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Psychopharmacological approaches to modulating attention in the five-choice serial reaction time task: implications for schizophrenia

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Abstract *Rationale:* In schizophrenia, attentional disturbance is a core feature which may not only accompany the disorder, but may precede the onset of psychiatric symptoms. *Objectives:* The five-choice serial reaction time task (5CSRTT) is a test of visuo-spatial attention that has been used extensively in rats for measuring the effects of systemic and central neurochemical manipulations on various aspects of attentional performance, including selective attention, vigilance and executive control. These findings are relevant to our understanding of the neural systems that may be compromised in patients with schizophrenia. *Methods:* The 5CSRTT is conducted in an operant chamber that has multiple response locations, in which brief visual stimuli can be presented randomly. Performance is maintained using food reinforcers to criterion levels of accuracy. Various aspects of performance are measured, including attentional accuracy and premature responding, especially under different attentional challenges. *Results:* The effects of systemic and intra-cerebral infusions of selective dopamine, serotonin and cholinergic receptor agents on the 5CSRTT are reviewed with a view to identifying attention-enhancing effects that may be relevant to the treatment of cognitive deficits in schizophrenia. In addition, some novel agents such as modafinil and histamine receptor agents are also considered. Examining the effects of selective neurochemical lesions helped define the neural locus of attentional effects. Similarly, findings from microdialysis studies helped identify the extracellular changes in neurotrans-

mitters and their metabolites in freely moving rats during performance of the 5CSRTT. *Conclusions:* The monoaminergic and cholinergic systems have independent but complementary roles in attentional function, as measured by the 5CSRTT. These functions are predominantly under the control of the prefrontal cortex and striatum. These conclusions are considered in the context of their application towards therapeutic approaches for attentional disturbances that are typically observed in schizophrenic patients.

Keywords Attention · Rat · Schizophrenia · Dopamine · Serotonin · Acetylcholine · Noradrenaline · Striatum · Prefrontal cortex · 5CSRTT

Introduction

Attentional deficits in schizophrenia have been investigated intensively since Bleuler (1950) and Kraepelin's (1971) accounts of attentional disturbances in their patients. Nevertheless, impaired attentional processing has only recently gained respectability as one of the core deficits in this most elusive disorder. Attentional disturbances are grossly evident in encounters with schizophrenic patients: not only do attentional deficits accompany the disorder, they may have causal roots in the natural progression of subtle cognitive impairments that may precede the onset of the psychiatric symptoms (Jones et al. 1994; an der Heiden and Hafner 2000). Typically, patients with schizophrenia are unable to select and interpret incoming sensations leading to inappropriate responding. They find it difficult to sustain and shift attention in response to situational demands and illogically leap from one subject to another mid-conversation. At other times, they may orient to or fixate on trivial aspects of the environment, or perhaps engage compulsively in some activity. Furthermore, patients with flattened affect are typically unable to direct and sustain attention to emotionally meaningful goals and events. Indeed, autistically withdrawn schizophrenics are essentially unaware of

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the outside world and attend to stimuli in the environment only periodically in an unpredictable manner. Typically, clinical observations such as these have been examined in the laboratory using tests such as the continuous performance test (Epstein et al. 1996; Keefe et al. 1997; Harvey et al. 2003), on which schizophrenic patients often perform poorly (for review, see Nestor and O'Donnell 1998). Furthermore, performance deficits such as those observed on the continuous performance test may be differentially related to other schizophrenic symptoms and neuropsychological constructs (see Nieuwenstein et al. 2001).

Nevertheless, the constellation of symptoms described above characterizes the very nature of attention as a non-unitary construct and its different manifestations. It is therefore possible that different patients may exhibit different attentional impairments that emerge as a function of context or task demands depending upon the experimental conditions (Parasuraman and Davis 1977; Nuechterlein et al. 1983; Nestor and O'Donnell 1998). Although the diversity of attention is recognized (see, e.g. Parasuraman 1998) and a number of different sub-forms have been described including focused, divided, effortful and controlled, there are at least three fundamental components that appear to be largely independent: selection, whereby some informational elements are given priority over others; vigilance, which ensures attentional persistence over time; and control, which serves to optimise performance particularly, for example, by inhibition of concurrent activities (see Parasuraman 1998; Robbins 2002). These attentional processes facilitate cognitive and behavioural performance in several ways, thus allowing for the selection and integration of sensory inputs, learning and remembering, and the organisation and preparation of appropriate responses. Therefore, impaired attentional processing may be associated with inattention, distractibility, memory impairment, confusion, perseveration, or disinhibition, behaviours that are typically associated with schizophrenic episodes.

In practice, different sub-forms of attention, such as selection, vigilance and control, are often recruited together. This not only reflects the complexity and centrality of attention for behavioural performance, but also proves problematic in attempts to model attentional dysfunctions related to schizophrenia. For example, information processing theories, based on defective sensory filters (for review, see Nuechterlein and Dawson 1984), have been closely related to operational measures of sensorimotor gating, i.e. prepulse inhibition (PPI) of the startle response (see articles by D.L. Braff and B.A. Ellenbroek in this issue). Nonetheless, it is often difficult to relate these pre-attentive measures to conventional notions of voluntary attention (see Robbins 1998).

