). However, another study reported the opposite result, finding that adults with ADHD had reduced methylphenidate-induced DA release relative to healthy volunteers (Volkow et al., 2007). A recent study from this group also reported lower DAT binding as well as reduced D<sub>2</sub>/D<sub>3</sub> binding in a large sample of adults with ADHD (Volkow et al., 2009). Therefore the mechanism by which DA transmission contributes to the pathogenesis and treatment of impulsivity in ADHD remains unclear.

Experimental psychopharmacology studies using the stimulants amphetamine and methylphenidate to investigate the role of DA transmission in impulsivity have also generated conflicting results. This may be driven in part by their lack of specificity for the DA system, and likely concomitant release of other transmitters such as 5-HT. This complexity is highlighted by theories of ADHD that propose that the balance between 5-HT and DA transmission is critical in the aetiology of this disorder (Oades, 2002; Winstanley et al., 2005). de Wit and colleagues (de Wit et al., 2000, 2002) reported that a high dose (20 mg) of amphetamine improved SSRT, commission errors and delay discounting in healthy volunteers; however, other studies reported conflicting results (Kelly et al., 2006; Acheson and de Wit, 2008). Methylphenidate has been found to reduce some, but not all, laboratory measures of impulsivity in ADHD patients (Aron et al., 2003; Scheres et al., 2003; Turner et al., 2005; DeVito et al., 2008, 2009). One explanation for this pattern of results is an "inverted-U" model of response, in which an optimal amount of DA transmission is required to adequately perform a given cognitive process (Cools and D'Esposito, 2011). This model may explain why studies using acute tyrosine and phenylalanine depletion, a procedure by which DA synthesis can be decreased by restricting dietary intake of these amino acids (Montgomery et al., 2003; Leyton et al., 2004), have generally not reported reliable effects on any measures of impulsivity (Harmer et al., 2001; McLean et al., 2004; Lythe et al., 2005; Roiser et al., 2005).

An individual's position on the 'inverted-U', and hence whether a hypothetical increase in DA transmission might be likely to make them more or less impulsive or may be related to environmental factors (e.g. prior stimulant abuse) or genetic factors (e.g. polymorphisms in genes affecting DA transmission), or possibly a combination of the two. Hamidovic and colleagues (Hamidovic et al., 2009) reported that individuals homozygous for the A allele at a single nucleotide polymorphism (SNP) in the D<sub>2</sub> receptor gene (rs12364283), which results in reduced transcription relative to the G allele (Zhang et al., 2007; SNPs termed T and C respectively in that report), performed less impulsively on the SSRT following amphetamine administration, while the converse was true in G allele carriers. Also consistent with an inverted-U account, possession of the low-transcription A allele was also



associated with more impulsive performance under placebo.

Recent PET studies have confirmed this pattern, reporting that lower  $D_2/D_3$  autoreceptor binding (using [ $^{18}\text{F}$ ]fallypride) in the midbrain was associated with greater questionnaire-measured impulsivity (Buckholtz et al., 2010), replicating an earlier finding in the caudate in stimulant-dependent individuals (Lee et al., 2009). Stimulant-dependent individuals, who have lower  $D_2/D_3$  binding relative to healthy volunteers (Volkow et al., 2001), are also reliably more impulsive, whether assessed through behavioural (Monterosso et al., 2005; Clark et al., 2006; Hoffman et al., 2006) or questionnaire (Ersche et al., 2010) measures. Importantly, increased impulsivity is likely not solely a consequence of stimulant use, since increased questionnaire-measured impulsivity is also present in first-degree relatives of stimulant users (Ersche et al., 2010). In the study by Buckholtz and colleagues discussed above there was also a positive correlation between questionnaire-measured impulsivity and amphetamine-induced DA release in the striatum, assessed using raclopride displacement (Buckholtz et al., 2010), though this finding conflicts with an earlier study, which reported the opposite result (Oswald et al., 2007). Similarly, elevated striatal DA release has been reported in PD patients with treatment-induced pathological gambling (Steeves et al., 2009).

In summary the relationship between DA transmission and impulsive behaviour is complex, and contradictory results have been reported. The majority of the questionnaire-based and clinical evidence (i.e. studies in Parkinson's disease patients with treatment-induced impulsivity, substance-dependence and at least some in ADHD), supports an account by which abnormal transmission at the  $D_2$  and  $D_3$  receptors contributes to impulsivity. However, the evidence from ADHD muddies the waters somewhat, and the apparently contradictory therapeutic effects of DA-releasing stimulant drugs remain difficult to understand. One possible explanation is that there is an inverted-U response between DA levels; additionally, consideration of the critical modulatory role of 5-HT may provide some resolution of this paradox (Oades, 2007). Alternatively, different aspects of impulsivity may contribute to different clinical syndromes. This latter explanation is partly supported by psychopharmacological investigations, in which different laboratory measures of impulsivity appear to be differentially sensitive to experimental DA manipulations: for example, L-dopa appears to increase delay discounting (Pine et al., 2010), but has no effect on SSRT performance (Overtoom et al., 2003; Obeso et al., 2011). It is also possible that clinical syndromes expressing impulsive symptoms result from regional abnormalities in DA transmission; for example targeting differentially the prefrontal and striatal networks.

### The serotonin systems

The majority of the clinical data relating 5-HT and impulsivity have been provided by investigations of suicide. Early studies reported lower CSF and plasma 5-HIAA levels (Asberg et al., 1976, 1986) as well as blunted prolactin response to fenfluramine (Mann et al., 1992) in both

suicide attempters and completers, as well as lower brain 5-HT, 5-HT transporter (5-HTT) and abnormal 5-HT receptor binding at post-mortem in suicide completers (Mann et al., 2001). Suicide attempters score higher on questionnaire measures of impulsivity (Klonsky and May, 2010) as well as certain behavioural measures, specifically premature responses (Horesh, 2001; Dougherty et al., 2004; Swann et al., 2005). Importantly this association occurs across a variety of different psychopathologies, including depression, bipolar disorder and schizophrenia. Research into individuals with antisocial personality disorder categorised according to whether their violent behaviour was aggressive or non-aggressive has revealed similar results, with impulsive aggressive individuals reported to have lower levels of CSF 5-HIAA (Linnoila et al., 1983) and blunted prolactin response to fenfluramine (Coccaro et al., 1989; Dolan et al., 2002). This latter effect has also been reported in first degree relatives of individuals with antisocial personality disorder (Coccaro et al., 1994), in individuals with borderline personality disorder (Soloff et al., 2003), and in impulsive men without a personal or familial psychiatric history (Manuck et al., 1998).

