SECTION VI

Serotonin–Dopamine Interactions in Attentional Processes, Learning and Memory

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CHAPTER 25

Serotonergic and dopaminergic modulation of attentional processes

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Abstract: Disturbances in attentional processes are a common feature of several psychiatric disorders such as schizophrenia, attention deficit/hyperactivity disorder and Huntington's disease. The use of animal models has been useful in defining various candidate neural systems thus enabling us to translate basic laboratory science to the clinic and vice-versa. In this chapter, a comparative and integrated account is provided on the neuroanatomical and neurochemical modulation of basic behavioural operations such as selective attention, vigilance, set-shifting and executive control focusing on the comparative functions of the serotonin and dopamine systems in the cognitive control exerted by the prefrontal cortex. Specifically, we have reviewed evidence emerging from several behavioural paradigms in experimental animals and humans each of which centres on a different aspect of the attentional function. These paradigms offering both human and animal variants include the five-choice serial reaction time task (5CSRTT), attentional set-shifting and stop-signal reaction time task. In each case, the types of operation that are measured by the given paradigm and their neural correlates are defined. Then, the role of the ascending dopaminergic and serotonergic systems in the neurochemical modulation of its behavioural output are examined, and reference is made to clinical implications for neurological and neuropsychiatric disorders which exhibit deficits in these cognitive tests.

Keywords: attention; 5CSRTT; shifting; inhibition; dopamine; serotonin

Introduction

Attention refers to the processes determining an organism's receptivity to external or internal excitation and hence the probability that it will engage in the processing of that excitation (Parasuraman, 1998). Although it is often treated as a cognitive function, it is distinct in encompassing a multitude of manifestations which underlie and sustain the activity of the other cognitive functions. Attentional processes facilitate cognitive and behavioural performance in several ways, through the selection and integration of sensory inputs which is essential for efficient learning and remembering, as well as for the organisation of appropriate responses. Impaired attentional processing may therefore become manifested as inattention, distractibility, memory impairment,

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confusion, perseveration or disinhibition. Recognition of the diversity of attention has led to the identification of three distinct fundamental qualities: selection, which enables the allocation of priority to certain informational elements to the exclusion of others; vigilance, which refers to the capacity for attentional persistence over time; and control, which optimises performance, for example, by inhibition of concurrent activities (Parasuraman, 1998; Robbins, 2002, 2005).

Impaired attentional processing leads to unfocused cognitive function and consequent failure to regulate behaviour efficiently in response to environmental changes. Behavioural inflexibility may take the form of impulsivity (hasty responding with no regard for consequences) or compulsivity (needless response repetition). Such cognitive and behavioural deregulations are often noted within the normal state, for example in periods of severe stress or fatigue. They are also encountered as a core deficit in several neuropsychiatric abnormalities such as Parkinson's and Huntington's diseases, schizophrenia, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and drug addiction. In fact, important information on the neuroanatomical and neurochemical substrate of attention has been gained by the study of attentional deficits in these neuropsychiatric conditions, which share attentional and executive deficits reminiscent of those induced by prefrontal lesions.

Given that attentional failures can both compromise normal behaviour and underlie psychopathology, the understanding of the neuroanatomical and neurochemical substrate of the attentional function is crucial both in a theoretical and a clinical context.

Neuropsychiatric disorders involving deficits in attentional processes

The subcortical dementias

Huntington's and Parkinson's diseases are both characterised by attentional deficits. Early deficits in Huntington's disease include impairments in concentration and mental tracking, as well as in set maintenance and shifting (Folstein et al., 1990). Similarly, in Parkinson's disease attentional deficits initially emerge in complex tasks requiring shifting or sustained attention and mental tracking (Huber and Shuttleworth, 1990; Owen et al., 1992). In both disorders, attention span is spared in the early stages (Brown and Marsen, 1988; Huber and Shuttleworth, 1990). Executive deficits accompanying Huntington's disease also bear similarities to those of prefrontal symptomatology, including impaired behavioural regulation and planning (Folstein et al., 1990). Correspondingly, prefrontal-like executive dysfunctions such as difficulty in response initiation, set maintenance and switching, serial and temporal ordering and executive planning have been reported in Parkinson's patients (Freedman, 1990; Dubois et al., 1991).

Huntington's disease is associated with atrophy of the striatal structures of the caudate nucleus and putamen, while thalamic nuclei and the cerebellum may also be affected. Parkinson's disease involves loss of dopaminergic neurons in the pars compacta of the substantia nigra, accompanied by reduction of dopamine (DA) in the basal ganglia (caudate and putamen). Although Parkinson's disease is mostly associated with DA, other neurotransmitter systems are also involved. Cell loss is noted in the locus coeruleus (noradrenergic source to cortex), the nucleus basalis (major cholinergic input to cortex), the dorsal raphé nucleus, hypothalamus, mamillary bodies and reticular formation.

As mentioned above, the attentional and executive deficits encountered in these subcortical dementias bear similarities to those produced by frontal lobe damage with involvement of the prefrontal cortex (PFC). However, magnetic resonance imaging (MRI) data from Huntington's patients have not revealed specific frontal volume loss (Aylward et al., 1998). It seems likely, therefore, that the prefrontal symptomatology results from disconnection of fronto-striatal loops due to caudate atrophy. Similarly in Parkinson's disease cortical involvement appears to be in part caused by frontal disconnections due to DA loss (Jacobs et al., 2003).

Schizophrenia

Clinical observation of schizophrenic patients outlines a number of attentional disturbances such

as deficits in information selection and utilisation as well as in sustaining and shifting attention in response to changing environmental demands. Compulsive activity or fixation to trivial environmental stimuli may also be evident. Although these marked deficits lead to inappropriate responding and illogical discontinuities in behavioural course, nevertheless impaired attentional processing has only recently been accepted as one of the core deficits of the disorder.

Brain malfunction in schizophrenia is still not understood, though subtle brain abnormalities have been described in schizophrenic patient populations. The hippocampus, entorhinal and cingulate cortices have been implicated by structural and functional neuroimaging data (Tamminga et al., 2002; Pincus and Tucker, 2003) and there are reports of decreased cortical grey matter (Sullivan et al., 1998). Converging evidence suggests frontal lobe dysfunction (Weinberger et al., 1991). It has been proposed that schizophrenia may be the result of dysfunction in the neural circuitry linking the PFC with the thalamus, cerebellum and possibly the basal ganglia (Andreasen et al., 1998).

Attention deficit hyperactivity disorder (ADHD)

This disorder of executive attention is characterised by a persistent pattern of inattention and/or hyperactivity, as well as forgetfulness, poor impulse control and distractibility. It is considered neurodevelopmental due to the apparent lag in the development in impulse control. Frontal as well as striatal abnormalities have been associated with ADHD (Ernst et al., 1998; Rubia et al., 2000; Mehta et al., 2001; Solanto et al., 2001). As in schizophrenia, hypoactivity of the mesocortical DA projection has been implicated in its pathogenesis.

Role of the PFC in the anatomical substrate of attention: fronto-striatal loops

Adaptive behaviour requires selection of responses appropriate to current environmental demands, in tandem with the capacity to suppress responding which is no longer relevant. The maintenance and updating of relevant information is therefore essential, as is the imposition of top-down control over incoming information and executive functions (Robbins, 2005). The activity of systems of the brainstem, which modulate processing in their terminal fields in diverse forebrain areas including the cortex, also appear to be under cortical monitoring (Roberts et al., 1994). This top-down control has been associated with the PFC (Fuster, 1989; Chao and Knight, 1995; Miller and Cohen, 2001). A crucial function of the PFC in response selection emerges in situations requiring the selection of rapid responses to novel, often stressful situations; then the 'supervisory attentional system' of Shallice and Norman (Shallice, 1982) becomes especially important, for example by adding more 'weight' to particular representations. Some such situations are changes in reward–error feedback (e.g. see Wisconsin Card Sort Test below), changes in background distractors or instructions (e.g. contextual control; Cohen et al., 1999), dual-task control and attentional conflict (e.g. Stroop interference).

