Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans

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Abstract

A comparative and integrated account is provided of the evidence that implicates frontostriatal systems in neurodegenerative and neuropsychiatric disorders. Specifically, we have made detailed comparisons of performance following basal ganglia disease such as Parkinson's disease, with other informative groups, including Alzheimer's disease, schizophrenia and attention deficit/hyperactivity disorder and structural damage to the frontal lobes themselves. We have reviewed several behavioural paradigms including spatial attention and set-shifting, working memory and decision-making tasks in which optimal performance requires the operation of several cognitive processes that can be successfully dissociated with suitable precision in experimental animals. The role of ascending neurotransmitter systems are analysed from the perspective of different interactions with the prefrontal cortex. In particular, the role of dopamine in attentional control and spatial working memory is surveyed with reference to its deleterious as well as facilitatory effects. Parallels are identified in humans receiving dopaminergic medication, and with monkeys and rats with frontal dopamine manipulations. The effects of serotonergic manipulations are also contrasted with frontal lobe deficits observed in both humans and animals. The main findings are that certain tests of frontal lobe function are very sensitive to several neurocognitive and neuropsychiatric disorders. However, the nature of some of these deficits often differs qualitatively from those produced by frontal lobe lesions, and animal models have been useful in defining various candidate neural systems thus enabling us to translate basic laboratory science to the clinic, as well as in the reverse direction.
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1. Introduction

The frontal cortex mediates those cognitive functions, usually referred to as executive, that are needed to optimise performance in complex tasks and include a number of psychological processes, namely: (1) selection and perception of pertinent information; (2) maintenance, retrieval and manipulation of information held 'on-line' in working memory; (3) self-directed planning and organisation in relation to specific contingencies; (4) behavioural control and adaptation to changes in the environment; and (5) appropriate decision-making on the basis of positive and negative outcomes. A disruption of cognitive function often results in a heterogeneous pattern of deficits including distractibility and perseveration, social irresponsibility, lack of initiative, impulsivity and profound disinhibition. These cognitive symptoms are characteristic of many neurodegenerative disorders such as Alzheimer's and Parkinson's disease, psychiatric illness including schizophrenia, depression and obsessive compulsive disorder (OCD), as well as pervasive developmental disorders such as attention-deficit hyperactivity disorder (ADHD).

It is now apparent that cognitive-executive functions are mediated by independent and interacting neural systems that may be compromised by different forms of pathology, leading to a range of cognitive profiles. The frontostriatal network is particularly relevant because its dysfunction results in a pattern of deficits that distinguishes the basal ganglia diseases
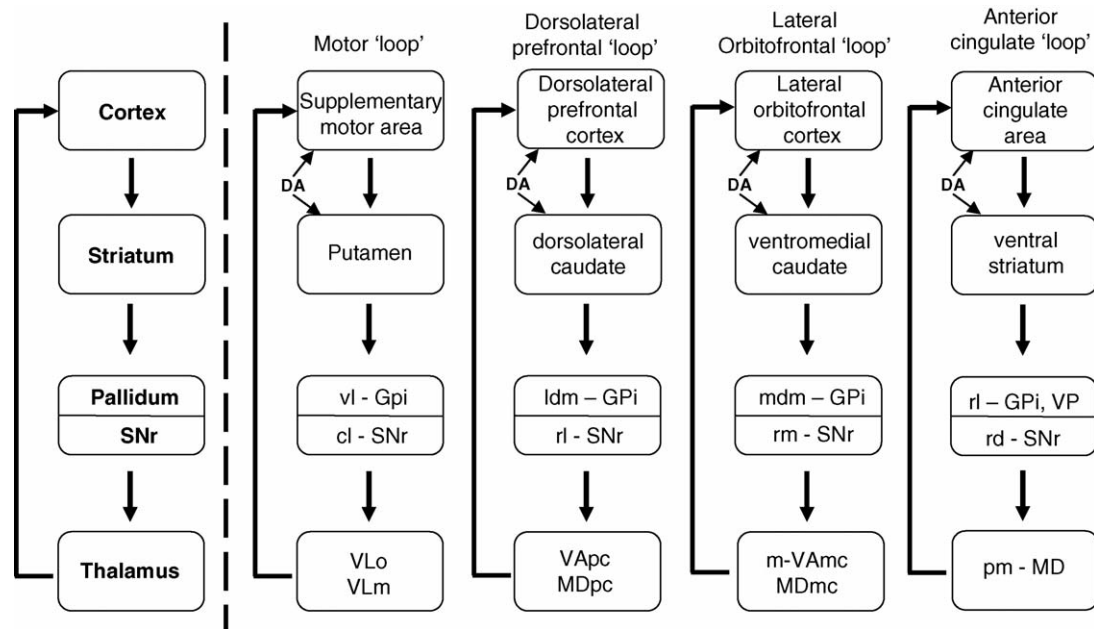
Fig. 1. Parallel organisation of functionally segregated circuits connecting the frontal cortex and striatum based on original scheme by Alexander et al. (1986). Four frontostriatal 'loops' are shown. Each 'loop' starts in a specific region of the frontal cortex and innervates different levels of the striatum before being relayed back to its cortical origin, via the thalamus. NB: short thin black arrows indicate dopaminergic (DA) innervation of the cortex and striatum. The diagram to the left of the dashed line indicates the general organisation of the cortico-striatal-pallidal-thalamic loop.

(e.g. Parkinson's and Huntington's disease) from dementia of the Alzheimer's type which typically comprises disruption, at least in the early stages, to the medial temporal lobe regions. These findings coincide with the anatomical and structural organisation of corticostriatal 'loops' (Alexander et al., 1986) largely derived from anatomical and electrophysiological studies in non-human primates, which involves the parallel processing of descending cortical information that is relayed back to the cortex via the thalamus (see Fig. 1). The parallel organisation of these circuits has proved useful in clarifying not only normal functions of the basal ganglia, but also in efforts to understand the behavioural disturbances that occur in basal ganglia disorders. To the extent that this framework is an accurate representation of functional organisation in the normal brain, it can be used successfully to implicate pathological mechanisms, including dysfunctional neurochemical systems (e.g. dopamine), which may account for the clinical manifestation of basal ganglia disorders.

Significant advances in neuroanatomy have further refined the descriptions of the frontostriatal circuits and their interaction with other complex, cortical-subcortical circuits relevant to behaviour, such as the visual association regions of the temporal cortex (Middleton and Strick, 1996), the hippocampus (Goldman-Rakic, 1987) and the amygdala (Kelley et al., 1982). Together with the increasing sophistication of neuropsychological assessment, advances in molecular pharmacology, and highly developed imaging techniques for studying physiological correlates of activity in the human brain, there has been much progress in understanding the frontostriatal contribution to the nature and extent of cognitive deficits that may underlie some of the behavioural symptoms observed in disorders of brain and behaviour. Nonetheless, animal studies

in the neurobiology of cognition provide some necessary inherent advantages over human studies. In addition to large individual differences in intelligence, education, health and experience, a more serious difficulty with human patients is to determine the relevance of individual neuropathological deficits (i.e. brain structures, neurotransmitter systems) to distinct features of the functional deficit (i.e. behaviour). For example, although it is accepted that there exists a well defined profile of intellectual impairment in Parkinson's disease (PD) that is related to the primary pathology of the nigro-striatal dopamine pathway, it is difficult to disentangle the contribution of additional factors such as degeneration of the basal forebrain or locus ceruleus or indeed cortical Lewy bodies that may also play a role in the overall cognitive deficit syndrome. Furthermore, the role of medication, such as L-Dopa, may also contribute to the cognitive impairment.