The link between 5-HT and impulsivity in suicide attempters has also been assessed more directly using PET, where reduced 5-HTT levels were reported specifically in more impulsive suicide attempters as assessed by questionnaire measures (Lindstrom et al., 2004; Ryding et al., 2006). At first glance, this relationship, which was not evident in healthy volunteers, may seem paradoxical as, assuming that the same number of 5-HT terminals are present, reduced 5-HTT should increase synaptic 5-HT; however, it is also possible that this finding may reflect a reduced density of 5-HT terminals. A similar reduction in 5-HTT binding in impulsive aggressive individuals has also been reported (Frankle et al., 2005). Another link between suicide and 5-HT, though more indirect, comes from reports of small but statistically significant increased rates of suicide in depressed adolescents prescribed SSRIs (Hetrick et al., 2007). Again, this finding is somewhat inconsistent with other data, since the pharmacological action of SSRIs is to increase 5-HT transmission. Moreover, a small number of studies reported that SSRIs reduced clinical measures of impulsivity in patients with personality disorders (Soloff, 1997; Butler et al., 2010; Silva et al., 2010), though others found no such beneficial effect (Moeller et al., 2001; Rinne et al., 2002).

The most widely utilised experimental technique to investigate the role of 5-HT transmission in impulsivity in humans is acute tryptophan depletion. Similar to acute tyrosine and phenylalanine depletion, participants ingest an amino acid mixture selectively lacking tryptophan, the precursor to 5-HT, resulting in a robust reduction in synthesis (Williams et al., 1999). Numerous studies have reported that acute tryptophan depletion increases a variety of behavioural measures of impulsivity as assessed using a variety of measures, including: premature responses (LeMarquand et al., 1998, 1999; Walderhaug et al., 2002, 2007; Booij et al., 2006; Dougherty et al., 2007); impaired conditioned suppression (Crockett et al., 2009; Robinson et al., 2012); and delay discounting

(Crean et al., 2002; Schweighofer et al., 2008). However, consistent with data in experimental animals, tryptophan depletion has generally not been found to impair SSRT (Clark et al., 2005), other than possibly in individuals with a family history of impulse control disorders (Crean et al., 2002). The reported effects of tryptophan depletion on risky decision-making have been inconsistent (Rogers et al., 1999; Anderson et al., 2003; Talbot et al., 2006).

A few studies have investigated the effect of boosting 5-HT transmission on impulsivity, using either SSRIs or fenfluramine; unfortunately this latter compound is no longer available for research in humans following its withdrawal from the market due to concerns over heart disease. Fenfluramine was found to reduce delay discounting in males with (Cherek and Lane, 1999, 2001) but not those without (Cherek and Lane, 2000) a history of conduct disorder. Similar results were reported for chronic SSRI treatment (Cherek et al., 2002). The 5-HT<sub>1A</sub> agonist buspirone has not been found to alter impulsivity in humans (Chamberlain et al., 2007), but the 5-HT<sub>2A</sub> antagonist quetiapine was found to decrease both questionnaire-measured impulsivity and Stroop interference in individuals with borderline personality disorder (Van den Eynde et al., 2008).

There is a substantial literature investigating cognitive deficits in recreational users of the drug 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'), which acutely releases but may in the long term deplete 5-HT (see Green et al., 2003 for a review). Many of these studies also included assessments of impulsivity. However, such studies are complicated by the potential for pre-existing differences between groups or the possible impact of drugs other than ecstasy. Like other drug users, ecstasy users score higher than non-drug-using controls on questionnaire-based impulsivity measures (Morgan, 1998; Morgan et al., 2002; Butler and Montgomery, 2004; Schilt et al., 2010), and also some behavioural measures (Morgan et al., 2006; Quednow et al., 2007). These group differences have even been observed in chronic ecstasy users with minimal exposure to other drugs (Halpern et al., 2004, 2011). It is possible that this association may reflect pre-existing differences between groups, since recreational users of drugs other than ecstasy also tend to have elevated scores on such questionnaires (Roiser et al., 2007). Indeed, in one study ecstasy users performed less impulsively than cannabis users, and similarly to non-drug-using controls, on a test of information-sampling impulsivity (Clark et al., 2009).

A number of studies have examined whether functional polymorphisms impacting on 5-HT transmission may influence impulsivity in humans. A polymorphism in the 5-HT transporter gene (5-HTTLPR), which alters transcription *in vitro* (Hu et al., 2006) and prolactin response to fenfluramine *in vivo* (Reist et al., 2001) has been examined most frequently. The *s* allele at this locus is believed to result in reduced 5-HT transmission relative to the *l* allele. Some studies have reported that the *s* allele is over-represented in individuals with antisocial personality disorder (Sakai et al., 2006). The *s* allele has also been associated with increased premature responding in men (Walderhaug et al., 2010), though conflicting findings

have been reported (Lage et al., 2011; Malloy-Diniz et al., 2011).

Other studies have examined polymorphisms in the tryptophan hydroxylase-2 (TPH2) gene. One found an association with SSRT in healthy volunteers (Stoltenberg et al., 2006); another reported an association with questionnaire-measured impulsivity in adolescents with ADHD, though the polymorphisms implicated did not overlap with those identified in the former study (Oades et al., 2008). However, one of the TPH2 polymorphisms reported in the latter study (rs6582071) has been associated with reduced brain 5-HT synthesis in humans (Booij et al., 2011), lending credence to this association. Finally, a recent study reported that a polymorphism in the 5-HT<sub>2B</sub> gene, which is exclusive to the Finnish population and completely blocks expression of the receptor, is associated with antisocial and borderline personality disorders (Bevilacqua et al., 2010). While no behavioural or questionnaire measures of impulsivity were administered to the patients in this study, follow-up studies in 5-HT<sub>2B</sub> knockout mice in the same paper revealed elevated impulsivity on a delay discounting measure.

In summary, while fewer studies are available, the human experimental and clinical data relating abnormal 5-HT transmission to impulsivity are quite consistent: most studies report that impulsivity is related to lower 5-HT transmission. However, as with the literature examining DA, not all measures of impulsivity are equally affected. Few studies of specific 5-HT receptors, either through psychopharmacological or PET investigations, have been reported, and more work is needed in this area.

## CONCLUSIONS

The clinical and preclinical data reviewed above are notable for their consistency. First, as outlined in the introduction, it is clear that "impulsivity" is not a single psychological construct. As noted by numerous previous authors (Evenden, 1999b; Moeller et al., 2001; Winstanley et al., 2004), there are several different dimensions of impulsivity, with many commonalities between the clinical and preclinical literature. For example, 5-HT depletion, whether via acute tryptophan depletion in humans or selective neurotoxic lesions in rats, appears to have little effect on certain forms of motoric inhibitory control (e.g. as measured by the SSRT), but reliably increases the likelihood of premature responding. SSRT performance is similarly unaffected by DA agonists and L-dopa in humans, and when administered systemically in rats, the same drugs increase delay discounting. Together with the dissociations noted in factor analyses of human behavioural data, these findings strongly indicate that "impulsivity" is a multi-faceted phenomenon.

Second, it is increasingly clear, especially from preclinical data, that a simple monotonic influence of either DA or 5-HT on any given aspect of impulsivity is unlikely. Indeed in the case of DA, both clinical and preclinical data suggest that "inverted-U" shape curve may exist. Moreover, the diversity of effects of agonists and antagonists at receptor subtypes of these two monoamines is striking:

for example, the selective 5-HT<sub>2C</sub> antagonist SB242084 increases premature responses on 5-CSRTT, while the selective 5-HT<sub>2A</sub> antagonist M100907 reduces impulsivity on the same measure (Winstanley et al., 2004; Fletcher et al., 2007). However, further work is needed in human studies to assess whether similar dissociations can be identified.