Shallice and Norman's model attributed to the PFC the role of a 'supervisory attentional system'. The ventromedial orbitofrontal cortex (OFC) was subsequently implicated in emotional decision making (Damasio, 1998). This promoted speculations about how these PFC regions, with their limbic connectivity, interact with dorsolateral PFC regions in the control of cognition and behaviour. Investigation, largely using functional brain imaging, focused on the hypothesis that parts of the human medial cortex and OFC mediate 'reward' or 'goal' representations (O'Doherty et al., 2001). This view had to integrate accumulating evidence involving specified subcortical circuitry, notably DA-dependent functions of the nucleus accumbens, in the mediation of reward processes (Robbins and Everitt, 1992). This led to the recognition of the PFC as a nodal part of 'loop' circuitries, involving connections between the OFC, other limbic structures, the nucleus accumbens, mediodorsal thalamus and ventral pallidum. Such neuroanatomical loops link with other sectors of the PFC and functionally related regions of the striatum in a cascading series of serial as

well as parallel circuitries (Alexander et al., 1986; Haber et al., 2000). Functionally, these cortico-striatal loops can be understood as incorporating mechanisms for the optimal selection of goals and responses, and for the optimal preparation of appropriate response outputs (Robbins, 2007).

Neurochemical modulation of the PFC in attention

The functioning of cortico-striatal loops is influenced by a number of ascending neurotransmitter systems, notably the catecholamines (DA and noradrenaline), the indoleamine serotonin (5-HT) and acetylcholine (ACh) (Robbins, 2000). It is also likely that descending influences from the PFC may, to some extent, regulate these neurochemical systems (Amat et al., 2005) which are implicated in stress, arousal and mood as well as in reward processes (Robbins and Everitt, 1992; Arnsten and Robbins, 2002). These neurotransmitter systems are of fundamental importance to the aetiology of the neuropsychiatric conditions mentioned earlier, which share the core deficit of failure to regulate behaviour adequately in response to changing environmental demands.

As would be expected given the plethora of diffuse ascending inputs from the major monoaminergic and cholinergic neurotransmitter systems, the PFC needs to be highly sensitive to neurochemical state. Furthermore, it is now clear that the different functions of these ascending neurotransmitter systems need to be studied not only in general terms, but also when they project to a common substrate such as the PFC (Robbins, 2005), where they act in a neuromodulatory rather than in an 'on-off' manner. There is considerable evidence that the effects of pharmacological manipulations of many of these systems on tests of attention and memory can effectively be described by the characteristic inverted U-shaped curve. Thus, a specific manipulation may lead to improvement when superimposed on low baseline performance (e.g. due to fatigue or aging), whereas higher baseline performance may conceal such improvement or even show deterioration upon the same manipulation (Robbins, 2005).

Phasic activity in some of the neuromodulatory systems, especially the mesolimbic DA pathway, has been implicated in the mechanisms of learning (Schultz and Dickinson, 2000). Their tonic levels of activity can be understood as representing different states (e.g. arousal, fatigue or mood). Tasks requiring executive control may be optimally performed in different states (Robbins, 2000). Executive control encompasses mechanisms serving to optimise behavioural and cognitive output and includes the regulation of input (e.g. over posterior cortical processing), output (e.g. via the basal ganglia and the associated cortico-striatal loops) and also the activity of the ascending neuromodulatory systems (Robbins, 2007).

Indexing attentional deficits in humans

Analysis of attentional deficits in disorders presenting prefrontal involvement has relied on a number of neuropsychological instruments. For example, sustained attention or vigilance has traditionally been examined through the continuous performance test (CPT; Rosvold et al., 1956; Parasuraman and Davies, 1977). In its original form the CPT requires sustained monitoring of sparse, unpredictable targets (e.g., letters) presented amongst distractors; performance deterioration over time is taken to reflect a vigilance decrement. Subsequent CPT modifications provide measures of visuo-spatial attention by requiring the subject continually to monitor the location of a brief visual target randomly occurring in one of the several spatial locations. Working memory can also be indexed by requiring responses only when the target is preceded by another stimulus.

A test broadly used in the investigation of the role of the PFC in cognitive flexibility is the Wisconsin Card Sort Test (WCST), which assesses deficits in attentional shifting. Initially, the test requires matching new stimuli to compound stimulus exemplars, following a constant rule or perceptual dimension. Thereafter, a category shift is required, that is the subject is required to start responding to a new rule, switching attention to a new perceptual dimension. Neuroimaging data confirm that completing the task primarily involves activation of the dorsolateral PFC. Finally, impaired behavioural inhibition, which is another common feature of neuropsychiatric

disorders such as Parkinson's, schizophrenia and most notably, ADHD has been studied by 'go-no go' procedures, such as the stop-signal reaction time (SSRT) task. It has even been argued that the form of inhibition represented by the SSRT is the only indisputable form of behavioural inhibition (MacLeod et al., 2003). In this task subjects are required to make fast responses on 'go' trials in a choice reaction time procedure, but to inhibit responding on signalled 'no-go' trials. The stop-signal occurs at different delays after the onset of the response process, thereby progressively taxing a subject's ability to impose response suppression.

Performance of patients with disorders involving attentional deficits (such as schizophrenia or ADHD) on neuropsychological instruments as those mentioned above is characterised by very high inter- and intra-individual variation. This variability, in addition to the multivariate nature of the attentional process, makes the task of exploring causal relations between neuropsychological data and the underlying neural substrate of attentional impairments extremely difficult, in spite of the armoury of neuroimaging techniques now available. This problem becomes especially acute when such causal relationships address neurochemical modulation, as systemic or localised infusion of selective pharmacological agents is not feasible in patients or healthy volunteers. Methods of pharmacological manipulation of neurotransmitter systems available for research in humans, such as tryptophan depletion (Rogers et al., 1999) have produced useful but essentially limited results. Studies on gene polymorphisms (Mattay et al., 2003) also have increasing potential. However, in order to ascertain neuroanatomical and neurochemical specificity of experimental interventions, it is necessary to resort to the use of experimental animal models. This endeavour has been facilitated by the current availability of comparable cross-species tests of cognitive function. These enable the identification of common neural substrates that subserve similar functions across species, increasing the likelihood that the same cognitive functions are being studied in each species.

In this chapter, the neural substrates and the neuromodulation of basic operations such as vigilance, set-shifting and executive control are surveyed, with a focus on the comparative functions of the DA and 5-HT systems and their interaction in the cognitive control exerted by the PFC. The survey is based on evidence from experimental animals and humans. It encompasses data generated by three different experimental conditions, each of which centres on a specific aspect of the attentional function (although of course not to the exclusion of other aspects). The three paradigms examined offer both animal and human variants.

The first paradigm is the five-choice serial reaction time task (5CSRTT) which provides a direct measure of sustained attention and bears good analogy to the CPT, a traditional index of human vigilance. The second paradigm is attentional set-shifting, which has been used to decompose the types of processes engaged by tests of attentional flexibility such as the WCST. The third paradigm is stop-signal inhibition, which models certain components of executive control.

In each case, the types of operation that are measured by the given paradigm and their neural correlates will be defined. Then, the role of the ascending dopaminergic and serotonergic systems in the neurochemical modulation of its behavioural output will be examined, with reference to clinical implications for neurological and neuropsychiatric disorders.

The five-choice serial reaction time task (5CSRTT)

5CSRTT, an animal test widely used with rodents, provides substantial validity as a direct measure of attention and bears good analogy to the CPT. The paradigm indexes different components of attention, so that the effects of various pharmacological treatments on these different attentional processes may be compared or contrasted. The 5CSRTT (Robbins et al., 1993; Robbins, 2002) is conducted in an operant chamber equipped with an arc of nine holes, four of which are occluded and five exposed. Each trial is initiated by the rat pushing open the food magazine door. This response is followed by a fixed 5-s intertrial interval (ITI), after which a 0.5 s light stimulus is presented

randomly in one of the five exposed holes. A nose-poke, within a 5-s hold period, in the hole where the light appeared is rewarded, while wrong responses are typically not punished.

Optimal performance on this apparently simple task requires the integration of several cognitive processes. Sustained attention to the goal area for the duration of the ITI is required in order not to miss the target, while divided attention across all five exposed holes is essential in order to scan the entire visual array. Good attentional performance is reflected by high response accuracy (a high number of correct target detections with a minimum of wrong responses), accompanied by few omissions and relatively fast response latencies. Generally speaking, deficient attention would result in low response accuracy. The likelihood that other factors, such as sensory, motor or motivational processes, also affect response accuracy can be assessed on the basis of the overall response profile on the task (Robbins, 2002; Chudasama and Robbins, 2003). Motivation can be indexed through the latency to collect reward; errors of omission with no change in reward collection latency indicate gross attentional impairments; while a concurrent reward collection latency increase suggests motivational or motor involvement. Changes in response latency without concurrent increase in reward collection latency possibly tap decisional processes. Finally, response inhibitory control (executive functioning) can also be assessed: the measure of premature responses during the ITI in anticipation of the visual target provides an index of impulsivity; while the inhibitory deficit of perseveration is also accessible through the measure of repeated responding at the holes, offering a putative index of compulsivity. Manipulations of task difficulty can be harnessed to explore the nature of any processing deficits. For example, response selection mechanisms can be excluded through use of a one-choice version, while a more robust assessment of sustained attention can be obtained by increasing the length of the ITI. Finally, sensory deficits can be examined by varying the intensity of the visual stimuli (Robbins, 2002). Thus, the 5CSRTT is capable of measuring several different types of performances, which include aspects of attention and impulse control. The task is also capable of dissociating performance elements which usually co-vary, although they probably rely on processes that are under the control of different neural mechanisms.

