Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 90 (2008) 250–260
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Neurobehavioral mechanisms of impulsivity: Fronto-striatal systems and functional neurochemistry

Jeffrey W. Dalley [a,b,c,*], Adam C. Mar [a,b], Daina Economidou [a,b], Trevor W. Robbins [a,b]

[a] *Behavioral and Clinical Neuroscience Institute, University of Cambridge, Downing St, Cambridge, CB2 3EB, UK*
[b] *Department of Experimental Psychology, University of Cambridge, Downing St, Cambridge, CB2 3EB, UK*
[c] *Department of Psychiatry, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK*

Available online 27 December 2007

Abstract

Impulsive acts and decisions are a part of everyday normal behavior. However, in its pathological forms, impulsivity can be a debilitating disorder often associated with a number of neuropsychiatric disorders, including attention-deficit hyperactivity disorder (ADHD). This article reviews recent progress in our understanding of the neurobiology of impulsivity using examples from recent investigations in experimental animals. Evidence is reviewed from several well-established paradigms with putative utility in assessing distinct forms of impulsive behavior in rodents, including the 5-choice serial reaction time (5CSRT) task and the delay discounting paradigm. We discuss, in particular, recent psychopharmacological and in-vivo neurochemical data in task-performing rats showing functional heterogeneity of the forebrain dopamine (DA), noradrenaline (NA), serotonin (5-HT) and acetylcholine (ACh) systems and identify how these systems normally function to facilitate flexible goal-directed behavior in situations that tax basic attentional functions and inhibitory response control mechanisms. We also discuss future research needs in terms of understanding the functional diversity of different sub-regions of prefrontal cortex (PFC) and how these systems normally interact with the striatum and main nuclei of origin of DA and NA neurons. Finally, we argue in line with others that animal paradigms are unlikely to model all aspects of complex psychiatric conditions such as ADHD but components of such syndromes may be amenable to investigation using sophisticated animal models based on highly-defined psychiatric endophenotypes.

Keywords: Attention; Prefrontal cortex; Nucleus accumbens; 5-choice serial reaction time task; Delay-discounting; Stop-signal reaction time; Dopamine; Serotonin; Noradrenaline

1. Introduction

Pathological forms of impulsive behavior are prevalent disorders of probable developmental origin which share high co-morbidity with a number of neuropsychiatric disorders including most notably attention-deficit hyperactivity disorder (ADHD) (Solanto, 2002). Understanding the relationship of impulsivity to complex brain disorders such as ADHD presents a major challenge for future research not least because ADHD is a heterogeneous disorder comprising at least three diagnostic symptoms; impulsivity, inattentiveness and hyperactivity, some or all of which may be present in varying degrees of severity (DSM-IV-TR, American Psychiatric Association, Newcorn et al., 2001; Solanto, 2002).

The precise cause of ADHD is unknown but there is considerable evidence that this brain disorder involves dysfunctional modulation of cortico–limbic–striatal circuitry by the brain neurotransmitters dopamine (DA), noradrenaline (NA) and serotonin (5-HT) (Arnsten and Li, 2005; Castellanos et al., 1996; Fone and Nutt, 2005; Krause et al., 2003; Solanto, 2002; Stein et al., 1993). Consistent with this view the first line of treatment for ADHD has for many years been psychostimulant drugs such as amphetamine and methylphenidate which act by increasing NA and DA activity in the brain (Elia et al., 1999; Kutcher et al., 2004; Solanto, 2002; McKittrick and Abercrombie, 2007). Amphetamine also increases 5-HT release in the brain unlike methylphenidate (Kuczenski and Segal, 1997).

More recently the selective NA reuptake inhibitor (SNRI) atomoxetine has been introduced as the first non-stimulant

* Corresponding author. Department of Experimental Psychology, University of Cambridge, Downing St, Cambridge CB2 3EB, UK. Tel.: +44 1223 765 291; fax: +44 1223 333 564.
E-mail address: jwd20@cam.ac.uk (J.W. Dalley).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.12.021

based medication with proven efficacy in ADHD (Caballero and Nahata, 2003; Thomason and Michelson, 2004). Indeed, atomoxetine also improves response inhibition in normal healthy human volunteers (Chamberlain et al., 2006). The concept that drugs with predominately NA-ergic activity may be an effective alternative to stimulant drugs in ADHD is bolstered by the clinical efficacy of guanfacine in this disorder which, like atomoxetine, significantly improves impulsivity and hyperactivity as well as inattentiveness in children with ADHD (Scahill et al., 2001; Caballero and Nahata, 2003). Guanfacine is a selective alpha-2 adrenergic agonist which is longer acting and less sedating than clonidine (Sorkin and Heel, 1986) and which has beneficial effects on prefrontal cortex (PFC) functioning in non-human primates (Avery et al., 2000).

Notwithstanding the fact that several therapeutic options are available in ADHD it is clear the continued development of novel therapeutic interventions in ADHD requires ever more sophisticated animal models and an increased understanding of the neurobiological and psychological distinction between different forms of impulsivity. The present review surveys the various tasks and procedural strategies that are currently used to investigate different forms of impulsivity in experimental animals. We focus, in particular, on the underlying neurobiology of distinct classes of impulsive behavior and the application and utility of in-vivo microdialysis in task-performing animals to resolving the likely neurochemical substrates of different forms of impulsive behavior.

2. Operant tests of impulsivity in rodents

There have been several excellent reviews on the taxonomy of impulsivity where recent conceptualizations have highlighted its multifaceted nature (Evenden, 1999; Winstanley et al., 2006a). Typically, definitions of impulsivity broadly include a lack of behavioral inhibition, including actions that are premature, mistimed, or difficult to suppress or control, and impulsive choice where actions are initiated without due deliberation of other possible options or outcomes.

A number of behavioral paradigms are used to assess impulsive behavior in rodents. The 5-choice serial reaction time (5CSRT) task was developed originally as an analogue of the continuous performance test in humans and assesses visuo–spatial attention and impulsivity in a specially-adapted operant chamber (Robbins, 2002). In the 5CSRT task a large number of discrete consecutive trials are presented in which subjects are required to wait during a fixed or variable inter-trial interval (ITI) while scanning a horizontal array of five apertures, and to nose poke in the spatial location of a brief visual stimulus in order to earn food reinforcement. Nose pokes occurring within the ITI, prior to the presentation of the visual stimulus, are classified as premature responses. Elevations in the probability of premature responses are commonly thought to reflect higher levels of impulsivity (Harrison et al., 1997; Muir et al., 1996). One important strength of the 5CSRT task is that it provides several relatively independent measures of attentional performance, including visual discrimination, response speed and response inhibition (Robbins, 2002), the latter fulfilling the basic requirement of an inhibition task by subjects needing to deliberately suppress a response in order to achieve a later goal (in this case food reward). A further important strength of the 5CSRT task is that it recruits many of the same frontal neural systems implicated in ADHD (see below), including the PFC, orbitofrontal cortex (OFC), striatum, and the ascending monoaminergic neurotransmitter systems (Dalley et al., 2004; Robbins, 2002).

Analogous forms of premature responses are measured on other behavioral tests of impulsivity, including a differential reinforcement of low rate of responding (DRL) and a fixed consecutive number (FCN) schedule. On a DRL schedule of reinforcement, the subject is required to space operant responses by a specified time interval to obtain reinforcement (O'Donnell and Seiden, 1982). On a FCN schedule, the subject is required to perform a minimum number of responses on one operandum before a response on a second operandum will deliver reinforcement. A reduction in the number of consecutive responses made on the first operandum before responding on the second is typically interpreted as increased impulsivity. On a variant of this task – the paced FCN – the two levers are withdrawn from the chamber each time the rat responds (Evenden, 1998). The paced FCN schedule helps to control for the potential confounding effects of alterations in general levels of activity. A key methodological distinction between the 5CSRT task and standard DRL and FCN schedules is that in the 5CSRT task the end of the waiting period (i.e., the time after which an operant response will be reinforced) is explicitly signaled.