Our own approach has been to compare cognitive performance of brain damaged human patients with animal models of their disorder, using tasks that can be theoretically decomposed into their constituent cognitive elements (see Table 1). Thus, one major advantage of animal studies is that we can reproduce in experimental animals particular features of the neuropathological and neurochemical changes observed in humans and establish their consequences. The major disadvantage however, is the difficulty of relating the behavioural deficit in animals to cognitive deficits in humans. For example, planning deficits in humans entail some level of evaluation and the effective sequence of mental responses relative to specific goals; cognitive processes which can be difficult to model in animals. However, the elements of planning which constitute a working memory load, the capacity to sequence responses, to shift on the basis of rewarding and punishing feedback, and

Table 1
Comparable tests of cognition in rats, monkeys and humans

Cognitive process	Species	Cognitive test	References
Visuospatial attention/sustained attention	Rats	5 choice serial reaction time task	Carli et al. (1983), Muir et al. (1996), Granon et al. (2000), Chudasama et al. (2003a)
	Monkeys	5 choice serial reaction time task; reaction time task	Weed et al. (1999), Spinelli et al. (2004)
	Humans	Continuous performance test	Rosvold et al. (1956), Orzack and Kornetsky (1966), Sahakian et al. (1993), Jones et al. (1995)
Spatial working memory	Rats	Delayed alternation	Olton (1982), Dunnett (1985, 1993), Zahrt et al. (1997), Floresco and Phillips (2001), Chudasama and Robbins (2004b), Chudasama et al. (2004c)
	Monkeys	Spatial delayed response; self-ordered working memory	Rosvold et al. (1961), Brozoski et al. (1979), Arnsten et al. (1994), Passingham (1985), Sawaguchi and Goldman-Rakic (1991), Collins et al. (1998)
	Humans	Subject-ordered working memory	Petrides and Milner (1982), Owen et al. (1990, 1996), Sahakian et al. (1990), Diamond et al. (1997), Mehta et al. (2004a, 2004b)
Set-shifting and reversal	Rats	Attentional set-shifting; discrimination and reversal learning	Bussey et al. (1994), Birrell and Brown (2000), Barense et al. (2002), Chudasama and Robbins (2003)
	Monkeys	Intra- and extra-dimensional (ED/ID) set-shifting; discrimination and reversal learning	Roberts et al. (1994), Dias et al. (1996), Collins et al. (2000), Crofts et al. (2001)
	Humans	WCST; intra- and extra-dimensional (ED/ID) set-shifting; discrimination and reversal learning	Milner (1963), Downes et al. (1989), Owen et al. (1992), Swainson et al. (2000), Pantelis et al. (2004), McLean et al. (2004), Cools et al. (2001a, 2001b)
Decision-making and impulsivity	Rats	Delayed reward; temporal discounting; stop-signal task	Mazur (1987), Richards et al. (1999), Mobini et al. (2000), Cardinal et al. (2001), Winstanley et al. (2004a, 2004b)
	Monkeys	Go/No-go task; stop-signal task	Pribram and Mishkin (1955), Iversen and Mishkin (1970), Petrides (1986), Schall et al. (2002)
	Humans	Iowa gambling task; Cambridge Gamble Task	Damasio (1994), Bechara et al. (1994), Rahman et al. (1999), Rogers et al. (1999b, 1999c), Manes et al. (2002), Clark et al. (2003)

Note: Some references in Table 1 may not be cited in the main text.

respond according to conditional rules can be readily addressed by primate and rodent neuropsychological studies and are included in our own battery of tests for monkeys and humans (i.e. CANTAB; Cambridge Neuropsychological Test Automated Battery). Although several cognitive tests used with humans has been derived from animal cognitive learning theory, such as the delayed-matching tests of recognition memory, in some cases, the cross-species comparison has been made in the opposite direction whereby a human neuropsychological test, the WSCT (Wisconsin Card Sorting Test), was made more accessible for use with monkeys, specifically by turning it into a series of simpler tests that decomposed its elementary cognitive constituents. Of course, this approach facilitates our understanding of the nature of the deficit in humans because it enables us to report with specificity, the precise difficulty an individual patient might have with the requirement of that particular task.

In addition to isolating the neural substrates of cognitive deficits in clinical patients, is the evidence that disorders of brain and behaviour include neurochemical pathology of the modulatory catecholaminergic (dopamine, serotonin and noradrenalin) and cholinergic neurotransmitters, also known to play an important role in cognitive functions. This evidence is derived from experimental studies in animals that have made relatively selective lesions of these projection pathways and have reported deficits in a variety of cognitive tasks (e.g. Brozoski et al., 1979). Furthermore, the main effect of drug therapy such as Ritalin, neuroleptics or selective serotonin reuptake inhibitors (SSRIs), is to alter the activity of the modulatory systems so as to bring about cognitive improvement. Nevertheless, the degree of overlap of dysfunctional neuropathological and neurochemical systems has implicated abnormalities in frontostriatal circuitry in virtually all neurological and neuropsychiatric disorders and thus animal models provide important experimental tools for understanding the mechanisms of drug action, as well as the development and screening of appropriate treatments for the alleviation of symptoms arising from brain disorders such as dementia and psychiatric illness.

2. Modeling attentional dysfunction

There is considerable evidence that changes in attention can influence a number of cognitive processes such as awareness of signals and objects as in disorders of neglect and selection, and interpretation of incoming signals as in schizophrenia. Advances in the neurobiology of animal behaviour have made it possible strategically to apply theoretical notions of attention such as selection, vigilance and control, formally derived from paradigms used in cognitive psychology to experimental animals including the mouse and rat. However, studies in experimental animals have been biased towards understanding the syndrome of sensorimotor neglect that commonly occurs following unilateral striatal-dopamine lesions (Ungerstedt, 1971; Marshall and Teitelbaum, 1977; Annett et al., 1992) using covert orienting paradigms (e.g. Posner, 1980; Bowman

et al., 1993; Ward and Brown, 1997) in which typically the animal is required to hold its head in a specific location while peripheral target stimuli are presented. Thus, observed deficits in animals with unilateral striatal lesions on these types of tasks were considered failures in organising orienting responses, although it was not immediately clear from the results if these deficits were compromised by impairments in response control given the long history of the role of the striatum in the cognitive control over action (Reading et al., 1991; McDonald and White, 1993; Mink, 1996). Indeed, from our own analysis, it became increasingly apparent that striatal neglect was more likely a response-related deficit, rather than a pure attentional one (Carli et al., 1985, 1989; Brasted et al., 1999; Brown and Robbins, 1989).

Nonetheless, attentional deficits form a prominent part of the cognitive profile associated with many psychiatric disorders that are typically characterised using tests of frontal lobe function such as shifting functions that are engaged in the WCST, and sustained attentional demands in the continuous performance test (CPT). Originally derived from research in human experimental psychology and included in CANTAB, attentional shifting, which will be discussed in a later section, and continuous performance can now both successfully be applied to experimental animals including rats and monkeys (Roberts et al., 1994; Chudasama and Robbins, 2004a; Brown and Bowman, 2002). These functions have important translational properties in view of the assumption that experimental animals have the basic building blocks of cognition that are seen in complex cognitive capabilities in humans. In this section, we will show that many attentional symptoms in humans can be modelled by simpler versions of what are considered to be human analogues in experimental animals (see Robbins, 1998).

2.1. 5 Choice serial reaction time task

An example of an animal test that has translational properties is the five choice serial reaction time task (5CSRTT; Carli et al., 1983) that was modelled after its human analogue, the continuous performance test (CPT; Rosvold et al., 1956; Wilkinson, 1963) and has been shown to recruit several attentional operations that depend on specific neural networks. Formally devised for assessing generalised brain damage (Rosvold et al., 1956), the CPT is considered a sensitive measure of attention; patients with right frontal lobe damage show long reaction times and miss more targets relative to controls (Rueckert and Grafman, 1996), and Berman and Weinberger (1990) showed greater activation in the right frontal cortex during performance of CPT compared with other 'frontal' prototypical tasks such as the WCST. In addition, the CPT has been used to assess attention in several clinical groups including patients with schizophrenia who typically show a reduction in performance over time when required to continuously monitor infrequent and unpredictable targets (e.g. letters). Although it is thought that impaired performance in the CPT is indicative of a vigilance decrement (Parasuraman and Davis, 1977), the precise nature of the attentional deficit in

schizophrenia has been difficult to resolve (Davis and Parasuraman, 1982; Nestor and O'Donnell, 1998). In the paradigm used for rats however, different forms of attention can be readily investigated and dissociated following selective neuroanatomical or neurochemical manipulations, thus a neural system that is presumably pathological in schizophrenia may be different from the neural system that is compromised in, for example, ADHD.

In rats, the 5CSRTT is conducted in an automated operant chamber equipped with five exposed apertures located opposite a food magazine. The rat is required to sustain and divide its attention across five spatial locations in order to detect a brief visual light target that occurs randomly in one of the five locations. As well as measuring accurate target detection (response accuracy), the 5CSRTT allows us to measure different mechanisms of behavioural inhibition such as premature 'impulsive' responses related to response preparation, as well as 'compulsive' perseverative responses that may occlude the animals' ability to monitor ongoing behaviour. Finally, measures of latency provide some overall assessment of motor and motivational status and even decision time, depending on the overall profile of results (for detailed description of apparatus, training protocol and behavioural profiles, see Carli et al., 1983; Robbins et al., 1993; Robbins, 2002).