It has been proposed that the 5CSRTT is particularly suited for testing attentional dysfunction in schizophrenia (Chudasama and Robbins, 2004). Several popular models of schizophrenic symptomatology are based on treatment with glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine (PCP) and ketamine (Steinpreis, 1996). The 5CSRTT appears to be sensitive to such psychotomimetic agents: systemic administration of PCP reduces choice accuracy, concurrently increasing premature and perseverative responding (Jin et al., 1997).

Effects of fronto-striatal lesions on the 5CSRTT

Attentional deficits accompanying schizophrenia have been consistently associated with frontal dysfunction, possibly as a result of dysfunction in the neural circuitry linking the PFC with the thalamus, cerebellum and possibly the basal ganglia. The hippocampus has also been implicated (see Introduction). This hypothesis can be readily investigated in rats by means of excitotoxic lesions to circumscribed areas of the PFC by means of the 5CSRTT.

There has been no consistent evidence for any hippocampal involvement in the 5CSRTT (Kirkby and Higgins, 1998). In contrast, medial PFC lesions involving the dorsal anterior cingulate cortex, medial prelimbic cortex and ventral infralimbic cortex reduce response accuracy, retard response latencies and increase perseverative responding (Muir et al., 1996). Selective lesions to these sub-regions in the rat demonstrated that they have quite specific functions, which must be coordinated to sustain optimal performance in the 5CSRTT. Specifically, accuracy impairments emerged only after dorsal anterior cingulate cortex lesions (Passetti et al., 2002; Chudasama et al., 2003); medial prelimbic or orbitofrontal cortical lesions produced selective increases in perseverative responding (Chudasama and Muir, 2001; Passetti et al., 2002) while, in contrast, lesions to

the ventral infralimbic cortex produced selective increases in premature responses (Chudasama et al., 2003). Evidence that the 5CSRTT engages fronto-striatal systems comes from the observation that bilateral lesions of the medial PFC or dorsal striatum result in deficits reproducible by the combination of unilateral medial prefrontal cortical and contralateral dorsal striatal lesion (Christakou et al., 2001). On the basis of neuroanatomical substrate, the 5CSRTT therefore appears to be most appropriate for modelling those aspects of cognitive dysfunction in schizophrenia which are thought to depend on 'fronto-executive' processes.

Neurochemical modulation of the 5CSRTT

Several drugs of established therapeutic value in schizophrenia, in fact most atypical antipsychotic drugs such as clozapine or reserpine, are thought to exert their actions on 5-HT as well as on DA receptors. These agents appear preferentially to increase DA release in the medial prefrontal cortex (mPFC) (Meltzer et al., 1989; Moghaddam and Bunney, 1990; Kuroki et al., 1999). Experimental evidence suggests that discrete behavioural elements in the 5CSRTT may be differentially regulated by dopaminergic and serotonergic projections to the PFC (Dalley et al., 2002a, b; Winstanley et al., 2003).

Effects of dopaminergic manipulations

Subcortical DA systems. Subcortical manipulations of the DA systems have produced performance deficits on the 5CSRTT that are mainly expressed in terms of effects on the speed and probability of responding (Cole and Robbins, 1989; Baunez and Robbins, 1999).

The D2 receptor system. Systemic treatment with preferential D2 receptor antagonists such as sulpiride produced accuracy deficits at certain doses (Harrison et al., 1997). As DA D2 receptors are found in much higher numbers in subcortical loci such as the striatum rather than in the PFC, this effect is possibly consistent with effects of dorsal striatal DA depletion (Baunez and Robbins, 1999). Intriguingly, however, systemic administration of sulpiride, which impaired performance in control animals, actually alleviated a response accuracy deficit noted in animals with mPFC lesions (Passetti et al., 2003). It can be hypothesised that the accuracy deficit noted in this study resulted from lesion-induced over-activity of subcortical dopaminergic systems, an explanation consistent with the lack of any effect of intra-mPFC infusions of sulpiride on the 5CSRTT (Granon et al., 2000).

The prefrontal D1 receptor system. Direct intra-mPFC infusions of a DA D1 receptor agonist (SKF 38393) significantly enhanced response accuracy in animals with low baseline accuracy but had no effect on animals with higher baseline performance. Conversely, intra-mPFC D1 antagonist (SCH 23390) infusions had no effect on animals with low baseline accuracy but reduced accuracy in animals with high baseline performance (Granon et al., 2000). This pattern suggests that the prefrontal D1 receptor system might normally be engaged to attain optimal task performance. The data also suggest that, under certain test conditions, it is 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 antipsychotic drugs which block D2 receptors concurrently down-regulating frontal D1 receptors (Lidow and Goldman-Rakic, 1994; Florijn et al., 1997; Lidow et al., 1997, 1998; Castner et al., 2000).

Taken together, these data indicate that dopaminergic projections to the rat mPFC have specific functions in modulating response accuracy in the 5CSRTT, while other aspects of performance such as response vigour or speed may be influenced by subcortical DA systems (Cole and Robbins, 1989).

Effects of serotonergic manipulations

As the dopaminergic system, the serotonergic system, the 5-HT1A and 5-HT2A receptors in

particular, is affected by atypical antipsychotics like clozapine (Meltzer, 1999; Millan, 2000; Winstanley et al., 2003). The serotonergic system, as a whole, has been strongly implicated in the regulation of impulsivity (Linnoila et al., 1983; Soubrié, 1986).

The 5CSRTT is demonstrably sensitive to serotonergic manipulations. Global, 5,7-dihydroxytryptamine (5,7-DHT) lesion-induced 5-HT depletion consistently appears to spare response accuracy while it increases impulsivity as reflected by increased premature responding and decreased omissions as well as correct response latency (Harrison et al., 1997; Koskinen et al., 2000; Winstanley et al., 2003, 2004). However, systemic administration of the 5-HT1A receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetraline (8-OH-DPAT), which also decreases 5-HT release (Bonvento et al., 1992; Hajós et al., 1999; Celada et al., 2001), does not affect impulsive responding and improves attentional performance (Winstanley et al., 2003). At higher doses the selective 5-HT1A receptor agonist 8-OH-DPAT reportedly increased impulsivity, possibly by activating presynaptic 5-HT1A receptors (Carli and Samanin, 2000). There is an incongruence, then, between the effects of chronic lesion-induced global 5-HT decreases and acute global decreases as those affected by systemic administration of a 5-HT1A receptor agonist.

The apparent inconsistency is compounded by the observation that systemic and intra-PFC administration of the 5-HT2A receptor antagonist M100907 decreases impulsive responding (Winstanley et al., 2003). Moreover, infusions of M100907 in the mPFC counteracted the loss of executive control (impulsivity induced by the competitive NMDA receptor antagonist 3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid, CPP), while 8-OH-DPAT decreased compulsive perseveration (Carli et al., 2006). Thus, an antagonist of the 5-HT system effectively produces effects opposite to those of global decrease in 5-HT transmission. This paradox, along with the observation that DOI, a 5-HT2A/2C agonist does increase premature responding, probably through activation of the 5-HT2A receptor (Koskinen et al., 2000), suggests dissociable behavioural contribution of 5-HT receptor subtypes in the 5CSRTT. Indeed, evidence suggests that the 5-HT2A and 5-HT2C receptors have opposing neurochemical effects. 5-HT2C receptor activation inhibits, whereas 5-HT2A activation enhances DA release (Millan et al., 1998; Di Matteo et al., 2000, 2001). Antagonism of 5-HT2C and 5-HT2A receptors has opposite effects on some behavioural effects of cocaine (Fletcher et al., 2002). Furthermore, it has been demonstrated that 5-HT2C and 5-HT2A receptors also have contrasting and dissociable behavioural contribution on impulsivity in the 5CSRTT. The selective 5-HT2C antagonist SB 242084 increases premature responding and decreases correct response latency (Higgins et al., 2003; Winstanley et al., 2004). When the antagonist was administered to 5,7-DHT-lesioned animals, the increase in premature responding emerged over and above the similar effects of the 5,7-DHT lesion (Winstanley et al., 2004; Fig. 1A2). In contrast, the selective 5-HT2A antagonist M100907 had no effect on response latency and actually reduced premature responding (Fig. 1A1). This effect was abolished by 5,7-DHT lesions (Winstanley et al., 2004). This dissociation challenges the hypothesis that general decreases in 5-HT neurotransmission increase impulsivity. Furthermore, the fact that antagonism of the 5-HT2C receptor produces a behavioural profile closer to 5,7-DHT lesions than any other receptor so far tested including the 5-HT2A receptor, suggests that the 5-HT2C receptor is central in the serotonergic regulation of behavioural inhibition.