Other operant-based paradigms, such as the go/no-go and stop signal reaction time (SSRT) tasks, similarly index impulsivity in terms of the ability of a subject to withhold or inhibit a pre-potent response. However, in these paradigms an explicit signal (i.e., auditory, visual or olfactory) is used to indicate trials requiring inhibition (or stop trials), and the absence of an operant response earns reinforcement. By contrast, in the 5CSRT task the absence of a response results in a loss of food delivery and a short darkened time-out period. In the go/no-go task, subjects are presented with a series of trials and learn to make a response in the context of certain stimuli, or withhold that response in the context of different stimuli, in order to receive reinforcement. A similar set-up is employed in the SSRT task where subjects must inhibit an already triggered motor response (Eagle et al., 2007). In both the go/no-go and SSRT tasks increased operant responding (i.e. a failure to withhold or inhibit) on so-called stop trials is inferred as increased impulsivity. However, the focus of the SSRT task is an inferred latency to 'stop' responding. By contrast, the focus of go/no-go tasks is on selection of 'go' versus 'no-go' responses, rather than a reaction time measure.

A final category of procedures used to assess impulsivity relates to decision-making or impulsive choice. Impulsive choice is typically measured in the delay discounting paradigm where impulsivity is defined by a greater tendency to value or choose smaller, more immediate reinforcers over larger, more delayed reinforcers — even where it is economically advantageous to value or choose the latter (Cardinal et al., 2001; Evenden, 1999). This tendency to devalue delayed reinforcers appears highly consistent across species, exemplified by

characteristic hyperbolic discounting curves for reinforcer as a function of increasing delay (Ainslie, 1975; Cardinal et al., 2004). While this obviously implies that delay discounting has adaptive value in natural environments, it is also clear that when the tendency to show preference for immediate reinforcers over more lucrative delayed reinforcers is exaggerated, it may lead to maladaptive behavior.

3. Neural substrates of impulsivity

The core pathology of ADHD is widely hypothesized to include a network involving the PFC and basal ganglia (Arnsten and Li, 2005; Castellanos et al., 1996; Faraone and Biederman, 1998). Brain imaging studies have shown subnormal activation and volume of the PFC and distinct regions of the basal ganglia in ADHD patients, as well as dysfunction of the frontal-striatal system, especially in the right hemisphere (Casey et al., 1997; Castellanos et al., 1996; Rubia et al., 1999; Vaidya et al., 1998). Results of a PET study in unmedicated ADHD patients show diminished uptake of the DA precursor [18F]-L-dopa in the PFC (Ernst et al., 1998). Furthermore, an involvement of the striatal dopamine transporter (DAT) has been implicated in ADHD with increased DAT availability reported in adult ADHD patients (Dougherty et al., 1999; Krause et al., 2000; Spencer et al., 2007), an abnormality that is reversed by methylphenidate treatment (Krause et al., 2000). Such findings, overall, highlight the complexity of ADHD with diverse deficits in the fronto-striatal DA systems, some or all of which may be secondary to a primary sub-cortical deficit (Ernst et al., 1998; Krause et al., 2000).

The main neural loci implicated in different forms of impulsivity in rodents, including SSRT performance, have recently been reviewed (Cardinal, 2006; Winstanley et al., 2006a; Aron et al., 2007). The following section considers the main distinctions between putative cortical and sub-cortical substrates of impulsivity measured on the delay discounting paradigm and 5CSRT task, the main purpose of which is to clarify our rationale for targeting certain key brain regions in subsequent in-vivo microdialysis studies in task-performing rats.

It has been known for many years that the PFC plays an important role in the inhibitory control over behavior. For example, selective lesions of the rat medial PFC impair simple measures of behavioral inhibition, including novelty and stimulant-induced locomotor activity (Dalley et al., 1999; Jaskiw et al., 1990; Whishaw et al., 1992), as well as responding in extinction (Morgan et al., 1993; Quirk et al., 2006). However, more complex forms of inhibition, especially those involving delays to reinforcement, appear remarkably insensitive to lesions of the medial PFC, including selective lesions of the anterior cingulate cortex (Cgl) (Cardinal et al., 2001). By contrast, impulsivity on the 5CSRT task is generally increased by PFC lesions, most especially lesions involving Cgl (Muir et al., 1996) and infralimbic cortex (IL) (Chudasama et al., 2003), and lesions that disconnect medial PFC from the anterior medial striatum (Christakou et al., 2001).

Based on recent studies the cortical loci of impulse control on the 5CSRT task has been refined. Whereas focal lesions of anterior Cgl impair visual discriminative accuracy they appear to have little effect on impulsivity on this task (Chudasama et al., 2003; Passetti et al., 2002), consistent with analogous tasks involving a 'wait to respond' period (Broersen and Uylings, 1999; Risterucci et al., 2003). By contrast, lesions of postgenual Cgl (Muir et al., 1996) and IL (Chudasama et al., 2003) increase impulsivity, an effect also observed following local NMDA receptor antagonism in the IL (Murphy et al., 2005). Notably, the OFC appears to play no significant role in the control of impulsivity on the 5CSRT task (Chudasama et al., 2003).

The striatum, with its high connectivity with the PFC, not surprisingly contributes to several forms of impulsive behavior. Bilateral excitotoxic lesions of the nucleus accumbens (NAcb) core (NAcbC), but not shell (NAcbS), increase impulsive choice for small immediate rewards (Cardinal et al., 2001; Pothuizen et al., 2005), whereas combined NAcbC/NAcbS lesions reportedly increase preference for larger delayed rewards (or decrease impulsivity) (Acheson et al., 2006). These differing effects may be due to procedural discrepancies, the most prominent being the manner in which delays are actually presented. It has been argued, for example, that NAcb lesions disrupt the ability of animals to predict the timing of delayed reward when the delay to reward is changed frequently, suggestive of an adaptive role of this structure in delay discounting (Acheson et al., 2006). This idea is consistent with other findings that NAcbC lesions mainly affect impulsivity on the 5CSRT task when the ITI (or 'waiting period') is unexpectedly altered (Murphy ER et al., unpublished data; Christakou et al., 2004). Finally, prominent roles of medial and lateral striatum in 5CSRT task performance have been shown with lesions of the medial striatum, in particular, resembling those targeting medial cortical structures (Christakou et al., 2001; Rogers et al., 2001).

As discussed above, lesions of the anterior Cgl do not appear to impair choice for delayed, large magnitude, rewards (Cardinal et al., 2001; Rudebeck et al., 2006). However, supragenual Cgl lesions do reduce choice for a larger reward alternative which requires higher effort versus a smaller reward/lower effort option (Rudebeck et al., 2006; Walton et al., 2003, 2002). Selective lesions of the OFC, which have minimal effect on impulsive responding on the 5CSRT task, have been shown to disrupt choice behavior in delay discounting paradigms. However, the effects have been rather inconsistent. Thus, in two studies, rats with bilateral OFC lesions showed increased preference for choosing a smaller, immediate reward over a larger, delayed reward (Mobini et al., 2002; Rudebeck et al., 2006). However, in a third study, OFC-lesioned rats actually showed decreased impulsive choice (i.e. increased preference for the large delayed reward) (Winstanley et al., 2004b). The cause of this anomaly is unknown but again potentially involves the precise way in which delay discounting procedures such as these are empirically defined and carried out. Thus, although the weight of evidence supports a role of OFC in choice for delayed rewards, its specific role in this process requires further clarification. The important point overall is that OFC is apparently sensitive to delays to reinforcement whereas Cg1 is sensitive to required effort, regardless of delay (Rudebeck et al., 2006).