The effect of large medial prefrontal (mPFC) lesions on the 5CSRTT performance is profound (Muir et al., 1996); rats show inaccurate target detection, they are highly perseverative, and are slow responders. Recent studies have refined the lesions to discrete regions of the prefrontal cortex which has helped define the complementary roles of the different frontal sectors (Passetti et al., 2002; Chudasama et al., 2003a; see Table 2). For example, damage to dorsal mPFC leads to impairments in discriminative accuracy whereas lesions to the more ventral mPFC regions promote impulsivity, and damage to the orbitofrontal cortex (OFC) causes perseveration (Chudasama et al., 2003a). Clearly, the rodent frontal cortex has a complex role in integrating aspects of attention and behavioural inhibition in order to optimise performance in the 5CSRTT. The diversity of the behavioural effects following selective frontal lesions is consistent with the scheme of partially segregated frontostriatal 'loops' (Alexander et al., 1986); different frontal regions project to different sectors of the striatum. Hence, the lateral striatum (LS) receives its projections from the lateral frontal and sensorimotor regions of the neocortex (Donoghue and Herkenham, 1986; McGeorge and Faull, 1989), whereas the medial striatum (MS) is innervated by the medial prefrontal cortex (Divac and Diemer, 1980; McGeorge and Faull, 1989; Sesack et al., 1989), but it is only the medial portion of the striatum that is implicated in cognitive function (e.g. Dunnett, 1990; Eagle et al., 1999). Thus, similar to large mPFC lesions, MS lesions produce long-lasting deficits in several aspects of 5CSRTT performance including diminished response accuracy and increased premature and perseverative responding (Rogers et al., 2001; see Table 2) that is probably monitored by different regions of the mPFC (Chudasama et al., 2003a). Similar results are also

Table 2
Summary of main behavioural effects following excitotoxic lesions, or pharmacological treatments to different regions of the rat prefrontal cortex and striatum on performance of the 5CSRTT

	Different regions of the frontal cortex			Different regions of the striatum		
	Dorso-medial	Ventral	Lateral	Dorso-medial	Ventral	Lateral
Accuracy 'attention'	3, 5 ↓ (↑4) a, b, c	—	—	↓ d, e	—	—
Premature 'impulsive'	1 ↑ (↓2)	1 ↑ (↓2) a	—	↑ d, e	6 ↑	—
Perseverative 'compulsive'	↑ c, g	↑ a	—	↑ d, e	↑ f	—
Latency 'decision speed'	↑ a, b, c	—	↑ c	↑ d	—	7 ↑ d

Definitions of different regions of the frontal cortex: the dorsomedial region includes the dorsal Cg1 and PL cortex; the ventral region comprises the IL cortex and OFC that includes ventromedial and ventrolateral orbitofrontal sectors; the lateral frontal cortex includes motor areas (M1 and M2).

Key to effects relative to sham or baseline: ▲, increase; ▼, decrease; ——, no change.

Small letters represent key to references for lesion studies only. (a: Chudasama et al., 2003a; b: Passetti et al., 2002; c: Muir et al., 1996; d: Rogers et al., 2001; e: Christakou et al., 2001; f: Christakou et al., 2004; g: Chudasama and Muir, 2001).

Numbers represent key to drug treatments only: 1: global 5-HT depletion (Harrison et al., 1997; Koskinen and Sirvio, 2001; Winstanley et al., 2003); 2: intra-mPFC infusions of $5\text{-HT}_{2a/2c}$ antagonists (Passetti et al., 2003; Winstanley et al., 2003); 3: intra-mPFC infusions of D_1 receptor antagonist (Granon et al., 2000); 4: intra-mPFC infusions of D_1 receptor agonist (Granon et al., 2000; Chudasama and Robbins, 2004b); 5: cortical acetylcholine depletion (McGaughy et al., 2002); 6: intra-accumbens infusion of d-amphetamine (Cole and Robbins, 1989); 7: DA depletion from dorsolateral striatum (Baunez and Robbins, 1999).

obtained using the more direct approach of disconnecting the mPFC-dorsomedial striatum communication (Christakou et al., 2001). By comparison, lesions of the lateral striatum produce a very different pattern of deficits in the 5CSRTT, namely increased omissions and retarded learning (Rogers et al., 2001) that is reminiscent of the latency deficit observed after lesions of the lateral frontal cortex (Muir et al., 1996). Of course, some of these deficits may well be due to damage to structures of striatal outflow such as the subthalamic nucleus (Baunez and Robbins, 1997) the function of which is also critically dependent on the frontal cortex (Chudasama et al., 2003b). Finally, lesions made to the ventral striatum (VS) subsuming the nucleus accumbens (Nac) produce a compulsive tendency of perseverative responding that is specifically related to the inability to successfully integrate behaviour according to the reward schedule of the task (Christakou et al., 2004). Together, these findings are useful in understanding how 'intact' prefrontal cortico-striatal systems may function to integrate complex behaviours such as the selection and suppression of planned response sequences; this behavioural syndrome of dysexecutive control is evident in a variety of disorders in which the frontal cortex is seriously implicated such as patients with dementia or psychiatric disturbances of schizophrenia and ADHD.

Psychopharmacological studies that have focused on selective neurochemical manipulations of the ascending monoaminergic and cholinergic systems within the PFC and related structures, has enabled us to show dissociations in the way in which the PFC may modulate different aspects of discrimination and control (Robbins and Everitt, 1995). For example, manipulations of serotonin (5-HT) produce a pattern of behaviour in the 5CSRTT suggestive of its likely interactions with the DA system (Meltzer, 1989). Thus, global 5-HT depletion markedly increases impulsive responses (Harrison et al., 1997; Koskinen and Sirvio, 2001; Winstanley et al., 2003) mimicking the effects of d-amphetamine when directly infused into the Nac (Cole and Robbins, 1989). In addition, in-vivo microdialysis studies that can sample changes in neurotransmitters and their metabolites engaged during task performance, have revealed that cortical DA is particularly engaged during 5CSRTT task performance, whereas 5-HT correlates with the performance of impulsive responses (Dalley et al., 2002) suggesting that variations in 5-HT levels may help distinguish impulsive characteristics from attentional ones.

There is evidence, however, that the DA mediated functions within the ventral striatum are regulated by glutamatergic afferents from the PFC (Gariano and Groves, 1988; Jaskiw et al., 1990; Murase et al., 1993; Taber and Fibiger, 1995). Thus, electrical stimulation of the PFC (Taber and Fibiger, 1995) or local application of glutamate (Moghaddam et al., 1990) increases extracellular levels of DA in the striatum, and

Dalley et al. (1999) has reported that lesions of the PFC produce alterations in CREB (cAMP response element binding protein) phosphorylation in the Nac following d-amphetamine treatment. These findings are particularly relevant to altered mesocorticolimbic DA transmission produced by prolonged or intermittent exposure to stimulant drugs (e.g. methylphenidate or amphetamine); the behavioural deficits of inattention and impulsivity appear to be strikingly similar to the core deficits in ADHD.

These neurochemical observations are consistent with other pharmacological approaches such as microinfusions of selective DA receptor agents directly into the mPFC; these findings have been useful in modeling patterns of behaviour that appear to adjust via dopaminergic mechanisms depending on overall control levels of performance. Thus, while D_1 receptor agonists infused directly into the mPFC enhance accuracy in low performing animals, D_1 receptor antagonists impair performance when it is relatively high (Granon et al., 2000). Furthermore, enhancing attentional arousal using mPFC D_1 stimulation can have a subsequent modulatory effect on memory performance by either *impairing* it when it is 'high,' and *improving* it when it is 'low' (Chudasama and Robbins, 2004b). These findings have implications for human clinical conditions such as ADHD where psychostimulant therapy, such as Ritalin (methylyphenidate), has beneficial effects on patients that are essentially already 'stimulated.'