Compulsivity, another form of motor disinhibition is indexed by the 5CSRTT via perseverative responding. Winstanley et al. (2004) demonstrated that 5,7-DHT lesions increased perseverative as well as impulsive responding, a finding consistent with increased perseverative errors during reversal in the marmoset after localised 5-HT depletion within the PFC (Clarke et al., 2004) and after OFC damage (Jones and Mishkin, 1972; Rogers et al., 1999; Schoenbaum et al., 2002; Chudasama et al., 2003; Chudasama and Robbins, 2004). Neither 5-HT2A antagonism (M100907) nor 5-HT2C antagonism (SB 242084) appear to affect perseverative responses (Higgins et al., 2003; Winstanley et al., 2003, 2004). These data suggest that different kinds of motor disinhibition differ in their neurobiological bases, as impulsivity and compulsivity appear to be differentially regulated by the 5-HT system.

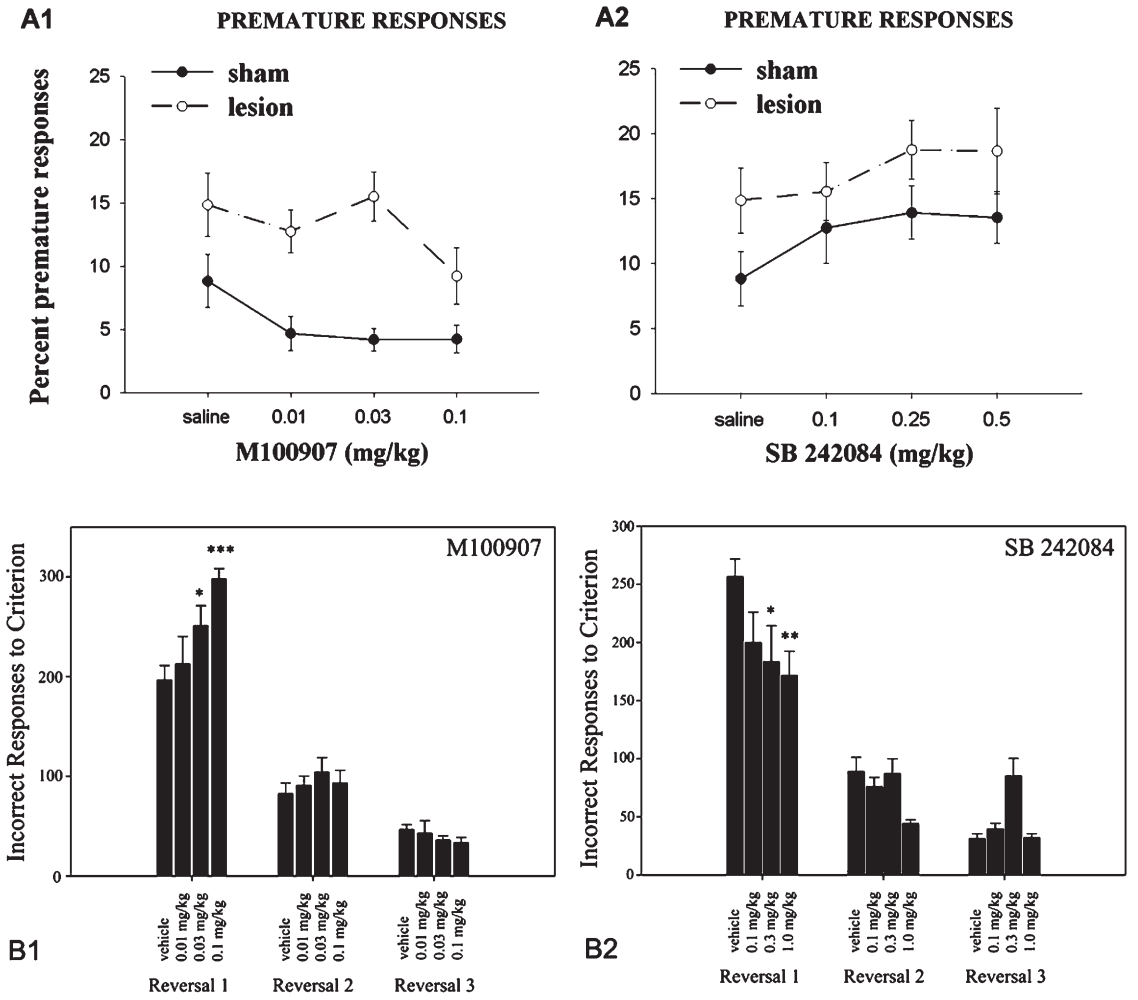

Fig. 1. Effects of M100907 (A1) and SB 242084 (A2) on the percentage of premature responses performed during the five-choice serial reaction time task (5CSRT) in ICV 5,7-dihydroxytryptamine (5,7-DHT)-lesioned animals and sham-operated controls. (Adapted with permission from Winstanley et al., 2004.) Effects of M100907 (B1) and SB 242084 (B2) on perseverative and learning errors performed during spatial reversal learning. (Adapted with permission from Boulougouris et al., 2007b.)

Taken together, the available evidence suggests that serotonergic modulation in the mPFC can increase attentional selectivity and decrease impulsivity via 5-HT1A and 5-HT2A receptors.

DA–5-HT interaction on the regulation of 5CSRTT performance

5,7-DHT lesions increase the number of premature responses and reduce correct response latency in the 5CSRTT. Administration of amphetamine causes a similar pattern of behavioural effects (Cole and Robbins, 1987; Harrison et al., 1997). This amphetamine-induced increase in impulsivity is attenuated by serotonergic lesions (Harrison et al., 1997) and is dependent on the ability of amphetamine to increase DA release in the nucleus accumbens (Cole and Robbins, 1987, 1989). In contrast, the D1 receptor antagonist SCH 23390 decreases premature responding and reduces the increased impulsivity produced by 5,7-DHT

lesions (Harrison et al., 1997). These data implicate interactions between the 5-HT and DA system in regulating this form of impulsive behaviour.

During performance of a simplified version of the 5CSRT, in vivo microdialysis showed a marked increase of DA levels in the mPFC and a higher DA turnover was observed in the frontal cortex of more impulsive animals' post-mortem (Dalley et al., 2002a, b). It is possible that M100907 and SB 242084 may exert their opposite effects on impulsivity in this task via their contrasting modulation of the dopaminergic system. 5-HT2C receptor antagonism increases basal levels of DA and noradrenaline (NA) efflux (Millan et al., 1998; Di Matteo et al., 2000; Gobert et al., 2000) while, in contrast, 5-HT2A antagonism does not affect levels of DA and NA (Gobert and Millan, 1999). The increase in impulsive behaviour by SB 242084 (Winstanley et al., 2004) might therefore be mediated by enhanced DA release triggered by SB 242084. In contrast, a decrease in task-related dopaminergic activation potentially caused by M100907 may account for the decrease in premature responding observed.

Clinical implications

Improved attentional performance on the 5CSRTT following 8-OH-DPAT and M100907 may be due to cortical ACh release mediated by dopaminergic and serotonergic interactions at 5-HT1A and D1 receptors (Winstanley et al., 2003), given that systemic 8-OH-DPAT as well as systemic DA D1 agonists increase prefrontal ACh release (Day and Fibiger, 1993; Consolo et al., 1996; Steele et al., 1997). These interacting mechanisms may facilitate attentional and cognitive improvements via atypical antipsychotic treatment in schizophrenic patients.

The evidence at hand therefore suggests that serotonergic modulation in the mPFC can increase attentional selectivity and decrease impulsivity via 5-HT1A and 5-HT2A receptors. These findings bear clinical relevance, given that some atypical antipsychotics have 5-HT2A receptor antagonist actions that may potentially contribute to a pro-cognitive effect in schizophrenia (Meltzer, 1999).