Among the most sensitive and commonly used paradigms for measuring attention in schizophrenia is the continuous performance test (CPT), first developed by Rosvold et al. (1956) for use in assessing generalized brain damage. The task is generally referred to as a test of "sustained attention" because in its original form, the

patient was required to continuously monitor infrequent and unpredictable targets (e.g. letters) that were typically presented amongst distractors. Thus, reductions in performance over time in the CPT are considered to reflect a vigilance decrement (Parasuraman and Davies 1977). Since its original development, the CPT has been modified (e.g. Wilkinson 1963; Kornetsky and Mirsky 1966; Wohlberg and Kornetsky 1973) in order to tap into different aspects of attention by manipulating various parameters such as inter-trial intervals (stimulus onset asynchrony) and stimulus modality. In its simplest version, subjects are required to continually monitor the location of a brief visual target in one of five spatial locations that occur randomly (Wilkinson 1963; Carli et al. 1983; Cohen et al. 1999), therefore providing a measure of visuo-spatial attention. Some variants of the CPT have manipulated task complexity to include a condition in which the patient has to respond only when the target stimulus was preceded by another stimulus, thus also incurring a working memory load (see Nestor and O'Donnell 1998). However, although schizophrenic patients show an overall performance decrement on the CPT, suggesting that attentional processes are indeed compromised, a vigilance decrement is not always so obvious (Davies and Parasuraman 1982; Nestor et al. 1990). Furthermore, while neuroleptic medication may improve performance of the CPT, it does not normalize it (Orzack et al. 1967).

There is little doubt that patients with schizophrenia have attentional impairments, but it is quite difficult to specify their neural and neurochemical basis, and hence develop new forms of pharmacotherapy for controlling them. In order to define causal relations between behavioural symptoms and their underlying neural substrates, it is necessary to study the effects of suitably selective pharmacological agents in a way that is not constrained as is the case for normal human volunteers, thus necessitating the use of experimental animals. The ability to extrapolate findings in animals to humans has improved with the use of comparable cross-species tests of cognitive function. Such tests enable the identification of common neural substrates that subservise similar functions, increasing the likelihood that the same cognitive functions are being studied in each species. The relative ease with which brain neurotransmitter and neural systems can be manipulated in the rat makes this species an obvious choice for pharmacological screening (Muir 1996). Furthermore, in animals, the administration of specific receptor agents is easier to control and manipulate especially by local infusions rather than systemic treatment. Although the systemic administration is the preferred route for patients, in animal studies (and in human studies), it fails to provide us with any direct locus of action. Thus, from the point of view of drug development, it would be highly advantageous (plausible but perhaps ambitious) to be able to produce a novel class of drugs that have their targets in specific cortical and subcortical areas that may work differentially for regulating cognitive processes (see below).

In this review, we focus on a prominent animal test of attention, the five-choice serial reaction time task (5CSRRT) that is analogous to the CPT. We summarize the effects of relevant drugs (e.g. D_1 agonists, 5-HT antagonists) acting at specific receptors on aspects of attention that may be relevant to the cognitive deficits in schizophrenia. The relevance of this test for treating attentional deficits in human disorders, such as attention deficit hyperactive disorder (ADHD) and Alzheimer's disease has already been extensively reviewed by Robbins (2002). The present paper considers the effects of pharmacological agents on aspects of attention that may be relevant to disturbances specific to schizophrenia. Importantly, we focus on drug manipulations that have been shown to modulate attentional deficits and consequently may be suitable drug targets for treating cognitive deficits in schizophrenia.

The five-choice serial reaction time task

The five-choice serial reaction time task (5CSRRT) is now among the most widely used tests of attentional function in animals. A previous review of the developmental history and application of the 5CSRRT for measuring the effects of drugs and other manipulations on attentional performance (Robbins 2002) provides the basis for much of what is included in this review. The value of the 5CSRRT is that this model makes clear links with its human analogue, the CPT and therefore provides substantial validity as a direct measure of attention. Furthermore, the 5CSRRT enables the investigation of different components of attention (selection, vigilance and control) in detail and therefore permits the testing of many forms of pharmacological treatments on these different attentional processes.

The 5CSRRT is conducted in what is essentially an operant chamber without levers. Instead, the chamber is equipped with nine apertures or holes, of which four are occluded by metal caps and five are exposed (see Fig. 1). Each hole can be illuminated briefly through light-emitting diodes located at the rear of each aperture. The nose-poke response of the rat in an exposed hole is detected by an infrared photocell beam that is located at the entrance of each aperture (for a detailed description of the apparatus and basic training protocol, see Robbins et al. 1993). The rat initiates each trial by pushing open the food magazine Perspex panel door that is monitored by a microswitch. This response is followed by a fixed 5-s intertrial interval (ITI), after which a light stimulus, the visual target (usually 0.5 s duration), is presented randomly in one of the five holes. The rat is rewarded if it makes a nose-poke response in the hole in which the target light stimulus appeared within a 5-s limited hold period.

Although the task is deceptively simple in its design, optimal performance on this task requires the integration of a number of component cognitive processes. For example, during the ITI the rat must divide its attention across all five locations in order to scan the visual array, as well as sustain its attention for the entire interval so as not

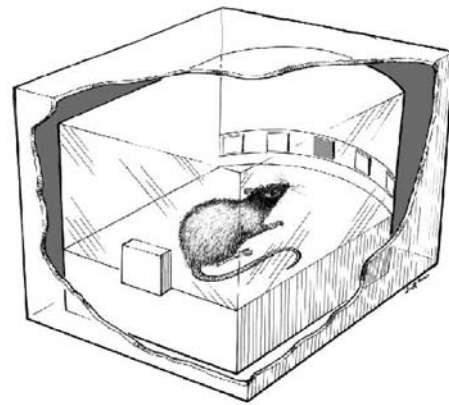


Fig. 1 A schematic illustration of the experimental chamber of the 5CSRRT in cross section (adapted from original illustration by John Romford, Department of Zoology, Cambridge University, UK)

to miss the target. Thus, high response accuracy scores indicate good attentional performance that is reflected by a high number of correct target detections with few omissions and a relatively fast latency to respond. Low response accuracy (chance performance=20%) suggests inattention that may indeed be influenced by other sensory, motor, or motivational processes, although these interpretations can be disambiguated by considering the overall profile of the results (for a detailed explanation of behavioural profiles, see Robbins 2002).