4. Behavioral pharmacological studies

Pre-clinical research into the neurochemistry of impulsive behavior has focused almost exclusively on the brain DA and 5-HT systems (for review see Winstanley et al., 2006a). However, in light of the growing interest and acceptance of an important role of NA in the aetiology and treatment of ADHD it is clear that earlier studies may need to be re-evaluated and perhaps repeated to clarify the precise mode of action of stimulant drugs like amphetamine which discriminate poorly between the NA, DA and 5-HT systems (Kuczenski and Segal, 1997). Indeed, even supposedly selective compounds like atomoxetine increase both NA and DA levels in the medial PFC (Bymaster et al., 2002). Added to this complexity the cortical versus sub-cortical loci of drug effects in ADHD remain poorly understood.

Nevertheless, it is instructive that a recent study reports decreased impulsivity on the SSRT, delay discounting and 5CSRT tasks in rats treated systemically with atomoxetine (Robinson et al., 2007a). This is the first report of convergence across broadly different measures of impulsivity involving delay aversion and response inhibition and implies that a common brain mechanism may be involved. Stimulants, by contrast, generally increase impulsivity on the 5CSRT task, go/no-go and DRL paradigms (Blackburn and Hevenor, 1996; Robbins, 2002; Wiley et al., 2000) but decrease impulsive behavior in the delay discounting and SSRT tasks (Winstanley et al., 2006a). Such divergent effects are perhaps best explained by the fact that unlike stimulant drugs, atomoxetine has no effect on DA release in the striatum (Bymaster et al., 2002; Kuczenski and Segal, 1997) and thus has negligible effects on behavioral invigorating mechanisms mediated by NAcb DA (Robbins and Everitt, 2007). Thus, stimulant and non-stimulant drugs may both exert their beneficial effects in ADHD via the fronto-cortical NA and DA systems, an idea clearly compatible with recent speculations (e.g., see Arnsten and Li, 2005). It is also consistent with reports that increased impulsivity on the 5CSRT task following acute amphetamine treatment in rats can be reversed by selective NAcb DA depletion (Cole and Robbins, 1989) and intra-NAcb infusions of DA receptor antagonists (Pattij et al., 2007).

However, there are some obvious caveats to this notion, not least the role of 5-HT itself which has for many years been implicated in the brain mechanisms underlying inhibitory response control (Soubrié, 1986). Indeed, $5HT_{2a}$ and $5\text{-}HT_{2c}$ receptors, in particular, appear to be promising targets for therapeutic drug action in disorders of impulse control (Robinson et al., 2007b; Carli et al., 2006; Higgins et al., 2003; Koskinen et al., 2000; Passetti et al., 2003; Winstanley et al., 2003a; Fletcher et al., 2007). Nevertheless, many of the effects of selective 5-HT manipulations on impulsivity; for example, produced by depleting brain 5-HT through intracerebroventricular infusions of the serotonergic neurotoxin 5,7-DHT or the administration of selective 5-HT receptor antagonists, appear to involve interactions with the brain DA systems (Harrison et al., 1997; Lucki and Harvey, 1979; McMahon et al., 2001; Segal, 1976). Indeed, there is direct support for the notion that 5-HT/DA interactions may contribute to the expression of certain impulsive behaviors (e.g., delay aversion on a delay discounting paradigm — Winstanley et al., 2003b). Challenges for future research will be (1) to establish the cortical versus sub-cortical loci of this interaction (see Robinson et al., 2007b) and (2) to determine the significance of 5-HT/DA interactions to the aetiology and treatment of ADHD (e.g., see Oades, 2002).

5. In-vivo neurochemical studies

In general elucidating the causal involvement of individual chemical neuromodulatory systems in cognitive functions mediated by the PFC and striatum requires direct neural intervention. However, targeted manipulations such as these can be problematic — for example, in leading to non-specific neuroadaptive or compensatory changes, which may in turn affect function locally as well as more globally at a network-wide level. An alternate, yet complementary, approach to infer the involvement or otherwise of an individual neurotransmitter system in motivated behavior is to measure directly its release or presence in the extracellular fluid of the brain during task performance. Applying this principle to rats trained on either the 5CSRT task or the delay discounting paradigm, we have carried out a number of studies using the technique of in-vivo microdialysis to measure levels of different neurochemicals in both the medial PFC and OFC of task-performing rats (Dalley et al., 2001, 2002a,b; McGaughy et al., 2002; Passetti et al., 2000; Winstanley et al., 2006b). By measuring several neurotransmitters on the same task and allowing changes in brain release to be determined by the animals' own performance we were able to determine the functional specificity of neurochemical inputs to the PFC and OFC, as well as the general nature of processes underlying the activation of discrete neurotransmitter systems. These studies were conducted with the working hypothesis that different neurotransmitter systems likely modulate distinct psychological and behavioral processes that are themselves determined and constrained by the different cortical areas to which they project (Everitt and Robbins, 1997).

On a practical level there are a number of factors that can affect the quality of data obtained using this approach. It is undesirable for example to use general anesthetic agents that have a slow offset of action (e.g., barbiturates). The best anesthetic agent in our hands is a ketamine/xylazine mix given by the intra-muscular route of administration. Inhalational agents such as isoflurane and methoxyflurane are also very suitable for this work allowing animals to be tested within 48 h of surgery. It is also important that animals are well-habituated to the in-vivo microdialysis system and that behavioral performance is not unduly affected by the tethering arrangement, especially on the 5CSRT task where animals shuttle continuously between the front and the back of the box to collect food reward on correct trials. This is best achieved by ensuring that response latencies, omissions and other behavioral measures are no different to pre-surgical performance levels. Significant discrepancies in behavior may require minor modifications to the testing apparatus — for example, by removing the front panel from the food magazine to facilitate head entry or adjusting the length and counterbalancing of the tether. Finally, since the 5CSRT

task requires a nose-poke operant the probe assembly on the skull should ideally be kept as small as possible.

The main results of this approach are summarized in Table 1. The first series of studies measured levels of ACh and NA in the medial PFC of rats performing the 5CSRT task over a 60 min period (Dalley et al., 2001; McGaughy et al., 2002; Passetti et al., 2000). In all studies, large and sustained increases in ACh efflux were found in animals actively performing the task, similar to findings in a related sustained attention task (Himmelheber et al., 2000). To ensure that such changes depended on active responding and not food reward we used a yoked design procedure whereby previously trained rats received food reward that was contingent on the performance of a second 'master' rat (Dalley et al., 2001). Although ACh efflux increased in yoked rats this was significantly attenuated compared with master rats thus indicating that reward contingent responding was an important component of the cholinergic response in the PFC. Importantly, these neurochemical data accord with a large number of studies implicating the basal forebrain cholinergic system in sustained attention (Everitt and Robbins, 1997; Sarter and Bruno, 1997). A further important finding was that in well-trained rats there was no marked increase in NA efflux — consistent with previous reports of a lack of effect of forebrain NA depletion on baseline performance (Carli et al., 1983; Cole and Robbins, 1992). NA efflux was, however, increased in yoked animals when food was no longer contingent on performance (Dalley et al., 2001). Such effects were dissociable from ACh efflux and consistent with a special involvement of the coeruleo-cortical NA system in novel settings, presumably related to a shift in attention (focused or scanning, e.g., (Usher et al., 1999) and the facilitation of more adaptive behavioral strategies. We return to this point later.