Unlike the effect of DA D_1 agents, the infusion of the D_2 receptor agent, sulpiride, was without effect in the 5CSRTT, but remarkably ameliorated an accuracy deficit in animals with mPFC lesions when administered systemically (Passetti et al., 2003). This effect may possibly reflect a striatal mode of action caused hypothetically by over-activity of sub-cortical DA that may have contributed to the lesion induced disruption of performance. Although intra-mPFC infusions of DA receptor agents had little or no effects on other response measures such as premature or perseverative responding, there is evidence that changes in DA levels caused by, for example, amphetamine, produce a syndrome of stereotyped behaviour that is mediated by DA release in the dorsal striatum (e.g. Creese and Iversen, 1975; for review see, Robbins et al., 1990) and this may be related to many of the psychotic symptoms thought to be precipitated following amphetamine abuse in schizophrenia (Connell, 1958; Snyder, 1973), which is significant for this group of patients compared with patients with dementia.

Observations following manipulations to the cholinergic system have also been useful in predicting patterns of attentional dysfunction and subsequent effects of pro-cognitive drugs used with patients. Thus, acetylcholine depletion in the PFC caused by basal forebrain lesions, produces accuracy deficits in the 5CSRTT together with disinhibitory deficits, particularly when engaging sustained attentional mechanisms in high attention demanding conditions (McGaughy et al., 2002). While anti-muscarinic agents such as scopolamine aggravate these effects, they can be ameliorated by pro-cholinergic drugs such as physostigmine or nicotine (Muir et al., 1995). However, the modulatory role of acetylcholine in cognitive function is particularly interesting given its role in maintaining working memory, as well as serving to optimise attentional processing (Chudasama et al., 2004c). These findings are relevant to the attention enhancing action of pro-cholinergic drugs used with patients with Alzheimer's disease known to be deficient in cholinergic markers performing a CANTAB version of the human 5CSRTT (Sahakian et al., 1993) and their deteriorating performance in the learning of several forms of material and short-term memory function (Sahakian et al., 1990).

Hence, the 5CSRTT has proven to be useful for analysing the functions of the different neurotransmitters in the rodent brain, and their interactions with each other which need to be considered when predicting their impact on performance. Although currently, there are no primate studies that have directly examined the effects of frontal or striatal manipulations during CPT performance, there now exist versions of the 5CSRTT for use with rhesus monkeys (Weed et al., 1999) marmosets (Spinelli et al., 2004), as well as mice (Humby et al., 1999) which will hopefully enable integrative cross-species comparisons to be made. But attentional deficits form only part of the impaired cognitive profile in human clinical conditions. For example, certain tasks used to index working memory in experimental animals such as spatial delayed response, are functionally related to the 5CSRTT paradigm in that the animal is required not only to detect a visual target in space but also to remember its location over a short delay (see Chudasama and Robbins, 2004b). Moreover, 5CSRTT performance also requires other 'building blocks' of cognitive function, such as the capacity to initiate responses but to prevent impulsive behaviours, but also repeated, maladaptive perseveration. These mechanisms of executive control also contribute to the overall temporal scheduling, or planning, of behaviour from trial to trial. We therefore consider these more complex processes in the context of other tests of the 'CANTAB' battery.

3. CANTAB (Cambridge Neuropsychological Test Automated Battery)

CANTAB was originally devised for the assessment of cognitive function in elderly and dementing patients (Robbins et al., 1994). It is a battery of computerised tests administered with the aid of a touch-sensitive monitor. Its guiding principle was two-fold: (1) to design tests in which could be broken down into their constituent cognitive components in order to define which aspect of cognition was impaired and which was spared that was relevant to performance for that particular task; and (2) the tasks could be performed by monkeys, as well as humans using the same basic hardware and software so that the perceptual processing required to perform the task is likely to be similar across species. The battery has now been used extensively in the testing of patients with AD and other forms of dementia (Sahakian et al., 1988, 1990), basal ganglia disorders including PD (Downes et al., 1989; Owen et al., 1992, 1993), Korsakoff's syndrome (Joyce and Robbins, 1991), depression (Abas et al., 1990; Swainson et al., 2001), schizophrenia (Elliott et al., 1995) as well as children with learning difficulties or

autism (Hughes et al., 1994). The main rationale of CANTAB is to seek illuminating functional dissociations of executive and non-executive mechanisms, via comparative studies of brain damaged humans and monkeys and results have indicated that some of the tests are sensitive to frontal or temporal lobe dysfunction. In this way, CANTAB has been very useful in accurately distinguishing, for example, AD patients from depressed patients (Swainson et al., 2001) thus providing a potential means of early diagnosis. Ultimately, the observed deficits can be related to studies with animals with neuronal and neurochemical abnormalities produced by the disease process to get a better idea of how to target the deficit by pharmacological means.

Although several tasks constitute the CANTAB test battery, for the purpose of this review, we will focus on three main CANTAB tests: extra- and intra-dimensional attentional set shifting (ED/ID), self-ordered spatial working memory, and the Cambridge Gamble Task.

4. Modeling the WCST: extra- and intra-dimensional attentional set-shifting

An example of a paradigm that has been made useful for both human and monkeys in detecting different executive impairments is the extra-dimensional shift (EDS; Slamecka, 1968; Downes et al., 1989; Roberts et al., 1994). In EDS the subject is first trained to respond to one stimulus dimension (e.g. lines or shapes) of a complex, multidimensional compound stimulus and is then required to respond instead to a previously irrelevant dimension. The critical comparison is when the subject is required to make an intra-dimensional shift (IDS) which requires the ability to transfer responses to novel exemplars within the same stimulus dimension thus requiring the establishment of an 'attentional-set.' In addition, reversals (when the reward contingencies of the relevant dimension are reversed), can be introduced at both EDS and IDS stages in order to assess control over behaviour by the dimension rather than by a specific exemplar of it (for detailed description and experimental protocol, see Roberts and Sahakian, 1993; Roberts et al., 1994). The salient features of the ED/ID set-shifting test are: (1) it constitutes the main requirement in the WCST, the primary clinical index for frontal lobe dysfunction (Milner, 1963); (2) it allows the separation of two levels of cognitive flexibility; *perseveration* to a specific exemplar or a stimulus dimension, as well as *attentional set-shifting*; processes which constitute the complexity of the WCST; and (3) a parallel version has been devised for testing monkeys (Roberts et al., 1988), thus providing significant advantages for understanding the neural and neurochemical nature of the deficits in humans, as well as in experimental animals. It is particularly relevant, therefore, that disorders of neurocognitive decline and neuropsychiatric illness such as schizophrenia and ADHD, all show deficits in set shifting ability (Owen et al., 1992; Pantelis et al., 2004; McLean et al., 2004), and all show some disturbance of frontostriatal neural networks (Rogers et al., 2000; Liddle et al., 1992; Castellanos et al., 1994; Castellanos, 1996).

4.1. Clinical and neuropsychological findings

The ability to perform the various stages of ED/ID set shifting and reversal learning appears to be mediated by selective prefrontal regions and associated subcortical structures. Studies using primates with excitotoxic fibre-sparing localised lesions of different regions of the PFC indicate that dorsolateral prefrontal cortex (DLPFC) mediates EDS, while reversal learning is associated with the more ventral OFC (Dias et al., 1996). This analysis is consistent with results from a recent neuroimaging study in humans in which shifting an attentional set activated the DLPFC and putamen, whereas only reversal learning which involved switching between two exemplars of the same dimension, differentially activated the ventral caudate nucleus/ventral striatum (Rogers et al., 2000). Together, these data are important in demonstrating that set-shifting ability is dependent on ventral orbitofrontal as well as dorsolateral regions via parallel segregated frontostriatal circuits (Alexander et al., 1986) and task performance may well be compromised by striatal pathology, which occurs relatively early in basal ganglia disorders, and may therefore disrupt function of these neural loops.

One of the most valuable features of ED/ID testing is that not only is it validated as being sensitive to frontal lobe damage, but it is also the only 'frontal' test that is sensitive to the early stages of PD; unmedicated and early stage PD patients exhibit a specific deficit at the EDS stage because they are unable to form and maintain an attentional set (Downes et al., 1989; Owen et al., 1992). However, unlike early PD patients, clinically asymptomatic HD patients are impaired at shifting attentional set at the EDS stage, whereas patients with advanced HD exhibit a dramatic increase in perseverative responding at the simple reversal stage, preventing them from even reaching the EDS stage (Lange et al., 1995). These observations are similar in some ways to patients with frontotemporal dementia (FTD) who have more selective ventral OFC pathology and show much greater deficits on reversals rather than the EDS stage (Rahman et al., 1999). This suggests therefore, that 'shifting,' which has been associated with the DLPFC, and 'reversal learning,' thought to be sensitive to medial orbital damage (Dias et al., 1996) are distinct operations which express according to the stage of the disease process, presumably as a result of how HD affects the striatal sectors that receive differential projections from these prefrontal areas (Lawrence et al., 1998a). Thus, this comparison of deficits that occur either early or late in the course of the illness is consistent with the dorsal-to-ventral progression of the neuropathology in the striatum (Hedreen and Folstein, 1995; Lawrence et al., 1998a).