In addition, during the ITI, the rat must withhold making inappropriate premature nose-poke responses (that lead to time-out and re-set the ITI) in the apertures. Increased premature responding is particularly interesting because it occurs while the rat is anticipating the occurrence of the visual target, presumably when the ability to control pre-potent responding is impaired. Therefore, this measure provides a valuable index of impulsivity, the tendency to act without foresight, which can be a product of impaired response inhibitory control. Premature responses can be distinguished from perseverative nose-poke responses that occur repeatedly in the apertures following a correct response and signaled food presentation, and which also lead to time-out. Thus, increased perseverative responses reflect the dysfunction of another inhibitory mechanism engaged by the 5CSRRT, which is perhaps more akin to compulsivity in that the repetitive tendency occludes the animal's ability to monitor ongoing behaviour.

The difficulty of the task can be manipulated in various ways so as to uncover the potential nature of any processing deficits. For example, the rat's ability to sustain attention can be further challenged by increasing the length of the ITI, thus providing a more robust measure of vigilance. A one-choice version can be administered, whereby only one spatial location is used, thus placing less stress on response selection mechanisms. Sensory processing can also be examined by varying the brightness of the stimulus. Thus, the 5CSRRT is capable of measuring several types of performance that include aspects of attention and behavioural inhibition, and

although these measures co-vary in certain circumstances, they appear to be dissociable and probably rely on processes that are under the control of different neural mechanisms. The 5CSRRT was originally developed to test the effects on performance of a number of pharmacological agents, administered systemically or intracerebrally. This work has provided significant insights into the functional dissociations of each of the neurotransmitter (noradrenergic, dopaminergic, serotonergic, and cholinergic) systems (Robbins and Everitt 1995a, 1995b). A detailed review of these effects can be found in Robbins (2002).

Modeling attentional dysfunction in schizophrenia using the 5CSRRT

Effects of fronto-striatal lesions and testing effects of glutamatergic agents

Attentional deficits in schizophrenia have been consistently associated with frontal dysfunction which can readily be investigated in rats, for example, by excitotoxic lesions of the medial prefrontal cortex (mPFC) (Muir et al. 1996a; Miner et al. 1997; Granon et al. 1998; Birrell and Brown 2000). Lesions of the mPFC that include the dorsal pre-genu anterior cingulate cortex (area Cg1), medial prefrontal cortex (PrL), and sometimes the ventral infralimbic cortex (IL), produce profound deficits in the 5CSRRT. These animals show poor response accuracy, increased perseverative responses, and retarded response latencies on the 5CSRRT (Muir et al. 1996a). More recently, it has been shown that a combination of a unilateral mPFC lesion with a dorsal striatal lesion on the contralateral side of the brain, produces deficits comparable to bilateral lesions of either structure (Christakou et al. 2001), suggesting that the task engages fronto-striatal systems, although there has been no consistent evidence for any hippocampal involvement (Kirkby and Higgins 1998). Thus, it is apparent that the use of the 5CSRRT is most appropriate for modeling those aspects of cognitive dysfunction in schizophrenia thought to depend on “fronto-executive” processes.

Selective lesions of different sectors of the rat mPFC are helping to define the precise relationship between these sub-regions. Thus, accuracy impairments are only observed following lesions made to the dorsal Cg1 area (Passetti et al. 2002; Chudasama et al. 2003). By comparison, PrL as well as orbitofrontal (OFC) lesions, produce selective increases in perseverative responses (Chudasama and Muir 2001; Passetti et al. 2002), this being in contrast to animals with lesions centred on the IL cortex that showed selective increases in premature responses only (Chudasama et al. 2003). Evidently, these sub-regions have quite specific functions that have to be coordinated in a manner that allows accurate target detection and control of responding in order to produce optimal performance in the 5CSRRT.

Understanding the nature of the contribution of the prefrontal cortex to 5CSRRT performance, as well as the contribution of other structures such as the hippocampus and amygdala that have been implicated in developmental models of schizophrenia, enables the localization of specific receptors for certain systemic treatments. Characterising the effects of glutamatergic agents is particularly important given the popularity of models of schizophrenic symptomatology produced by treatment with glutamate NMDA receptor antagonists such as ketamine and phencyclidine (PCP) (Steinpreis 1996), although the effects of selective glutamate receptor agents have been little explored. In the 5CSRRT, psychotomimetic agents such as PCP increase premature and perseverative responding as well as reduce choice accuracy (Jin et al. 1997). However, given the motor stimulant properties of PCP that include locomotor activity and stereotypy (e.g. Murray and Horrita 1979; Verebey et al. 1981; Iwamoto 1984; Jacobs et al. 2000), the precise effects of systemic PCP on attentional processes is unclear. In some recent studies, however, PCP exacerbated attentional deficits in neonatal hippocampal lesioned animals (Le Pen et al. 2003), as well as increase locomotor activity (Hori et al. 2000; Kato et al. 2000), suggesting a neurodevelopmental pathology of the hippocampus in schizophrenia. Intriguingly, however, the detrimental effect on attentional accuracy in neonatal or adult hippocampal lesioned animals, without PCP administration, was less robust than that exhibited by animals with entire medial prefrontal lesions (Le Pen et al. 2003). Instead, these animals showed a deficit more similar to animals with restricted lesions of the frontal cortex that included the dorsal Cg1 portion that is known to be selectively involved in discriminative accuracy (Muir et al. 1996a; Passetti et al. 2002; Chudasama et al. 2003; Le Pen et al. 2003). Clearly, attentional deficits that result from neurodevelopmental changes may have to be considered with respect to their projections to the frontal cortex. Indeed, one study has argued a possible role for the central nucleus of the amygdala (also implicated in developmental models of schizophrenia) in modulating visual attention via its projections to the basal forebrain cortical cholinergic system (Holland et al. 2000), although neurochemical manipulations of the amygdala have yet to be explored systematically.