Table 1
Dissociable changes in extracellular levels of the primary neuromodulatory input systems of the medial PFC during stable performance on the 5CSRT and delay discounting tasks, as measured by in-vivo microdialysis

	5-choice serial RT		Delay-discounting	
ACh	↑	Sustained [a]	§	–
5-HT	↔ [b]	–	↑	Sustained [e]
NA	↑	Transient [c]	§	–
DA	↑	Sustained [d]	↑	Sustained
DOPAC	↑	Sustained [d]	↑	Sustained

An indication of whether changes were transient (i.e., less than 20 min) or sustained (up to 60 min) is shown. § denotes not measured; ↑ increase; ↔ no change.

[a] (Passetti et al., 2000); (Dalley et al., 2001); (McGaughy et al., 2002).

[b] (Dalley et al., 2002a). 5-HT levels were unaffected during performance of a simple choice reaction time procedure. However, 5-HT levels were related positively to levels of premature responding on this task.

[c] (Dalley et al., 2001). Sustained increases in NA levels were, however, found when the predictive relationship between instrumental responding and food reinforcement was extinguished.

[d] (Dalley et al., 2002a). Sustained elevations in DA and DOPAC levels were found during performance of a one-hole variant of the 5CSRT task.

[e] (Winstanley et al., 2006b). No change in 5-HT efflux was observed in OFC under similar test conditions.

Serotonin efflux has also been measured in the medial PFC of rats during continuous performance of a simplified one-hole variant of the 5CSRT task (Dalley et al., 2002a). This version of task assesses impulsivity in the same way as the 5CSRT task and is as sensitive as the 5CSRT task in detecting changes in impulsive responding caused, for example, by the selective depletion of brain 5-HT (Winstanley et al., 2004a). At baseline, 5-HT efflux was remarkably unaffected in the majority of animals during 60 min of sustained task performance. However, in a small subset of subjects, 5-HT levels were found to correlate positively with levels of premature responding on this task. Though seemingly at odds with the prevailing dogma of reduced 5-HT in impulsivity this finding is nevertheless consistent with an earlier report of increased 5-HT utilization in right frontal cortex of impulsive rats on this task (Puumala and Sirvio, 1998). Further support was provided in a later follow up study where reduced impulsivity was found in isolation-reared rats treated systemically with amphetamine which was linked to decreased 5-HT efflux in PFC (Dalley et al., 2002b). These findings thus imply that inadequate or excessive stimulation of 5-HT receptors in the PFC can interfere with inhibitory response control (see also Passetti et al., 2003).

To date, it has been difficult to dissociate changes in extracellular levels of DA in PFC from those of ACh. During task performance DA efflux generally increases by about 2-fold in line with similar increases in the DA metabolite 3,4-dihydroxyphenyacetic acid (DOPAC) (Dalley et al., 2002a). These changes presumably relate, to some extent, to reinforcement mechanisms as DA and DOPAC efflux increase even when 'free' food is provided non-contingently upon behavior under a yoked schedule (Winstanley et al., 2006b).

However, based on a recent study where in-vivo microdialysis was coupled to performance of rats on a delay discounting procedure extracellular levels of DOPAC were found to increase selectivity in the OFC, effects that could not be attributed to instrumental responding or reward delivery (Winstanley et al., 2006b). The precise origin of increased DOPAC in this study is unknown but potentially could arise from NA afferents in this region (see Nisenbaum et al., 1991). A further original finding of this study was that 5-HT efflux increased in medial PFC but not OFC. This effect was clearly related to task demand, not reward density or the level of instrumental responding, and was further dissociable from the lack of effects on 5-HT efflux during performance of a fixed ITI simple reaction time task (Dalley et al., 2002a). This may imply an involvement of PFC 5-HT in aspects of temporal discrimination, consistent with earlier reports (e.g., see Dietrich and Allen, 1998).

6. Individual differences in impulsivity

An important consideration in relating research into inhibitory response mechanisms to clinical psychopathology is the relative contribution of genetic and environmental determinants to underlying neurobiological mechanisms, which presumably largely account for inter-individual variability in behavior. Recently, we and others have taken advantage

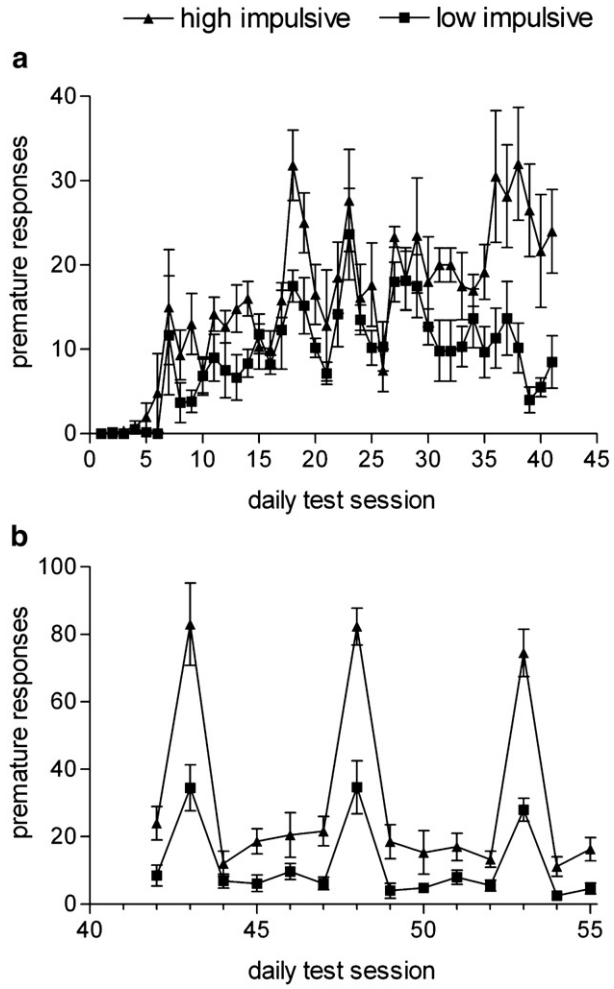

Fig. 1. Temporal profile of premature responding on the 5CSRT task as a function of training. It can be seen that rats destined to be impulsive on the 5CSRT task ('high impulsive', $n=6$) show a delayed elevation in premature responding compared with low-impulsive rats ($n=6$). The separation of future high- and low-impulsive rats is most obvious after approximately 30 days of training (6 daily sessions/week) during the post-acquisition stage when the visual target stimuli are 0.5 s in duration (a). Screening for high impulsivity is carried out in trained animals by measuring their level of premature responding during three challenge sessions (sessions 43, 48 and 53) when the inter-trial interval (ITI) is increased from 5 s to 7 s (b). High impulsivity is defined by levels of premature responding greater than 50 on each of the three challenge sessions. ANOVA results (a): session: $F_{40,400}=7.8$; $p<0.001$; group: $F_{1,10}=16.9$; $p=0.002$; session x group: $F_{40,400}=1.64$; $p=0.01$ (b): session: $F_{13,130}=51.2$; $p<0.001$; group: $F_{1,10}=20.48$; $p=0.001$; session x group: $F_{13,130}=8.69$; $p<0.001$.

of the fact that high impulsivity on the 5CSRT task is a naturally occurring phenotype present in a low but stable frequency, typically 10% or less in its extreme form (Blondeau and Dellu-Hagedorn, 2006; Dalley et al., 2007; Diergaarde et al., 2007; Puumala et al., 1996). The phenotype itself is remarkably selective in behavioral terms with errors of omission, response latencies and food latencies generally no different compared with non-impulsive rats (Dalley et al., 2007). High impulsive (HI) rats are also not hyperactive in most test settings (Blondeau and Dellu-Hagedorn, 2006); indeed they actually show reduced levels of locomotor activity when placed in a novel environment (Dalley et al., 2007). They also show no obvious impairment in the acquisition of the 5-CSRT task and they exhibit no obvious learning deficits.