Specific impairments in the ability to perform the ID shift have also been identified in advanced stages of certain illnesses (see Table 3) although the neural correlate of IDS performance have not yet definitively been identified. Nonetheless, an apparent progression of deficit has been observed in cross-sectional studies of patients with schizophrenia; well preserved high functioning schizophrenic patients show deficits at the EDS stage (Elliott et al., 1995, 1998), whereas increased severity of the illness is associated with impaired performance

Table 3
Impaired performance on EDS, IDS set-shifting and reversal learning paradigm: comparison of clinical groups and candidate neural systems

EDS	IDS	Reversal
Dorsolateral prefrontal lesions	Neural substrate unknown	Orbitofrontal lesions
High functioning schizophrenics	Low functioning schizophrenics	Low functioning schizophrenics
Early/unmedicated Parkinson's disease	Advanced Parkinson's disease	Advanced Parkinson's disease
Attention-deficit hyperactivity disorder	Frontotemporal dementia	Frontotemporal dementia
Chronic amphetamine abusers	Chronic heroin abusers	Low serotonin (Normals)
Preclinical Huntington's disease	Low prefrontal Dopamine	Advanced Huntington's disease
Obsessive-compulsive disorder[a]		Cortical cholinergic depletion

[a] Watkins et al. (2005).

at the IDS stage (Pantelis et al., 1999, 2004). Importantly, these deficits in set stability are not merely functions of test sensitivity or global cognitive impairment. For example, patients early in the course of AD can perform set shifting as well as controls despite a major deficit in short-term memory (Sahakian et al., 1990) and patients with damage to the temporal cortex or have amygdala-hippocampectomies are unimpaired on ED/ID testing (Owen et al., 1991). Clearly, the clinical relevance of the ED/ID test is that it is more specifically a test of anterior cortical function including the frontostriatal circuitry rather than a test of posterior cortical deficits, involving, for example the temporal lobe.

4.2. Effects of medication

In human neuropsychological testing, an important factor is the effect of medication on behavioural performance. For example, DA-ergic drugs such as levodopa (L-Dopa) are efficacious in the treatment of motor symptoms of PD (e.g. Yahr, 1990; Growdon et al., 1998) and controlled withdrawal of the L-Dopa in PD patients produces a generalised impairment in tasks sensitive to frontal lobe function including attentional-set shifting (Lange et al., 1992; Kulisevsky et al., 1998). However, early-in-the-course unmedicated PD patients show greater deficits in set shifting performance than late-in-the-course medicated patients, strongly suggesting a positive effect of medication (Downes et al., 1989; Owen et al., 1992).

The precise relationship between cognitive impairment and catecholamine dysregulation of frontostriatal circuits is somewhat complex; there is some evidence that DA-ergic medication may have the effect of modulating the overall behavioural response by producing both deleterious as well as beneficial effects depending on several factors including drug dosage, task demands and control rates of responding (Robbins and Sahakian, 1979; Gotham et al., 1988; Arnsten et al., 1994; Swainson et al., 2000; Cools et al., 2001a; Chudasama and Robbins, 2004b). Thus, during a probabilistic reversal learning task, where reinforcement contingencies were degraded such that only 80% feedback (instead of the normal 100%) was received on the correct stimulus, and 20% feedback being 'incorrect' (see Lawrence et al., 1999), medicated PD patients were significantly impaired because of their inability to reach a learning criterion at the reversal stage (Swainson et al., 2000). It is also possible, that learning deficits can contribute to the set shifting deficit on the ED/ID task; PD patients have difficulties

in the development and maintenance of attentional sets (Flowers and Robertson, 1985; Owen et al., 1992) in addition to their deficits in shifting to an alternative set, when the demands for new rule learning are increased. As such, the ED/ID task confounds learning and set-shifting (Swainson et al., 2000). The task-set switching paradigm (Rogers and Monsell, 1995; Cools et al., 2001a, 2001b; Mehta et al., 2004b) minimizes these effects by reducing the load on rule learning by having subjects switch between well established sets (well practiced tasks) which therefore increases the premium on set shifting. Using this task, Cools et al. (2001a) showed that L-Dopa withdrawal in PD patients, while having a detrimental effect on task-set switching, had a beneficial effect on probabilistic reversal learning. In addition, although the PD patients showed the classic EDS impairment, there was no difference between those patients that were 'on' or 'off' medication and thus the specific impairment on the task set switching at the 'off' stage indicates a specific deficit in re-engaging a well established attentional set, a finding also observed in monkeys with 6-hydroxydopamine (6-OHDA) lesions of the caudate nucleus (Collins et al., 2000; Crofts et al., 2001). Indeed, L-Dopa is thought to work by elevating DA levels in the worst affected regions, namely the dorsal striatum (Hornykiewicz, 1974; Maruyama et al., 1996) and the effects of medication on task-set switching and reversal learning have been interpreted in terms of the 'normalization' of DA levels when potentially depleted from the fronto-dorsal striatal circuit (associated with task-set switching performance), whilst at the same time potentially 'overdosing' DA levels in a relatively intact fronto-ventral striatal circuit that is associated with reversal learning (Swainson et al., 2000). The 'DA overdosing' effect has also been observed in healthy volunteers who are impaired in probabilistic reversal learning following administration of the D_2 agonist, bromocriptine while showing an improvement in spatial working memory performance (Mehta et al., 2004b). There is also evidence that DA based psychostimulant drugs may modulate set-shifting behaviour in other clinical conditions. For example, chronic amphetamine abusers are sensitive to the ED shift whereas heroin abusers are impaired in learning the ID component in the ED/ID test (Ornstein et al., 2000), and methylphenidate improves set-shifting performance in ADHD patients (Mehta et al., 2004a). Together, these data argue for a specific influence of DA on the modulation of performance on tasks sensitive to frontal lobe damage and highlight the necessity to understand the state of

patients under study in terms of clinical response as well as neurochemical pathology. Importantly, the mechanism by which DA-ergic medication in PD patients may facilitate and impede cognitive performance serves as a useful model for understanding how DA modulation may contribute to normal and abnormal cognitive states.

Nonetheless, the influence of L-Dopa medication poses difficulties of interpretation of the deficits observed in PD patients as well as other forms of neurochemical pathology seen in this condition, and there is now accumulating evidence that some of the deficits seen in PD may be related to non-dopaminergic pathology, for example in the cortical differentiation of the monoaminergic and cholinergic neurotransmitter systems. Consequently, the ED/ID test suite has been employed in studies using non-human primates because of the ease with which specific neurotransmitter manipulations can be made in this species. These studies have helped elucidate the nature of the selective neurotransmitter manipulations on several aspects of cognitive performance. For example, it has been demonstrated that basal forebrain lesions that cause up to 70% cortical cholinergic depletion (Roberts et al., 1990, 1992), equivalent to that seen in non-demented cases of PD (Perry et al., 1985), selectively impaired serial reversal learning (when reversals occur consecutively within a session), implicating the relative importance of cholinergic mechanisms of the frontal cortex in the cognitive deficits associated with this disease. Thus, cortical cholinergic loss is unlikely to account for the attentional set-shifting deficit in PD patients, although it may account for other cognitive deficits including memory and learning difficulties which correlate well with cholinergic loss in patients with AD.