A recent paper by Higgins et al. (2003) has shown a very interesting pattern of deficits in the 5CSRRT in animals following systemic treatments with either MK-801 or the NR2B selective NMDA receptor antagonist Ro 63-1908, although the latter agent did not affect hippocampal dependent mnemonic function (neither delayed matching to sample nor acquisition of the Morris water-maze). Specifically, systemic Ro 63-1908 led to a dramatic increase in premature responses and concomitant reductions in accuracy on the 5CSRRT. MK-801 had qualitatively similar effects but also significantly increased errors of omission. The pattern of effects of Ro 63-1908, together with the effects of regional excitotoxic lesions, suggest a specific prefrontal substrate for these deficits, which may provide a useful model for pharmacological amelioration.

Neurochemical modulation of the 5CSRRT

The above findings are consistent with recent evidence suggesting that dopaminergic and serotonergic projections to the prefrontal cortex may differentially regulate these behaviours in the 5CSRRT (Dalley et al. 2002a, 2002b; Winstanley et al. 2003). Indeed, most atypical antipsychotic drugs, such as clozapine, are thought to exert their actions on serotonin (5HT) receptors as well as dopamine (DA) receptors, and appear to preferentially increase DA release in the mPFC (Altar et al. 1986; Meltzer et al. 1989; Moghaddam and Bunney 1990; Kuroki et al. 1999). In addition, the mPFC has also been shown to be involved in the attention-enhancing effects of nicotine (Hahn et al. 2003), implicating a role for the cholinergic innervation of the mPFC in attentional function. Accordingly, the 5CSRRT has been used extensively to examine the neuromodulatory effects of DA, 5-HT, and ACh receptor manipulations on attentional function.

Effects of dopaminergic agents

Thus far, subcortical manipulations of the DA systems have produced performance deficits on the 5CSRRT that are mainly expressed in terms of effects on the speed and probability of responding (Cole and Robbins 1989; Baunez and Robbins 1999). Systemic treatment with preferential D₂ receptor antagonists such as sulpiride produces accuracy deficits at certain doses (Harrison et al. 1997), possibly consistent with effects of dorsal striatal DA depletion (Baunez and Robbins 1999).

Direct infusions of DA D₁ receptor agents into the mPFC produce selective, baseline dependent effects on response accuracy in the 5CSRRT (Granon et al. 2000). Thus, intra-mPFC infusions of the D₁ receptor agonist SKF 38393 significantly enhances response accuracy in animals with relatively low (about 70% correct) baselines but had no effect on animals that were performing at higher levels. Conversely, infusions of the D₁ antagonist SCH 23390, but not the D₂ receptor antagonist sulpiride, reduced response accuracy only in animals with relatively high baselines whilst having no effect on animals that were performing at low levels (Granon et al. 2000). These data suggest that the prefrontal D₁ receptor system might normally be engaged to attain optimal task performance. They also suggest that it is indeed feasible to enhance attentional performance in normal rats with a D₁ receptor

agonist, and provides additional support for the efficacious use of D₁ agonists in aged monkeys (Arnsten 1997) or monkeys treated chronically with typical psychotic drugs, whose main mode of action is to block D₂ receptors, whilst concurrently down-regulating frontal D₁ receptors (Lidow and Goldman-Rakic 1994; Florijn et al. 1997; Lidow et al. 1997, 1998; Castner et al. 2000). The clear implication of these data is that it may be feasible to enhance cognitive performance under certain test conditions using D₁ receptor agonists.

Intriguingly, however, the systemic administration of sulpiride, a DA D₂ receptor antagonist, alleviated a response accuracy deficit in animals with mPFC lesions (Passetti et al. 2003) whilst impairing performance in control animals (see Table 1 for summary). Hypothetically, the mPFC lesion resulted in over-activity of sub-cortical dopaminergic systems that may contribute to the accuracy deficit. This notion is consistent with evidence that intra-mPFC infusions of sulpiride in non-lesioned animals do not impair performance on the 5CSRRT (Granon et al. 2000), or on other tasks that are known to depend on mPFC such as spatial delayed response (Druzin et al. 2000). The fact that DA D₂ receptors are found in much higher numbers in the striatum rather than the prefrontal cortex suggests that sulpiride is exerting its D₂ antagonism effects at subcortical loci such as the dorsal striatum. Importantly, however, there has been very little exploration of the effects of other D₂-like receptors (i.e. D₃ and D₄) in rats performing the 5CSRRT, given their complex interactions. Nonetheless, taken together, these data clearly indicate that dopaminergic projections to the rat mPFC have specific functions in modulating response accuracy in the 5CSRRT, rather than other aspects of performance such as response vigour or speed that instead may be influenced by subcortical DA systems (Cole and Robbins 1989).