However, one curious feature of HI rats is that the phenotype emerges only at the latter stages of training when task demand is high. Thus, the number of premature responses appears to increase quite dramatically in HI rats when the stimulus duration is reduced to 0.6 s or less (see Fig. 1a). Moreover, once identified, subjects displaying a high impulsive phenotype go on to show persistent and stable elevations in premature responding on this task (Fig. 1b). We and others have also found that high impulsivity on the 5CSRT task is inversely related to attentional accuracy with low accuracy scores being associated with the high levels of premature responding (Fig. 2) (Blondeau and Dellu-Hagedorn, 2006; Puumala et al., 1996; Puumala and Sirvio, 1998). However, while it is feasible to distinguish between a combined inattentive/impulsive cluster and an attentive/non-impulsive cluster, equivalent to the distinction of Blondeau and Dellu-Hagedorn (2006), the division between mildly inattentive/impulsive sub-groups is less easily made in our hands. This appears to be due, in part, to the generally higher performance of Lister hooded rats (present study) compared with albino rat strains (Blondeau and Dellu-Hagedorn, 2006; Puumala et al., 1996), making subsequent hierarchical cluster analysis more difficult. Nevertheless, the clear congruence between the different studies suggests that impulsivity and inattentiveness are to some extent related behavioral variables.

Several studies have examined the neurobiological correlates of high impulsivity on the 5CSRT task. The main deficits appear localized to PFC, especially Cgl, with specific abnormalities in metabolic activity, DA turnover and 5-HT release (Barbelivien et al., 2001; Dalley et al., 2002a). Diffuse abnormalities in 5-HT utilization in right frontal cortex have also been reported (Puumala and Sirvio, 1998). More recently using PET we found reduced availability of $D_{2/3}$ receptors in the NAcb and a significant inverse relationship between $D_{2/3}$ availability in NAcb and impulsivity (Dalley et al., 2007). There was no accompanying

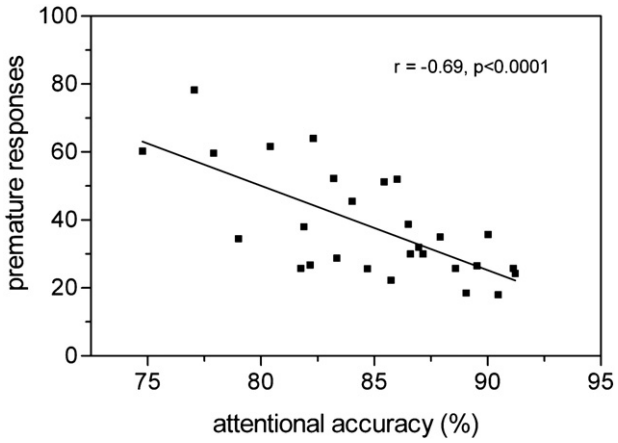

Fig. 2. Significant negative correlation between impulsivity on the 5CSRT task and attentional accuracy ($n=28$). Data shown are the mean number of premature responses and attentional accuracy (%) averaged across the three long-ITI challenge sessions. Challenge sessions were presented at weekly intervals and consisted of 100 discrete trials, each of a fixed long ITI of 7 s.

change in DA release in the NAcbC implying that such receptor changes likely reflected reduced $D_{2/3}$ receptor number (or Bmax). These changes appear consistent with the hypothesis that $D_{2/3}$ receptors in this region mediate motivated behavior for distal versus proximal rewards (Smith et al., 2005). It is also worth pointing out that this form of impulsivity is attenuated by low systemic doses of atomoxetine (Blondeau and Dellu-Hagedorn, 2006). These findings thus implicate a neural circuitry that overlaps to some extent with the spontaneous hypertensive rat model of ADHD (Russell et al., 1995) with disturbances in dorsomedial PFC/Cgl and NAcb, and corresponding abnormalities in NA, DA and 5-HT function.

7. Synthesis and implications for clinical psychopathology

There has been considerable convergence in recent years on the neuroanatomical substrates of impulsivity in experimental animals and clinical patient groups. Primary areas of interest include the PFC, OFC and distinct sub-regions of the striatum and there is evidence, as reviewed above, of functional specialization in the neural systems mediating the two major sub-forms of impulsivity — delay aversion and response inhibition.

Our research to date implicates an abnormal underlying neuromodulation of Cgl and NAcb in the expression and persistence of high impulsivity on the 5CSRT task. The notion that such behavior is determined by Cgl–NAcb interactions and attentional demand is supported by several lines of evidence, in addition to recent neurobiological findings reviewed above. Firstly, lengthening the duration of the visual stimulus from 0.25 s to 1 s significantly decreases premature responding on this task (Blondeau and Dellu-Hagedorn, 2006), thereby suggesting the core deficit to be unrelated to impaired timing and temporal discrimination per se. Secondly, focal excitotoxic lesions of Cgl selectively impair attentional accuracy (Chudasama et al., 2003; Passetti et al., 2002), effects reminiscent of impaired accuracy of HI rats tested at baseline (Blondeau and Dellu-Hagedorn, 2006; Puumala et al., 1996). Thirdly, as discussed below, premature responses increase after trials where errors are made in rats with disconnection lesions of NAcbC and medial PFC that include Cgl (Christakou et al., 2004).

The anterior cingulate cortex has been widely implicated in processes of cognitive control, specifically in adjusting behavior in demanding task situations involving response conflict, errors in performance, and negative feedback (Barch et al., 1997; Duncan and Owen, 2000; Kerns et al., 2004; Yeung et al., 2005). The notion that HI rats on the 5CSRT task carry an underlying abnormality in Cgl function is supported by at least two behavioral observations. Firstly, it may explain the late onset in impulsivity at a time when visual target stimuli are more difficult to discriminate. Secondly, it may explain the reported increase in premature responding after negative feedback in PFC lesioned rats (Christakou et al., 2004).

How such a primary deficit in Cgl causally mediates impulsivity on the 5CSRT task is poorly understood at present. However, one hypothesis gaining prominence is that via strong convergent excitatory projections to the locus coeruleus (LC) noradrenergic system Cgl and OFC exert a powerful control over the adaptive need to adjust behavior in situations that are either novel, non-routine or difficult (Aston-Jones and Cohen, 2005; Tait et al., 2007). Such a concept is entirely compatible with previous speculations on the role of the LC noradrenergic system in 'effortful' processing (Cole and Robbins, 1992; Dalley et al., 2004) and suggests the hypothesis that deficits in Cgl–LC interactions may in part underlie impaired impulse control on the 5CSRT task. This hypothesis is clearly testable by the direct measurement of NA efflux in NA-rich brain areas of high impulsive rats, including Cgl and the NAcbS during task performance.

