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The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry

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Abstract *Rationale:* The developmental history and application of the 5-choice serial reaction time task (5CSRTT) for measuring effects of drugs and other manipulations on attentional performance (and stimulus control) in rats is reviewed. *Objectives:* The 5CSRTT has been used for measuring effects of systemic drug treatments and also central manipulations such as neurochemical lesions on various aspects of attentional control, including sustained, selective and divided attention – and is relevant to the definition of neural systems of attention and applications to human disorders such as attention deficit/hyperactivity disorder (ADHD) and Alzheimer's disease. *Methods:* The 5CSRTT is implemented in a specially designed operant chamber with multiple response locations ('nine-hole box') using food reinforcers to maintain performance on baseline sessions (about 100 trials) at criterion levels of accuracy and trials completed. The 5CSRTT can be used for measuring various aspects of attentional control over performance with its main measures of accuracy, premature responding, correct response latencies and latency to collect earned food pellets. *Results:* The data reviewed include studies mainly of systemic and intra-cerebral effects of adrenoceptor, dopamine receptor, serotonergic receptor and cholinergic receptor agents. These are compared with investigations of effects of selective chemical neurotoxins and excitotoxins applied to discrete parts of the forebrain, in order to define the neural and neurochemical substrates of attentional function. Furthermore, these results are integrated with findings from *in vivo* microdialysis in freely moving rats or metabolic studies. *Conclusions:* The monoaminergic and cholinergic systems appear to play separable roles in different aspects of performance controlled by the 5CSRTT, in neural systems centred on the prefrontal cortex, cingulate cortex and striatum. These

conclusions are considered in the methodological and theoretical context of other psychopharmacological studies of attention in animals and humans.

Keywords Five-choice serial reaction time task · Attention · Catecholamines · Dopamine · Noradrenaline · Serotonin · Acetylcholine · Amphetamine · Nicotine · Prefrontal cortex · Striatum · Nucleus accumbens · ADHD · Alzheimer's disease · Schizophrenia

Introduction: the problem

The development of the new test paradigm to be described in this Review was initially stimulated by the need to understand the nature of the deficits shown by children with attention deficit/hyperactivity disorder (ADHD) and the effects of psychomotor stimulant drugs such as methylphenidate used in their treatment. One simple way of accounting for the seemingly paradoxical effects of psychomotor stimulants to reduce initially high levels of locomotor activity in ADHD children was to invoke the rate-dependency principle that had been introduced by Dews and his colleagues (Dews 1958; Kelleher and Morse 1968; Dews and Wenger 1977) from studies on experimental animals (Robbins and Sahakian 1979).¹ However, whilst the rate of behavioural output is certainly an important consideration in understanding ADHD-like syndromes, so too is the direction and

¹ That article arose in part from a sabbatical visit to Harvard Medical School in 1977 to work with Peter Dews, Bill Morse and Roger Kelleher. My colleague Barbara Sahakian at the same time worked post-doctorally at MIT with Richard Wurtman (who had much earlier himself been affiliated with the Harvard group). Suffice it to say that understanding the therapeutic effects of stimulant medication certainly was not solved by the Robbins and Sahakian paper, but it has at least stimulated others in the field (Grace 2001). Another main outcome of my visit to Harvard was my introduction to a simple nose-poke operant procedure for mice working under various schedules of reinforcement with condensed milk as the reinforcer (Wenger and Dews 1976), which was one of the main stimuli for my concept of a multi-choice test chamber for rats with an array of response apertures

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efficiency of such behaviour. Psychiatrists and experimental psychologists have tended to use such theoretical notions as “attention” to characterise such behavioural deficits in children with ADHD. Attention is a complex construct with several meanings (see below) and operant psychologists and behavioural pharmacologists, including Dews and colleagues, have often preferred to eschew such constructs in favour of operational formulations such as “stimulus control”. The concept of stimulus control can indeed be helpful for describing the special role of discriminative stimuli in engendering different contingencies of responding, but it has not been so useful for extending our understanding of the transient changes in discriminative performance that occur even in highly trained animals or for inefficiency of performance in situations where stimulus processing demands are high.

When I began this project in about 1977, a number of test procedures had been developed for assessing in animals different aspects of attention (sometimes called continuous performance), such as those introduced by Rosvold and Mirsky (Rosvold et al. 1956; Mirsky and Rosvold 1960) and Kornetsky and Eliasson (1969). However, although some basic drug effects had been described using these procedures, neither of these groups had begun to address the possible roles of central neurotransmitter systems upon which such drugs most probably acted. Thus, I designed a test chamber for rats with a front curved wall containing a number (in fact, nine) of adjacent apertures allowing the measurement of possible nose-poke operants through the use of infra-red beams. Food pellets were presented as reinforcers at a magazine at the rear of the chamber, and to which access was monitored via a hinged Plexiglas panel equipped with a micro-switch. The basic idea was that it would be feasible to measure the response of rats to presentations of brief visual events – in particular, whether the rats could “report” the occurrence of such targets.

Having devised the so-called “nine-hole box”, the challenge was to show that it might be useful and, to that end, John Evenden, Mirjana Carli and myself spent 2–3 years devising a number of procedures for measuring different aspects of performance in rats and, in collaboration with Barry Everitt, using them to quantify effects of manipulations of central neurotransmitters. In particular, we were interested in attentional processes. Just as attention cannot be considered as a unitary construct in humans, so too does it probably consist of several distinct mechanisms in other animals. One form is sustained attention or vigilance, a continuous allocation of processing resources for the detection of rare events. Deficits in vigilance or sustained attention are typically manifested towards the end of a long test session. Another form is divided attention, where an animal has to respond according to several different contingencies in the same test setting, for example having to monitor simultaneously several different sensory channels, thus requiring optimal allocation of limited information processing resources. A third form of attention is selective (focused) attention, where an animal has to focus resources on a restricted

number of sensory channels, whilst ignoring the rest. In practice, many situations require a mixture of these different processes. In order to examine performance that reflected these different forms of attention, Carli, Evenden and myself devised several test procedures, making use of the various ways in which the test chamber could be configured, including some of the earliest attempts to measure reaction time performance in rats (Carli et al. 1985, 1989) and several devoted to quantifying various aspects of the so-called “neglect” syndrome deriving from unilateral brain lesions or other manipulations.

Development of the 5-choice serial reaction time task

The bulk of this review considers a test procedure called the 5-choice serial reaction time task (5-CSRTT) which has been among the most widely adopted of the tasks configured in the nine-hole box (Fig. 1). This test has a basic form which is akin to the continuous performance tests of Rosvold and Mirsky (Rosvold et al. 1956; Mirsky and Rosvold 1960; and still much used in clinical settings to quantify attentional deficits in ADHD and schizophrenia) and which assesses sustained attention to a number of distinct locations over a 30-min or so test session. In this

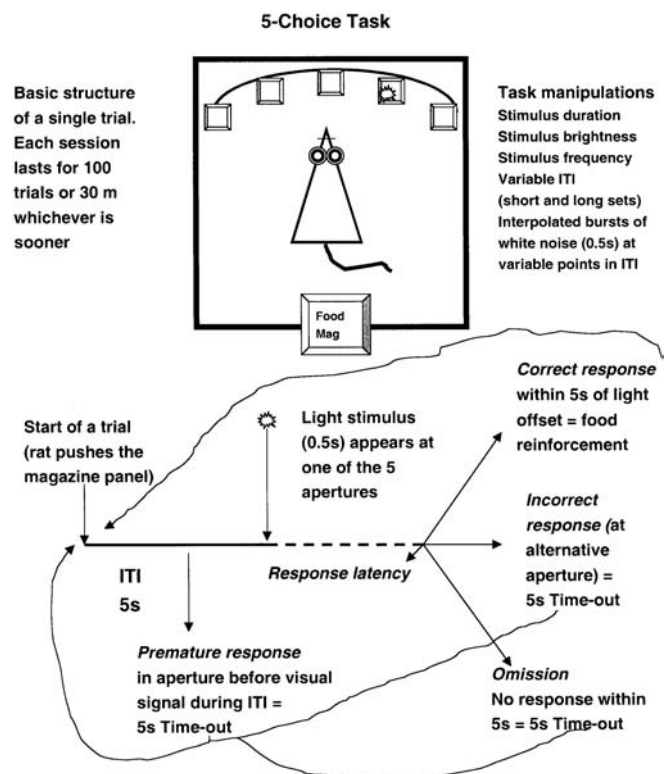


Fig. 1 Schematic of the apparatus used for the nine-choice task (not to scale) and the structure of a trial on the baseline version of the task, with typical parameters of performance. For details of the apparatus and training procedure, see Carli et al. (1983) and also the methodological review by Robbins et al. (1993), which contains detailed descriptions of task contingencies

format, the test is most relevant to quantifying effects on sustained and divided attention. However, as will be detailed below, the test schedule can also be modified to include tests of the ability of rats to ignore brief bursts of white noise while detecting the visual targets.

In the U.K., Leonard (see for example Wilkinson 1963) had previously devised a 5-CSRTT for humans in which subjects again had to continually monitor the location of a visual target stimulus over repeated trials in one of five locations. Immediately upon reporting its occurrence, another of the five locations was randomly chosen as the next target. This task thus also has elements of a continuous performance test, but has an obvious spatial component. The main application of this test was in measuring the effects of stressors and other agents, including drugs, that affected arousal and formed much of the empirical basis for Broadbent's (1971) seminal work on human performance, *Decision and stress*.