There is also considerable evidence that the dopaminergic system (particularly prefrontal DA) may be critical in working memory processes; 6-OHDA lesions of prefrontal cortex of macaques, produce delayed response impairments (Brozoski et al. 1979), as do infusions of D₁ but not D₂ receptor antagonists into the principal sulcus of the PFC (Sawaguchi and Goldman-Rakic 1991). Similar findings have been reported following infusions of D₁ antagonist in the medial PrL area of the rat mPFC (Seamans et al. 1998). However, it is becoming increasingly apparent that the dopamine-working memory association is far from simple. Thus, there is evidence that high

Table 1 Neuropharmacology of the five-choice serial reaction time test: effects on accuracy

Enhanced	Impaired
Intra-mPFC D ₁ agonist	Intra-mPFC D ₁ antagonist
Intra-mPFC 5-HT _{2A} antagonist	Intra-mPFC scopolamine
Intra-mPFC 5-HT _{1A} agonist	Systemic D ₂ antagonist
Systemic nicotine	Systemic MK-801
Systemic physostigmine	Systemic NR2B NMDA antagonist
Systemic alpha ₁ agonist	Cortical ACh loss
Systemic D ₂ antagonist in animals with mPFC lesions	Cortical NA loss (certain conditions)

levels of DA turnover/utilisation (e.g. Sahakian et al. 1985) or higher doses of D₁ receptor agonists (Zahrt et al. 1997) impair memory in delayed alternation tasks, according to an “inverted U” hypothesis of the relationship between efficiency of performance and level of D₁ receptor stimulation. However, the inverted-U or Yerkes-Dodson relationship may vary as a function of task. For example, the original form of the Yerkes-Dodson function (Eysenck 1982) proposed that ‘easy’ tasks might have optimal levels of performance at higher levels of arousal than more ‘difficult’ tasks.

We thus extended the 5CSRRT to include a discrete memory component, therefore allowing us to assess pharmacological manipulations on attention and memory within the same task in the nine-hole box. In the combined attention-memory task (CAM), the rat is required to detect the visual target, which is typically 0.7 s duration (‘attentional’ phase) and then nose-poke the food magazine for the entire length of a variable delay (0–16 s). After the delay, the rat is presented with a choice of two stimulus lights (‘memory’ phase). One light is the same as the visual target and the second stimulus light is a random other. In the matching paradigm, the rat is rewarded for nose-poking the light that was identical to the target (Chudasama et al. 2001).

In the CAM task, a preliminary investigation showed that systemic administration of *d*-amphetamine, a psychostimulant that releases DA, NA, and 5HT in the brain (Rang et al. 1995), significantly enhanced attentional accuracy in animals with selective dorsal Cg1 lesions. Nevertheless, unlike sulpiride, *d*-amphetamine had no effect on the performance deficit in animals with mPFC lesions. Nor did *d*-amphetamine differentially affect these lesioned groups in the memory phase of the task (Chudasama, Nathwani and Robbins unpublished observations). However, direct intra-mPFC infusions of the D₁ agonist SKF 81297 not only enhanced attentional accuracy, but also affected performance of animals during the memory phase in a delay-dependent manner specifically by impairing good performance at the short delay and improving poor performance at the long delays (Chudasama and Robbins, unpublished observations). Thus, increased DA activity in the PFC may make the animal selectively attend or focus more effectively on the stimuli controlling behavioural performance, which may therefore explain the beneficial effects of D₁ agonists on attention (Granon et al. 2000) and subsequently on memory. Importantly, these data suggest that DA receptor stimulation sufficient to improve attentional accuracy, can also disrupt and facilitate working memory. One possibility is that different cognitive processes require different levels of DA, a possibility that may be relevant when considering drug therapies for schizophrenic patients who show slightly different cognitive disturbances. Taken together, these data are compatible with the level of mesofrontal DA activity, possibly normally dependent on such factors as previous exposure to stress, producing costs as well as benefits, in different aspects of cognitive performance (see Robbins 2000). Thus, any attempt to enhance cognitive

function in schizophrenic individuals should take such findings into account.

Effects of serotonergic agents

The serotonergic system is also a target for antipsychotic agents, particularly at 5-HT_{1A} and 5-HT_{2A} receptor sites (e.g. clozapine) (Meltzer 1999; Millan 2000; Winstanley et al. 2003). It is now well recognized that global 5-HT depletion increases impulsive premature responding in the 5CSRRT without affecting response accuracy (Harrison et al. 1997; Koskinen et al. 2000; Koskinen and Sirvio 2001; Winstanley et al. 2003). However, with the introduction of more selective agents, the contribution of different serotonergic receptors in the mPFC has provided significant insights into how this system regulates performance on the 5CSRRT via its likely interactions with the DA system (Meltzer 1989). Thus, the systemic administration of DOI, a 5-HT_{2A/2C} receptor agonist increases impulsivity and reduces accuracy in the 5CSRRT (Koskinen et al. 2000), whereas direct intra-mPFC infusions of ketanserin, a 5-HT_{2A/2C} antagonist reduces impulsivity but has no effect on accurate responding (Passetti et al. 2003). Similarly, infusions of the 5-HT_{2A} antagonist M100907 into the mPFC also reduce impulsivity as well as omissions, whilst improving accuracy under certain conditions (Winstanley et al. 2003; for summary of effects on accuracy, see Table 1). By contrast, systemic administration of 8-OH-DPAT, a 5-HT_{1A} agonist, selectively improves performance at the lowest doses, an effect that is blocked by the 5-HT_{1A} antagonist WAY 100635 (Winstanley et al. 2003). Similarly, in-vivo microdialysis studies indicate that cortical DA and its metabolite DOPAC, but not 5-HT, increased during performance of the 5CSRRT. Furthermore, cortical 5-HT, but not DA, correlates with impulsive premature responses both under basal and task related levels (Dalley et al. 2002a). Taken together, these data demonstrate that serotonergic modulation in the mPFC can both increase attentional selectivity and decrease impulsivity via 5-HT_{1A} and 5-HT_{2A} receptors. These findings in normal rats are particularly exciting given that some atypical antipsychotics have 5-HT_{2A} receptor antagonist actions that may potentially contribute to a pro-cognitive effect in schizophrenia (Meltzer 1999). That systemic 8-OH-DPAT and systemic DA D₁ agonists increase prefrontal acetylcholine release (ACh) (Day and Fibiger 1993; Consolo et al. 1996; Steele et al. 1997), suggests that attentional performance on the 5CSRRT following 8-OH-DPAT and M100907 may be due to cortical ACh release mediated by dopaminergic and serotonergic interactions at 5-HT_{1A} and D₁ receptors (see Winstanley et al. 2003). Importantly, these interacting mechanisms may facilitate attentional and cognitive improvements via atypical antipsychotic treatment in patients with schizophrenia. Evidently, dopaminergic and serotonergic systems interact probably via distinct receptor mechanisms, in a manner that controls the vigour of responding and the accuracy of responding to visual targets.