A schematic representation of the key frontal cortical–ventral striatal systems implicated in impulsivity in experimental animals is shown in Fig. 3. For clarity focus is placed on the modulation of this circuitry by NA and DA. Clearly, though, other neuromodulatory systems likely play an important role as well, including 5-HT, glutamate and histamine (e.g., see Day et al., 2007). The main frontal cortical systems implicated in impulsivity include Cg1, OFC and IL. These project to the NAcb in an heterogeneous manner with the NAcbC and NAcbS receiving preferential inputs from the Cg1 and IL, respectively (Voorn et al., 2004). Impulsive choice on delay discounting procedures depends on the functional integrity of the OFC and NAcbC (Winstanley et al., 2004b; Mobini et al., 2002; Cardinal et al., 2001). Other forms of impulsivity, including impulsive actions, depend on the medial PFC – especially Cg1 and IL – as well as the nucleus accumbens and areas of the medial striatum considered homologous to the caudate nucleus in humans (Eagle and Robbins, 2003; Robbins, 2002; Rogers et al., 2001).

At the core of this model is the NAcb which receives a heterogeneous distribution of catecholaminergic inputs from the

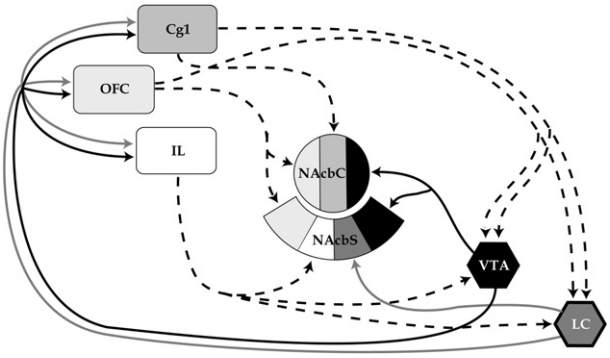

Fig. 3. Frontal cortical–ventral striatal systems underlying the control and regulation of impulsive behavior in rodents. Descending pathways from the anterior cingulate cortex (Cg1), orbitofrontal cortex (OFC) and inframbic cortex (IL) terminate in the nucleus accumbens core (NAcbC) and shell (NAcbS) as well as the main nuclei of origin of the brain noradrenergic and dopaminergic systems (locus coeruleus 'LC' and ventral tegmental area, 'VTA', respectively). The NAcbC and NAcbS receive inputs from the VTA but only the NAcbS receives a significant innervation from the LC. Cortical inputs to the nucleus accumbens are topographically organized with differential inputs from Cg1 and IL to the NAcbC and NAcbS, respectively (Voorn et al., 2004). Rats showing high levels of impulsivity on the 5CSRT task exhibit Cgl dysfunction and putatively impaired gating of PFC control over striatal output via impaired Cgl–NAcbC functioning and abnormal Cgl modulation of LC inputs to the NAcbS and other functional nodes.

VTA and LC. The NAcbC and NAcbS are both densely innervated by DA terminals (Brog et al., 1993) but only the NAcbS receives a prominent NA-ergic innervation (Berridge et al., 1997; McKittrick and Abercrombie, 2007). The significance of this heterogeneous innervation is that it potentially connects two independent sources of inhibitory control over NAcb output and behavior, namely a circuitry that includes Cg1 and NAcbC and a circuitry that includes IL and NAcbS. Thus, optimal impulse control may require the recruitment of one or more inhibitory control modules in a manner dependent on task demand and the adaptive imperative to adjust or control behavior in changing situations. Challenges for future research on brain mechanism of impulsivity will be (1) to determine the functional significance of NA and DA in the NAcbC, NAcbS and PFC and (2) to elucidate how drugs with putatively selective actions on the brain noradrenergic systems (i.e., atomoxetine and guanfacine) act to alleviate different forms of impulsive behavior via interactions with cortical and sub-cortical NA.

Finally, understanding the psychobiological mechanisms of impulsivity has important implications for human drug abuse and addiction. Several recent studies have examined how chronic drug exposure affects different measures of impulsivity in rats (Dalley et al., 2005; Jentsch and Taylor, 1999; Paine et al., 2003). Although significant effects have been observed (e.g., on delay discounting) it appears from recent findings that impulsivity may be causally involved in drug abuse vulnerability rather than the other way around (Dalley et al., 2007; Diergaarde et al., 2007; Perry et al., 2005). Thus, rats selected for high impulsivity on both the delay discounting and 5CSRT tasks maintain significantly higher levels of intravenous cocaine and nicotine self-administration than non-impulsive control rats. They also show significantly reduced levels of $D_{2/3}$ receptors in the NAcb (Dalley et al., 2007), which extends earlier findings in human drug addicts (Volkow et al., 2002) by showing that such receptor changes may, in part, pre-date drug use. Finally, our working hypothesis of Cgl hypofunction in HI rats may be relevant to the finding that cocaine addicts show reduced activity of the anterior cingulate cortex and impaired inhibitory response control when task demand (i.e., working memory load) is high (Hester and Garavan, 2004).

Summing up, this review emphasizes the tremendous progress that has been made in defining the nature of neural systems mediating distinct forms of impulsivity. Further advances will be made by continuing to facilitate the already considerable translation that exists between pre-clinical and clinical models of impulsivity. Central to this aim should be a greater refinement of animal models to define more precisely distinct sub-forms of impulsivity (see Gottesman and Gould, 2003), and a more focused effort to understand the role and functional significance of NA in the aetiology and treatment of ADHD.

Acknowledgements

This work was funded by an MRC Pathfinder Award (G0401068), the Wellcome Trust (076274/z/04/z), and by a consortium joint award from the MRC and Wellcome Trust (G0001354) within the Cambridge University Behavioral and Clinical Neuroscience Institute.

References

Acheson A, Farrar AM, Patak M, Hausknecht KA, Kieres AK, Choi S, et al. Nucleus accumbens lesions decrease sensitivity to rapid changes in the delay to reinforcement. Behav Brain Res 2006;l73:217–28.

Ainslie G. Specious reward: a behavioral theory of impulsiveness and impulse control. Psychol Bull 1975;82:463–96.

Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 2005;57:1377–84.

Aron AR, Durston S, Eagle DM, Logan GD, Stinear CM, Stuphorn V. Converging evidence for a fronto–basal–ganglia network for inhibitory control of action and cognition. J Neurosci 2007;27:11860–4.

Aston-Jones G, Cohen JD. Adaptive gain and the role of the locus coeruleus norepinephrine system in optimal performance. J Comp Neurol 2005;493: 99–1 10.

Avery RA, Franowicz JS, Studholme C, van Dyck CH, Arnsten AF. The alpha-2A-adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. Neuropsychopharmacology 2000;23:240–9.

Barbelivien A, Ruotsalainen S, Sirvio J. Metabolic alterations in the prefrontal and cingulate cortices are related to behavioral deficits in a rodent model of attention-deficit hyperactivity disorder. Cereb Cortex 2001;11:1056–63.

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 1997;35:1373–80.

Berridge CW, Stratford IL, Foote SL, Kelley AE. Distribution of dopamine betahydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens. Synapse (New York, N.Y 1997;27:230–41.

Blackburn JR, Hevenor SJ. Amphetamine disrupts negative patterning but does not produce configural association deficits on an alternative task. Behav Brain Res 1996;80:41–9.

Blondeau C, Dellu-Hagedorn F. Dimensional analysis of ADHD subtypes in rats. Biological Psychiatry 2006;61:1340–50.

Broersen LM, Uylings HB. Visual attention task performance in Wistar and Lister hooded rats: response inhibition deficits after medial prefrontal cortex lesions. Neuroscience 1999;94:47–57.