Some of our own early attempts to examine attentional processes in animals (Carli et al. 1983) were based on this task, which we configured in the nine-hole box, in which the rat had to monitor the occurrence of a brief (0.5-s) target stimulus (light) projected at the rear of one of five holes set in an arc of nine holes at the front of the chamber. Nose-poke responses in the holes were monitored by infra-red photocell beams placed at their entrance (Fig. 1). Correct responses were rewarded by the presentation of food pellets in a magazine at the rear of the chamber, monitored by a movable flap with a micro-switch attached. Errors of commission (i.e. responding in a hole in which the stimulus had not been presented), errors of omission (failing to respond to the occurrence of a stimulus within a prescribed time limit) and premature responses [prior to the onset of the target stimulus, in the 5-s inter-trial interval (ITI)], were all punished by a brief period of darkness (time-out), after which the trial had to be initiated by a response in food magazine.

The basic task essentially tests the ability of the rat to sustain spatial attention divided among a number of locations over a large number of trials (about 100). This capacity is measured by the accuracy of reporting the stimuli; the choice or response accuracy measure is simply the proportion of correct detections over total correct detections plus errors of commission (i.e. incorrect responses in apertures where the visual target had not been presented), expressed as a percentage. It is important to realise that this measure does not include errors of omission (i.e. failures to respond within the 5-s limited-hold period following the presentation of the brief visual target) or premature responses (i.e. responses occurring before the visual target occurs in the period following the initiation of the trial). Chance performance is thus 20% – and this is a useful baseline which is far less constrained in detecting significant changes than the 50% random performance level of 2-choice procedures. If accuracy is impaired, this is difficult to explain as a simple motor effect because the two responses on average have equivalent motor requirements. It is possible to conceive

any changes in this measure reflecting effects on basic visual sensory function. However, this interpretation can be tested by varying the brightness or illuminance of the stimuli and observing possible disproportionate changes, for example at the lower levels of brightness of the visual targets. In rats that are reasonably well trained, it is evident that they adopt “scanning strategies” for monitoring the five locations, which is consistent with the interpretation that they are allocating attention in order to detect and locate brief stimuli, usually of only 0.5-s duration.

The response latency for correct detections can also be measured to the nearest centisecond, but the interpretation of this measure as a decision time, or as affected by motivational, sedative or motor factors depends on the pattern of changes in other variables. This is also true for the errors of omission measure, where again increases in omissions might hypothetically reflect sensory, motor or motivational factors. These differing interpretations can often be disambiguated by considering other control measures taken during performance, and by taking into account the overall profile or pattern of effects for measures on the task as a whole. For example, motivation can be indexed sensitively by the latency to collect earned food pellets (i.e. visiting the food magazine after a correct response). Therefore, if changes in response latency occur in the absence of changes of latency to collect earned pellets, the former more likely reflects decisional processes. Furthermore, if increases in omissions are similarly not accompanied by changes in magazine latency, the increased omissions may well be due to gross impairments in attention.

Finally, aspects of response inhibitory control (sometimes called executive functioning) are indexed by such variables as premature responses (occurring in the 5-s ITI) or perseverative responses (repeated responses at the response apertures). Premature responses occur inappropriately, before the visual targets have occurred and presumably during the period in which the rats are anticipating their occurrence. They thus appear to occur when inhibitory control of highly prepotent responses has been lost maladaptively, and, as such, are examples of impulsive behaviour (Evenden 1999). Perseverative behaviour, by contrast, represents another form of inhibitory deficit (more akin to “compulsive” rather than “impulsive” behaviour), in which rats continue to respond at the apertures even following signalled food presentation. This perseverative behaviour may be directed either at the aperture where responding has just earned reinforcement or at other locations. Thus, the 5-CSRTT is capable of measuring several different types of performance that include aspects of attention and impulse control. It might be considered that increases in premature and perseverative responses, as well as impairments in accuracy, all reflect changes in stimulus control. However, the concept of stimulus control then ceases to have much explanatory power when these various measures do not show well-correlated changes. In general, it appears that, although some of these measures can co-vary in certain circum-

stances, they often dissociate and appear to depend on different processes, probably under control of separable neural mechanisms. This is particularly true of measures such as response accuracy and premature responses, and we shall be considering the relevant evidence later in this review.

The difficulty of the 5-CSRTT can be varied by reducing or increasing the brightness, duration or frequency of the target visual stimuli. However, manipulations of the task parameters can be used to probe other aspects of attention or more general performance factors (Fig. 1). For example, the stimuli can be made temporally, as well as spatially, unpredictable, a manipulation that is equivalent to the non-paced version of the continuous performance task (versus the standard, or paced, version in which stimuli come at predictable intervals). The less predictable schedule (or stimulus-onset asynchrony – SOA) means that the rat or human cannot rely on automatic processing to control orientation to the location of the stimuli at a particular time and they thus have to monitor their readiness to respond on a continuous basis. If deficits only arise under conditions where stimuli are unpredictable, they are again more likely to reflect attentional rather than simple sensory functions.

Alternatively, distracting stimuli, such as bursts of white noise, can be interpolated into the inter-trial interval in order to distract the rat from the target visual stimuli (in unpublished studies of Carli, Evenden and Robbins, this has also been done in the visual modality by presenting irrelevant visual stimuli in the four locations not used for presenting targets). Such manipulations clearly test the ability of the animal to “screen out” irrelevant stimuli and thus constitute tests of selective attention. Finally, possible ‘vigilance decrements’ (Parasuraman et al. 1987) can be identified by recording attentional performance over the course of the session, to provide specific measures of sustained attention. However, one common problem with this type of paradigm is that it is difficult to separate out possible effects of vigilance decrement from simple satiety, due to the ability of the rat to earn large numbers of food pellets by working for long periods over large numbers of trials. However, this is in principle feasible if the latency to collect earned food pellets shows no sign of lengthening at the end of the session.

5-CSRTT: functional neural systems

The pattern of effects on the variants of the 5-CSRTT obtained from the manipulations of specific neurotransmitter systems to be described below, including systemic drug administration, presumably results from the disruption of modulation of particular neural systems in their terminal domains. Thus, before describing the specific pharmacological effects in the 5-CSRTT in more detail, it is worth reviewing what has been following direct interference with the functioning of these systems by lesioning (Muir et al. 1996a) or by correlating the metabolic activity of discrete areas using deoxyglucose

(DG) autoradiography (Barbelivien et al. 2001) – even though these studies have been relatively recent.

It is possible to make discrete lesions of different forebrain regions by local infusions of glutamate receptor agonists, which, at suitable doses and depending on the local concentrations and characteristics of glutamate receptor sub-types, act as cell-body excitotoxins, largely sparing fibres of passage (Muir et al. 1996a).

Following lesions of different cortical areas using quinolinic acid, there were transient deficits in choice accuracy following damage to the medial prefrontal cortex (PFC), peri- and post-genual anterior cingulate cortex, and the parietal cortex. These were significant, substantial, and lasting in the case of the medial PFC lesion. After performance recovered to control levels, rats with medial PFC lesions showed a strong tendency towards impairment following shortening of the stimulus and presentation of white noise just prior to the visual target. However, the most striking effect of these challenges was seen in the latencies of the medial PFC lesioned rats, which lengthened specifically and significantly in each case, suggesting that the lesion had caused deficits that resulted in the animals trading speed for accuracy. Although antero-dorsal PFC lesioned rats had no deficits on the baseline, they too responded to the attentional challenges with significantly lengthened latencies in the case of unpredictable or abbreviated stimuli, and for interpolated bursts of white noise in the ITI. None of the lesioned groups exhibited disproportionate impairments when the brightness of the discriminanda was varied, suggesting that none of the deficits resulted from primary sensory loss (as might perhaps reasonably also be inferred from what is already known about the functional neuroanatomy of these regions).

Of the other cortical areas studied, the most clear-cut results were found following lesions of the anterior cingulate cortex, which produced long-lasting and significant increases in impulsive responding, even though no other aspect of attentional performance was affected. This result is important because it supports the claim made above that the accuracy and “impulsivity” measures can be functionally dissociated – also supported by patterns of systemic drug effects, and by certain neurochemical measures and manipulations (see below).

The most surprising results from the study by Muir et al. (1996a) are the apparent lack of effects of parietal cortex lesions, as this region is known to be a major presumed locus of a “posterior attentional system” in primates which has been linked to attentional disturbances such as neglect (Posner and Petersen 1990). However, it is possible that neither the exact locus of damage nor the exact nature of the attentional requirements of the 5-choice task were appropriate for exposing attentional dysfunction dependent on the parietal cortex of the rat. More recent work using smaller lesions is helping to define precise relationships between sub-regions of the rat PFC and 5-CSRTT performance. For example, discrete lesions to the rat prelimbic cortex (Zilles’ area Cg3) appear to cause increases in perseverative responding,

with little effect on other measures (Chudasama and Muir 2001), whereas similar lesions to the Cg1 region produce selective impairments in accuracy (Passetti et al. unpublished observations) suggesting that these various sub-regions have quite specific functions that have to be coordinated in order to produce optimal 5-CSRTT performance. These data are also consistent with the pharmacological evidence we have reviewed which suggests that the different aspects of 5-CSRTT performance can be differentially affected by drug treatments.

From this work, it appears that the anterior cortex is particularly important for the control of performance on the 5-CSRTT. This is supported by evidence that manipulations of the hippocampus seem to have relatively little impact on trained performance on the task. For example, bilateral perforant path knife cut lesions, while producing a delay-dependent deficit in an operant delayed-matching-to-position task, had little effect on 5-CSRTT performance (Kirkby and Higgins 1998). This result is also important from a behavioural perspective, as it suggests that the very small delays and, hence hypothetically, the engagement of working memory itself, are not a major prerequisite for 5-CSRTT performance. Notwithstanding, it is possible that the hippocampus plays some role in task acquisition (Bratt et al. 1995) and in certain aspects of monitoring of performance (Barbelivien et al. 2001).