Attentional set-shifting

Tests such as the WCST which index cognitive flexibility, in fact address several similar yet distinct forms of attentional shifts. For example, if we consider discrimination learning based on compound stimuli involving two perceptual dimensions (e.g. shapes and lines), where exemplars of these dimensions occur in combination with one another on successive trials, one exemplar of one particular dimension being correct (e.g. vertical but not skewed line correct), then (1) when the relevant stimulus dimension (i.e. lines) stays constant but novel stimuli are used (e.g. straight but not curly line correct), this is an intradimensional (ID) shift; (2) when an exemplar from the previously irrelevant dimension (shapes) becomes correct (square but not triangle) then an extradimensional (ED) shift is demanded; finally (3) when the stimuli remain the same, but the previously correct exemplar is now incorrect (triangle but not square) then we refer to reversal learning, a shift which can occur either at the compound discrimination learning stage or after the ID- or ED-shift.

Different tests of attentional flexibility involving ID–ED shifts and reversal are available for humans, non-human primates and rodents. Such procedures by necessity engage other processes besides switching attention (e.g. ability to utilise feedback denoting that a shift is necessary, ability to overcome 'learned irrelevance' of a previously non-operative perceptual dimension). However, the precise nature of any failure to make a required shift can be further analysed (Owen et al., 1993).

Effects of fronto-striatal lesions on set-shifting and reversal

Research on the neural substrate of attentional shifting has demonstrated that the apparently similar switching requirements of ID- and ED-shift are in fact mediated by different regions of the PFC (Dias et al., 1996, 1997; Robbins, 1998). Marmosets with lateral PFC lesions were impaired when an ED-shift (from 'shapes' to 'lines', a category shift, in terms of the WCST) was required. However, they were unimpaired in

reversal learning, which suggests that their ED-shift deficit was not simply a failure to detect altered feedback. When marmosets with lesions to the OFC where tested, a double dissociation was noted: these animals had no deficit on the ED-shift, but were impaired in reversal learning.

The lateral PFC–OFC functional dissociation has also been demonstrated in rats (Brown and Bowman, 2002), supporting the existence of neuroanatomical homologies between rodent and primate PFC regions (Preuss, 1995; Brown and Bowman, 2002). Lateral OFC lesions in the rat produce impairments in reversal learning (Schoenbaum et al., 2002; Chudasama and Robbins, 2003; Boulougouris et al., 2007a). A similar involvement of the rat medial PFC and the primate lateral PFC in ED-shifting might also be expected on the grounds of the putative homology of these regions, although this is more controversial (Brown and Bowman, 2002).

Translating these basic findings to humans proved difficult, as reversal learning is much easier for humans than ED-shifting. Nevertheless, relatively selective reversal deficits have been shown in patients with frontal-variant fronto-temporal dementia, for whom hypoperfusion initially occurs in the OFC (Rahman et al., 1999). This finding, which suggests that the human OFC also mediates aspects of reversal learning, has been corroborated by other neuropsychological studies (Fellows and Farah, 2003; O'Doherty et al., 2003; Hornak et al., 2004).

However, data relating to specific PFC regions with ED-shifting are sparse. Patients with PFC damage of varied aetiology, but in whom the OFC had been spared, showed maximum deficit in ED-shifting, while reversals were not significantly affected (Owen et al., 1991).

Exploration of the neuroanatomical substrate of reversal learning and shifting in a functional imaging context (positron emission tomography, PET; Rogers et al., 2000) was initially unsuccessful in showing selective OFC activation, perhaps due to the nature of the task used. However, the Rogers et al. (2000) study demonstrated activation of the ventromedial caudate nucleus in the contrast between ID-shift and reversal, suggesting that reversal is mediated in part by a cortico-striatal loop: this would include the OFC, given the anatomical connectivity existing between these regions. In the same study, contrast between ED- and ID-shifting showed activity in the rostral and dorsolateral PFC. A recent study (Hampshire and Owen, 2006) employing event-related functional magnetic resonance imaging (fMRI) and methods allowing better resolution of activity within the OFC, demonstrated that reversal was associated with blood oxygen level-dependent (BOLD) signals in the OFC, with concurrent reduction in medial PFC activation. ED-shifting was most obviously associated with ventrolateral PFC activity. Although the dorsolateral PFC was not specifically associated with responding at any one stage, it was active during most of the task, which suggests an overall role in strategic processes contributing to problem solution.

In conclusion, if the lateral PFC region in the marmoset corresponds to the ventrolateral PFC highlighted in the Hampshire and Owen (2006) study, then there is concordance between the marmoset lesion data and human functional neuroimaging results. The lesion data suggest that both the lateral and OFC regions of the marmoset PFC are active during discrimination learning, but have different functions in behavioural plasticity. The lateral PFC appears to control the shifting of responding between entire, abstract perceptual dimensions (e.g. 'shape' vs. 'line'), whereas the OFC mediates the shifting of responding between simple concrete features with specific associations with reward. Over and above showing functional specialisation of PFC regions, these data imply a hierarchical organisation of function between lateral and OFC regions, analogous to other proposed hierarchical relations between PFC areas (Petrides, 1998; Koechlin et al., 2003). Indeed, an influential theory of discrimination learning holds that discrimination learning proceeds hierarchically (Sutherland and Mackintosh, 1971). The data suggest that the different stages of discrimination learning correspond to different functions mediated by the lateral PFC and the OFC.

The behavioural outcome of both lateral PFC and OFC lesions is perseverative responding, either to previous exemplars or to dimensions in the face of non-reward, both deficits reflecting defective behavioural inhibition. The Dias et al.

(1996, 1997) findings therefore suggest that both the lateral PFC and the OFC contribute to inhibitory functions in response selection. Thus, contrary to earlier opinions, response inhibitory functions appear to be distributed widely within the PFC, in analogy to Goldman-Rakic's view that working memory is organised on a modular basis within the PFC, subsuming processes of inhibition and selection, as well as holding stimuli online.

Neurochemical modulation of attentional set-shifting and reversal

As mentioned earlier, hypoactivity of the mesocortical DA projection has been implicated in clinical disorders such as schizophrenia and ADHD, as well as in working memory dysfunction (Goldman-Rakic, 1998). Consequently, the effects of dopaminergic manipulations on attentional shifting have been examined. The established contribution of prefrontal 5-HT in executive control also led to exploration of the serotonergic contribution to attentional flexibility.

Effects of dopaminergic manipulations

Profound DA depletion from the entire PFC in the marmoset actually enhanced rather than impairing ED-shifting (Roberts et al., 1994; Fig. 2). This unexpected finding was later attributed to an initial failure of the monkeys to form stable attentional sets, since DA depletion profoundly impaired serial ID-shifting (Crofts et al., 2001; Fig. 2), which normally leads to the establishment of an attentional set. Dopamine depletion had no other effects on discrimination acquisition or simple or serial reversal learning (Roberts et al., 1994; Clarke et al., 2007; Fig. 2). In the rat, pharmacological inhibition of catechol-*o*-methyltransferase (COMT: postulated to have a selective effect on PFC dopamine) by tolcapone, resulted in improvements in ED-shifting, possibly as a consequence of enhanced PFC dopamine activity (Tunbridge et al., 2004).

Selective orbitofrontal DA depletion in the marmoset was without effect in either acquisition of visual discriminations or reversal learning (Clarke et al., 2007). Similarly, selective striatal DA depletion in the marmoset caudate nucleus had no effect on discrimination learning, reversal, ID- or initial ED-shifting, though it reduced distractibility in the ID–ED-shift task (Collins et al., 1998; Crofts et al., 2001). However, a deficit was observed when, at the end of the series, an ED-shift back to the previously reinforced dimension was introduced. The finding suggests that, while the striatum and its dopaminergic innervation may not be involved in the formation of new sets, they may be important in the mediation of shifts between already established sets. Additionally, DA depletion of the rodent dorsomedial striatum selectively impaired reversal of odour discriminations, though discrimination acquisition was intact (O'Neill and Brown, 2007). This suggests that dopaminergic transmission in the dorsomedial striatum contributes to reversal.

In humans, an fMRI study on normal volunteers, revealed activations only in the PFC following rule alternation, while reversal produced activations in both the PFC and striatum (Cools et al., 2004). Also, patients with striatal lesions (though mainly comprising lesions of the putamen and not the caudate nucleus) were unimpaired in responding to rules but exhibited problems alternating between objects (Cools et al., 2006). Finally, a probabilistic reversal task activated not only regions of the OFC, medial PFC and inferior frontal cortex (IFC), but also the ventral striatum (Cools et al., 2002). These data suggest that the PFC controls set shifting, while both the PFC and the striatum are involved in the reversal. More direct assessment of the relative contributions of cortical and striatal DA in the two types of attentional shifting are difficult in humans, as it is hard to manipulate the mesocortical DA system selectively. Nevertheless, studies on polymorphism for a gene controlling COMT showed some deficits in WCST performance, suggesting a difficulty in ED-shifting rather than in ID-shifting (Mattay et al., 2003). In normal volunteers, a D2 receptor antagonist (sulpiride) produced weak and inconsistent effects only on set shifting latency (Mehta et al., 2004). Finally, a study on Parkinson's patients (Lewis et al., 2005) showed an impairment in set-shifting which was unaffected by L-DOPA, while a parallel working memory deficit was ameliorated by L-DOPA.