Finally, though a great deal of research over the past decade has focused on the role of DA in impulsivity, a return to 5-HT seems warranted. In particular it will be important to characterise further the nature of interactions between DA and 5-HT in influencing different types of impulsivity (Winstanley et al., 2005; Oades, 2007). Such research might help to resolve the paradox of why DA-releasing stimulant medications improve symptoms of ADHD, while at the same time drugs that boost DA transmission (agonists or L-dopa) appear to *increase* impulsivity, most dramatically in the case of medication-induced side-effects in PD. At the same time, it must be appreciated that other neurotransmitters also affect impulsivity. For example, SSRT performance in humans is modulated by manipulations of the noradrenergic system (Chamberlain and Sahakian, 2007), mu-opioid receptor function predicts impulsivity both in humans (Love et al., 2009) and mice (Olmstead et al., 2009), whilst GABA levels in dorsolateral prefrontal cortex are reportedly decreased in impulsive individuals (Boy et al., 2011). Improving our understanding of the interactions between these transmitters, and providing a more cognitively-informed nosology of impulsivity, may provide important insights into the aetiology of highly disabling syndromes such as ADHD, stimulant dependence and bipolar disorder.

## FINANCIAL DISCLOSURE

J.P.R. is a consultant for Cambridge Cognition.

*Acknowledgements*—Supported by the MRC (JD: G0701500; JR G0901275) and by a joint award from the MRC and Wellcome Trust to the Behavioural and Clinical Neuroscience Institute at Cambridge University. Fig. 1 was produced by Dr. Dawn Eagle, Department of Experimental Psychology, Cambridge University, and by Patrick (Dylan) Rich, Howard Hughes Medical Institute, Janelia Farm Research Campus, Ashburn, USA.

## REFERENCES

- Acheson A, de Wit H (2008) Bupropion improves attention but does not affect impulsive behavior in healthy young adults. *Exp Clin Psychopharmacol* 16:113–123.
- Adriani W, Canese R, Podo F, Laviola G (2007) 1H MRS-detectable metabolic brain changes and reduced impulsive behavior in adult rats exposed to methylphenidate during adolescence. *Neurotoxicol Teratol* 29:116–125.
- Ainslie G (1975) Specious reward: a behavioral theory of impulsiveness and impulse control. *Psychol Bull* 82:463–496.
- Anderson IM, Richell RA, Bradshaw CM (2003) The effect of acute tryptophan depletion on probabilistic choice. *J Psychopharmacol* 17:3–7.
- Aron AR, Dowson JH, Sahakian BJ, Robbins TW (2003) Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 54:1465–1468.
- Asberg M, Nordstrom P, Traskman-Bendz L (1986) Cerebrospinal fluid studies in suicide. An overview. *Ann N Y Acad Sci* 487:243–255.
- Asberg M, Traskman L, Thoren P (1976) 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Arch Gen Psychiatry* 33:1193–1197.
- Azmitia EC, Segal M (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *J Comp Neurol* 179:641–667.
- Baarendse PJ, Vanderschuren LJ (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. *Psychopharmacology* 219:313–326.
- Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW (2009) Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology (Berl)* 205:273–283.
- Bari A, Mar AC, Theobald DE, Elands SA, Oganya KC, Eagle DM, Robbins TW (2011) Prefrontal and monoaminergic contributions to stop-signal task performance in rats. *J Neurosci* 31:9254–9263.
- Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50:7–15.
- Bello EP, Mateo Y, Gelman DM, Noain D, Shin JH, Low MJ, Alvarez VA, Lovinger DM, Rubinstein M (2011) Cocaine supersensitivity and enhanced motivation for reward in mice lacking dopamine D2 autoreceptors. *Nat Neurosci* 14:1033–1038.
- Besson M, Belin D, McNamara R, Theobald DE, Castel A, Beckett VL, Crittenden BM, Newman AH, Everitt BJ, Robbins TW, Dalley JW (2010) Dissociable control of impulsivity in rats by dopamine d2/3 receptors in the core and shell subregions of the nucleus accumbens. *Neuropsychopharmacology* 35:560–569.
- Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, Zhou Z, Wedenoja J, Maroteaux L, Diaz S, Belmer A, Hodgkinson CA, Dell'osso L, Suvisaari J, Coccaro E, Rose RJ, Peltonen L, Virkkunen M, Goldman D (2010) A population-specific HTR2B stop codon predisposes to severe impulsivity. *Nature* 468:1061–1066.
- Bizarro L, Patel S, Murtagh C, Stolerman IP (2004) Differential effects of psychomotor stimulants on attentional performance in rats: nicotine, amphetamine, caffeine and methylphenidate. *Behav Pharmacol* 15:195–206.
- Bizot J, Le Bihan C, Puech AJ, Hamon M, Thiebot M (1999) Serotonin and tolerance to delay of reward in rats. *Psychopharmacology (Berl)* 146:400–412.
- Blokland A, Sik A, Lieben C (2005) Evaluation of DOI, 8-OH-DPAT, eticlopride and amphetamine on impulsive responding in a reaction time task in rats. *Behav Pharmacol* 16:93–100.
- Blondeau C, Dellu-Hagedorn F (2007) Dimensional analysis of ADHD subtypes in rats. *Biol Psychiatry* 61:1340–1350.
- Booij L, Swenne CA, Brosschot JF, Haffmans PM, Thayer JF, Van der Does AJ (2006) Tryptophan depletion affects heart rate variability and impulsivity in remitted depressed patients with a history of suicidal ideation. *Biol Psychiatry* 60:507–514.
- Booij L, Turecki G, Leyton M, Gravel P, Lopez De Lara C, Diksic M, Benkelfat C (2011) Tryptophan hydroxylase(2) gene polymorphisms predict brain serotonin synthesis in the orbitofrontal cortex in humans. *Mol Psychiatry*. <http://dx.doi.org/10.1038/mp.2011.79>.
- Bornovalova MA, Lejuez CW, Daughters SB, Zachary Rosenthal M, Lynch TR (2005) Impulsivity as a common process across borderline personality and substance use disorders. *Clin Psychol Rev* 25:790–812.
- Boy F, Evans CJ, Edden RA, Lawrence AD, Singh KD, Husain M, Sumner P (2011) Dorsolateral prefrontal gamma-aminobutyric acid in men predicts individual differences in rash impulsivity. *Biol Psychiatry* 70:866–872.
- Bubar MJ, Stutz SJ, Cunningham KA (2011) 5-HT(2C) receptors localize to dopamine and GABA neurons in the rat mesoaccumbens pathway. *PLoS ONE* 6:e20508.



- Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. *Science* 329:532.
- Butler GK, Montgomery AM (2004) Impulsivity, risk taking and recreational 'ecstasy' (MDMA) use. *Drug Alcohol Depend* 76:55–62.
- Butler T, Schofield PW, Greenberg D, Allnut SH, Indig D, Carr V, D'Este C, Mitchell PB, Knight L, Ellis A (2010) Reducing impulsivity in repeat violent offenders: an open label trial of a selective serotonin reuptake inhibitor. *Aust N Z J Psychiatry* 44:1137–1143.
- Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001) Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* 292:2499–2501.
- Cardinal RN, Robbins TW, Everitt BJ (2000) The effects of d-amphetamine, chloridiazepoxide, alpha-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology (Berl)* 152:362–375.
- Carli M, Baviera M, Invernizzi RW, Balducci C (2006) Dissociable contribution of 5-HT1A and 5-HT2A receptors in the medial prefrontal cortex to different aspects of executive control such as impulsivity and compulsive perseveration in rats. *Neuropsychopharmacology* 31:757–767.
- Castellanos FX, Elia J, Kruesi MJ, Marsh WL, Gulotta CS, Potter WZ, Ritchie GF, Hamburger SD, Rapoport JL (1996) Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 14:125–137.
- Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006) Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311:861–863.
- Chamberlain SR, Muller U, Deakin JB, Corlett PR, Dowson J, Cardinal RN, Aitken MR, Robbins TW, Sahakian BJ (2007) Lack of deleterious effects of buspirone on cognition in healthy male volunteers. *J Psychopharmacol* 21:210–215.
- Chamberlain SR, Sahakian BJ (2007) The neuropsychiatry of impulsivity. *Curr Opin Psychiatry* 20:255–261.
- Cherek DR, Lane SD (1999) Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. *Psychopharmacology (Berl)* 146:473–481.
- Cherek DR, Lane SD (2000) Fenfluramine effects on impulsivity in a sample of adults with and without history of conduct disorder. *Psychopharmacology (Berl)* 152:149–156.
- Cherek DR, Lane SD (2001) Acute effects of D-fenfluramine on simultaneous measures of aggressive escape and impulsive responses of adult males with and without a history of conduct disorder. *Psychopharmacology (Berl)* 157:221–227.
- Cherek DR, Lane SD, Pietras CJ, Steinberg JL (2002) Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. *Psychopharmacology (Berl)* 159:266–274.
- Clark L, Robbins TW, Ersche KD, Sahakian BJ (2006) Reflection impulsivity in current and former substance users. *Biol Psychiatry* 60:515–522.
- Clark L, Roiser J, Robbins T, Sahakian B (2009) Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstasy users. *J Psychopharmacol* 23:14–22.
- Clark L, Roiser JP, Cools R, Rubinstztein DC, Sahakian BJ, Robbins TW (2005) Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. *Psychopharmacology (Berl)* 182:570–578.
- Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry* 46:587–599.
- Coccaro EF, Silverman JM, Klar HM, Horvath TB, Siever LJ (1994) Familial correlates of reduced central serotonergic system function in patients with personality disorders. *Arch Gen Psychiatry* 51:318–324.
- Cole BJ, Robbins TW (1987) Amphetamine impairs the discriminative performance of rats with dorsal noradrenergic bundle lesions on a 5-choice serial reaction time task: new evidence for central dopaminergic-noradrenergic interactions. *Psychopharmacology (Berl)* 91:458–466.
- Cole BJ, Robbins TW (1989) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi on performance of a 5-choice serial reaction time task in rats: implications for theories of selective attention and arousal. *Behav Brain Res* 33:165–179.
- Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry* 69:e113–e125.
- Crean J, Richards JB, de Wit H (2002) Effect of tryptophan depletion on impulsive behavior in men with or without a family history of alcoholism. *Behav Brain Res* 136:349–357.
- Crean JP, de Wit H, Richards JB (2000) Reward discounting as a measure of impulsive behavior in a psychiatric outpatient population. *Exp Clin Psychopharmacol* 8:155–162.
- Crockett MJ, Clark L, Robbins TW (2009) Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. *J Neurosci* 29:11993–11999.
- Dahlstroem A, Fuxe K (1964) A method for the demonstration of monoamine-containing nerve fibres in the central nervous system. *Acta Physiol Scand* 60:293–294.
- Dahlstroem A, Fuxe K, Olson L, Ungerstedt U (1964) Ascending systems of catecholamine neurons from the lower brain stem. *Acta Physiol Scand* 62:485–486.
- Dalley JW, Everitt BJ, Robbins TW (2011) Impulsivity, compulsivity, and top-down cognitive control. *Neuron* 69:680–694.
- Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* 315:1267–1270.
- Dalley JW, Theobald DE, Pereira EA, Li PM, Robbins TW (2002) Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioural performance of a task assessing visuospatial attention and impulsivity. *Psychopharmacology (Berl)* 164:329–340.
- de Wit H, Crean J, Richards JB (2000) Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behav Neurosci* 114:830–837.
- de Wit H, Enggasser JL, Richards JB (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* 27:813–825.
- Devilbiss DM, Berridge CW (2006) Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. *J Pharmacol Exp Ther* 319:1327–1335.
- DeVito EE, Blackwell AD, Clark L, Kent L, Dezsery AM, Turner DC, Aitken MR, Sahakian BJ (2009) Methylphenidate improves response inhibition but not reflection-impulsivity in children with attention deficit hyperactivity disorder (ADHD). *Psychopharmacology (Berl)* 202:531–539.
- DeVito EE, Blackwell AD, Kent L, Ersche KD, Clark L, Salmond CH, Dezsery AM, Sahakian BJ (2008) The effects of methylphenidate on decision making in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 64:636–639.
- Dolan M, Deakin WJ, Roberts N, Anderson I (2002) Serotonergic and cognitive impairment in impulsive aggressive personality disordered offenders: are there implications for treatment? *Psychol Med* 32:105–117.
- Dom G, De Wilde B, Hultstijn W, Sabbe B (2007) Dimensions of impulsive behaviour in abstinent alcoholics. *Pers Individ Differ* 42:465–476.
- Dougherty DM, Marsh DM, Mathias CW, Dawes MA, Bradley DM, Morgan CJ, Badawy AA (2007) The effects of alcohol on laboratory-measured impulsivity after L-tryptophan depletion or loading. *Psychopharmacology (Berl)* 193:137–150.