Effects of cholinergic agents

The atypical antipsychotics such as clozapine and risperidone, in addition to increasing DA release in the mPFC, also increase ACh release in the mPFC (Meltzer 1989; Ichikawa et al. 2002) suggesting that ACh release may also contribute to the ability of atypical antipsychotics to improve cognitive symptoms in schizophrenia (Leucht et al. 1999; Meltzer and McGurk 1999; Ichikawa et al. 2002). Converging lines of evidence support an important role for the basal forebrain cortical cholinergic system in attention and arousal which is consistent with recent data that have reported a sustained elevation of extracellular ACh in the mPFC of unlesioned rats during contingent performance of the 5CSRTT (Passetti et al. 2000; Dalley et al. 2001). This finding suggests that ACh may mediate primary aspects of attention, including stimulus detection (Robbins 1997; Passetti et al. 2000; Sarter and Bruno 2000).

AMPA-induced lesions of the nucleus basalis magnocellularis (NBM) that depleted the neocortex of choline acetyltransferase (ChAT) by around 70% produced a long-lasting deficit in attentional accuracy in the 5CSRTT (Muir et al. 1994; Robbins and Everitt 1995a). Interestingly, physostigmine (an acetylcholinesterase inhibitor) and nicotine (which acts on nicotinic acetylcholine receptors) have been shown to exert beneficial effects on response accuracy in the 5CSRTT in rats with NBM lesions (Muir et al. 1995). Direct infusions of scopolamine, a muscarinic antagonist, into the mPFC induce significant attentional deficits (Robbins et al. 1998). In addition, systemic physostigmine has also been shown to alleviate an attentional deficit in the 5CSRTT following intra-NBM infusions of muscimol, a GABA agonist that also reduces cholinergic activity (Muir et al. 1992).

More recently, intrabasis infusions of high and low doses of the immunotoxin 192 IgG-saporin (Wiley et al. 1991) which has a greater specificity for cholinergic cells, produce different degrees of damage that appear to correlate with the degree of accuracy deficit (McGaughy et al. 2002). The specificity of the NBM cholinergic system is supported given that saporin-induced damage to the ventral diagonal band (VDB) or septum produce no reliable correlation with any aspect of performance on the 5CSRTT (Muir et al. 1996b; Lehmann et al. 2001). However, the finding that animals with less extensive NBM saporin lesions produced no change in ACh efflux during performance of the 5CSRTT and no impairment in attentional accuracy, suggests the possibility that the basal forebrain cortical cholinergic system may have compensated for the loss of ChAT-immunoreactive cells in the NBM in order to maintain accurate attentional performance (see McGaughy et al. 2002). However, the restricted lesioned animals were impaired in response accuracy when the sustained attentional requirements of the task were increased, suggesting that selective damage to the basal forebrain cholinergic neurons may be critical in optimizing performance in response to specific behavioural challenges, particularly when the attentional de-

mands are great (for discussion, see Baxter and Chiba 1999). Nonetheless, the restorative effects of systemic cholinergic drug administration in saporin-lesioned animals have yet to be explored systematically.

There is also evidence that nicotine can consistently enhance performance in paradigms with an attentional component (Wesnes and Warburton 1984; Sahakian et al. 1989; Jones et al. 1992; Koelega 1993; Stolerman et al. 1995). In the 5CSRTT, both systemic and intra-mPFC nicotine treatment, but not intra-hippocampal treatment, enhances accuracy and reduces omissions under certain conditions (Hahn et al. 2003) implicating the prefrontal cortex as a major target site for the attention-enhancing effects of nicotine. Mirza and Stolerman (2000) have also shown that the beneficial effects of nicotine are mostly evident when inter-trial interval is manipulated so as to challenge sustained attentional demands. However, it is becoming increasingly apparent that the enhancing effects of nicotine are more dependent on the ability to focus attentional resources on task-relevant stimuli therefore involving selective attentional mechanisms (Stolerman et al. 2000; Hahn et al. 2002; Robbins 2002). Together, these data are consistent with the modulatory effects of the NBM cholinergic system on the 5CSRTT (Sarter 1994; Everitt and Robbins 1997; Sarter and Bruno 1997; Robbins 2002) and have clear significance in their application for the use of cholinergic agents in the remediation of attentional deficits that are observed in patients with schizophrenia.