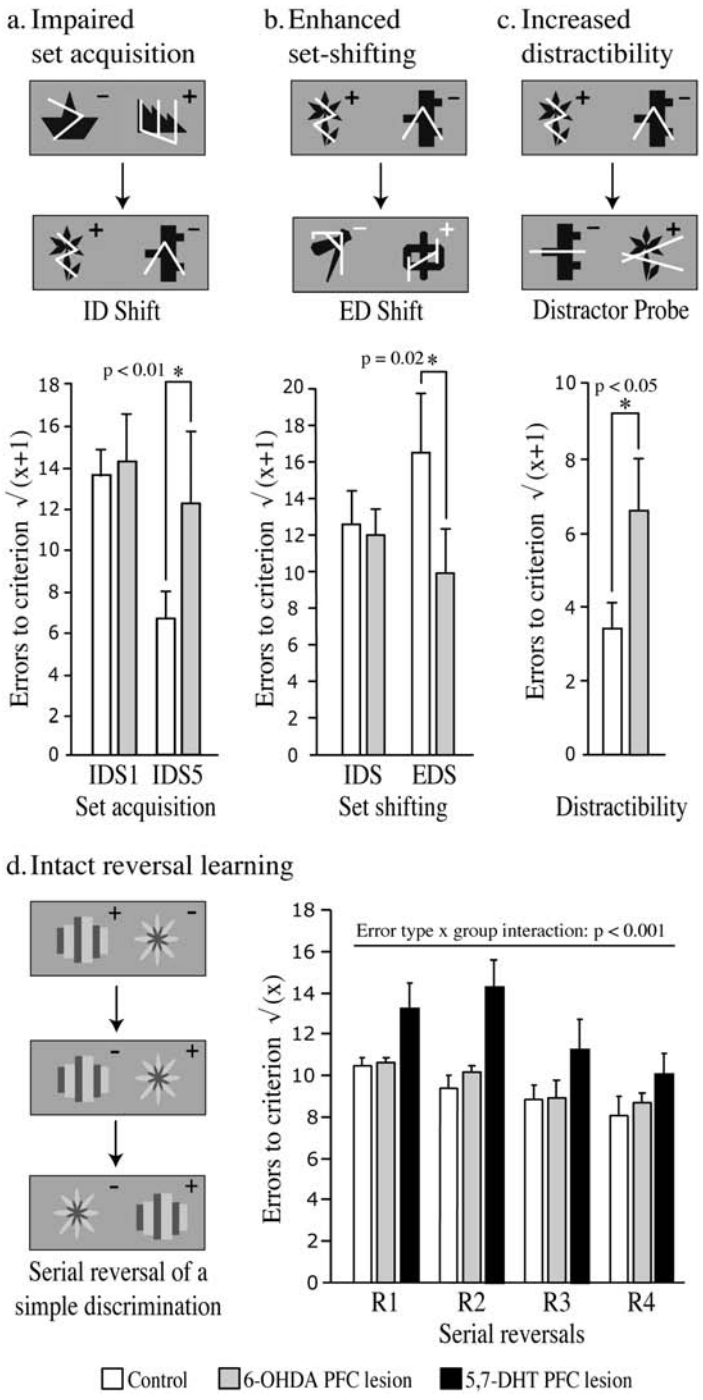

Fig. 2. The effects of 6-OHDA induced DA lesions of the marmoset PFC on the acquisition and shifting of attentional sets and on reversal learning. Examples of two discriminations in which the same dimension remains relevant, commonly called an IDS, are shown in (a); a discrimination requiring a shift of attentional set, called an EDS, is depicted in (b); a distractor probe test, shown in (c), in which the exemplars from the irrelevant dimension of a previously learned discrimination are replaced by novel exemplars. The '+' and '−' signs in (a), (b) and (c) indicate, respectively, whether the stimuli were associated with reward or not. Black lettering indicates that shapes were the relevant dimension and white lettering that lines were the relevant dimension. (Adapted with permission from Robbins and Roberts, 2007.)

Although clinical and preclinical evidence suggests that deregulation within the dopaminergic systems is involved in behavioural flexibility and inhibition, the particular receptor mechanisms underlying these effects are still not well understood. Studies on the effects of D-amphetamine, which increases DA release in the striatum, have produced equivocal results of either impairment or facilitation of reversal performance (Weiner and Feldon, 1986; Idris et al., 2005). Involvement of the D2 receptor seems likely, at least in reversal: the D2 receptor antagonist haloperidol impairs reversal performance (Ridley et al., 1981), as does blockade of the D2 receptor gene in knockout mice (Kruzich and Grandy, 2004). Reversal is also compromised by the D2/D3 receptor antagonist raclopride (monkeys: Lee et al., 2007) and the D2/D3 receptor agonist quinpirole (rat: Boulougouris et al., unpublished observations). There is also some indication of DA D2/D3 receptor involvement in the modulation of set shifting. Floresco et al. (2006) showed that administration of the D2/D3 receptor antagonist eticlopride impaired animals' ability to adjust their behaviour to a conditional change of rule in a set-shifting task.

Overall, the data suggest a separation of function between PFC and striatum with respect to various forms of attentional flexibility. While mesocortical DA was initially implicated in set-shifting, subsequent studies argue against the participation of either prefrontal or striatal DA, at least in the mediation of the ED-shift. It is possible that the ED-shift depends on PFC interactions with other cortical regions, especially in the parietal and temporal cortices (Rogers et al., 2000; Hampshire and Owen, 2006). On the other hand, while there is consensus of a lack of effect of cortical DA on reversal learning, several lines of evidence implicate subcortical systems in its mediation. D2 receptors in the striatum would appear to be implicated.

Effects of serotonergic manipulations

In contrast to PFC dopamine depletion, selective 5-HT depletion in the marmoset had no effect on ED- or serial ID-shifting, but produced a large deficit in reversal learning due to perseverative responding to the previously rewarded object (Clarke et al., 2004, 2005, 2007).

In human volunteers, transient depletion of central 5-HT by the tryptophan depletion technique produced effects on discrimination learning that were especially evident in reversal learning (Park et al., 1994). Another study (Rogers et al., 1999b) also reported that tryptophan depletion led to relatively selective effects on human reversal learning (but see also Talbot et al., 2006) with no effect on ED-shifting. Evers et al. (2005) showed that behavioural reversal was accompanied by significant signal change in the right ventrolateral and dorsomedial PFC of healthy volunteers performing a probabilistic reversal task. Tryptophan depletion enhanced reversal-related signal change in the dorsomedial PFC only, affecting the BOLD signal specifically associated with negative feedback. These data indicate that the 5-HT system has a modulatory role in reversal learning specifically.

On the receptor level, recent evidence suggests that different 5-HT receptor subtypes have distinct roles in the modulation of reversal learning. Boulougouris et al. (2007a) established a double dissociation in the role of 5-HT2C and 5-HT2A receptor subtypes in serial spatial reversal learning. Specifically, systemic administration of the 5-HT2C receptor antagonist SB 242084 facilitated spatial reversal learning in a dose-dependent manner (Fig. 1B2). Selective intra-OFC infusions of SB 242084 also promoted reversal learning, whereas infusions in the mPFC or nucleus accumbens did not. The facilitation of reversal learning therefore appears to be mediated by 5-HT2C receptors within the OFC (Boulougouris and Robbins, unpublished observation). In contrast, systemic treatment with the 5-HT2A receptor antagonist M100907 dose-dependently impaired reversal learning, on the first reversal of the series in particular (Fig. 1B1). This deficit emerged as increased perseveration of the previously correct response, reproducing the effects observed after selective orbitofrontal 5,7-DHT lesions (Clarke et al., 2004, 2005, 2007) as well as orbitofrontal cortical lesions in rats and non-human primates (Dias et al., 1996; Chudasama and Robbins, 2003; Boulougouris et al., 2007a).

These findings are of considerable theoretical and clinical importance. At a theoretical level, the opposing effects of 5-HT2A and 5-HT2C antagonism on perseverative responding in spatial reversal learning task (increase and decrease, respectively) contrast with the also reverse effects of these agents on impulsive responding in the 5CSRTT (see section The five-choice serial reaction time task (5CSRTT); Fig. 1). Specifically, intra-PFC 5-HT2A antagonism decreases impulsive responding (Winstanley et al., 2003) whereas 5-HT2C antagonism increases it (Higgins et al., 2003; Winstanley et al., 2004). These observations are relevant to the concept of an impulsivity–compulsivity spectrum in obsessive–compulsive spectrum disorders (Hollander and Rosen, 2000). At a clinical level, these data also bear on the issue of whether 5-HT2C receptor antagonists might be expected to be useful in the treatment of human obsessive–compulsive disorder (OCD).