- Dougherty DM, Mathias CW, Marsh DM, Papageorgiou TD, Swann AC, Moeller FG (2004) Laboratory measured behavioral impulsivity relates to suicide attempt history. *Suicide Life Threat Behav* 34:374–385.
- Durana JH, Barnes PA (1993) A neurodevelopmental view of impulsivity and its relationship to the superfactors of personality. In: McCown WG et al., editors. *The impulsive client: theory, research and treatment*. Washington, DC: American Psychological Association.
- Eagle DM, Bari A, Robbins TW (2008) The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology (Berl)* 199:439–456.
- Eagle DM, Lehmann O, Theobald DE, Pena Y, Zakaria R, Ghosh R, Dalley JW, Robbins TW (2009) Serotonin depletion impairs waiting but not stop-signal reaction time in rats: implications for theories of the role of 5-HT in behavioral inhibition. *Neuropsychopharmacology* 34:1311–1321.
- Eagle DM, Robbins TW (2003) Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. *Behav Neurosci* 117:1302–1317.
- Eagle DM, Tuft MR, Goodchild HL, Robbins TW (2007) Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology (Berl)* 192:193–206.
- Eagle DM, Wong JC, Allan ME, Mar AC, Theobald DE, Robbins TW (2011) Contrasting roles for dopamine D1 and D2 receptor subtypes in the dorsomedial striatum but not the nucleus accumbens core during behavioral inhibition in the stop-signal task in rats. *J Neurosci* 31:7349–7356.
- Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW (2010) Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biol Psychiatry* 68:770–773.
- Evenden J (1999a) Impulsivity: a discussion of clinical and experimental findings. *J Psychopharmacol* 13:180–192.
- Evenden JL (1999b) Varieties of impulsivity. *Psychopharmacology (Berl)* 146:348–361.
- Evenden JL, Ryan CN (1999) The pharmacology of impulsive behaviour in rats VI: the effects of ethanol and selective serotonergic drugs on response choice with varying delays of reinforcement. *Psychopharmacology (Berl)* 146:413–421.
- Eysenck HJ, Eysenck SBG (1991) *Adult impulsiveness, venturesomeness and empathy scale*. London: Hodder Soughton.
- Feola TW, de Wit H, Richards JB (2000) Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. *Behav Neurosci* 114:838–848.
- Fink KB, Gothert M (2007) 5-HT receptor regulation of neurotransmitter release. *Pharmacol Rev* 59:360–417.
- Fletcher PJ, Tampakeras M, Sinyard J, Higgins GA (2007) Opposing effects of 5-HT(2A) and 5-HT(2C) receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology (Berl)* 195:223–234.
- Floresco SB, Tse MT, Ghods-Sharifi S (2008) Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology* 33:1966–1979.
- Franken IH, van Strien JW, Nijis I, Muris P (2008) Impulsivity is associated with behavioral decision-making deficits. *Psychiatry Res* 158:155–163.
- Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang Y, Hwang DR, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [<sup>11</sup>C]McN 5652. *Am J Psychiatry* 162:915–923.
- Gerasimov MR, Franceschi M, Volkow ND, Rice O, Schiffer WK, Dewey SL (2000) Synergistic interactions between nicotine and cocaine or methylphenidate depend on the dose of dopamine transporter inhibitor. *Synapse* 38:432–437.
- Green AR, Mehan AO, Elliott JM, O'Shea E, Colado MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxyamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* 55:463–508.
- Hadamitzky M, Feja M, Becker T, Koch M (2009) Effects of acute systemic administration of serotonin2A/C receptor ligands in a delay-based decision-making task in rats. *Behav Pharmacol* 20:415–423.
- Halpern JH, Pope Jr HG, Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D (2004) Residual neuropsychological effects of illicit 3,4-methylenedioxyamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug Alcohol Depend* 75:135–147.
- Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope Jr HG (2011) Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. *Addiction* 106:777–786.
- Hamidovic A, Dlugos A, Skol A, Palmer AA, de Wit H (2009) Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: an exploratory study with d-amphetamine in healthy participants. *Exp Clin Psychopharmacol* 17:374–383.
- Hamidovic A, Kang UJ, de Wit H (2008) Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. *J Clin Psychopharmacol* 28:45–51.
- Hanna GL, Ornitz EM, Hariharan M (1996) Urinary catecholamine excretion and behavioral differences in ADHD and normal boys. *J Child Adolesc Psychopharmacol* 6:63–73.
- Harmer CJ, McTavish SF, Clark L, Goodwin GM, Cowen PJ (2001) Tyrosine depletion attenuates dopamine function in healthy volunteers. *Psychopharmacology (Berl)* 154:105–111.
- Harrison AA, Everitt BJ, Robbins TW (1997) Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology (Berl)* 133:329–342.
- Harrison AA, Everitt BJ, Robbins TW (1999) Central serotonin depletion impairs both the acquisition and performance of a symmetrically reinforced go/no-go conditional visual discrimination. *Behav Brain Res* 100:99–112.
- Hayes DJ, Greenshaw AJ (2011) 5-HT receptors and reward-related behaviour: a review. *Neurosci Biobehav Rev* 35:1419–1449.
- Helms CM, Reeves JM, Mitchell SH (2006) Impact of strain and D-amphetamine on impulsivity (delay discounting) in inbred mice. *Psychopharmacology* 188:144–151.
- Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M (2007) Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*:CD004851.
- Hoffman WF, Moore M, Templin R, McFarland B, Hitzemann RJ, Mitchell SH (2006) Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology (Berl)* 188:162–170.
- Hollander E, Cohen LJ (1996) *Impulsivity and compulsivity*. Washington, DC: American Psychiatric Press Inc.
- Horesh N (2001) Self-report vs. computerized measures of impulsivity as a correlate of suicidal behavior. *Crisis* 22:27–31.
- Housden CR, O'Sullivan SS, Joyce EM, Lees AJ, Roiser JP (2010) Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology* 35:2155–2164.
- Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* 78:815–826.
- Isles AR, Humby T, Wilkinson LS (2003) Measuring impulsivity in mice using a novel operant delayed reinforcement task: effects of behavioural manipulations and d-amphetamine. *Psychopharmacology (Berl)* 170:376–382.
- Kagan J, Rosman BL, Day D, Albert J, Phillips W (1964) Information processing in the child: significance of analytic and reflective attitudes. *Psychol Monogr* 78:1 (Whole No. 578).