Other neurotransmitter systems

Of course, conventional psychostimulants such as methylphenidate which involve dopaminergic activity have also been shown to be effective in enhancing performance in low-performing rats in the 5CSRTT (Puumala et al. 1996), a finding that parallels the improvements observed following central infusions of D₁ receptor agents (Granon et al. 2000). Systemic administrations of *d*-amphetamine typically affect indices of response vigour such as premature responding and speed rather than attentional accuracy (Cole and Robbins 1987, 1989). There is some evidence that the behavioural effects of non-selective catecholamine agents may reflect actions within both the noradrenergic and dopaminergic systems (Cole and Robbins 1987). Thus modafinil, a novel wake-promoting drug used in narcolepsy, has a clinical profile similar to that of traditional psychostimulants, but is thought to act as a hypocretin agonist that has an excitatory effect on the locus coeruleus adrenergic neurons (Hagan et al. 1999; Bourgin et al. 2000; Ivanov and Aston-Jones 2000). In the 5CSRTT, modafinil-treated animals maintain a high level of response accuracy while increasing premature responding at high doses (Burnham et al. 2003; Milstein et al. 2003), thus mimicking the effects of systemic *d*-amphetamine administration (Cole and Robbins 1987). Clearly, modafinil appears to promote arousal through a mechanism that does not involve dopaminergic activity (Lin et

al. 1992, 1996; Ferraro et al. 1997; Turner et al. 2003), although the biochemical effects of modafinil have yet to be clearly identified (Rush et al. 2002) and its precise mechanism of action is yet to be explored systematically. Further studies are required in order to examine the potential cognitive-enhancing effects of modafinil in the 5CSRTT.

With respect to NA, it is thought that boosting NA function may serve to enhance attentional performance and facilitate neural processing through actions primarily at α_1 and α_2 adrenergic receptors (Arnsten 2000; Robbins 2002). For example, the α_1 receptor agonist St-587, improved attentional performance in the 5CSRTT when the signal duration was shortened, an effect that was blocked by the α_1 receptor antagonist prazosin (Puumala et al. 1997). Similarly, only high doses of the α_2 antagonist, atipamezole improved detection of visual targets when brightness was reduced (Sirvio et al. 1993, 1994), presumably by enhancing central NA function. It is of particular interest, therefore, that rhesus monkeys treated with the α_2 agonist clonidine or guanfacine are less distracted when subjected to interpolated bursts of white noise during the delay period of a delayed-response task (Arnsten and Contant 1992, see also Arnsten 2000).

Nonetheless, the effects of adrenergic agents or modafinil are not directly compatible with the effects of lesions made to the dorsal noradrenergic bundle (which deplete cortical NA). Such lesions impair attention to the stimulus only under high-arousal conditions such as distracting bursts of white noise, temporal unpredictability of the stimulus, or increasing behavioural output caused by systemic or intra-accumbens infusions of *d*-amphetamine (Carli et al. 1983; Cole and Robbins 1987). Clearly, it is difficult to compare the effects of widespread NA depletion with systemic administration of drugs that are likely to affect multiple systems. Thus, it is necessary to examine the effects of direct infusions of adrenergic receptor agents into specific neuroanatomical locations, and to do so using the testing conditions that most clearly reveal the effects of DNAB lesions (see Robbins 2002).

There is some recent evidence showing that NA levels in the mPFC increased only when the task contingencies were manipulated such that the animal continued to receive reward in the absence of making a response to the visual target, and not during baseline performance (Dalley et al. 2001). Intriguingly, the profile of effects was the exact opposite for ACh release, which increased during baseline performance but not when the contingencies were changed. These findings provide a clear dissociation between the relative contributions of each of these neurotransmitters in optimizing attentional processing (see Dalley et al. 2001).

In addition to the effects of the cortical NA system, which may function to preserve attentional selectivity in highly arousing circumstances (for discussion, see Robbins and Everitt 1995a; Usher et al. 1999), other evidence indicates that agents acting at histamine receptors, particularly the H_3 -receptor antagonists, may have thera-

peutic applications in psychiatry (Schwartz et al. 1995). The novel potent H_3 -receptor antagonist ciproxifan has recently been shown to enhance attentional accuracy when the stimulus duration was reduced whilst having no effect on any other measure of the 5CSRTT (Ligneau et al. 1998). That H_3 receptors are abundant in the frontal cortex (Pollard et al. 1993) suggests that they may interact with other cortically projecting neurotransmitter systems (Leurs et al. 1998). For example, it has been shown that H_3 receptors may modulate the activity of cholinergic neurons. For example, activation of cortical H_3 receptors by local and systemic administration of imetit (a selective H_3 -receptor agonist) reduces K(+)-evoked ACh release in the cortex of freely moving animals (Blandina et al. 1996). Although theoperamide or clobenpropit (H_3 -receptor antagonists) attenuate the amnesic effects of scopolamine in maze tasks, the restorative effects of histaminergic agents in the 5CSRTT have not been examined thoroughly.

Relationship to other tests of attention

In cognitive testing, it is often advisable to use at least two different tests of similar functions in order to obtain converging data that enable generalizations to be made about the underlying processes. This approach is illustrated in the case of the 5CSRTT by examining parallel measures of vigilance and divided attention (see McGaughy et al. 1994; McGaughy and Sarter 1995; Muir 1996). There are in fact many other tests of attention used for rodents that probably tap into different aspects of attentional function, but which are largely beyond the scope of this review. In the rat, these tests include prepulse inhibition (PPI), latent inhibition (LI), and most recently extra-dimensional shifting (Birrell and Brown 2000). The latter is derived from tests designed for non-human primates as analogues of the Wisconsin Card Sorting Test, and is directly applicable to experimental animals (Dias et al. 1996; Pantelis et al. 1999). Seldom have these tests been employed in the same experimental design although the differential effects of dopaminergic drugs on these tasks suggest that they may be mediated by rather distinct neurochemical systems. One exception is the comparison of the effects of early social isolation (post-weaning) on LI and PPI. Social isolation produces many neurochemical effects, including significant increases in DA efflux within the nucleus accumbens following treatment with systemic *d*-amphetamine. Whereas isolation disrupted PPI, it had no effect on LI (Wilkinson et al. 1994). The more recent study of the effects of isolation rearing found no substantial deficits in the response accuracy measure in the 5CSRTT, but increased errors of omission and decreased premature responses, under certain circumstances (Dalley et al. 2002a). Evidently, isolation rearing has quite different effects on tests of attention that are mainly subserved at subcortical levels, possibly indexing 'implicit' aspects of attention or sensorimotor gating, whereas performance on the 5CSRTT