DA–5-HT interaction on the regulation of set-shifting and reversal

In summary, 5-HT neurotransmission in the OFC contributes to the modulation of reversal learning, with distinct and contrasting roles of the 5-HT2A and 5-HT2C receptors in this modulation of reversal. No impact on the performance of tasks such as ED-shifting has been discerned so far.

In contrast, the mesocortical DA projection has been implicated in set-shifting, while there is consensus on its lack of involvement on reversal learning. However, the striatal dopaminergic innervation appears to contribute to the modulation of reversal learning and possibly in the mediation of shifts between already established sets. Therefore, although both the dopaminergic and serotonergic systems innervate the entire PFC, they appear to have differential impact in distinct regions, since manipulation of the two monoamine pathways has distinct effects on PFC-dependent mechanisms of cognitive flexibility.

With respect to the functional dissociation of the 5-HT2A and 5-HT2C receptor role in the modulation of reversal, it is possible that M100907 and SB 242084 exert their opposite effects on compulsivity in this task via their contrasting modulation of the dopaminergic system. As mentioned earlier (see section The five-choice serial reaction time task (5CSRTT)) 5-HT2C receptor antagonism increases basal levels of DA and NA efflux (Millan et al., 1998; Di Matteo et al., 2000; Gobert et al., 2000) while, in contrast, 5-HT2A antagonism does not affect levels of DA and NA (Gobert and Millan, 1999). The facilitation of reversal, implying minimal perseveration to a previously rewarded response (Boulougouris et al., 2007b) might be mediated by enhanced DA release triggered by SB 242084, while a decrease in task-related dopaminergic activation potentially caused by M100907 may account for the increased perseveration caused by the 5-HT2A receptor antagonist.

Clinical implications

Patients with basal ganglia disorders, such as early Huntington's and Parkinson's diseases, show impairments in ED-shifting, suggesting some mediation by striatal structures. In late in-the-course Huntington's disease, impairments in simple reversal learning are prohibitive of attempts at examining ED-shifts. This pattern of initial deficits in ED-shifting followed by reversal learning deficits suggests a dorsal-to-ventral spread in pathology (Lange et al., 1995). In late in-the-course Parkinson's, performance in the early stages of ID- and ED-shift was remediated by L-DOPA, although there was no conclusive evidence on whether ED-shifting was affected (Lange et al., 1992). As mentioned earlier, the hypothesis that the ED-shift is DA-dependent now appears doubtful (Mehta et al., 1999, 2004; Cools et al., 2001; Lewis et al., 2005), raising the possibility that it may be modulated by PFC interactions with other cortical regions (Rogers et al., 2000; Hampshire and Owen, 2006). The deficits observed in ED-shifting in Parkinson's and Huntington's diseases may thus reflect extra-striatal pathology, possibly in the PFC.

Finally, the Boulougouris et al. (2007b) data suggest that 5-HT2C receptor antagonists may be useful in relieving reversal deficits such as those

noted in Huntington's disease. In fact, they may deserve consideration as a means of controlling compulsivity in the context of obsessive–compulsive disorder.

The stop-signal reaction time task (SSRT)

The SSRT task has been used as a measure of behavioural inhibition in humans, non-human primates and rodents, and is ideally suited for translational study. The SSRT is a sophisticated 'go-no-go' task in which subjects are required to make speeded responses on 'go' trials in a choice reaction time procedure, but to inhibit responding on 'no-go' trials. These are approximately 25% of the total trials and are signalled by a succinct auditory stimulus. This stop-signal is programmed to occur at different delays following the imperative signal, thus occurring at different times after the onset of the response process. Therefore, the ability of a subject to impose response suppression can be progressively more taxed.

The response outcome of a stop trial is dependent on which response process will finish first: if it is the 'stop' process the response will be inhibited, if is the 'go' process then the response will be performed. Consequently, trials in which the stop signal is presented late on in the response process are less likely to be inhibited than trials in which the stop signal is presented early in the response process. The central measure of the task is the speed of the response stopping process, that is the time taken by the subject to attend to, process and complete a response to the stop signal. The stop response has no physical outcome. The estimate of the end point of such a response is based on the theoretical framework provided by the 'horse-race model' (for details see Logan and Cowan, 1984), upon which the SSRT task is based.

The SSRT is particularly suited for testing executive aspects of attentional dysfunction. It has been argued, perhaps debatably, that the form of inhibition represented by the SSRT is the only indisputable form of behavioural inhibition (MacLeod et al., 2003).

Effects of fronto-striatal lesions on the SSRT

Both stopping and no-go impairments have been extensively associated with fronto-striatal dysfunction (Rubia et al., 2001; Robbins, 2007). Evidence comes from translational neuroanatomical studies which have highlighted regions of the frontal cortex and basal ganglia that are critical for response inhibition, and interplay between these regions may be necessary for attaining appropriate behavioural outcomes (Band and van Boxtel, 1999). Monkeys with lesions of the inferior convexity, a likely homologue of the human right inferior frontal gyrus, produced impairments in go/no-go performance (Iversen and Mishkin, 1970), while human subjects with frontal cortical damage were impaired in response inhibition (Drewe, 1975; Decary and Richer, 1995; Godefroy and Rousseaux, 1996). Recent neuroimaging studies have highlighted several cortical regions of interest with respect to both SSRT and go/no-go tasks. In particular, several studies report strong IFC activation in both stop and go/no-go tasks, thus underlining the importance of this region in behavioural inhibition (Aron et al., 2004).

In rats, the role of the PFC in SSRT control is not well understood. Recently, it has been shown that excitotoxic lesions of the rat OFC, but not the infralimbic or prelimbic cortex, slowed SSRT but had no significant effect on the go response (Eagle and Robbins, 2003; Eagle et al., 2007a). Although direct homology between the right IFC in humans and the ventral OFC in rats is not established, these regions are currently the only cortical regions, in the respective species, to be specifically implicated in the control of SSRT.

There has also been evidence for striatal involvement in the SSRT. In childhood and adolescent ADHD, subcortical structures have been shown to play an increased role in the processing of stop and no-go signals. Subjects with ADHD exhibited lower activation within the striatum than controls, while there was no difference in activation levels in the cortex between groups (Vaidya et al., 1998). There may be a reliance on subcortical structures in SSRT processing in younger subjects, with caudate activation in

adolescents that is not always seen in adult performance (Rubia et al., 1998, 2005b; Rubia and Smith, 2004; Nosarti et al., 2006). However, adult patients with basal ganglia lesions are impaired at stopping (Rieger et al., 2003).

Finally, the subthalamic nucleus (STN) is conventionally thought of as an output structure of the basal ganglia, acting as part of the potentially inhibitory indirect pathway within the cortico-striato-thalamic circuitry. Current interest in its function during the stopping process has led to a hypothesis that it links more directly with regions of the cortex involved in stopping, providing rapid information-processing during this form of inhibition. In human subjects, STN activation correlated with faster SSRTs (Aron and Poldrack, 2006) and STN activation on the SSRT task also correlated with activation of the right IFC. Additionally, SSRT deficits have been linked with abnormal STN function in Parkinson's disease (Gauggel et al., 2004) and stimulation within the STN, but not the surrounding structures, in these patients improved SSRT (van den Wildenberg et al., 2006). However, in the rat, lesions of the STN globally disrupted performance on the SSRT task, both when the stop signal was delayed, and when the stop signal was presented at the same time as the go signal, more strongly indicative of a generalised attentional or response selection (no-go-like) deficit following these lesions (Eagle et al., 2007a).

Neurochemical modulation of the SSRT

Effects of dopaminergic manipulations

As discussed previously, DA is strongly implicated in behavioural inhibition. It has been suggested that DA dynamically modulates the balance of go and no-go basal ganglia pathways during cognitive learning and performance (Frank et al., 2006). However, the effects Frank et al. (2006) define as increased inhibition may be construed as a negative modulation of the go pathway rather than as positive modulation of the no-go pathway and there is little evidence to support a role for either D1 or D2 receptors in no-go inhibition. Inase et al. (1997) investigated the effect of the D1 and D2 receptor agonists (SKF38393-quinpirole) and antagonists (SCH23390-sulpiride) on single unit activity in the putamen of monkeys performing a go/no-go task. D1 and D2 receptor agents could modulate the activity of neurons in both go and no-go trials but there was no selective difference between go and no-go trials in the effectiveness of D1 or D2 manipulations. Additionally, in rats, the mixed D1/D2 antagonist, cis-flupenthixol, had no significant effect on no-delay (no-go) stop-trial accuracy (Eagle et al., personal communication), which again fails to support a role for D1 and D2 receptors in no-go inhibition.