- Kelly TH, Robbins G, Martin CA, Fillmore MT, Lane SD, Harrington NG, Rush CR (2006) Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. *Psychopharmacology (Berl)* 189:17–25.
- Kirby KN, Finch JC (2010) The hierarchical structure of self-reported impulsivity. *Pers Individ Differ* 48:704–713.
- Klonsky ED, May A (2010) Rethinking impulsivity in suicide. *Suicide Life Threat Behav* 40:612–619.
- Kollins SH, March JS (2007) Advances in the pharmacotherapy of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 62:951–953.
- Koskinen T, Ruotsalainen S, Sirvio J (2000) The 5-HT<sub>2</sub> receptor activation enhances impulsive responding without increasing motor activity in rats. *Pharmacol Biochem Behav* 66:729–738.
- Kuczenski R, Segal DS (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem* 68:2032–2037.
- Lage GM, Malloy-Diniz LF, Matos LO, Bastos MA, Abrantes SS, Correa H (2011) Impulsivity and the 5-HTTLPR polymorphism in a non-clinical sample. *PLoS ONE* 6:e16927.
- Lane SD, Cherek DR, Rhodes HM, Pietras CJ, Tcheremissine OV (2003) Relationships among laboratory and psychometric measures of impulsivity: implications in substance abuse and dependence. *Addict Dis Treat* 2:33–40.
- Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009) Striatal dopamine d<sub>2</sub>/d<sub>3</sub> receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci* 29:14734–14740.
- LeMarquand DG, Benkelfat C, Pihl RO, Palmour RM, Young SN (1999) Behavioral disinhibition induced by tryptophan depletion in nonalcoholic young men with multigenerational family histories of paternal alcoholism. *Am J Psychiatry* 156:1771–1779.
- LeMarquand DG, Pihl RO, Young SN, Tremblay RE, Seguin JR, Palmour RM, Benkelfat C (1998) Tryptophan depletion, executive functions, and disinhibition in aggressive, adolescent males. *Neuropsychopharmacology* 19:333–341.
- Leyton M, Dagher A, Boileau I, Casey K, Baker GB, Diksic M, Gunn R, Young SN, Benkelfat C (2004) Decreasing amphetamine-induced dopamine release by acute phenylalanine/tyrosine depletion: a PET/[<sup>11</sup>C]raclopride study in healthy men. *Neuropsychopharmacology* 29:427–432.
- Lindstrom MB, Ryding E, Bosson P, Ahnide JA, Rosen I, Traskman-Bendz L (2004) Impulsivity related to brain serotonin transporter binding capacity in suicide attempters. *Eur Neuropsychopharmacol* 14:295–300.
- Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sci* 33:2609–2614.
- Logan G, Schachar R, Tannock R (1997) Impulsivity and inhibitory control. *Psychol Sci* 8:60–64.
- Logan GD (1994) On the ability to inhibit thought and action. In: Dagenback D, Carr TH, editors. *Inhibitory processes in attention memory and language*. San Diego: Academic Press. p. 189–239.
- Loos M, Pattij T, Janssen MC, Counotte DS, Schoffeleers AN, Smit AB, Spijker S, van Gaalen MM (2010) Dopamine receptor D1/D5 gene expression in the medial prefrontal cortex predicts impulsive choice in rats. *Cereb Cortex* 20:1064–1070.
- Love TM, Stohler CS, Zubieta JK (2009) Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. *Arch Gen Psychiatry* 66:1124–1134.
- Lythe KE, Anderson IM, Deakin JF, Elliott R, Strickland PL (2005) Lack of behavioural effects after acute tyrosine depletion in healthy volunteers. *J Psychopharmacol* 19:5–11.
- Malloy-Diniz LF, Neves FS, de Moraes PH, De Marco LA, Romano-Silva MA, Krebs MO, Correa H (2011) The 5-HTTLPR polymorphism, impulsivity and suicide behavior in euthymic bipolar patients. *J Affect Disord* 133:221–226.
- Mann JJ, Brent DA, Arango V (2001) The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. *Neuropsychopharmacology* 24:467–477.
- Mann JJ, McBride PA, Brown RP, Linnoila M, Leon AC, DeMeo M, Mieczkowski T, Myers JE, Stanley M (1992) Relationship between central and peripheral serotonin indexes in depressed and suicidal psychiatric inpatients. *Arch Gen Psychiatry* 49:442–446.
- Manuck SB, Flory JD, McCaffery JM, Matthews KA, Mann JJ, Muldoon MF (1998) Aggression, impulsivity, and central nervous system serotonergic responsivity in a nonpatient sample. *Neuropsychopharmacology* 19:287–299.
- Masaki D, Yokoyama C, Kinoshita S, Tsuchida H, Nakatomi Y, Yoshimoto K, Fukui K (2006) Relationship between limbic and cortical 5-HT neurotransmission and acquisition and reversal learning in a go/no-go task in rats. *Psychopharmacology (Berl)* 189:249–258.
- Mazur JE, Coe D (1987) Tests of transitivity in choices between fixed and variable reinforcer delays. *J Exp Anal Behav* 47:287–297.
- McLean A, Rubinsztein JS, Robbins TW, Sahakian BJ (2004) The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. *Psychopharmacology (Berl)* 171:286–297.
- McMahon LR, Filip M, Cunningham KA (2001) Differential regulation of the mesoaccumbens circuit by serotonin 5-hydroxytryptamine (5-HT)<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. *J Neurosci* 21:7781–7787.
- Meda SA, Stevens MC, Potenza MN, Pittman B, Gueorguieva R, Andrews MM, Thomas AD, Muska C, Hylton JL, Pearson GD (2009) Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. *Behav Pharmacol* 20:390–399.
- Miyazaki K, Miyazaki KW, Doya K (2011) Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. *J Neurosci* 31:469–479.
- Mobini S, Chiang TJ, Al-Ruwaitea AS, Ho MY, Bradshaw CM, Szabadi E (2000a) Effect of central 5-hydroxytryptamine depletion on inter-temporal choice: a quantitative analysis. *Psychopharmacology (Berl)* 149:313–318.
- Mobini S, Chiang TJ, Ho MY, Bradshaw CM, Szabadi E (2000b) Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology (Berl)* 152:390–397.
- Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC (2001) Psychiatric aspects of impulsivity. *Am J Psychiatry* 158:1783–1793.
- Moeller FG, Dougherty DM, Barratt ES, Oderinde V, Mathias CW, Harper RA, Swann AC (2002) Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. *Drug Alcohol Depend* 68:105–111.
- Monterosso JR, Aron AR, Cordova X, Xu J, London ED (2005) Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend* 79:273–277.
- Montgomery AJ, McTavish SF, Cowen PJ, Grasby PM (2003) Reduction of brain dopamine concentration with dietary tyrosine plus phenylalanine depletion: an [<sup>11</sup>C]raclopride PET study. *Am J Psychiatry* 160:1887–1889.
- Morgan MJ (1998) Recreational use of “ecstasy” (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* 19:252–264.
- Morgan MJ, Impallomeni LC, Pirona A, Rogers RD (2006) Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naive controls. *Neuropsychopharmacology* 31:1562–1573.
- Morgan MJ, McFie L, Fleetwood H, Robinson JA (2002) Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology (Berl)* 159:294–303.
- O’Sullivan SS, Evans AH, Lees AJ (2009) Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. *CNS Drugs* 23:157–170.
- Oades RD (2002) Dopamine may be ‘hyper’ with respect to noradrenaline metabolism, but ‘hypo’ with respect to serotonin