Surprisingly however, the effect of frontal catecholamine depletion produced by 6-OHDA leads to *enhanced* set-shifting at the EDS stage, a result opposite to that of lateral PFC lesions (Roberts et al., 1994; Dias et al., 1996). Further experiments showed that monkeys with PFC DA depletion were markedly impaired in acquiring and maintaining an attentional set towards a specific perceptual dimension (Crofts et al., 2001), a finding resembling that observed in PD patients (Owen et al., 1992) and chronic schizophrenia (Pantelis et al., 1999). However, the lack of set-shifting impairment in monkeys with DA depletion from the caudate nucleus (Collins et al., 2000; Crofts et al., 2001) implicates the involvement of other neurochemical mediators other than DA that may cause a disruption to circuits outside the caudate nucleus. Recently, this hypothesis has been applied directly to monkeys with PFC 5-HT (serotonin) depletion which resulted in increased perseverative responding to a previously rewarded stimulus in a visual discrimination reversal task (Clarke et al., 2004). Intriguingly, the 5-HT depletion was selective to PFC regions that included the OFC which is recruited during reversal learning (Dias et al., 1996). Furthermore, the analysis that PFC 5-HT depletion did not alter 5-HT or DA levels in sub-cortical structures including the dorsal and ventral striatum is consistent with the finding that striatal DA depletion does not affect the ability to reverse stimulus-reward associations (Collins et al., 2000; Crofts et al., 2001).

In humans, the effect of directly manipulating 5-HT levels has only been explored using dietary tryptophan depletion which has little effect on tasks that require the integrity of the DLPFC (Park et al., 1994) but does impair visual discrimination reversal (Park et al., 1994; Rogers et al., 1999a). These effects of neurochemical manipulations in the PFC provide some insight into the nature of the functional interactions between these neurochemical systems. It now seems likely that the central 5-HT system and its interactions with acetylcholine probably mediate reward-related information processing and this has implications for a number of neuropsychiatric disorders. For example, patients with OCD make perseverative errors (Lucey et al., 1997), they show OFC pathology (Insel and Winslow, 1992; Hermesh et al., 2003) and are often prescribed tricyclic antidepressant chlorimpramine and selective serotonin reuptake inhibitors as part of drug therapy (Zohar and Judge, 1996). Thus, the interactions between the ascending neurotransmitter systems may have to be taken into account when predicting their impact on performance.

The ED/ID test has been useful for understanding the cortical specificity and neurochemical selectivity of function in patients with frontal damage, basal ganglia disease as well as psychiatric illness. A similar discrimination and reversal paradigm has now been implemented for use with rats (Bussey et al., 1997) also using computer graphic stimuli on a touch-sensitive monitor, which has made is possible to dissociate the perseverative nature of the OFC cortex (Chudasama and Robbins, 2003) from the non-perseverative new learning deficit that is sensitive to the more dorsal and lateral PFC regions in the rat (Bussey et al., 1997; Chudasama et al., 2001). Other tasks used with rats that are formally similar to the ED/ID test include a set-shifting task that uses odours and texture as the stimuli dimensions to be discriminated (Birrell and Brown, 2000) which again is highly sensitive to the OFC damage (Brown and Bowman, 2002). In addition, behavioural flexibility has also been investigated using place reversal learning tasks (e.g. Ragozzino et al., 1999) by means of laboratory mazes and are sensitive to frontal manipulations (Ragozzino et al., 1999; Delatour and Gisquet-Verrier, 2000; Dias and Aggleton, 2000).

Therefore, understanding the basic function of these different frontal sectors provides a necessary foundation on which to interpret cognitive deficits in several clinical disorders, as well as understanding the effects of selective neurotransmitter manipulations on various aspects of cognitive performance. The recent findings that modafinil, a wake-promoting agent which has psychostimulant properties, enhanced attentional set-shifting performance in adult ADHD and schizophrenia (Turner et al., 2004a, 2004b), and methylphenidate improves set-shifting in ADHD patients (Mehta et al., 2004a) indicates the psychostimulant medication may have potential as important therapy for cognitive impairment because of its beneficial effects on attentional control.

5. Modeling spatial working memory

Studies of localisation of function within the prefrontal cortex have been more feasible in monkeys and rats, than in

humans, because of the advantage of being able to produce selective neuroanatomical and neurochemical manipulations. It is now accepted that deficits shown by animals on the delayed response procedure, formally a test of spatial short-term memory, is associated with damage to the DLPFC. The deficit is thought to relate to the way in which the PFC controls how internal representations come to affect action (Goldman-Rakic, 1987) specifically by holding information 'on-line.' Animals with frontal ablations are consistently impaired on this task which made it well suited for comparing the effects of frontal lesions in experimental animals with clinical conditions such as PD although it is difficult to decompose executive functions of response selection, strategy and organisation that may well contaminate the overall working memory deficit.

Nevertheless, the motivating factor in designing the self-ordered working memory task for CANTAB was the simple reason that a major aspect of executive function is attention to action, especially in behavioural circumstances that require planning and organisation. Its basic design, which is a modification of the original subject-ordered pointing task (Petrides and Milner, 1982), is derived from the spatial search task used with monkeys (Passingham, 1985) and is related to the radial maze working memory task for rats (Olton, 1982). In brief, the patient must search through a number of boxes on a screen to collect tokens and produce their own 'self-ordered' sequence of responses. Patients with frontal lobe damage continued to return to boxes in which a token had already been found making 'between search errors' (Owen et al., 1990). These patients were also less proficient at using a strategy to facilitate their performance, suggesting that their overall deficit in working memory may be confounded by a deficit in planning and organisational skills. Several other groups of patients such as AD and PD patients and temporal lobe patients also show between search errors indicating some level of frontal pathology, but they do not show the significant deficit in strategy (Sahgal et al., 1992; Owen et al., 1995, 1996) whereas Huntington's and Korsakoff's patients exhibit deficits in both strategy and memory performance (Joyce and Robbins, 1991; Lawrence et al., 1996); these deficits may arise due to a neural circuitry that associates the frontal cortex with diencephalic structures, rather than medial temporal lobe and basal ganglia.

The self-ordered test clearly requires the integrity of the frontal cortex and has been directly examined in monkeys with frontal lesions that have been shown to be profoundly impaired on this task, and are highly perseverative due to the disruption of inhibitory control mechanisms necessary to avoid reselecting the previously chosen stimulus (Roberts et al., 1994). That PFC DA depletion in monkeys had no effect on any aspect of performance on the self-ordered task (Collins et al., 1998) clearly dissociates its rather specific influence in facilitating shifting between attentional dimensions. Surprisingly, the only task in which DA depletion mimicked the effect of PFC lesions was in spatial delayed response, a classic working memory task. The specificity of this deficit in monkeys is relevant to children with the genetic developmental disorder of phenylketonuria or PKU, who are thought to show reduced levels of DA in the frontal cortex because of their inability to convert phenylala-

nine into the DA precursor, tyrosine (Diamond et al., 1997, 2004). In addition to showing widespread brain damage and severe mental retardation (e.g. Cowie, 1971), children with PKU show poor spatial working memory performance and set-shifting abilities (Luciana et al., 2001), but do not show impaired performance on the self-ordered pointing task (Diamond et al., 1997). However, a different pattern of behaviour is evidenced in normal developing children with homozygous Methionine (Met) polymorphism of the catechol-*O*-methyltransferase (COMT) gene, which results in slower prefrontal DA catabolism, thus allowing DA to remain active in extracellular space longer (Lotta et al., 1995; Diamond et al., 2004). Opposite to the effects of reduced DA in PKU, the Met polymorphism genotype resulted in children showing *better* performance on a task requiring working memory, but again not on self-ordered pointing (Diamond et al., 2004). These data clearly confirm that performance on the self-ordered pointing task is insensitive to levels of PFC DA and the differential sensitivity of PFC DA on distinct cognitive processes.

The above findings also support the accumulating evidence that DA in the frontal cortex has an important modulatory effect on working memory performance. In monkeys this is assessed using the delayed response tasks; DA receptor antagonists produce an impairment (Sawaguchi and Goldman-Rakic, 1991), low dose DA receptor agonists *enhance* performance (Arnsten et al., 1994; Cai and Arnsten, 1997) and increased DA turnover disrupts performance (Murphy et al., 1996) according to an inverted 'U' shaped function. Recently, these findings have been mimicked in rats using maze paradigms (Zahrt et al., 1997; Floresco and Phillips, 2001) and automated operant tasks that have highlighted an interesting attention-working memory interaction via PFC DA modulation (Granon et al., 2000; Chudasama and Robbins, 2004b). Evidently, although PFC DA depletion failed to show a direct role in various performance measures of the self-ordered task, it is possible that different cognitive processes may be differentially affected by fluctuations in prefrontal DA that may ultimately modulate behaviour. There is evidence in humans that DA manipulations influence certain cognitive processes in normal volunteers. Spatial short-term working memory tasks that require information to be held in memory and sequentially manipulated can be enhanced by low doses of DA D_2 receptor agonists such as bromocriptine, whilst impairing the ability to reverse a learned probabilistic reversal task (Mehta et al., 2001) both processes known to depend on the frontal lobes (Owen et al., 1995). In contrast, the DA D_2 receptor antagonist, sulpiride, impairs several spatial tasks of working memory as well as attentional set-shifting and the more robust task set-switching paradigm (Mehta et al., 1999, 2004b) and yet *improves* attentional selection in rats with PFC lesions (Passetti et al., 2003). These effects were in the absence of any sedative or motoric effects of the drug. The anatomical distribution of DA D_2 receptors in the brain suggests that the major site of action for sulpiride is in the striatum (Camps et al., 1989), coupled with the finding that preclinical HD patients show correlations between accurate performance on working memory tasks with D_2 receptor ligand binding potentials in the caudate and putamen (Lawrence et al., 1998b).