Brog JS, Salyanpongse A, Deutch AY, Zahm DS. The patterns of afferent innervation of the core and shell in the 'accumbens' part of the rat ventral striatum: immunohistochemical detection of retrogradely transported Fluoro-Gold. J Comp Neurol 1993;338:255–78.

Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2002;27:699–711.

Caballero J, Nahata MC. Atomoxetine hydrochloride for the treatment of attention-deficit/hyperactivity disorder. Clin Ther 2003;25:3065–83.

Cardinal RN. Neural systems implicated in delayed and probabilistic reinforcement. Neural Netw 2006;19:1277–301.

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ. Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 2001;292:2499–501.

Cardinal RN, Winstanley CA, Robbins TW, Everitt BJ. Limbic corticostriatal systems and delayed reinforcement. Ann NY Acad Sci 2004;1021:33–50.

Carli M, Robbins TW, Evenden JL, Everitt BJ. Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 1983;9:361–80.

Carli M, Baviera M, Invernizzi RW, Balducci C. 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 2006;3(1):757–67.

Casey BJ, Castellanos FX, Giedd IN, Marsh WL, Hamburger SD, Schubert AB, et al. Implication of right frontostriatal circuitry in response inhibition

and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psych 1997;36: 374–83.
Castellanos FX, Giedd TN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53:607–16.
Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 2006;311:861–3.
Christakou A, Robbins TW, Everitt BJ. Functional disconnection of a prefrontal cortical–dorsal striatal system disrupts choice reaction time performance: implications for attentional function. Behav Neurosci 2001;115:812–25.
Christakou A, Robbins TW, Everitt BJ. Prefrontal cortical–ventral striatal interactions involved in affective modulation of attentional performance: implications for corticostriatal circuit function. J Neurosci 2004;24:773–80.
Chudasama Y, Passetti F, Rhodes SE, Lopian D, Desai A, Robbins TW. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. Behav Brain Res 2003;146:105–l 19.
Cole BJ, Robbins TW. 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 1989;33:165–79.
Cole BJ, Robbins TW. Forebrain norepinepbrine: role in controlled information processing in the rat. Neuropsychopharmacology 1992;7:129–42.
Dalley JW, Thomas KL, Howes SR, Tsai TH, Aparicio-Legarza MI, Reynolds GP, et al. Effects of excitotoxic lesions of the rat prefrontal cortex on CREB regulation and presynaptic markers of dopamine and amino acid function in the nucleus accumbens. Euro J Neurosci 1999;11:1265–74.
Dalley JW, McGaughy J, O'Connell MT, Cardinal RN, Levita L, Robbins TW. Distinct changes in cortical acetyicholine and noradrenaline efflux during contingent and noncontingent performance of a visual attentional task. J Neurosci 2001;21:4908–14.
Dalley JW, Theobald DE, Eagle DM, Passetti F, Robbins TW. Deficits in impulse control associated with tonically-elevated serotonergic function in rat prefrontal cortex. Neuropsychopharmacology 2002a;26:716–28.
Dalley JW, Theobald DE, Pereira EA, Li PM, Robbins TW. 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) 2002b;164: 329–40.
Dalley JW, Cardinal RN, Robbins TW. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev 2004;28:771–84.
Dalley JW, Theobald DE, Berry D, Milstein JA, Laane K, Everitt BJ, et al. Cognitive sequelae of intravenous amphetamine self-administration in rats: evidence for selective effects on attentional performance. Neuropsychopharmacology 2005;30:525–37.
Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 2007;315:1267–70.
Day M, Pan JB, Buckley MJ, Cronin E, Hollingsworth PR, Hirst WD, et al. Differential effects of ciproxifan and nicotine on impulsivity and attention measures in the 5-choice serial reaction time test. Biochem Pharmacol 2007;73: 1123–34.
Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer AN, et al. Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. Biol Psychiatry 2007. doi:10.1016/j.biopsych.2007.07.011.
Dietrich A, Allen JD. Functional dissociation of the prefrontal cortex and the hippocampus in timing behavior. Behav Neurosci 1998;112:1043–7.
Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 1999;354:2132–3.
Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 2000;23:475–83.
Eagle DM, Robbins TW. Inhibitory control in rats performing a stop-signal reaction time task: effects of lesions of the medial striatum and *d*-amphetamine. Behav Neurosci 2003;117:1302–17.
Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW. Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cereb Cortex 2007. doi:10.1093/cercor/bhmo44.
Elia J, Ambrosini PJ, Rapoport JL. Treatment of attention-deficit-hyperactivity disorder. N Engl J Med 1999;340:780–8.
Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-l8]fluorodopa positron emission tomographic study. J Neurosci 1998;18:5901–7.
Evenden JL. The pharmacology of impulsive behaviour in rats III: the effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and ethanol on a paced fixed consecutive number schedule. Psychopharmacology (Berl) 1998;138:295–304.
Evenden JL. Varieties of impulsivity. Psychopharmacology 1999;146:348–6l.
Everitt BJ, Robbins TW. Central cholinergic systems and cognition. Annu Rev Psychol 1997;48:649–84.
Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998;44:951–8.
Fletcher PJ, Tampakeras M, Sinyard J, Higgins GA. 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 task. Psychopharmacology 2007;195:223–34.
Fone KC, Nutt DJ. Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. Curr Opin Pharmacol 2005;5:87–93.
Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636–45.
Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology (Berl) 1997;133:329–42.
Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. J Neurosci 2004;24:11017–22.
Higgins GA, Enderlin M, Haman M, Fletcher PJ. The 5-HT2A receptor antagonist M100,907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism. Psychopharmacology (Berl) 2003;170:309–19.
Himmelheber AM, Sarter M, Bruno JP. Increases in cortical acetylcholine release during sustained attention performance in rats. Brain research 2000;9:313–25.
Jaskiw GE, Karoum F, Freed WJ, Phillips I, Kleinman JE, Weinberger DR. Effect of ibotenic acid lesions of the medial prefrontal cortex on amphetamine-induced locomotion and regional brain catecholamine concentrations in the rat. Brain Res 1990;534:263–72.
Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl) 1999;146:373–90.
Kerns JG, Cohen JD, MacDonald 3rd AW, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. Science 2004;303:1023–6.
Koskinen T, Ruotsalainen S, Puumala T, Lappalainen R, Koivisto E, Mannisto PT, et al. Activation of 5-HT2A receptors impairs response control of rats in a five-choice serial reaction time task. Neuropharmacology 2000;39: 471–81.
Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 2000;285:107–10.
Krause KH, Dresel SH, Krause J, la Fougere C, Ackenheil M. The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. Neurosci Biobehav Rev 2003;27:605–13.
Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 1997;68:2032–7.
Kutcher S, Aman M, Brooks SJ, Buitelaar J, van Daalen E, Fegert J, et al. International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions. Eur Neuropsychopharmacol 2004;14:11–28.

Lucki I, Harvey JA. Increased sensitivity to *d*- and l-amphetamine action after midbrain raphe lesions as measured by locomotor activity. Neuropharmacology 1979;18:243–9.

McGaughy J, Dalley JW, Morrison CH, Everitt BJ, Robbins TW. Selective behavioral and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192 IgG-saporin on attentional performance in a five-choice serial reaction time task. J Neurosci 2002;22:1905–13.

McKittrick CR, Abercrombie ED. Catecholamine mapping within nucleus accumbens: differences in basal and amphetamine-stimulated efflux of norepinephrine and dopamine in shell and core. J Neurochem 2007;100:1247–56.

McMahon LR, Filip M, Cunningham KA. Differential regulation of the mesoaccumbens circuit by serotonin 5-hydroxytryptamine (5-HT)2A and 5-HT2C receptors. J Neurosci 2001;21:7781–7.