The striatum is an obvious component of the functional neural system engaged by 5-CSRTT performance, considering not only its connectivity with the PFC, but also evidence, to be described below, that it mediates many of the effects of systemic and intracerebral D-amphetamine on 5-CSRTT performance. This involvement of the striatum has been confirmed by recent studies that have compared the effects of discrete excitotoxic striatal lesions on 5-CSRTT performance. Thus, Rogers et al. (2001) have drawn a clear distinction between the effects of lesions of the medial and lateral striatum. Lesions to the latter, a homologue of the primate putamen, produce a remarkable syndrome in which performance of the task is virtually abolished, with only few trials being completed per session. A degree of recovery occurs over many subsequent training days, as though the rat is re-acquiring the task. However, this re-acquisition is significantly less efficient than the initial learning, and some form of lasting performance deficit seems likely. The nature of this striking impairment remains to be elucidated. Control tests and other considerations suggest that it is not simply a consequence of motor impairment or motivational dysfunction. One implication is that it represents a form of disturbance of the retrieval of response rules (i.e. a "reference memory" deficit) or of "stimulus-response habits". However, it is apparent that lateral lesioned rats continue to discriminate the visual targets at an above chance (20% correct) level of accuracy, even at an early post-operative stage, when they are completing very few trials.

Lesions of the medial striatum (which spare the underlying ventral striatum and also leave minimal

cortical damage) produce a considerable disruption of 5-CSRTT performance, which, however, is not as profound as that following lateral lesions inasmuch that the medial lesioned rats do continue to work at the task and generally complete the requisite number of trials. The medial lesion, however, leads to significant deficits on response accuracy, lengthened response latencies, and to increases in both premature and perseverative responses (Rogers et al. 2001). This broad syndrome is consistent with some convergence of input into the medial striatum from cortical systems controlling these separate elements of performance. This proposed functional interaction between the medial PFC and medial striatum is supported by recent evidence coming from the study of asymmetrical, disconnection preparations in which a lesion to the medial PFC in one hemisphere is combined with a lesion to the medial striatum in the other hemisphere. This combination of lesions produces a syndrome that is as powerful as that of bilateral lesions to either cortical or striatal structure, and cannot be mimicked by unilateral lesions of either structure alone, or within the same hemisphere (Christakou et al. 2001). Further work has also established that lesions of the core region of the nucleus accumbens affect some aspects of performance, such as an elevation in premature responses, but do not affect response accuracy (Christakou et al. unpublished data) consistent with the hypothesis that several components of 5-CSRTT performance are mediated by somewhat distinct cortico-striatal circuits. The subsequent translation of this processing into task-related performance clearly continues into brain stem circuitry. Increased premature responding occurs following lesions to the medial dorsal, but not the anterior, thalamus (Chudasama and Muir 2001), with rather more global deficits in performance being caused by lesions to the dorsal globus pallidus (Robbins et al. 1989), subthalamic nucleus (STN) (Baunez and Robbins 1997) or the pedunculopontine nucleus (Inglis et al. 2001). Although further discussion of these impairments is beyond the scope of this Review, it is notable that these findings have been used in an attempt to define further neurochemical influences influencing performance at these levels. For example, both muscimol and AP5 infusions have been employed within the STN to demonstrate the effects of manipulating neurotransmission respectively of GABAergic or glutamatergic inputs impinging on the STN (Baunez and Robbins 1999a).

The lesion approach to defining the critical neural systems substrate for 5-CSRTT performance has recently been complemented by the metabolic mapping study of Barbelivien et al. (2001) in low-performing and high-performing rats on the 5-CSRTT. Thus, [¹⁴C]DG uptake was measured during the performance of the 5-CSRTT, as an index of neuronal activity in many forebrain sites. Results showed that the poorly performing rats exhibited lower DG uptake in the cingulate and ventrolateral orbital cortices than did well-performing rats. There was an inverse correlation between the percentage of premature responses and DG uptake in the ventrolateral orbitofrontal

and cingulate cortices. There was also a positive correlation between choice accuracy and DG uptake in several other cortical areas, including the frontal and parietal regions. These findings are broadly consistent with the effects of lesions of the rat cortical regions summarised above (Muir et al. 1996a), although it is important to bear in mind that the DG evidence is essentially correlative and, as such, can never define the causal contribution of the structures showing DG uptake for 5-CSRTT performance. However, Barbelivien et al. (2001) pointed out the similarity of the neural network revealed using DG uptake as well as that implicated in attentional functioning in primates using other approaches. They also speculated about the possible role of the cingulate and ventrolateral orbital regions in models of ADHD.

The understanding of the central substrates of 5-CSRTT performance opens up the possibility of establishing the location of the key receptors for certain systemic drug effects. This understanding also enables us to define the probable terminal domains within which more specific manipulations of the ascending neurotransmitter systems exert their effects.

5-CSRTT: neuropharmacology

Following extensive training on the 5-CSRTT, performance generally reaches high (e.g. >80% accuracy; <15% omissions) levels, with low within- and between-subject

variance. Nevertheless, at 80% correct, performance is not at ceiling and it is still possible in theory to detect improvements in accuracy. The less than perfect performance presumably reflects attentional factors, rather than an inability to learn, or to retrieve from reference memory the “rule” (‘respond to the lit hole’). The stable baselines of performance engendered by the 5-CSRTT have made it quite a useful means for assessing repeated effects of systemically administered drugs in groups of well-trained rats, especially as performance often returns to baseline quite rapidly. This stability is characteristic of the methodology introduced by Dews, Morse and colleagues for quantifying the behavioural effects of systemically administered drugs. The disadvantage of studying peripherally administered drugs, of course, is that their actions can be mediated by receptors at multiple sites, and so the overall effect often comprises several, sometimes competing, components. This also means that it would not be surprising if the effects of generally more discrete intra-cerebral manipulations, such as central infusions, do not always correspond to effects observed peripherally. However, of course, systemically administered drugs correspond more readily to effects seen in humans, for example therapeutically, when attempting to produce so-called “cognitive enhancing” actions in patients with disorders such as dementia.

The 5-CSTTT paradigm was originally introduced to test the effects of a large number of neuropharmacological manipulations, summarised in Table 1. The major

Table 1 Summary of main neuropharmacological effects on the 5-choice serial reaction time task (CSRTT) and interactions with behavioural manipulations on measures of response or choice accuracy and premature (or impulsive) responses. Manipulations: *baseline* baseline task, *bright* variations of brightness, *Var ITI* variability of inter-trial interval, *Dur* reduced duration of visual target, *WN* bursts of white noise, *D-Amp* systemic d-amphetamine. Effects relative to sham control: *up* increase, *down* decrease, *0* no difference or no differential effect of lesion vs sham control, *nt* not tested. Treatments: *DNAB* dorsal noradrenergic bundle lesion (Carli et al. 1983; Cole and Robbins 1992), *nbm-ACh* saparin lesions of cholinergic projections of nucleus basalis magnocellularis (nbm) (McGaughy et al. 2002), *VS-DA* ventral striatal dopamine depletion (Cole and Robbins 1989), *DS-DA* (Baunez and Robbins 1999b), *5-HT* global and profound depletion of forebrain 5-HT (Harrison et al. 1997a, 1997b)

	Baseline	Bright	Var ITI	Dur	WN	D-Amp
% Correct						
DNAB	0	0	Down	nt	Down ^a	Down ^b
nbm-ACh						
Low dose sap	Down	0	0	0	nt	nt
High dose	Down for all manipulations tested					nt
VS-DA	0	0 ^c	0 ^d	nt	0	0
DS-DA	0	nt	Down	0	nt	0
5-HT	Up ^e	0	0 ^f	0	0	0
Premature responses						
DNAB	0	0	Down ^g	nt	0 ^h	0 ^h
nbm-ACh						
Low dose sap	0	nt	0	0	nt	nt
High dose	Up for all manipulations tested					
VS-DA	Down	0	0	nt	Down	Down
DS-DA	0	nt	0	0	nt	0
5-HT	Up	Up	Up	Up	Up ^g	Up ⁱ

^a WN just prior to target

^b At higher doses

^c Small improvement at lowest level

^d Small improvement at shortest ITI

^e Transient improvement following dorsal raphé lesions only

^f Performance improved at short ITIs following median raphé lesions

^g WN increased premature responses equally in lesioned and sham rats

^h Transient effect, not always replicated

ⁱ Less increase in 5-HT lesioned rats with increasing doses

findings, over almost a 20-year period, are dissociable effects observed following selective lesions to each of the monoaminergic neurotransmitter systems (noradrenergic, dopaminergic and serotonergic), as well as the cholinergic (ACh – acetylcholine) system (Robbins and Everitt 1995a). In the last few years, other approaches to establishing the roles of these systems have emerged, foremost among them being attempts to correlate post-mortem indices of neurotransmitter turnover with indices of 5-CSRTT performance (Puumala and Sirvio 1998) and direct measurement of neurotransmitter function during 5-CSRTT performance, using *in vivo* microdialysis in the freely moving animal (Passetti et al. 2000; Dalley et al. 2001, 2002).

Noradrenergic systems

Selective lesions of the dorsal noradrenergic ascending bundle and in vivo neurochemistry

In one of the initial investigations (Carli et al. 1983), almost complete depletion of cortical noradrenaline (NA), achieved by infusions of the catecholamine selective neurotoxin 6-hydroxydopamine into the trajectory of the dorsal noradrenergic ascending bundle (DNAB), only produced accuracy deficits under certain conditions (Table 1). These were when the stimuli were presented unpredictably in time, when distracting bursts of noise occurred just prior to the target stimuli, and when the behaviourally activating drug and indirectly acting catecholamine agonist D-amphetamine was infused into the region of the nucleus accumbens (Cole and Robbins 1987). A working hypothesis was developed to accommodate these findings that cortical NA was engaged in conditions of high arousal to preserve attentional selectivity (Robbins 1984; see Robbins and Everitt 1995b for a re-appraisal of this hypothesis in the light of subsequent evidence). A later study replicated and extended most of the original findings of the effects of DNAB lesions on performance in the 5-choice task. Of particular interest was the finding that the disruptive effects of white noise on choice accuracy were of similar magnitude over several values of illuminance for the visual signals, suggesting an effect of NA depletion relatively late in the course of processing, perhaps at the level of response preparation (Cole and Robbins 1992).

