Neuroscience 215 (2012) 42–58

REVIEW

DOPAMINE, SEROTONIN AND IMPULSIVITY

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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.

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

Contents

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

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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.

0306-4522/12 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2012.03.065

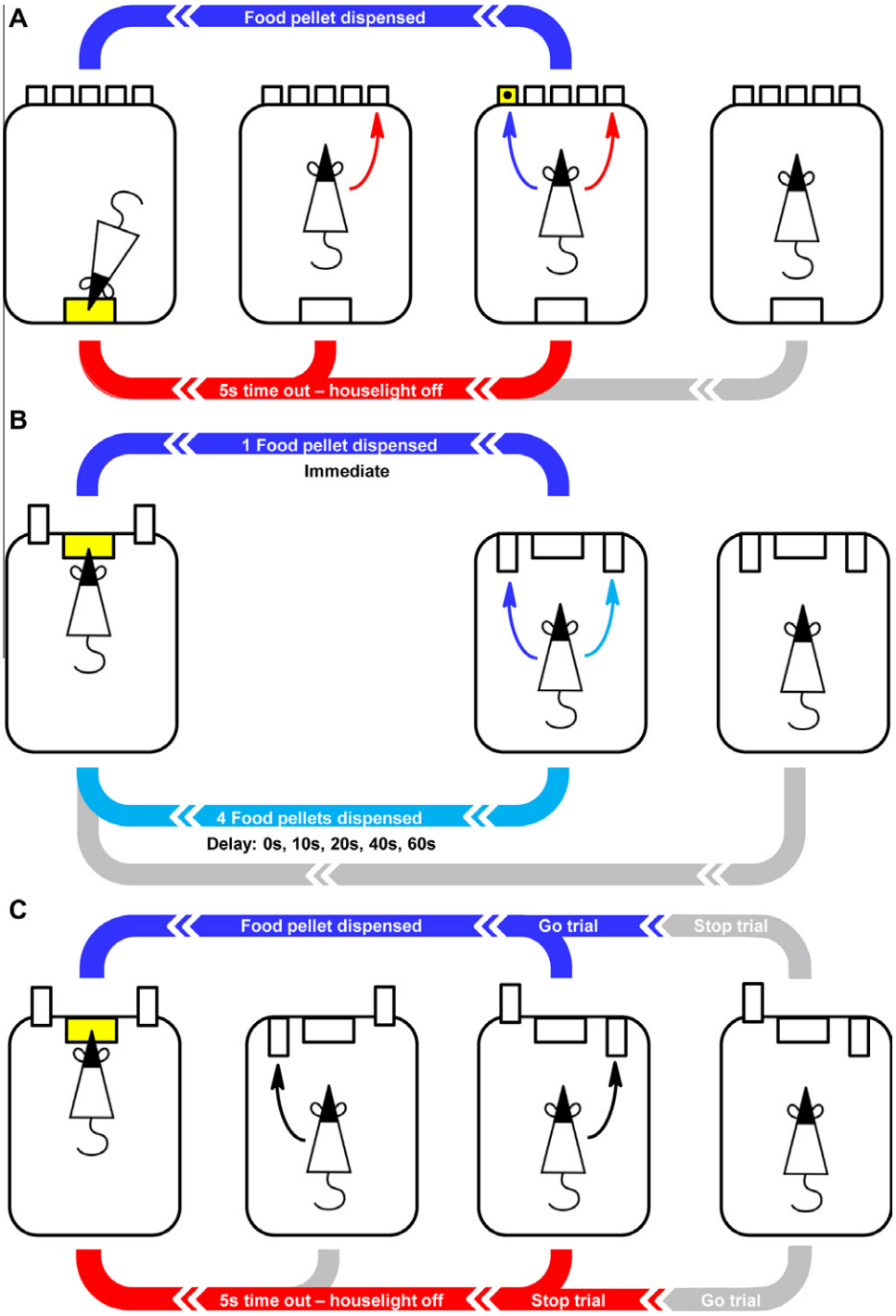

Fig. 1. Schematic representation of (A) 5-choice serial reaction time task, (B) delay discounting task and (C) stop-signal task. Each figure shows a representation, from above, of the 5-choice task (A) or operant-conditioning chamber (B, C). Blue arrows indicate correct responses and outcomes, red arrows 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 (Dahlstroem 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