It is also relevant that monkeys with striatal DA depletion are impaired on spatial working memory (Collins et al., 2000). Clearly, although the precise mechanisms by which DA modulates cognitive performance are still unknown, experimental studies in both humans and animals add to the growing body of evidence implicating central DA systems in cognitive processes dependent on intact frontostriatal connections.

Therefore, it appears that the executive deficit in spatial working memory observed in frontal patients has a considerable degree of selectivity but it is not simply produced by damage to the PFC. It seems likely that performance on this task is a product of interactions between cortical and subcortical structures, and their neurochemical innervations, especially DA which serves to regulate performance depending on the precise task requirement and baseline levels of DA. Much of this work has emerged from studies using experimental animals because of the availability of specific receptor agents that are not always available for use in humans. Importantly, the results of Collins et al. (1998) demonstrate that the effects of lesioning ascending DA projections in monkeys are not always equivalent to lesions of the prefrontal cortex itself.

6. Modeling decision-making and impulsivity

Converging neuropsychological and neuroimaging evidence suggests that abnormalities in practical real-life decision-making form a prominent part of the profile of the cognitive deficit associated with patients that have frontal damage restricted to the ventromedial PFC (VMPFC) that includes the orbitofrontal region (Damasio, 1994; Bechara et al., 1998, 1999; Rogers et al., 1999b; Rahman et al., 1999; Manes et al., 2002). Such cognitive deficits are considered in the context of risk-taking or impulsivity because patients tend to pursue inappropriate actions, often without foresight, that are immediately rewarding, but are likely to have undesirable consequences for the patient's well being in the long-term. In humans, abnormalities in decision-making have been quantified successfully using the Iowa gambling task (e.g. Bechara et al., 1994) which emphasizes the learning of reward and punishment associations by making a series of card selections that result in either a net gain or net loss. Patients with VMPFC damage are consistently impaired in this task because they persist in drawing cards from the high risk/high penalty decks leading to an overall reward loss (Damasio, 1994; Bechara et al., 1994, 2000). Patients with damage to the DLPFC perform within the normal range but are sensitive to tests of working memory showing a double dissociation of impairment in decision-making and working memory (Bechara et al., 1998). As such, measures of decision-making and impulsivity may be useful as functional markers of ventral prefrontal cortex damage in several patient groups that show sociopathological tendencies (Damasio et al., 1990; Lapierre et al., 1995; Blair et al., 2001) or substance abuse (Volkow and Fowler, 2000; Bechara et al., 2001; Bolla et al., 2003).

Some of the principles of the Iowa gambling task have been incorporated into the Cambridge Gamble Task and as part of CANTAB, has been decomposed to assess decision-making

abilities uncontaminated by learning and working memory confounds, simply by presenting all the information needed to make a decision on the computer screen. In brief, the subject is required to make a probability judgment of whether a token is hidden beneath a red or blue box presented on a screen and bet a proportion of their total points, reflecting confidence in their decision (for details, see Clark et al., 2004). The task also aims to dissociate motor impulsivity from risk-taking behaviour: fixed bets are displayed on the screen in either ascending or descending order, and the subject must make a response only when the amount displayed is the amount they would like to bet. A truly impulsive subject is less able to 'wait' and tends to respond too early thus placing high bets when they are descending, and place low bets when they are ascending resulting in overall loss in reward.

The Cambridge Gamble Task is sensitive to several patient groups with implicated VMPFC pathology; FTD patients (Rahman et al., 1999), those with aneurysms of the anterior communicating artery which supplies blood to the medial and ventral PFC (Mavaddat et al., 2000), and those with large frontal lesions (Manes et al., 2002) make accurate probability judgements and have slow deliberation times, but demonstrate high risk behaviour as evidenced by their need to place high bets in both ascending and descending conditions. By way of comparison, patients with borderline personality disorder who show fronto-executive deficits (O'Leary et al., 1991; Bazanis et al., 2002) also show slow deliberation times but were unable to suppress their responses thus placing bets too early in both ascending and descending conditions indicating maladaptive impulsive tendencies. Indeed, decision-making may recruit neural activity from multiple ventromedial frontal regions specifically within the inferior and orbital PFC (Rogers et al., 1999b) which may explain the apparently greater incidence of decision-making deficit in patients with OFC damage compared with those sustaining damage to dorsolateral or dorsomedial areas (Bechara et al., 1998; Rogers et al., 1999a). However, patients with early HD, who often have 'fronto-executive' cognitive deficits, show intact decision-making ability on the Cambridge Gamble Task (Watkins et al., 2000) although they may be impaired on the more complex Iowa gambling task (see Stout et al., 2001). They also show deficits during reversal learning (Lange et al., 1995) that is normally sensitive to OFC lesions (Dias et al., 1996). Decision-making requires the ability to select appropriate responses which require flexibility in adaptation to changing reward contingencies and thus, deficits in reversal learning may relate to high risk-taking or impulsive behaviours that lead to abnormal decision making abilities. The parallels between decision-making and reversal learning impairments have been provided in detail elsewhere (see Clark et al., 2004). Suffice to say, however, that PD patients, similar to HD patients, perform the Iowa gambling task within the normal range (Czernecki et al., 2002; Stout et al., 2001) suggesting that the reversal learning deficits may reflect the progression of the disease that has been observed in basal ganglia disorders through the striatum, and indicate a considerable degree of specificity of decision-making effects to ventral regions of the prefrontal cortex.

6.1. Studies with non-human primates

There is a paucity of lesion and pharmacological literature on primates and risk taking behaviour, but performance of monkeys on Go/No-go tasks is relevant not only because it is a task that assesses the ability to actively inhibit inappropriate impulses, but also because the same paradigm has been used extensively in clinical settings (e.g. Drewe, 1975) including patients with orbitofrontal damage (Leimkuhler and Mesulam, 1985; Malloy et al., 1993). In the Go/No-go procedure (e.g. McEnaney and Butter, 1969; Iversen and Mishkin, 1970), the monkey learns to make a response in the presence of a positive stimulus (a 'go' trial), and *inhibit* a response in the presence of a negative stimulus (a 'no-go' trial) for a fixed duration. No-go errors (responses that are made during the No-go trial) are committed because of the failure to inhibit or delay the pre-potent tendency to respond. In monkeys, this inhibitory deficit of impulse control is sensitive to damage to the inferior prefrontal convexity (Iversen and Mishkin, 1970) which is the critical tissue that was often included in lesions of the dorsolateral, as well as the ventral orbital surface of the prefrontal cortex. Dorsolateral lesions that spare the lateral portion of the inferior convexity, do not impair Go/No-go performance (Lawicka et al., 1975) but consistent with its role in spatial and mnemonic functions, produce severe deficits in delayed response tasks (Pribram, 1961; Goldman and Rosvold, 1970; Goldman-Rakic, 1987). By comparison, orbital lesions that are extended to include the inferior prefrontal convexity produce a marked difficulty in suppressing the No-go response (Lawicka et al., 1975; Iversen and Mishkin, 1970; Butters et al., 1973) similar to that observed in patients with OFC damage (Leimkuhler and Mesulam, 1985; Malloy et al., 1993; see also Casey et al., 1997a). That patient's with DLPFC damage do not impair Go/No-go performance (Drewe, 1975; Décary and Richer, 1995) further demonstrates the selectivity of the ventral orbitofrontal region in the inhibitory control of impulsive behaviour.