More recent work has used the novel approach of monitoring extracellular levels of NA within the medial PFC during performance of the 5-CSRTT, as well as that of other neurotransmitters, using *in vivo* microdialysis in the previously trained, freely-moving animal (Dalley et al. 2001, 2002). For NA, it was interesting to observe that, in well-trained rats on baseline, there were no increases in NA concentration – a finding that might have been predicted from the lack of effect of coeruleo-cortical NA depletion on baseline performance (Carli et al. 1983; Cole and Robbins 1992). However, NA levels were elevated when the task contingencies were manipulated so that the

rat still received the equivalent number of food presentations, but no longer had to respond to the visual signals. This result might be interpreted as reflecting the response of the coeruleo-cortical NA system to novel circumstances – the elevation in NA did show some attenuation on a second session. Its importance is that this result was not obtained in the same situation for ACh in the PFC (see below). Overall, it appears that the coeruleal-cortical NA system is engaged during particularly novel or arousing circumstances in a way that presumably optimises performance, including aspects of attentional function.

Effects of systemic adrenoceptor agents

To date, effects of systemic adrenergic alpha-1 and alpha-2 agonists and antagonists have been predominantly reported. Systemic doses of dexmedetomidine (e.g. 3.0 mg/kg s.c.), an alpha-2 agonist which probably reduces central noradrenergic function, mainly increased errors of omission and reduced premature responses (Sirvio et al. 1994; Ruotsalainen et al. 1997), possibly reminiscent of sedative actions, but possibly more dependent on post-synaptic actions as the effects on omissions were not blocked by central NA depletion effected using *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) (Ruotsalainen et al. 1997). These findings in rats are of interest in comparison with the apparently ameliorative effects of systemically administered alpha-2 agonists such as clonidine and guanfacine in reducing disruptive effects of interpolated white noise during the delay period of a delayed-response working memory task in monkeys (Arnsten and Contant 1992).

In contrast to the effect of the alpha-2 agonist dexmedetomidine, the alpha-2 receptor antagonist atipamezole, administered at doses (0.03–3.0 mg/kg) that might be expected to enhance central noradrenergic function, improved detection of visual signals when their brightness was reduced. There were, however, no significant effects when the signals were made unpredictable by varying the ITI, except at the highest doses, which impaired performance (Sirvio et al. 1993, 1994).

St-587, a putative alpha-1 agonist, also produced a small but significant improvement in response accuracy when the visual signals were shortened at low doses (0.1 mg/kg) (Puumala et al. 1997), again suggesting that under certain conditions boosting noradrenergic function can enhance attentional performance. Prazosin, the alpha-1 receptor antagonist, in complementary fashion, produced a mild disruptive effect on accuracy at 0.3 mg/kg and blocked the effect of St-587 on accuracy at 0.1 mg/kg, a dose that had no effect by itself. The specificity of these effects is shown from the fact that similar doses had no effects on a spatial delayed non-matching to position test of working memory (Puumala and Sirvio 1997). At the same 0.1-mg/kg dose of St-587, there was an increase in trials completed and reduction in premature responses on the 5-CSRTT, whereas prazosin (0.3 mg/kg) reduced trials completed and lengthened response latencies (Pu-

umala et al. 1997). However, these effects of St-587 and prazosin did not show mutual antagonism when combinations of the two agents were studied.

Taken together, these findings do not immediately seem to correspond to the effects of DNAB lesions, reviewed above, which produce profound depletion of telencephalic NA and mainly affect accuracy, and only under certain test conditions (Carli et al. 1983; Cole and Robbins 1992), although directly comparable data are not always available for some conditions (such as reduced target duration). The most relevant receptor appears to be the alpha-1 adrenoceptor which modulates response accuracy to a greater extent than the alpha-2 adrenoceptor compounds studied so far. However, it is clear that manipulation of a single receptor, especially via peripheral administration, cannot be expected to have directly comparable effects to those of widespread NA depletion, because of the multiplicity of systems affected, both centrally and peripherally by systemic administration. In order to reconcile the effects of the systemically administered adrenergic agents and central NA depletion, it will be necessary in future studies to infuse adrenoceptor agents (affecting beta as well as alpha subtypes) at specific central nervous system (CNS) locations and employ those testing conditions that most clearly reveal effects of DNAB lesions (Carli et al. 1983; Cole and Robbins 1992; Dalley et al. 2001, see below). For these reasons, it is unwise to make too many generalisations at this stage about the effects of systemically administered adrenoceptor agents on 5-CSRTT performance.

Dopaminergic systems

Central dopamine depletion, intracerebral infusions and in vivo neurochemistry

The consequences of manipulating central dopaminergic transmission on performance of this task have been studied for both the ventral striatum, including the nucleus accumbens and the dorsal striatum (caudate-putamen). Depletion of dopamine (DA) effected using 6-OHDA in both regions mainly affected indices of response vigour: the number of errors of omission were increased, response latencies were lengthened, whereas response accuracy was largely unaffected – see Table 1 (ventral striatum, Cole and Robbins 1989; dorsal striatum, Baunez and Robbins 1999b). In the case of the dorsal striatum, there is a small effect on response accuracy with variable ITI (Baunez and Robbins 1999b), as well as an increase in perseverative responses (Table 1). These results are broadly consistent with evidence from other tests carried out using this apparatus that manipulations of dorsal striatal DA affect mainly response-related processes (Carli et al. 1985; Brown and Robbins 1989, 1991). By contrast with effects of DA depletion from both the dorsal and ventral striatum, 6-OHDA lesions of the medial PFC (which typically reduce both DA and NA levels there) have relatively minor effects. However, under some

conditions, for example, variable and short ITIs, response accuracy is impaired by such lesions (Robbins et al. 1998), possibly consistent with an attentional role for the PFC, in addition to its well-known implication in working memory (Goldman-Rakic 1998).

These studies employing depletion of central DA have been complemented by others in which central infusions of drugs have been employed. For example, intra-accumbens infusions of the drug D-amphetamine had almost the opposite effects to those of mesolimbic DA loss (Cole and Robbins 1987). Dose-dependent increases in impulsive (premature) responses were the main effect, with no obvious change in response accuracy until relatively high doses of the drug were used. Depletion of nucleus accumbens DA reduced the impulsive responding produced both by systemic D-amphetamine and bursts of white noise (Cole and Robbins 1989). Both of the latter agents mainly enhance the vigour of responding, but, unlike cholinergic and noradrenergic treatments, did not significantly affect discrimination or choice accuracy. The effects of intra-accumbens amphetamine were also blocked by concomitant systemic treatment with 0.3 mg/kg of the mixed D1/D2 receptor antagonist alpha-flupenthixol, a dose which by itself had little effect on performance. Therefore, it seems likely that most of these effects of D-amphetamine are mediated by DA (see also above). In fact, NA depletion by DNAB lesions had no effect on response speed or premature responses induced by D-amphetamine (either systemically or via intra-accumbens infusions) – but did lead to impairments in response accuracy not seen in normal rats (Cole and Robbins 1987). This is consistent with the hypothesis (Robbins 1984) that the noradrenergic system preserves attentional selectivity in the face of stressful, arousing, or, in this case, activating effects. Thus, when the coeruleo-cortical system is compromised, the activating effects of amphetamine may lead to impairments in accuracy.

For the medial PFC, infusions of DA receptor agents have quite clear-cut effects, but almost entirely on response accuracy rather than on other measures (Granon et al. 2000). As might have been expected on the basis of the pharmacology of working memory, D1 receptor agents were more efficacious than D2 agents. Thus, for example, intra-PFC bromocriptine (D2 agonist) and sulpiride (D2 receptor antagonist) had no significant effects, over several doses. Importantly, D1 receptor agents did have significant effects on accuracy, with improvements following medial PFC infusions of the partial D1 receptor agonist SKF 38393 and impairments following the D1 receptor antagonist, SCH 23390. More intriguingly, these effects were both baseline dependent. Thus, the D1 receptor agonist enhanced accuracy in rats with relatively low (about 70%) accuracy, but had no effect on higher performance levels (about 80%). These baseline differences were obtained by a combination of taking poorly performing rats on the basic schedule and also titrating performance of other rats to a lower level by reducing the target signal duration; it did not appear much to matter how the low baseline was generated, but this

clearly needs further research to resolve. In a complementary manner, suitable doses of the D1 receptor antagonist SCH 23390 only impaired accuracy in rats performing at a relatively high baseline. The precise average values for the low and high baselines make it difficult to argue that the drug actions were limited by ceiling (or floor) effects. Rather, the data suggest that the dopaminergic projection to the rat PFC has specific functions in modulating response accuracy rather than aspects of performance such as speed and vigour of responding, which are mediated in part by subcortical DA systems. Based on these results, systemically administered DA receptor agents can clearly be expected to exert a mixture of these effects (see below).