Although D-amphetamine- and methylphenidate have been shown to induce speeding of SSRT, this may reflect action on striatally mediated DA function, as no firm evidence supports a role for DA in their action on the stopping process per se. Dopaminergic drugs can clearly increase impulsive behaviour on other tasks, for example delayed reward (Wade et al., 2000), but such drugs have little effect on stopping. Overtoom et al. (2003) found no effect of L-DOPA on stopping. Although Fillmore et al. (2002) reported that cocaine users were impaired on SSRT compared with non-cocaine-using control subjects, which suggests dopaminergic involvement in SSRT, it was not possible to determine whether these differences predated or resulted from cocaine use.

The mixed D1/D2 receptor antagonist, cis-flupenthixol, had no effect either on stopping or on the SSRT-speeding effects of methylphenidate and modafinil at doses that significantly slowed the go response (Eagle et al., 2007b). While it is possible that methylphenidate or D-amphetamine might act via other DA receptors, there is no clear evidence to support a dopaminergic mechanism of SSRT control on the receptor level. Although polymorphisms in the DA receptor D4 (DRD4) gene in ADHD are thought to be critical for cognitive function, a comparison of ADHD children with or without at least one DRD4 7-repeat allele, found no difference in stopping behaviour, although there was a difference in GoRTs (Langley et al., 2004). Altogether, the evidence, at present, is against a direct role for DA in the stopping process.

Effects of serotonergic manipulations

As discussed previously, central 5-HT function is widely acknowledged as an important factor of behavioural inhibition and response control. Accumulating evidence implicates 5-HT on the modulation of no-go inhibition and stopping performance. Global 5-HT depletion in rodents following intracerebroventricular (i.c.v.) infusions of 5-7-DHT profoundly impaired the ability of rats to adequately inhibit responding to a no-go signal and also impaired the ability of pre-trained rats to subsequently respond correctly to a no-go signal (Harrison et al., 1999). This impairment was selective to an animal's ability to withhold responding following 5-HT depletion, without affecting other behavioural measures. Similarly, impaired acquisition of a go/no-go task has been reported after parachloroamphetamine administration (Masaki et al., 2006).

Neuroimaging studies in humans have implicated the OFC in relation to the effects of 5-HT on no-go inhibition. Acute tryptophan depletion has been reported to decrease right orbito-inferior prefrontal activation in fMRI during the no-go condition, although there was no significant alteration in inhibitory performance on the task (Rubia et al., 2005a). Moreover, fMRI data indicate that citalopram enhanced the response to the no-go condition in the medial orbitofrontal region (Del-Ben et al., 2005). Additionally, an fMRI investigation of healthy subjects' neural responses with or without the antidepressant mirtazapine during performance of a go/no-go task reported significant activation in the right dorsolateral PFC, middle frontal gyrus and OFC bilaterally, right anterior cingulate, right temporal and right parietal cortex and left occipital cortex and thalamus. Mirtazapine, however, enhanced activation in the right lateral OFC (Vollm et al., 2006). Treatment with *m*-clorophenylpiperazine (mCPP; a non-specific 5-HT agonist) has also been shown to increase BOLD signal in the right OFC during go/no-go in healthy adults (Anderson et al., 2002).

Finally, there is evidence implicating the 5-HT2A receptor in the no-go inhibition. A polymorphism in the promoter of the 5-HT2A receptor gene has been proposed to underlie some forms of behavioural inhibition. Subjects with the A-1438A allele of the 5-HT2A receptor gene made more commission errors under the punishment–reward condition in a go/no-go task than those in the G-1438G group (Nomura and Nomura, 2006). The specific contribution of other 5-HT receptor subtypes in no-go responding is still unknown.

Although there is strong evidence on the role of 5-HT in no-go, there is no evidence regarding 5-HT role in the modulation of stopping performance. Depletion of brain 5-HT has relatively little effect on SSRT, even in subjects stratified according to 5-HT transporter polymorphism. Neither buspirone (a 5-HT1A receptor agonist) nor citalopram (selective 5-HT reuptake inhibitor) had any effects on SSRT in healthy volunteers (Chamberlain et al., 2006a, b). Studies in rats corroborate the lack of effect with citalopram, additionally demonstrating that global (i.c.v.) 5, 7-DHT lesions have no effect on SSRT or any other behavioural measures (Eagle et al., personal communication). Moreover, 5-HT transporter knockout mice did not differ from wild type controls in the SSRT task (Hausknecht et al., 2006). Under these lines of reports and the use of SSRT in modelling impulsivity in juvenile and adult ADHD (Aron et al., 2003a, b), one might conclude that serotonergic agents do not seem to be useful for the treatment of this disorder where attentional deficits are a feature.

Conclusions

This survey provides an integrative account of the differential contributions of 5-HT and DA to specific aspects of attentional processes as they emerge from 'animal to human' approaches. Three tasks allowing translational study have been used to that purpose, to address three fundamental qualities of attention. (1) The 5CSRTT, an analogue of the human CPT, is designed to measure several attentional operations with an emphasis on sustained attention or vigilance. (2) Attentional set-shifting including reversal, intra- and extradimensional shifts, as the human WCST, tap attentional flexibility, that is the ability of humans and animals to develop and maintain higher-order rules and shift attention according to changing reward

Table 1. Neuropharmacology of the five-choice serial reaction time task (5CSRTT), intradimensional (ID)/extradimensional (ED) shift, reversal learning and serial reaction time task (SSRTT)

Task	Enhancement	Impairment
5CSRTT	Intra-mPFC D1 agonist (SKF 38393)	Systemic D2 antagonist (sulpiride)
	Systemic D2 antagonists in mPFC-lesioned animals	Intra-mPFC D1 antagonist (SCH 23390)
	Intra-mPFC 5-HT2A antagonist (M100907)	Systemic D-amphetamine
	Intra-mPFC 5-HT1A agonist (8-OH-DPAT)	Global 5-HT depletion
		Systemic 5-HT2C antagonist (SB242084)
ID-shift	Dopamine depletion	
ED-shift	D2/D3 antagonist eticlopride	Dopamine depletion
Reversal	D2 antagonist (haloperidol)	Dorsomedial striatal dopamine depletion
	D2/D3 antagonist (raclopride)	Systemic D2/D3 agonist (quinpirole)
	Systemic 5-HT2C antagonist (SB 242084)	OFC serotonin depletion
	Intra-OFC 5-HT2C antagonism (SB 242084)	Systemic 5-HT2A antagonist (M100907)
SSRTT	D-amphetamine	Cocaine; parachloroamphetamine

contingencies. (3) Finally, the SSRT addresses the issue of behavioural control by means of inhibition of activities which no longer serve environmental demands. Taken together, the findings detailed above highlight the specificity of influences that these neurotransmitter systems have on overall prefrontal executive control, acting to promote distinct components of prefrontal processing in a context-dependent manner (Table 1). Future directions must focus towards the definition of the specific aspects of attentional functions in which these neuromodulatory systems are acting to influence prefrontal processing. Of cardinal importance for the elucidation of the function of those neurotransmitters is their top-down regulation by the very system that they themselves modulate, that is the fronto-executive system.

Abbreviations

5,7-DHT	5,7-dihydroxytryptamine
5CSRTT	five-choice serial reaction time task
5-HT	5-hydroxytryptamine (serotonin)
8-OH-DPAT	8-hydroxy-2-(di-*n*-propylamino)-tetraline
ACh	acetylcholine
ADHD	attention deficit/hyperactivity disorder
BOLD	blood oxygen level-dependent
COMT	catechol-*o*-methyltransferase
CPP	3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid
CPT	continuous performance test
DA	dopamine
ED	extradimensional
fMRI	functional magnetic resonance imaging
i.c.v.	intra-cerebroventricular
ID	intradimensional
IFC	inferior frontal cortex
ITI	intertrial interval
mCPP	*m*-chlorophenylpiperazine
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NA	noradrenaline
NMDA	*N*-methyl-D-aspartate
OCD	obsessive–compulsive disorder
OFC	orbitofrontal cortex
PCP	phencyclidine
PET	positron emission tomography
PFC	prefrontal cortex
SSRT	stop-signal reaction time
STN	subthalamic nucleus
WCST	Wisconsin Card Sort Test

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