Hence, the Go/No-go task has useful translational properties; it is a laboratory test that can be used with humans and monkeys, and rats (e.g. Setlow et al., 2003), and is a test of inhibitory-impulsive control capable of distinguishing orbitofrontal from dorsolateral pathology. However, in addition to with-holding a pre-potent response, a critical aspect of Go/No-go performance is the ability to select the appropriate action based on anticipated reward (Petrides, 1982, 1986; Balleine and Dickinson, 1998). Such stimulus-response associations are thought to rely, in part, on the integrity of the basal ganglia (Mishkin et al., 1984; Reading et al., 1991; Knowlton et al., 1996) and their projections to selective regions of the frontal cortex (Johnson et al., 1968; Killcross and Coutureau, 2003). Thus, rhesus monkeys with lesions to the periarcuate region of the DLPFC only exhibit deficits in tasks where they are required to select between alternative responses as in a conditional motor task (for review, see Petrides, 1987) or indeed, delayed alternation (see Fuster, 1980), a finding mimicked by lesions made to the dorsal part of the head of the caudate nucleus (Battig et al., 1960). Likewise, similar to the performance deficit in Go/No-go tasks, monkeys with lesions to the ventral sector of the caudate nucleus, retard operant extinction such that these monkeys continue to emit a bar response even though they are not rewarded for doing so (Butter et al., 1963; Divac et al., 1967); another task that is sensitive to ventral orbital damage, and is not affected by DLPFC ablations (Divac et al., 1967). Together, these observations suggest that the frontostriatal system of projections may ultimately provide two independent mechanisms; a dorsal mechanism for the coordination of motor actions and 'habits' (Mishkin et al., 1984; Killcross and Coutureau, 2003) that is known to deteriorate in patients with striatal pathology (e.g. Saint-Cyr et al., 1988), and a ventral mechanism for the inhibition of stimulus-response-reward associations that is associated with pathological conditions such as OCD (Baxter et al., 1988; Swedo et al., 1989) and ADHD (Trommer et al., 1991; Casey et al., 1997b).

6.2. Studies in rats

There is increasing evidence suggesting that abnormalities in serotonergic innervation of the frontal cortex may contribute to the decision-making deficit (Park et al., 1994; Rogers et al., 1999c). In rodents, it has been possible to examine with specificity, the direct effects of manipulating the serotoninergic system. In support of the general hypothesis that decreased 5-HT function increases impulsivity (e.g. Soubrié, 1986), global 5-HT lesions in rats using 5–7 dihydroxytryptamine (5,7-DHT) reliably increases impulsive responding in several tasks including Go/No-go tasks and the 5CSRTT, which incorporate a 'waiting' component during which the animal must resist the immediate impulse to respond (e.g. Wogar et al., 1993; Fletcher, 1995; Harrison et al., 1997, 1999; Winstanley et al., 2004a), and is similar to the effects of lesioning the ventromedial prefrontal cortex (Chudasama et al., 2003a). Unlike the requirement to withhold or inhibit an impulsive response, the responding parameters are different in the delay discounting procedure in which the animal is presented with a choice of selecting a response that results in a small but immediate reward, or a response that leads to a larger delayed one (Mazur, 1987; Evenden and Ryan, 1996) and therefore, similar to human decision-making, the delay discounting task requires the animal to use experience of reward to guide future selection of responses. Consistent with the human literature, rats with OFC lesions increase their preference for smaller, immediate rewards (Mobini et al., 2002) whereas lesions made to dorsomedial regions remain unimpaired on this task (Cardinal et al., 2001). However, consistent impairments in impulsive choice following 5-HT depletion in rats have not been observed (e.g. Bizot et al., 1999; Mobini et al., 2000; Winstanley et al., 2004b). Evidently, not all measures of impulsivity are uniformly affected by 5-HT depletion, supporting the view that impulsivity is a non-unitary construct which can be fractionated into several varieties (Evenden, 1999; Winstanley et al., 2004a). For example, another aspect of impulsivity is the ability to stop a response that has already been initiated (Logan, 1994; Logan et al., 1997) and can be assessed using the stop-signal reaction time (SSRT) task in rats (Eagle and Robbins, 2003a, 2003b), and in humans (e.g. de Wit et al., 2000). Patients with impulsive disorders, such as

ADHD (Oosterlaan et al., 1998; Rubia et al., 1998; Aron et al., 2003a), or frontal and striatal pathology (Aron et al., 2003b; Rieger et al., 2003), produce significant impairments in their ability to stop in the SSRT. However, although rats with dorsomedial striatal lesions are also slow to stop, lesions of the dorsomedial PFC are without effect in the SSRT task (Eagle and Robbins, 2003a, 2003b). Furthermore, unlike the behavioural effects on impulsive choice, rats with lesions of the ventral striatum (Nac) do not affect any aspect of SSRT performance. Clearly, different striatal regions mediate different forms of impulsivity that can be measured by different inhibitory-impulsive tasks.

In rats, 5-HT depletions have also shown to increase speed and number of responses in a pavlovian autoshaping task in which animals learn to approach reward predictive of reward (Winstanley et al., 2004a) and selective lesions of the OFC impair pavlovian autoshaping task (Chudasama and Robbins, 2003) suggesting that the pathology of the OFC and its serotonergic innervation may contribute to a dysfunctional reward system. It follows therefore, that aspects of impulsivity may be present in behaviours that are elicited through stimulus-reward associations and it has been suggested that such associations may play an important role in the maintenance and relapse of drug seeking behaviour (Childress et al., 1992; Jentsch and Taylor, 1999; Everitt and Robbins, 2000; Volkow and Fowler, 2000). However, unlike the impulsive tendency to seek reward in drug abusers, children with ADHD show an impulsive tendency specific to seeking stimulation by needing immediate, frequent and intense reinforcers to maintain appropriate behaviour (Haenlein and Caul, 1987; Barkley, 1989).

The effects of DA drugs on reward-related behaviour as a measure of impulsivity has been addressed in rats; amphetamine administration (a non selective DA releaser) increases the value of delayed rewards (i.e. decreased impulsivity), whereas DA D_2 but not D_1 receptor antagonists decreased the value of delayed rewards and thus increased impulsivity (Wade et al., 2000; de Wit et al., 2002). Although it is clear that DA modulates choice between rewards, the effects of DA manipulations are quite complex, particularly with respect to drug dosage, rate dependency and neuroanatomical locus of action. For example, the Nac has also been implicated in regulating choice between reinforcers that may be under the control of dopaminergic mechanisms (Cardinal et al., 2001). That drug abusers show deficits in decision-making tasks (Bechara et al., 2001; Rogers and Robbins, 2001; Clark and Robbins, 2002) and children with ADHD are often insensitive to promise of reward and threat of punishment (Pelham and Murphy, 1986; Solanto, 2001), suggest that frontal pathology may be a core problem in disorders of addiction and ADHD (Bechara et al., 2001; Rogers and Robbins, 2001; Clark and Robbins, 2002; Solanto, 2001).

7. Concluding comments

In this survey, we have provided an integrative cognitive and comparative account of the evidence that implicates frontostriatal modulation in neurodegenerative and psychiatric disorders. Specifically, we have illustrated the view that there are certain cognitive functions where extrapolation from animal behaviour has positively informed our investigation of cognitive functions in humans (see Table 1). We have discussed specific examples of 'animal to human approaches' where paradigms originally established for use in animals (e.g. delayed response), have directed the design and development of analogous tests for use in humans (e.g. self-ordered working memory). In addition, although human experimental psychology has provided several ways of operationalizing perhaps conceptual and abstract cognitive constructs, it has now become apparent that many of these constructs can be adapted quite easily for use in experimental animals, the obvious example being the animal ED/ID test based upon the principles of the human WCST. Thus, animal experimental psychology has benefited in the opposite direction by means of 'human to animal' approaches. Together, these advances have been particularly useful in terms of establishing the necessary and sufficient form of neuroanatomical and neurochemical pathology for specific cognitive deficits in a range of brain and behaviour disorders. For the purpose of this paper, however, we have focused on behavioural tasks sensitive to frontal lobe function and as such appear to be useful markers for characterising frontal lobe pathology in several clinical groups. The observation of common cognitive deficits in patient groups with different diagnoses, such as schizophrenia, ADHD and dementia, reinforces the possibility that the same neural substrates are being compromised in these different disorders, at least at some level, for example, either early or late in the course of the disease.

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