The precise role of the PFC DA system in 5-CSRTT performance has not yet been fully established, but there is converging evidence from other approaches including direct neurochemical measurements. DA depletion from the medial PFC using 6-OHDA produces relatively minor deficits in performance, although accuracy is impaired with unpredictable ITIs (Robbins et al. 1998). However, these 6-OHDA lesions also had reduced PFC NA levels and probably also exhibited considerable recovery or functional compensation. A study of post-mortem neurochemical changes underlying individual differences in 5-CSRTT performance showed a significant correlation between 3,4 dihydroxyphenylacetic acid (DOPAC)/DA ratios and choice accuracy in the right frontal cortex (Puumala and Sirvio 1998). This is probably consistent with preliminary evidence that extracellular PFC DA is elevated during a simplified, 1-choice variant of the task; the relationship to choice accuracy cannot yet be determined but, unlike PFC 5-hydroxytryptamine (5-HT), there is none with premature responses (Dalley et al. 2002).

*Effects of systemic catecholamine agents:
D-amphetamine, methylphenidate and haloperidol*

For rats well-trained on the 5-CSRTT, the most striking effect of systemically administered drugs, such as the indirectly acting catecholamine agonist D-amphetamine, has generally been to affect indices of response vigour such as premature responding and correct latency, but not response accuracy, except at higher doses, at which impairments are sometimes observed (Cole and Robbins 1987, 1989). The effects of these non-selective catecholamine agents are considered under the heading of dopaminergic systems because there is evidence that at least some of their behavioural effects on the 5-CSRTT are mediated by dopaminergic systems, although it is likely that their effects often reflect actions within both the noradrenergic and dopaminergic systems (Cole and Robbins 1987).

Improvements in choice accuracy with psychomotor stimulant drugs that are commonly seen in human subjects, and which have been the empirical basis of tests of connectionist modelling of the actions of the

central catecholamines (Servan-Schieber et al. 1990), have proven difficult to observe using the 5-CSRTT. This is probably because the apparent improvements seen following D-amphetamine in humans are generally seen in vigilance situations, it having long been known that D-amphetamine counteracts the effects of fatigue and the so-called vigilance decrement (Mackworth 1965). As noted above, it has proven quite difficult to devise comparable paradigms for the rat, although recent investigations have shown that such a decrement may be evident under certain conditions. Poor accuracy of performance on the 5-CSRTT is sometimes correlated with elevated premature responses in intact, but "poorly performing" rats (Puumala et al. 1996). These authors have, in fact, related this apparent association of enhanced impulsivity and impaired attention to the ADHD syndrome and further shown that a low dose of the stimulant drug methylphenidate (100 µg/kg) reduces premature responses and mildly enhances accuracy in poorly performing animals. However, a higher dose of methylphenidate (1000 µg/kg) in the same poorly performing rats produced significantly improved accuracy, but in conjunction with the usual increase in premature responding that is seen following D-amphetamine. Whilst the improvements in accuracy are distinct from what is seen in normal high-performing rats, the fact that premature responding was also elevated fails to support the hypothesis that impulsivity somehow leads to attentional deficit. Overall, these findings suggest that it may be possible to detect improvements in accuracy with psychomotor stimulant drugs, in low performing rats, possibly paralleling the improvements observed with intra-cerebrally administered D1 receptor agents, described above (Granon et al. 2000). However, it is also possible that there are subtle differences in the effects of D-amphetamine and methylphenidate which have not yet been studied systematically.

The main effects of both systemically (0.3–2.3 mg/kg) and intra-cerebrally (1–10 µg, bilaterally, intra-accumbens) administered D-amphetamine on well-trained 5-CSRTT performance are to increase premature responding, generally at doses having no significant effects on response accuracy (Cole and Robbins 1987, 1989). One difference between systemic and central administration is that the latency to respond correctly is speeded by systemic amphetamine but slowed by intra-accumbens amphetamine (Cole and Robbins 1987). This intriguing difference presumably reflects an alternative site to the ventral striatum for some of the behavioural effects of amphetamine in this situation. These data also indicate that there can be a separation of effects between measures of speed and overall probability of responding (i.e. premature responding), and hence a dissociation of the processes underlying response vigour.

Premature responding induced by systemic D-amphetamine is blocked by DA depletion from the nucleus accumbens (Cole and Robbins 1989). In contrast, there is evidence that the "speeding" of response latency component of the amphetamine response is mediated by dorsal striatal DA. Baunez and Robbins (1999b) challenged

dorsal striatal DA-depleted rats with systemic D-amphetamine (0.6 mg/kg) and showed that the usual speeding produced by this dose in normal rats was not found to be significant in rats with dorsal striatal DA depletion. In contrast, similar depletion did not block the elevation in premature responding produced by D-amphetamine, unless there was an additional lesioning of the STN. As excitotoxic lesions of the STN produce many behavioural effects similar to those observed following manipulations of the ventral striatum (Baunez et al. 2002), this is consistent with the mediation of such impulsive responses via this circuitry, and also with the suggested dissociation of measures of speed and probability of responding.

Complementary to the effects of D-amphetamine, systemic haloperidol (a DA and also adrenoceptor blocker) has also been reported to lengthen response latency and increase errors of omission (Carli and Samanin 1992). The latter findings are consistent with the effects of haloperidol in a related task in which motor requirements were minimised (Skjoldager and Fowler 1991).

Effects of selective DA receptor agents

As we have seen, many of the effects of D-amphetamine can be ascribed to effects at central DA receptors, but there have been some further investigations using more selective agents. There are now extensive dose-response data for the D1 and D2 receptor antagonists (Harrison et al. 1997a) to supplement the effects reported for the mixed D1/D2 antagonist alpha-flupenthixol (Cole and Robbins 1987). The Harrison et al. data were collected in the context of a study of effects of i.c.v. lesions of the central 5-HT systems but were also obtained for sham-operated control rats. The findings were quite clear. Systemic administration of the D1 receptor antagonist SCH23390 (0.05 mg/kg and 0.075 mg/kg) mainly produced effects on the vigour, rather than the accuracy of performance, affecting, for example, premature responses, omissions and latencies to respond. The D2 receptor antagonist sulpiride (40 mg/kg and 60 mg/kg), by contrast, impaired response accuracy and latency measures but did not significantly reduce premature responding. A recent study has shown the same difference between D1 and D2 receptor antagonists in terms of effects on accuracy, raclopride on this occasion being the D2 receptor agent (Shoaib et al. 2001). These findings have recently been complemented by studies in monkeys of effects of selective DA receptor antagonists (and also D-amphetamine), using a version of the 5-CSRTT implemented on a video monitor with a touch-sensitive screen (Weed and Gold 1998). The main effects were to generally increase reaction times at both phases of the required response sequence (release and respond).

In summary, when given systemically [with the exceptions of effects of amphetamine (at high doses only) and sulpiride] DA agents mainly affect indices of response vigour, such as premature responding, omissions

and latency, rather than accuracy. This makes it difficult to argue that their primary effects are on attentional function. From the evidence of manipulations of central DA systems, it appears likely that many of the effects of DA agents on vigour of performance (i.e. speed, premature responses, etc.) are mediated by dorsal and ventral striatal systems, although the deficits in accuracy produced by sulpiride might relate to those impairments in accuracy occurring following dorsal striatal DA depletion in some conditions. By contrast, there is direct evidence for a role for PFC DA systems specifically to modulate the accuracy of 5-CSRTT performance.

Serotonergic systems

Central 5-HT depletion and in vivo neurochemistry

The effects of central 5-HT depletion have mainly been studied using the neurotoxins para-chlorophenylalanine (PCPA) and 5,7 dihydroxytryptamine (DHT). Unfortunately, they do not produce the same picture. PCPA has been reported to reduce accuracy if the stimuli are presented at a faster rate than normal or at low intensity (Jakala et al. 1992). These effects are somewhat reminiscent of the effects of DNAB lesions (Carli et al. 1983, see above), and may reflect in part some non-specific actions of PCPA. The effects of forebrain 5-HT depletion following intra-ventricular administration of the neurotoxin 5,7 DHT provide a complex pattern that contrasts with that resulting from PCPA or manipulations of the other neurochemical systems (Harrison et al. 1997a). The most striking, and seemingly permanent, effect is to increase premature or "impulsive" responding, rather like intra-accumbens amphetamine. This effect is very long-lasting, occurring essentially over the entire post-operative period of several months, and irrespective of various task manipulations, such as alterations in ITI (similar effects have since been observed by other groups; Carli and Samanin 2000). The increases in premature responding following i.c.v. 5,7 DHT were antagonised by systemic administration of SCH 23390, a D1 receptor antagonist. Additional effects included a speeding of the latency to collect food pellets, an effect, however, which does not appear to result merely from enhanced primary motivation.

More selective patterns of depletion, produced by infusions of 5,7 DHT from the medial and dorsal nuclei led to dissociable profiles of effects. The enhancement of impulsivity is especially apparent following infusions in the dorsal raphé, which mainly innervates the neocortex and striatum, but this depletion also uncovers a transient but significant enhancement of choice accuracy. Medial raphé lesions, by contrast, which produce widespread 5-HT depletions in the forebrain, especially in the hippocampus, are probably responsible for the speeded latencies to collect earned food pellets (Harrison et al. 1997a, 1997b). These varied effects of 5-HT depletion clearly indicate that this neurotransmitter, like the other mono-

amines, has multiple functions in mediating different aspects of performance on this task, depending on the anatomical locus of depletion. This might also explain the qualitatively different functional effects seen after systemic administration of different 5-HT receptor agents.