- metabolism in children with attention-deficit hyperactivity disorder. *Behav Brain Res* 130:97–102.
- Oades RD (2007) Role of the serotonin system in ADHD: treatment implications. *Expert Rev Neurother* 7:1357–1374.
- Oades RD, Lasky-Su J, Christiansen H, Faraone SV, Sonuga-Barke EJ, Banaschewski T, Chen W, Anney RJ, Buitelaar JK, Ebstein RP, Franke B, Gill M, Miranda A, Roeyers H, Rothenberger A, Sergeant JA, Steinhausen HC, Taylor EA, Thompson M, Asherson P (2008) The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): findings from a family-based association test (FBAT) analysis. *Behav Brain Funct* 4:48.
- Obeso I, Wilkinson L, Jahanshahi M (2011) Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. *Exp Brain Res* 213:435–445.
- Olmstead MC, Ouagazzal AM, Kieffer BL (2009) Mu and delta opioid receptors oppositely regulate motor impulsivity in the signaled nose poke task. *PLoS ONE* 4:e4410.
- Oswald LM, Wong DF, Zhou Y, Kumar A, Brasic J, Alexander M, Ye W, Kuwabara H, Hilton J, Wand GS (2007) Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. *Neuroimage* 36:153–166.
- Overtoom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, van der Molen MW, van der Gugten J, Westenberg H, Maes RA, Koelega HS (2003) Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. *Behav Brain Res* 145:7–15.
- Pattij T, Janssen MC, Vanderschuren LJ, Schoffelmeer AN, van Gaalen MM (2007) Involvement of dopamine D1 and D2 receptors in the nucleus accumbens core and shell in inhibitory response control. *Psychopharmacology (Berl)* 191:587–598.
- Pattij T, Schettens D, Schoffelmeer AN, van Gaalen MM (2012) On the improvement of inhibitory response control and visuospatial attention by indirect and direct adrenoceptor agonists. *Psychopharmacology (Berl)* 219:327–340.
- Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 51:768–774.
- Pezze MA, Dalley JW, Robbins TW (2009) Remediation of attentional dysfunction in rats with lesions of the medial prefrontal cortex by intra-accumbens administration of the dopamine D(2/3) receptor antagonist sulpiride. *Psychopharmacology (Berl)* 202:307–313.
- Pine A, Shiner T, Seymour B, Dolan RJ (2010) Dopamine, time, and impulsivity in humans. *J Neurosci* 30:8888–8896.
- Pothuizen HH, Jongen-Relo AL, Feldon J, Yee BK (2005) Double dissociation of the effects of selective nucleus accumbens core and shell lesions on impulsive-choice behaviour and salience learning in rats. *Eur J Neurosci* 22:2605–2616.
- Puumala T, Ruotsalainen S, Jakala P, Koivisto E, Riekkinen Jr P, Sirvio J (1996) Behavioral and pharmacological studies on the validation of a new animal model for attention deficit hyperactivity disorder. *Neurobiol Learn Mem* 66:198–211.
- Puumala T, Sirvio J (1998) Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. *Neuroscience* 83:489–499.
- Quednow BB, Kuhn KU, Hoppe C, Westheide J, Maier W, Daum I, Wagner M (2007) Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). *Psychopharmacology (Berl)* 189:517–530.
- Reist C, Mazzanti C, Vu R, Tran D, Goldman D (2001) Serotonin transporter promoter polymorphism is associated with attenuated prolactin response to fenfluramine. *Am J Med Genet* 105:363–368.
- Reynolds B, Ortengren A, Richards JB, de Wit H (2006) Dimensions of impulsive behavior: personality and behavioral measures. *Pers Indiv Differ* 20:305–315.
- Richards JB, Zhang L, Mitchell SH, de Wit H (1999) Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *J Exp Anal Behav* 71:121–143.
- Rinne T, van den Brink W, Wouters L, van Dyck R (2002) SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am J Psychiatry* 159:2048–2054.
- Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. *Psychopharmacology (Berl)* 163:362–380.
- Robbins TW, Sahakian BJ (1979) "Paradoxical" effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioural pharmacology. *Neuropharmacology* 18:931–950.
- Robinson ES, Dalley JW, Theobald DE, Glennon JC, Pezze MA, Murphy ER, Robbins TW (2008a) Opposing roles for 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. *Neuropsychopharmacology* 33:2398–2406.
- Robinson ES, Eagle DM, Economidou D, Theobald DE, Mar AC, Murphy ER, Robbins TW, Dalley JW (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: specific deficits in 'waiting' versus 'stopping'. *Behav Brain Res* 196:310–316.
- Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW (2008b) Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology* 33:1028–1037.
- Robinson OJ, Cools R, Sahakian BJ (2012) Tryptophan depletion disinhibits punishment but not reward prediction: implications for resilience. *Psychopharmacology (Berl)* 219:599–605.
- Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JF, Sahakian BJ, Robbins TW (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoamine mechanisms. *Neuropsychopharmacology* 20:322–339.
- Roiser JP, McLean A, Ogilvie AD, Blackwell AD, Bamber DJ, Goodyer I, Jones PB, Sahakian BJ (2005) The subjective and cognitive effects of acute phenylalanine and tyrosine depletion in patients recovered from depression. *Neuropsychopharmacology* 30:775–785.
- Roiser JP, Rogers RD, Sahakian BJ (2007) Neuropsychological function in ecstasy users: a study controlling for polydrug use. *Psychopharmacology (Berl)* 189:505–516.
- Rosa-Neto P, Lou HC, Cumming P, Pryds O, Karrebaek H, Lunding J, Gjedde A (2005) Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *Neuroimage* 25:868–876.
- Rosa Neto P, Lou H, Cumming P, Pryds O, Gjedde A (2002) Methylphenidate-evoked potentiation of extracellular dopamine in the brain of adolescents with premature birth: correlation with attentional deficit. *Ann N Y Acad Sci* 965:434–439.
- Rossi M, Gerschovich ER, de Achaval D, Perez-Lloret S, Cerquetti D, Cammarota A, Ines Nouzeilles M, Fahrer R, Merello M, Leiguarda R (2010) Decision-making in Parkinson's disease patients with and without pathological gambling. *Eur J Neurol* 17:97–102.
- Ryding E, Ahnide JA, Lindstrom M, Rosen I, Traskman-Bendz L (2006) Regional brain serotonin and dopamine transporter binding capacity in suicide attempters relate to impulsiveness and mental energy. *Psychiatry Res* 148:195–203.
- Sakai JT, Young SE, Stallings MC, Timberlake D, Smolen A, Stetler GL, Crowley TJ (2006) Case-control and within-family tests for an association between conduct disorder and 5HTTLPR. *Am J Med Genet B Neuropsychiatr Genet* 141B:825–832.
- Schachar R, Logan GD, Robaey P, Chen S, Ickowicz A, Barr C (2007) Restraint and cancellation: multiple inhibition deficits in