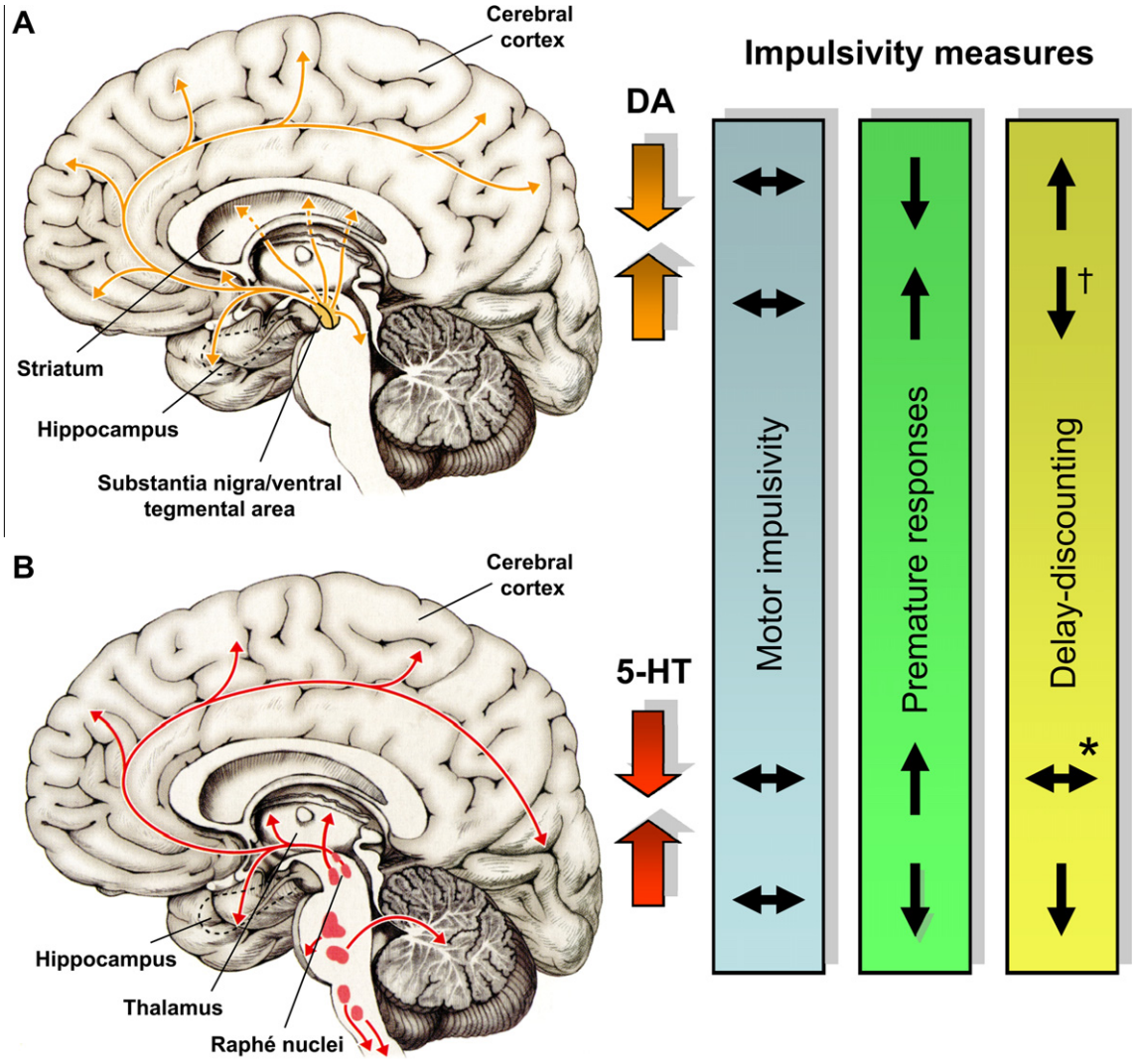

Fig. 2. Distribution of dopamine (A) and serotonin (B) neurotransmitters in the human brain. Diagrams show the distribution of cell bodies in the ventral tegmental area/substantia nigra (DA) and raphé nuclei (5-HT) together with their ascending projections (arrows) to structures in diencephalon and telencephalon. 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). †L-DOPA increases delay discounting impulsivity in humans whilst amphetamine and other stimulants increase impulsivity when delays to reinforcement are unsignalled. *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 $D_{2/3}$ 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 $D_{2/3}$ 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_2 and D_3 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 $D_{2/3}$ 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_1 and D_2 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_1 receptors in medial prefrontal cortex (Loos et al., 2010) and by D_1 and D_2 receptors in the orbitofrontal cortex (Zeeb et al., 2010). Interestingly, the effects of D_1 and D_2 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_1 receptors in medial prefrontal cortex instead. Such findings resonate with the demonstration that increasing DA transmission at D_1 and D_2 receptors favours choice towards larger, probabilistic rewards, whereas D_3 receptor activation has the opposite effect (St Onge and Floresco, 2009). Intriguingly, DA may act via D_2-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_1 nor D_2 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_1 and D_2 receptors *are* reported to modulate SSRT but in an opposing manner (Eagle et al., 2011), thereby implicating competing interactions between the direct (D_1 receptor modulated striatonigral neurons) and indirect (D_2 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-$HT_{2A/2C}$ agonist (±)-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_{2A} antagonists (Evenden and Ryan, 1999; Koskinen et al., 2000; Blokland et al., 2005; Hadamitzky et al., 2009). The selective 5-HT_{2C} 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-$HT_{2A/2C}$ 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_{2A} 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_{2A} 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_{1A} 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_2 and D_3 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_2/D_3 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_2/D_3 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_2/D_3 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_2 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}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 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_{1A} agonist buspirone has not been found to alter impulsivity in humans (Chamberlain et al., 2007), but the 5-HT_{2A} 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_{2B} 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_{2B} 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_{2C} antagonist SB242084 increases premature responses on 5-CSRTT, while the selective 5-HT_{2A} 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.

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