These effects of i.c.v. 5,7 DHT have to be assessed in the context of results of other studies, sometimes employing systemic drug treatments with this paradigm, or others that attempt to measure 5-HT involvement in specific anatomical locations. This has led in some instances to some apparently paradoxical findings. For example, Puumala and Sirvio (1998) found a correlation between one index of 5-HT utilisation in the right frontal cortex, and the proportion of premature responses across individual animals. This then suggests that, in apparent contradistinction to findings of 5-HT depletion increasing impulsive responding reviewed above (Harrison et al. 1997a, 1997b), elevated 5-HT activity within the frontal cortex is also associated with such responding. Nevertheless, the findings of Puumala and Sirvio (1998) are supported by several other observations. They are consistent with the effects of certain systemic effects [e.g. of the 5-HT_{2A/C} receptor agonist DOI, see above, although these effects of DOI could not be reproduced by central infusions into either the nucleus accumbens or the cingulate cortex (Koskinen et al. 2000b)]. In fact, consistent with systemic effects of DOI, either systemic or intra-PFC ketanserin (the 5-HT_{2A/C} receptor antagonist) reduces premature responding (Passetti et al. unpublished data). Furthermore, a recent study focused on measuring 5-HT via a microdialysis probe within the medial PFC in a simplified 1-choice version of the 5-CSRTT, suitable for eliciting individual differences in premature responses, has also shown a significant positive correlation between extracellular 5-HT and the number of premature responses (Dalley et al. 2002). Thus, while it appears that there is a definite relationship between 5-HT function and the control of premature responses on the 5CSRTT, the precise nature of this is unknown. There is some evidence to suggest that excessive stimulation of 5-HT₂ receptors at certain locations interferes with mechanisms of response control rather than attention. However, it seems possible that different forms of inhibitory control may be exerted by the 5-HT systems at different receptors within distinct brain regions: to test this will require further research.

One conclusion that does appear to hold across studies is that, under certain circumstances, elevated 5-HT function is associated with impaired response accuracy and, correspondingly, that diminished 5-HT function, can lead to improved accuracy (e.g. following dorsal raphé lesions, Harrison et al. 1997b). This finding is consistent with the negative correlation between accuracy and 5-HT utilisation in the left PFC (Puumala and Sirvio 1998). It is intriguing to consider the suggestion that such improved accuracy following reduced 5-HT function may depend on interactions with other neurotransmitter systems, for example, within the PFC, DA (Puumala and Sirvio 1998) and ACh, increases in both DA-ergic and cholinergic

neuromodulation being associated with enhanced attentional performance (Granon et al. 2000, and below).

Effects of systemic serotonergic agents

The diverse behavioural effects of agents affecting 5-HT transmission on the 5-choice task are also not always consistent with what has been seen following global central 5-HT depletion (Harrison et al. 1997a, below). The situation is complicated by the large number of 5-HT receptor subtypes, several of which have now been implicated in sometimes different aspects of 5-CSRTT performance, by the non-selectivity of many of the agents, and to some small degree some inconsistencies in findings with particular drugs. In the earliest study there were deficits in accuracy following the non-selective 5-HT_{2A/C} agonists LSD (0.1 mg/kg, i.p.) and quipazine (2.5 mg/kg, i.p.) that were remediated by the 5-HT_{2A/C} receptor antagonist ritanserin (Carli and Samanin 1992). A follow-up study of the 5-HT_{2A/C} agonist DOI (0.05–0.2 mg/kg s.c.), however, led to only mild impairments in accuracy in one study (Koskinen et al. 2000a) and none at all in another (Koskinen et al. 2000b) under a range of test conditions. However, DOI markedly increased premature responding, with no effects on response latencies or open-field activity (Koskinen et al. 2000a, 2000b; Koskinen and Sirvio 2000). The effects on premature responses were blocked by both ritanserin and ketanserin, another 5-HT_{2A/C} receptor antagonist, and only partially so by the selective 5-HT_{2C} receptor antagonist SER082 (Koskinen et al. 2000a). In fact, m-chlorophenylpiperazine (mCPP), a 5-HT_{2C} agonist, produced (at 2.5 mg/kg, i.p.) completely different effects to those of DOI, mainly reducing trials completed and increasing omissions, possibly via a sedative action.

In the early study by Carli and Samanin (1992), the blockade of effects on accuracy by ritanserin was complete for quipazine, but partial for LSD, it being inferred that additional 5-HT receptor agonist activity, possibly at the 5-HT_{1A} receptor, might be responsible for some of the effects of LSD. This consideration has motivated a subsequent, detailed study of the effects of systemic 8-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin (8-OH-DPAT), the 5-HT_{1A} receptor agonist with actions at both pre- and post-synaptic receptors (Carli and Samanin 2000). A dose of 0.1 mg/kg s.c. (but no lower) significantly impaired response accuracy, while also increasing errors of omission, premature responses, as well as latencies to respond correctly and to collect earned food pellets. All of these effects were blocked by co-administration of the selective 5-HT_{1A} receptor antagonist WAY 100635, administered systemically (30–100 µg/kg s.c.), there being no effects of the WAY compound by itself. Depleting central 5-HT using 5,7 DHT or infusing the WAY compound into the dorsal raphé nuclei only blocked the effects of 8-OH-DPAT on accuracy. The effects on accuracy of 8-OH-DPAT were also ameliorated by lengthening the target stimulus duration. These

findings help to dissociate the effects on accuracy from those resulting in possible changes in motivational or motor function. Overall, the main conclusion from these studies is that stimulation of pre-synaptic 5-HT_{1A} receptors is implicated in the attentionally disruptive effects of 8-OH-DPAT. However, the effects to lengthen response latencies and increase omissions may depend on stimulation of post-synaptic receptors. The likely mechanism of action for the effect of 8-OH-DPAT to elevate premature responses is more difficult to summarise. This effect was blocked by central, intra-dorsal raphé infusions of the 5-HT_{1A} antagonist, indicating the involvement of pre-synaptic receptors, but not following 5-HT depletion by 5,7 DHT, which by itself elevates premature responding (see also below). However, the combination of 5,7 DHT and 8-OH-DPAT led to reductions in the number of premature responses produced by the neurotoxin.

There has been less study of agents affecting other 5-HT receptors. Carli and Samanin (1992) reported that m-CPP, a non-selective 5-HT_{1B/C} agonist at 2.5 mg/kg i.p. increased the latencies to respond and omissions without affecting response accuracy. It seems likely, in fact, that these effects are mediated by 5-HT_{2C} receptors, as a later study (Koskinen et al. 2000a) showed that they were blocked by the selective 5-HT_{2C} receptor antagonist SER082. Muir et al. (1995) found few effects of ondansetron, the 5HT₃ receptor antagonist on performance of the 5-CSRTT, either in intact rats or in rats with lesions of the cholinergic nbm. However, certain doses of ondansetron did reduce premature responses, especially those induced by D-amphetamine or by cholinergic nbm lesions induced by α -amino-3-hydroxy-5-methyl-4-isoxazoleprionic acid (AMPA; see below). D-Fenfluramine, which effects 5-HT release, mainly lengthened response latencies and increased omissions, consistent with its anorectic, and hence motivational reducing, effects (Carli and Samanin 1992). However, it was also shown by these authors that the effects of the specific receptor agents they examined could not be simulated by pre-feeding, suggesting that they were not caused by reduced motivation. The differences between D-fenfluramine and some of the 5-HT compounds used, e.g. at the 5-HT₂ receptor, may possibly indicate differences in affinity of released 5-HT for its various receptors.

In summary, accuracy is affected most clearly by agents affecting 5-HT_{1A} receptors, possibly but much less clearly 5-HT_{2A} receptors, but not 5-HT_{2C} or 5-HT₃ receptors. Premature responses currently implicate 5-HT_{1A} and 5HT_{2A} receptors. It appears that a third class of variables relating to omissions, trials completed and response latencies may represent sedative or possible motivational functions that are apparently modulated by 5HT_{2C} receptors. Other receptor sub-types, notably 5HT_{1B}, have been studied much less extensively, if at all. This classification is clearly provisional, but may be useful in accounting for the complex pattern of effects observed following central 5-HT depletion, which, under certain circumstances, can reflect each of the main clusters of variables specified here.

Cholinergic systems

Cholinergic neurotoxins, intracerebral administration and in vivo neurochemistry

Until recently it has been impossible to effect neurochemically selective cholinergic depletions in discrete brain regions because of the absence of a suitably specific neurotoxin. Thus, it was necessary initially to attempt to lesion the cholinergic systems with relatively non-specific infusions of excitotoxins such as ibotenic acid into the regions containing the principal cholinergic cell groups, such as the nbm, projecting mainly to the neocortex and amygdala, and the medial septum or diagonal band, projecting mainly to the hippocampus and cingulate cortex. A good deal of early work showed that the different excitotoxins varied considerably in their potency and selectivity for targeting cholinergic cells – thus, in fact, the potency of effects on cholinergic neurons was ibotenate < quisqualate < AMPA (Everitt and Robbins 1997). This rank ordering of cholinergic neurotoxicity did not always correlate with behavioural effects, for example, on learning. Consequently, it was important to determine which behavioural paradigms were most sensitive to this rank order. Fortunately, it became apparent that one variable in particular on the 5-CSRTT, namely response accuracy, did reflect this ordering. Thus, excitotoxic lesions of the nbm in rats (using initially quisqualic acid and later AMPA) produced impairments of basic discrimination performance (Robbins et al. 1989; Muir et al. 1994), especially if the duration of the stimuli was reduced, although the impairments could not be attributed to sensory loss per se. The deficit was reduced if the duration of the stimuli was lengthened (Muir et al. 1994). There are ancillary deficits in the accuracy of responding when bursts of white noise are presented simultaneously with the discriminanda, but not during other variations of the task (Robbins et al. 1989; Muir et al. 1994). The effects of basal forebrain lesions were shown to be remediated by systemic treatment with physostigmine (0.05 mg/kg, but not 0.1 mg/kg) or nicotine (0.06–0.1 mg/kg), supporting a cholinergic basis for these effects (Muir et al. 1995). Finally, no significant effects on performance on the 5-CSRTT were found after AMPA lesions of the vertical limb of the diagonal band, suggesting that the effects of cholinergic depletion were anatomically specific (Muir et al. 1996b).