- attention deficit hyperactivity disorder. *J Abnorm Child Psychol* 35:229–238.
- Scheres A, Oosterlaan J, Swanson J, Morein-Zamir S, Meiran N, Schut H, Vlasveld L, Sergeant JA (2003) The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. *J Abnorm Child Psychol* 31:105–120.
- Schilt T, Koeter MW, Smal JP, Gouwetor MN, van den Brink W, Schmand B (2010) Long-term neuropsychological effects of ecstasy in middle-aged ecstasy/polydrug users. *Psychopharmacology (Berl)* 207:583–591.
- Schmidt CA, Fallon AE, Coccaro EF (2004) Assessment of behavioral and cognitive impulsivity: development and validation of the Lifetime History of Impulsive Behaviors Interview. *Psychiatry Res* 126:107–121.
- Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K (2008) Low-serotonin levels increase delayed reward discounting in humans. *J Neurosci* 28:4528–4532.
- Shaywitz BA, Cohen DJ, Bowers Jr MB (1977) CSF monoamine metabolites in children with minimal brain dysfunction: evidence for alteration of brain dopamine. A preliminary report. *J Pediatr* 90:67–71.
- Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jimenez M, Galleguillos F, Bustamante ML (2010) Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. *Psychiatr Genet* 20:25–30.
- Slezak JM, Anderson KG (2009) Effects of variable training, signaled and unsignaled delays, and d-amphetamine on delay-discounting functions. *Behav Pharmacol* 20:424–436.
- Solanto MV, Abikoff H, Sonuga-Barke E, Schachar R, Logan GD, Wigal T, Hechtman L, Hinshaw S, Turkel E (2001) The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. *J Abnorm Child Psychol* 29:215–228.
- Soloff P (1997) Special feature: psychobiologic perspectives on treatment of personality disorders. *J Pers Disord* 11:336–344.
- Soloff PH, Kelly TM, Strotmeyer SJ, Malone KM, Mann JJ (2003) Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder. *Psychiatry Res* 119:11–24.
- Soubrié P (1986) Reconciling the role of central serotonin neurons in human and animal behavior. *Behav Brain Sci* 9:319–335.
- St Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology* 34:681–697.
- St Onge JR, Floresco SB (2010) Prefrontal cortical contribution to risk-based decision making. *Cereb Cortex* 20:1816–1828.
- Stanis JJ, Marquez Avila H, White MD, Gulley JM (2008) Dissociation between long-lasting behavioral sensitization to amphetamine and impulsive choice in rats performing a delay-discounting task. *Psychopharmacology* 199:539–548.
- Stanislaw H, Todorov N (1999) Calculation of signal detection theory measures. *Behav Res Methods Instrum Comput* 31:137–149.
- Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP (2009) Increased striatal dopamine release in parkinsonian patients with pathological gambling: a [<sup>11</sup>C] raclopride PET study. *Brain* 132:1376–1385.
- Stoltenberg SF, Glass JM, Chermack ST, Flynn HA, Li S, Weston ME, Burmeister M (2006) Possible association between response inhibition and a variant in the brain-expressed tryptophan hydroxylase-2 gene. *Psychiatr Genet* 16:35–38.
- Swann AC (2009) Impulsivity in mania. *Curr Psychiatry Rep* 11:481–487.
- Swann AC, Bjork JM, Moeller FG, Dougherty DM (2002) Two models of impulsivity: relationship to personality traits and psychopathology. *Biol Psychiatry* 51:988–994.
- Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG (2005) Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am J Psychiatry* 162:1680–1687.
- Swanson JM, Volkow ND (2009) Psychopharmacology: concepts and opinions about the use of stimulant medications. *J Child Psychol Psychiatry* 50:180–193.
- Talbot PS, Watson DR, Barrett SL, Cooper SJ (2006) Rapid tryptophan depletion improves decision-making cognition in healthy humans without affecting reversal learning or set shifting. *Neuropsychopharmacology* 31:1519–1525.
- Talpos JC, Wilkinson LS, Robbins TW (2006) A comparison of multiple 5-HT receptors in two tasks measuring impulsivity. *J Psychopharmacol* 20:47–58.
- Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989) Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473–491.
- Turner DC, Blackwell AD, Dowson JH, McLean A, Sahakian BJ (2005) Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. *Psychopharmacology (Berl)* 178:286–295.
- Tye NC, Everitt BJ, Iversen SD (1977) 5-Hydroxytryptamine and punishment. *Nature* 268:741–743.
- Van den Eynde F, Senturk V, Naudts K, Vogels C, Bernagie K, Thas O, van Heeringen C, Audenaert K (2008) Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. *J Clin Psychopharmacol* 28:147–155.
- van Gaalen MM, van Koten R, Schoffelemeier AN, Vanderschuren LJ (2006) Critical involvement of dopaminergic neurotransmission in impulsive decision making. *Biol Psychiatry* 60:66–73.
- Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N (2001) Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry* 158:2015–2021.
- Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM (2009) Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA* 302:1084–1091.
- Volkow ND, Wang GJ, Newcorn J, Telang F, Solanto MV, Fowler JS, Logan J, Ma Y, Schulz K, Pradhan K, Wong C, Swanson JM (2007) Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 64:932–940.
- Voon V, Pessiglione M, Brezing C, Gallea C, Fernandez HH, Dolan RJ, Hallett M (2010a) Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. *Neuron* 65:135–142.
- Voon V, Reynolds B, Brezing C, Gallea C, Skaljic M, Ekanayake V, Fernandez H, Potenza MN, Dolan RJ, Hallett M (2010b) Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl)* 207:645–659.
- Wade TR, de Wit H, Richards JB (2000) Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. *Psychopharmacology (Berl)* 150:90–101.
- Walderhaug E, Herman AI, Magnusson A, Morgan MJ, Landro NI (2010) The short (S) allele of the serotonin transporter polymorphism and acute tryptophan depletion both increase impulsivity in men. *Neurosci Lett* 473:208–211.
- Walderhaug E, Lunde H, Nordvik JE, Landro NI, Refsum H, Magnusson A (2002) Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. *Psychopharmacology (Berl)* 164:385–391.
- Walderhaug E, Magnusson A, Neumeister A, Lappalainen J, Lunde H, Refsum H, Landro NI (2007) Interactive effects of sex and 5-HTTLPR on mood and impulsivity during tryptophan depletion in healthy people. *Biol Psychiatry* 62:593–599.
- Whiteside SP, Lynam DR (2001) The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Pers Individ Differ* 30:669–689.
- Williams WA, Shoaf SE, Hommer D, Rawlings R, Linnoila M (1999) Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. *J Neurochem* 72:1641–1647.
- Winstanley CA, Cocker PJ, Rogers RD (2011) Dopamine modulates reward expectancy during performance of a slot machine task in rats: evidence for a 'near-miss' effect. *Neuropsychopharmacology* 36:913–925.

- Winstanley CA, Dalley JW, Theobald DE, Robbins TW (2003) Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology (Berl)* 170:320–331.
- Winstanley CA, Dalley JW, Theobald DE, Robbins TW (2004) Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. *Neuropsychopharmacology* 29:1331–1343.
- Winstanley CA, Eagle DM, Robbins TW (2006a) Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clin Psychol Rev* 26:379–395.
- Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW (2006b) Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb Cortex* 16:106–114.
- Winstanley CA, Theobald DE, Dalley JW, Robbins TW (2005) Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. *Neuropsychopharmacology* 30:669–682.
- Wogar MA, Bradshaw CM, Szabadi E (1993) Effect of lesions of the ascending 5-hydroxytryptaminergic pathways on choice between delayed reinforcers. *Psychopharmacology (Berl)* 111:239–243.
- Wolff MC, Leander JD (2002) Selective serotonin reuptake inhibitors decrease impulsive behavior as measured by an adjusting delay procedure in the pigeon. *Neuropsychopharmacology* 27:421–429.
- Wooters TE, Bardo MT (2011) Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in Spontaneously Hypertensive, Wistar–Kyoto and Sprague–Dawley rats. *Brain Res* 1396:45–53.
- Zeeb FD, Floresco SB, Winstanley CA (2010) Contributions of the orbitofrontal cortex to impulsive choice: interactions with basal levels of impulsivity, dopamine signalling, and reward-related cues. *Psychopharmacology (Berl)* 211:87–98.
- Zeeb FD, Robbins TW, Winstanley CA (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology* 34:2329–2343.
- Zermatten A, Van der Linden M, d'Acremont M, Jermann F, Bechara A (2005) Impulsivity and decision making. *J Nerv Ment Dis* 193:647–650.
- Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, Lee ML, Xiao T, Papp A, Wang D, Sadee W (2007) Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proc Natl Acad Sci USA* 104:20552–20557.

*(Accepted 10 March 2012)*  
*(Available online 25 April 2012)*