Mobini S, Body S, Ho MY, Bradshaw CM, Szabadi E, Deakin JF, et al. Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl) 2002;160:290–8.

Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett 1993;163:109–13.

Muir JL, Everitt BJ, Robbins TW. The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. Cereb Cortex 1996;6:470–8l.

Murphy ER, Dalley JW, Robbins TW. Local glutamate receptor antagonism in the rat prefrontal cortex disrupts response inhibition in a visuospatial attentional task. Psychopharmacology (Berl) 2005;179:99–107.

Newcorn JH, Halperin JM, Jensen PS, Abikoff HB, Arnold LE, Cantwell DP, et al. Symptom profiles in children with ADHD: effects of comorbidity and gender. J Am Acad Child Adolesc Psych 2001;40:137–46.

Nisenbaum LK, Zigmond MJ, Sved AF, Abercrombie ED. Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. J Neurosci 1991;11:1478–84.

Oades RD. 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 2002;130:97–102.

O'Donnell JM, Seiden LS. Effects of monoamine oxidase inhibitors on performance during differential reinforcement of low response rate. Psychopharmacology 1982;78:214–8.

Paine TA, Dringenberg HC, Olmstead MC. Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. Behav Brain Res 2003;147:135–47.

Passetti F, Dalley JW, O'Connell MT, Everitt BJ, Robbins TW. Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attentional task. Euro J Neurosci 2000;12:3051–8.

Passetti F, Chudasama Y, Robbins TW. The frontal cortex of the rat and visual attentional performance: dissociable functions of distinct medial prefrontal subregions. Cereb Cortex 2002;12:1254–68.

Passetti F, Dalley JW, Robbins TW. Double dissociation of serotonergic and dopaminergic mechanisms on attentional performance using a rodent five-choice reaction time task. Psychopharmacology (Berl) 2003;165:136–45.

Pattij T, Janssen MC, Vanderschuren U, Schoffelmeer AN, van Gaalen MM. Involvement of dopamine Dl and D2 receptors in the nucleus accumbens core and shell in inhibitory response control. Psychopharmacology (Berl) 2007;191:587–98.

Perry JL, Larson EB, German JP, Madden GJ, Carroll ME. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology (Berl) 2005;178:193–201.

Pothuizen HH, Jongen-Relo AL, Feldon J, Yee BK. Double dissociation of the effects of selective nucleus accumbens core and shell lesions on impulsive-choice behaviour and salience learning in rats. Euro J Neurosci 2005;22: 2605–16.

Puumala T, Ruotsalainen S, Jakala P, Koivisto E, Riekkinen Jr P, Sirvio J. Behavioral and pharmacological studies on the validation of a new animal model for attention deficit hyperactivity disorder. Neurobiol Learn Mem 1996;66:198–211.

Puumala T, Sirvio J. 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 1998;83:489–99.

Quirk GJ, Garcia R, Gonzalez-Lima F. Prefrontal mechanisms in extinction of conditioned fear. Biol Psychiatry 2006;60:337–43.

Risterucci C, Terramorsi D, Nieoullon A, Amalric M. Excitotoxic lesions of the prelimbic-infralimbic areas of the rodent prefrontal cortex disrupt motor preparatory processes. Euro J Neurosci 2003;17:1498–508.

Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl) 2002;163: 362–80.

Robbins TW, Everitt BJ. A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology (Berl) 2007;191: 433–7.

Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, et al. Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 2007a. doi:10.1038/sj.npp.1301487.

Robinson ES, Dalley JW, Theobald DEH, Glennon JC, Pezze MA, Murphy ER, et al. Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. Neuropsychopharmacology 2007b. doi:10.1038/sj.npp.1301636.

Rogers RD, Baunez C, Everitt BJ, Robbins TW. Lesions of the medial and lateral striatum in the rat produce differential deficits in attentional performance. Behav Neurosci 2001;115:799–811.

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 1999;156:891–6.

Rudebeck PH, Walton ME, Smyth AN, Bannerman DM, Rushworth MF. Separate neural pathways process different decision costs. Nat Neurosci 2006;9:1161–8.

Russell V, de Villiers A, Sagvolden T, Lamm M, Taljaard J. Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder — the spontaneously hypertensive rat. Brain Res 1995;676:343–51.

Sarter M, Bruno JP. Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. Brain Res Brain Res Rev 1997;23:28–46.

Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 2001;158:1067–74.

Segal DS. Differential effects of para-chlorophenylalanine on amphetamine-induced locomotion and stereotypy. Brain Res 1976;116:267–76.

Smith AJ, Becker S, Kapur S. A computational model of the functional role of the ventral–striatal D2 receptor in the expression of previously acquired behaviors. Neural Comput 2005;17:361–95.

Soubrié P. Reconciling the role of central serotonin neurons in human and animal behavior. Behav Brain Sci 1986;9:319–64.

Solanto MV. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res 2002;130:65–71.

Sorkin EM, Heel RC. Guanfacine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. Drugs 1986;31:301–36.

Spencer TJ, Biederman J, Madras BK, Dougherty DD, Bonab AA, Livni E, et al. Further evidence of dopamine transporter dysregulation in ADHD: A controlled PET imaging study using altropane. Biol Psychiatry 2007;62 (9):1059–61.

Stein DJ, Hollander E, Liebowitz MR. Neurobiology of impulsivity and the impulse control disorders. J Neuropsychiatry Clin Neurosci 1993;5:9–17.

Tait DS, Brown VJ, Farovik A, Theobald DE, Dalley JW, Robbins TW. Lesions of the dorsal noradrenergic bundle impair attentional set-shifting in the rat. Euro J Neurosci 2007;25:3719–24.

Thomason C, Michelson D. Atomoxetine-treatment of attention deficit hyperactivity disorder: beyond stimulants. Drugs Today (Barc) 2004;40:465–73.

Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. Science 1999;283: 549–54.

Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci USA 1998;95:14494–9.

Volkow ND, Fowler JS, Wang GJ, Goldstein RZ. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem 2002;78:610–24.

Voorn P, Vanderschuren U, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal–ventral divide of the striatum. Trends Neurosci 2004;27:468–74.

Walton ME, Bannerman DM, Rushworth MF. The role of rat medial frontal cortex in effort-based decision making. J Neurosci 2002;22:10996–1003.

Walton ME, Bannerman DM, Alterescu K, Rushworth MF. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci 2003;23:6475–9.

Whishaw IQ, Fiorino D, Mittleman G, Castaneda E. Do forebrain structures compete for behavioral expression? Evidence from amphetamine-induced behavior, microdialysis, and caudate-accumbens lesions in medial frontal cortex damaged rats. Brain Res 1992;576:l–11.

Wiley JL, Compton AD, Golden KM. Separation of drug effects on timing and behavioral inhibition by increased stimulus control. Exp Clin Psychopharmacol 2000;8:451–61.

Winstanley CA, Chudasama Y, Dalley JW, Theobald DE, Glennon JC, Robbins TW. Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats. Psychopharmacology (Berl) 2003a;167:304–14.

Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. Psychopharmacology (Berl) 2003b;170:320–31.

Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. Neuropsychopharmacology 2004a;29:1331–43.

Winstanley CA, Theobald DE, Cardinal RN, Robbins TW. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. J Neurosci 2004b;24:4718–22.

Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clin Psychol Rev 2006a;26:379–95.

Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins 1W. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. Cereb Cortex 2006b;16:106–14.

Yeung N, Hoiroyd CB, Cohen JD. ERP correlates of feedback and reward processing in the presence and absence of response choice. Cereb Cortex 2005;15:535–44.