When infused into the rat nbm, the largest effect on cortical cholinergic markers (e.g. ChAT activity) is generally observed in the PFC. This is consistent with the fact that the most typical behavioural effect of such lesions is impaired accuracy and this form of deficit also occurs after excitotoxic lesions of the PFC. Therefore, it is logical to assume that the impaired accuracy seen after cholinergic nbm lesions is a result of de-afferentation (and subsequent dysmodulation) of the rat PFC.

Despite this consistent vein of evidence for a role for the cholinergic system in attentional function, which has been substantiated by a wealth of evidence using other

procedures, and in other species (McGaughy et al. 1994, 1996; Voytko et al. 1994; Marrocco and Davidson 1998), we (McGaughy et al. 2002) have recently begun to re-examine the effects of nbm lesions on performance of the 5-CSRTT using the immunotoxin 192 IgG-saporin, which has much greater specificity for cholinergic cells in the nbm. A previous study (Waite et al. 1999) did find some evidence for response accuracy and other deficits in the 5-CSRTT following i.c.v. saporin infusion, but this could not be specifically related to destruction of cholinergic cells in the nbm, as distinct from the cerebellum. In our recent study, using both low and high doses of saporin, to effect different degrees of damage to the cholinergic cells, we have been able to demonstrate significant correlations between response accuracy and the degree of damage to cholinergic cells in the nbm, quantified using immunocytochemical methods. We have not yet, however, been able to test systematically the possible restorative effects of cholinergic drugs in the saporin-lesioned rats.

Converging evidence from other methodologies has generally been consistent with a modulatory effect of nbm cholinergic systems on 5-CSRTT performance, particularly in terms of response accuracy:²

- i. Intra-nbm doses of the GABA agonist muscimol, sufficient to produce reductions in cholinergic activity, also induce dose-related decrements in response accuracy (Muir et al. 1992a).
- ii. Neural grafts enriched with cholinergic cells from the nbm re-mediate deficits in accuracy produced by excitotoxic lesions when implanted into fronto-parietal areas (Muir et al. 1992b).
- iii. Intra-PFC scopolamine infused into the medial PFC region induces significant deficits in response accuracy at doses lower than those inducing elevated omissions, although this separation was not obtained at an anterodorsal PFC site (Robbins et al. 1998).
- iv. Large increases in ACh release within the PFC occur following exposure to rats of the 5-CSRTT, as measured using *in vivo* microdialysis (Passetti et al. 2000; Dalley et al. 2001). These increases appear to be stronger in rats that have been trained to discriminate the visual targets and are weakened when the task contingencies change [opposite to effects on PFC NA release (Dalley et al. 2001)].

Overall, there appears to be overwhelming evidence for a role for cholinergic systems innervating the PFC to have a vital role in attentional function, as well as possibly other processes. These findings have clear clinical significance in their application in the cholinergic deficits of Alzheimer's disease, and the use of cholinergic agents for its remediation (Sahakian et al. 1993), as well as for disorders with parallel loss of cholinergic function,

such as Levy Body dementia and Parkinson's disease (Perry et al. 1999).

Effects of systemic cholinergic agents

Jones et al. (1995) have reported differences in response accuracy in aged rats that are exacerbated by systemic treatment with scopolamine, the anti-muscarinic agent or mecamylamine, the nicotine receptor antagonist. However, it should also be pointed out that scopolamine often produces a variety of effects on the different behavioural variables of the 5-CSRTT and that there is not a complete consensus on the precise pattern of effects (Jakala et al. 1992; Jones and Higgins 1995), Jones et al. 1995; Mirza and Stolerman 1998). For example, systemic scopolamine (0.03–0.1 mg/kg s.c.) did not much impair choice accuracy in young rats except in a condition employing interpolated bursts of white noise in the ITI, leading Jones and Higgins (1995) to suggest that it mainly impaired selective attention. This increase in distractibility may explain the deleterious effects of a single dose of scopolamine on the accuracy of detecting one of three spatially separated visual stimuli observed by the rat after inserting its head into an "observation tunnel" (Skjoldager and Fowler 1991). The apparently enhanced distractibility observed in the Jones and Higgins (1995) study could not be reproduced by doses of methylscopolamine, thus excluding possible peripheral actions.

However, Mirza and Stolerman (2000) reported impairments of accuracy (but not correct response latency) at low doses of scopolamine (0.1 mg/kg s.c.) on the basic task, although, as in the case of central administration above (Robbins et al. 1998) it was difficult to obtain such effects at doses that did not also increase omissions. In fact, omissions were increased, and anticipatory errors decreased, at lower doses still (e.g. 0.01 mg/kg). The effects on omissions could only partly be reproduced by methylscopolamine, suggesting that these result from a mixture of central and peripheral actions.

These somewhat variable effects of scopolamine are of interest, insofar as they can be generally reproduced in another species – the mouse. Humby et al. (1999) tested two strains of mice on the 5-CSRTT, showing, as for the rat, that systematic manipulation of the task parameters produced changes in behaviour consistent with altered visuo-spatial attention. The mice were of known genetic constitution in that F1 crosses were obtained from breeding C57BI/6A with either the 129sv or DBA/2 strains. The C57BI/6XDBA/2 hybrid showed greater sensitivity to systemic scopolamine on the 5-CSRTT although not for effects on locomotor activity. Specific effects on accuracy in the baseline condition of the 5-CSRTT were observed at doses of 0.02 mg/kg and 0.2 mg/kg. These effects then, seem to be obtained more readily than in the rat, where additional distraction is apparently necessary to elicit reliable effects or elevated omissions are observed (Jones et al. 1992; Mirza and Stolerman 1998). At 2 mg/kg, however, large reductions in accuracy

² Risbrough et al. (2002) recently also examined effects of saporin lesions of nbm and found mainly elevated errors of omission; however, this was the main variable to have been affected, and the authors interpreted the deficit as being attentional in nature)

in the mice were associated with marked effects on other measures, with increased omissions and elevated response latencies. The disruptive effects of scopolamine were much attenuated on a 1-choice, as distinct from 5-choice variant of the task (consistent with Jones and Higgins (1995)), again suggesting a specific interaction of scopolamine with task requirements, with the drug impairing performance when there was an explicit choice requirement that challenged response selection mechanisms. Methylscopolamine had minimal effects, largely ruling out peripheral effects. These results are also consistent for the main part with the effects of central manipulations of the cholinergic systems described above, in particular of neurochemical lesions of the nbm projection to the PFC.

Although physostigmine and nicotine have been shown to exert beneficial effects on 5-CSRTT performance in rats with nbm lesions (Muir et al. 1995), and scopolamine, a muscarinic receptor antagonist also evidently impairs performance, until recently there have been reported no clear-cut effects of muscarinic receptor agonists, either for lesioned or for normal rats. Nor have anti-cholinesterases such as physostigmine, or nicotine, been shown to have any beneficial effects on normal performance, although few studies have been able to control for possible ceiling effects. Mirza and Stolerman (2000) have now however tested several systemically administered compounds, including physostigmine, the muscarinic agonist oxotremorine, and also nicotine, on a baseline titrated to be lower by reducing the duration of the visual signal. For both physostigmine and oxotremorine, there were somewhat equivocal results, however. In the case of physostigmine (0.05/0.1 mg/kg) no beneficial effects were seen; although the high dose substantially reduced trials completed. At a low (0.01 mg/kg s.c.) dose of oxotremorine, there were no effects: at a higher dose (0.03 mg/kg), insufficient trials were completed for meaningful data to be obtained. Clearly, these drugs may well be producing confounding peripheral actions, and the dose-response curves also seem quite steep, and in all probability, based on our own unpublished observations (JL Muir, H Marston, BJ Everitt, TW Robbins) individually variable. In future studies, it would be useful to test combined treatments of scopolamine and oxotremorine, or some other suitable muscarinic agonist, or alternatively to test possible remedial actions of muscarinic agonists in rats with nbm lesions.

Systemic nicotine also had little effect in sham-operated rats in the study by Muir et al. (1995); in fact their performance tended to show dose-related declines in accuracy, at doses enhancing the previously inferior performance of rats with nbm lesions. More recently, however, Mirza and Stolerman (1998) have shown that it is possible to obtain improvements in response accuracy following low doses of systemic nicotine in normal rats; indeed this is now among the best-studied of pharmacological effects on the 5-CSRTT. In their study, they investigated various ways of manipulating the basic task so as to optimise the conditions under which nicotine

effects may be seen. They did this in a systematic and elegant fashion by manipulating the task parameters, a manoeuvre also aimed at further validating the task for assessing vigilance, in accordance with previous knowledge and theory from human experimental psychology (Parasuraman et al. 1987). In the first study, they tested nicotine (0.05, 0.15 and 0.4 mg/kg) under weak stimulus (signal duration 0.25 s) conditions. In the second, they lengthened the ITI to 20 s to reduce the signal frequency and enhance the load on vigilance (with a consequent lengthening of session). Finally, they tested nicotine with short ITIs (1 s) to increase event rate.