depends more directly on prefrontal cortical mechanisms that are perhaps less severely disrupted by this form of rearing experience (Dalley et al. 2002b). This comparison illustrates that we may need several "animal models" in order to adequately represent the complexity of attentional dysfunction in schizophrenia.

The beneficial effects described above of D₁ receptor agents on 5CSRTT performance are consistent with other evidence that this receptor system helps to "stabilise" representations at the level of the PFC (Dustewitz et al. 2000). In fact, recent data on the effects of prefrontal DA depletion in monkeys are especially consistent with this hypothesis about the action of prefrontal DA at a cellular level. With regard to certain forms of cognitive impairment in schizophrenia, this hypothesis may explain the deficits found in schizophrenic subjects related to abstracting rules in complex discrimination learning tasks (Pantelis et al. 1999). Such deficits appear to be similar to those in monkeys with mesocortical DA loss (Crofts et al. 2001). Similarly, mesocortically DA-depleted monkeys are more distractible than normal (Crofts et al. 2001). However, while this evidence is consistent with that from rats, there have been no attempts yet to ameliorate these deficits in monkeys, for example, using D₁ receptor agonists (as was achieved by Castner et al. 2000 for working memory performance).

Conclusion and future directions

We are on the threshold of understanding how the attentional deficits in schizophrenia are related to the other profound cognitive deficits and psychotic symptoms associated with this severe neuropsychiatric disorder. The present generation of antipsychotic drugs is indeed very effective in relieving many of the symptoms of schizophrenia, particularly in its acute phase. Nevertheless, little is known about their efficacy in patients with ongoing symptoms, for example in the elderly where there is an increased propensity for drug interactions (Neil et al. 2003). What is clear, however, is that concepts regarding the psychopharmacology of schizophrenia are currently changing, with serotonergic transmission being a focus of interest. In addition, while most existing drugs possess antagonistic properties, the most recent approach has been to focus on partial agonists particularly at DA (e.g. Tamminga and Carlsson 2002; Grunder et al. 2003) and serotonin 5-HT_{1A} receptor sites (Millan 2000) because of their capacity to behave like agonists and antagonists in conditions of low and high receptor stimulation respectively. Thus, the testing of partial agonists in animals may illuminate the functionally important role of how regulating dopaminergic or serotonergic transmission may modulate attention and other cognitive processes.

It is now becoming increasingly apparent that existing antipsychotics possess many pharmacological activities, suggesting that they exert their therapeutic actions by interacting receptor mechanisms. In rodents, there is a need to examine the effects of receptor interactions on

attentional regulation using drugs that combine, for example, DA or serotonin blockade with anticholinergic properties, given that some antipsychotic drugs possess cholinergic activity in addition to their actions on monoaminergic receptors (Iversen 1975, 1985; Ichikawa et al. 2002). Another interesting interaction would be to test a drug that combines a D₁ agonist and a D₂ antagonist action in the same molecule. One may predict that the resulting drug would not only block psychotic symptoms via its D₂ receptors, but may also reduce negative (i.e. cognitive) symptoms via its D₁ receptors. Indeed, it may well be that such interactions contribute to the heterogeneity of the attentional deficits observed in patients with schizophrenia.

Interestingly, the effects of cortical and subcortical lesions on attentional function raise the clear possibility that these interactions may occur at different levels of the cortex and its connections with the striatum. Thus, there is a need to examine the effects of neurochemical manipulations made to selective frontal regions as well as other temporal lobe structures such as the amygdala and hippocampus that are also innervated by the frontal cortex and implicated in the neuropathology of schizophrenia. In this context, drugs that differentially target receptors in specific brain regions may have promising therapeutic applications for schizophrenia, as well as other disorders of inattention.

It seems likely that a range of animal behavioural test paradigms will be suitable for testing possibly beneficial effects of drugs on attention and cognition. Here, we have concentrated mainly on a rodent test that has some advantages because of its capacity to assess several aspects of attention simultaneously and produce data relevant to the effects of antipsychotic drugs (e.g. Passetti et al. 2003; Winstanley et al. 2003) as well as putative "cognitive enhancers" (e.g. Granon et al. 2000; Hahn et al. 2003) and neuromodulators (Chudasama and Robbins, unpublished manuscript). We predict that it will become increasingly necessary to relate such effects in animals directly to those observed in human subjects, including those with schizophrenia, whether for pharmacological screening of candidate compounds (e.g. in rats), the testing of construct validity (in non-human primates), or following genetic manipulations (i.e. in mice). The 5CSRTT has proved to be a useful paradigm for measuring sustained and divided attention in the rat under a variety of test conditions and for testing a large number of drugs. Its use will be enhanced when a similarly large body of data is available in patients with schizophrenia, as well as in normal subjects employing the "human" version of the test (e.g. Sahakian et al. 1993), and, where appropriate, in monkeys (Weed and Gold 1998) and mice (Humby et al. 1999).

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