When stimulus duration was decreased nicotine failed to enhance accuracy at any dose tested, even though performance declined in the last quarter of the session. However, 0.05 mg/kg did speed latencies in this last quarter. Nicotine also increased premature responses in the last part of the session, but had no effect on errors of omission. When the ITI was lengthened, 0.15 mg/kg nicotine improved response accuracy, with no changes in correct response latency. Under these test conditions, the drug did reduce omission errors, but produced the same increase in premature responses. Effects at the short ITI were much weaker but with some trends for improved accuracy. Recently, Hahn et al. (2001a) have shown that the attentional enhancement obtained with nicotine (0.1 mg/kg) survives chronic treatment; indeed, it is the disruptive effects of the drug which exhibit tolerance. Analogous findings have been reported by Grottick and Higgins (2000). They found in rats performing below the normal baseline that nicotine (optimally at 0.2 mg/kg) increased response accuracy and speeded latency. Furthermore, a chronic regimen of nicotine administration enhanced accuracy, even under normal stimulus parameters. Finally, the acute effects of nicotine were mimicked by the α_4 , β_2 selective agonist SIB 1765F, but not the α_7 agonist ARR-R 177779. Some other workers have been less successful in finding beneficial effects on accuracy in the 5-CSRTT (Blondel et al. 1998, 2000). Nevertheless, Blondel et al. (1998) reproduced many of the other aspects of nicotine's beneficial effects, for example, the speeding of response latency at comparable acute and repeated dosing regimes to those used by the Stolerman group. They also found the normal increase in premature responses and concluded that this was probably an independent effect of the drug. A possible reason for the failure to find effects on accuracy may derive from the use of short duration stimuli, which appears to weaken, rather than enhance, the effect of nicotine on accuracy (see Stolerman et al. 2000 for analysis).

Subsequent, parametric studies of the basis of the changes in performance by nicotine, reviewed in detail by Stolerman et al. (2000), have largely substantiated the robust nature of the effects. However, the performance-enhancing effects of nicotine have now been shown to be less dependent on the ITI used than was suggested from the initial studies. Thus, these authors' interpretation of the nature of the performance enhancement produced by nicotine has shifted from their initial emphasis on

reducing the vigilance decrement to other possible attentional mechanisms. For example, nicotine appears to prevent some of the disruptive effects of interpolated bursts of distracting white noise upon accuracy, suggestive of effects on selective attention (Hahn et al. 2002). Further work, studying the interaction of food deprivation and nicotine, has also tended to rule out possible motivational interpretations (Bizarro and Stolerman 2001).

Many of the effects of nicotine are reminiscent of those of stimulant drugs such as D-amphetamine: however, no consistent effects of D-amphetamine to improve accuracy have yet been reported in this test (Cole and Robbins 1989, 1992; Muir et al. 1995). In fact, in the presence of a DNAB lesion leading to widespread depletion of telencephalic NA, systemic or intra-accumbens D-amphetamine produces significant deficits in response accuracy at quite low doses (e.g. 0.6 mg/kg), while producing equivalent effects on premature responses in DNAB lesion and sham-operated groups (Cole and Robbins 1987). This difference between D-amphetamine and nicotine encourages the speculation that the beneficial effects of nicotine on response accuracy are not mediated by any actions that nicotine exerts on the activity of the mesolimbic DA projection. However, it should be noted that the same effort to optimise possible beneficial effects, as made by Mirza and Stolerman (1998) for nicotine, has not yet been applied to D-amphetamine.

The effects of nicotine receptor antagonists have been perhaps a little less consistent than those of nicotine itself. Jones et al. (1995) reported task-specific deficits of the non-competitive antagonist mecamylamine in 15-month (but not 3-month)-old rats, similar to those observed by Ruotsalainen et al. (2000). These findings broadly agree with the results of Grottick and Higgins (2000) who found that mecamylamine (3 mg/kg) generally produced effects opposite to those of nicotine, including deficits in accuracy. Complementing their studies of nicotine, Mirza and Stolerman (2000) also examined systemic effects of the nicotine receptor antagonist mecamylamine. In their hands, this drug did not impair accuracy, but did induce a significant dose-dependent increase in the percentage of omission errors at both 1.6 mg/kg and 5.0 mg/kg (s.c.), increasing response latency at the highest dose. Grottick and Higgins (2000), however, found no effects of other nicotine receptor antagonists such as DNBE and MLA. Moreover, the effects of mecamylamine on accuracy, which has some additional NMDA receptor activity, could be mimicked to some degree by systemic dizolcipine, the NMDA receptor antagonist; however, this agent also increased premature responses and reduced latency. Overall, there is some doubt to whether specific nicotine receptor antagonists impair accuracy in this procedure.

In combination with sub-threshold doses of scopolamine (0.01–0.03 mg/kg), similarly sub-threshold doses of mecamylamine did not strongly support the hypothesis that a functional interaction between the two receptor subtypes produces synergistic effects on performance; how-

ever, there was a marginally significant effect of the drug combination to impair response accuracy. Stolerman et al. (2000), in reviewing these data, made the interesting point that, in their studies, scopolamine tends to affect accuracy rather than latency, whereas mecamylamine has the opposite effect, suggesting that muscarinic and nicotinic receptors are implicated at different stages of information processing.

In summary, there seems little doubt that the anti-muscarinic agent scopolamine is very disruptive to 5-CSRTT performance, with most studies showing impairments in accuracy in some conditions, consistent with effects of nbm lesions (McGaughy et al. 2002) and often more general disruptions of performance. In contrast, systemic nicotine does apparently enhance accuracy under some conditions, in normal as well as in nbm-lesioned rats, while also affecting some aspects of the vigour of performance in a manner probably distinct from that produced by amphetamine-like drugs. It has proven difficult to show beneficial effects of anti-cholinesterases such as physostigmine on 5-CSRTT performance in normal rats, although improvements in accuracy have been shown following nbm lesions.

Although the effects of systemically administered cholinergic drugs in rodents are sometimes hard to interpret, there are nevertheless implications of this body of data for the treatment of human patients with dementia of the Alzheimer type (DAT), particularly in the light of novel agents emerging for this purpose, for example, nicotine agonists that are being tested in the 5-CSRTT (Blondel et al. 2000; Grottick and Higgins 2000; Hahn et al. 2001b). The anticholinesterase tacrine has been shown to improve attentional performance (accuracy and latency) in a direct analogue of the 5-choice task taken from the CANTAB battery in patients with probable DAT (Sahakian et al. 1993). Moreover, subcutaneous nicotine similarly improves performance in terms of both accuracy and latency in a related, but much more complex, rapid visual information processing (RVIP) task, which stresses sustained attention (Wesnes and Warburton 1983) – for both elderly volunteers and also patients diagnosed as having DAT (Sahakian et al. 1989; Jones et al. 1992).

Conclusions

This review has chronicled the development of a paradigm that has been developed to assess several aspects of attentional performance, primarily in rats but more recently in other species, including mice and monkeys. The main test requires a specialised multi-choice apparatus and also involves several distinct indices of performance whose inter-relationships and pharmacological, neural and neurochemical separability have been given especial emphasis in this Review. In fact, although there is likely to be considerable interplay among these systems in modulating the manner in which the frontal cortex and striatum optimise performance on this task, it is also apparent that we have been able to use the task to

demonstrate considerable specificity of effects of the different systems (Table 1). In general terms, there are two apparently different forms of control over the vigour of performance which includes, for example, inhibitory control over premature responding and the accuracy of responding to the visual targets. Nevertheless, it was interesting to observe for the monoamines how different receptors within each system appeared to modulate these two main functions differentially. Thus, for example, D1 receptor antagonists affected premature responses but not accuracy, whereas D2 receptor antagonists had the opposite effects. This type of pattern was also evident, respectively, for 5HT₂ vs 5HT_{1A} receptors, and alpha-2 vs alpha-1 receptors. For ACh, this picture was less clear, with nicotine usually affecting both measures. Overall, the significance of these differential effects of different receptor classes is intriguing, but presently unclear.

Some consideration has also been given to the validation of the task, which has been used in humans in another form, but probably needs further exploration to isolate distinct processes of attention (and other contributory psychological processes; Bushnell 1998). Such validation is normally done by drawing upon findings in human experimental psychology (such as the vigilance decrement) and investigating whether they can be reliably produced in this setting for the rat (or mouse or monkey). Another form of validation for particular hypotheses about a drug (or lesion) effect is to compare manipulations on other tasks putatively employed to evaluate similar processes. Converging evidence of a drug or lesion effect using the 5-CSRTT that extends, where appropriate, to other paradigms [e.g. models of the Posner covert orienting task (Marrocco and Davidson 1998)] or other tests of impulsivity, such as delayed reinforcement (Evdenden 1999) clearly strengthens any conclusions that can be made about that manipulation on a particular behavioural process. Conclusions clearly cannot rest on effects on single variables in a single behavioural test, as Dews, Morse and colleagues have constantly reminded us from their own analyses of drug effects in the context of schedule-controlled behaviour. We have not had the space to consider this essential further analysis, which is beyond the scope of this review, but we employ it in our own research. For example, we have used the nine-hole box in another configuration (e.g. with the head location fixed to measure the effect of central DA depletion on lateralised reaction times in a signal detection task; Carli et al. 1985, 1989; Brown and Robbins 1989, 1991) and thus to make further inferences about the functions of these systems.

The development of the 5-CSRTT, partly inspired by the problems of measuring changes relevant to clinical populations such as ADHD, and partly to the methodological lead from the Harvard group, has led to a number of operational measures of behaviour, which I have argued embody abstract qualities as attention and impulsivity. The test may well be applicable to measuring other forms of attentional deficits relevant to the clinic, including those observed during Alzheimer's disease, schizophrenia and as sequelae of drug abuse, including

withdrawal (Shoaib et al. 2000). However, it is clear that these are only convenient labels until we are able to explain them in more detailed terms. Such explanation, I maintain, will include not only a full behavioural characterisation of performance on such tasks as the 5-CSRTT, but also the identification of the neural and neurochemical systems which exert distinct contributions on performance engendered by it. The use of a standardised test, which has now been employed in different laboratories, has already resulted in the large amount of basic data relevant to these aims reviewed here. Although the design and implementation of the 5-CSRTT has come in part from studies in human experimental psychology, these aims have also been entirely consistent with the programme initiated by Dews and his colleagues in behavioural pharmacology.

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