Review

Chemical neuromodulation of frontal-executive functions in humans and other animals

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Abstract. Neuromodulation of frontal-executive function is reviewed in the context of experiments on rats, monkeys and human subjects. The different functions of the chemically identified systems of the reticular core are analysed from the perspective of their possible different interactions with the prefrontal cortex. The role of dopamine in spatial working memory is reviewed, taking account of its deleterious as well as facilitatory effects. Baseline-dependent effects of dopaminergic manipulation are described in rats on an attentional task, including evidence of enhanced function following infusions of D1 receptor agonists into the prefrontal cortex. The precise nature of the cognitive task under study is shown to be a powerful determinant of the effects of mesofrontal dopamine depletion in monkeys. Parallels are identified in human subjects receiving drugs such as the indirect catecholamine agonists L-dopa, methylphenidate and the dopamine D2 receptor blocker sulpiride. The effects of these drugs on different types of cognitive function sensitive to frontal lobe dysfunction are contrasted with those of a manipulation of 5-HT function, dietary tryptophan depletion. Hypotheses are advanced that accord the ascending systems a greater deal of specificity in modulating prefrontal cortical function than has hitherto been entertained, and clinical and theoretical implications of this hypothesis are discussed.
Key words. Prefrontal cortex - Orbitofrontal cortex - Dorsolateral prefrontal cortex - Dopamine - Serotonin - Noradrenaline - Acetylcholine - Methylphenidate - Executive function - Working memory - Planning - Set shifting

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Introduction

Mapping the functions of the prefrontal cortex (PFC) onto the richness and heterogeneity of its constituent anatomical regions poses a major conceptual problem. The prefrontal cortex is often said to have 'executive functions', which can be defined as that set of cognitive control processes that serve to optimize performance in complex tasks engaging the dedicated processing modules (for example, within the posterior cerebral cortex). The anatomical relationships of the prefrontal cortex are characterized by its contribution of inputs to several levels of the neuraxis, which presumably enable this region to participate in many aspects of control. These prefrontal outputs include backprojections to the posterior cortex and projections to the striatal feedback loop

circuitry, the hypothalamus and the brain stem (Goldman-Rakic *1987*; Pandya and Yeterian *1995*). However, of especial relevance to the present chapter, the prefrontal cortex also targets the main sources of the forebrain monoaminergic and cholinergic neurotransmitter systems - including dopamine-containing cells of the ventral tegmental area, noradrenergic neurons of the locus coeruleus, serotoninergic neurons of the raphé nuclei, and the cholinergic basal forebrain (Goldman-Rakic *1987*). Presumably, therefore, through their diffuse ascending inputs, these projections enable the prefrontal cortex to exert profound control over global influences such as arousal, stress, reinforcing feedback and mood, on processing within all of the main telencephalic structures, including the limbic system, thalamus and striatum, as well as the cortical mantle itself. Specific functions such as error signals in reinforcement learning (Schultz et al. *1997*), and selective attention and vigilance (Aston-Jones et al. *1991*), have also been proposed. The theoretical challenge therefore is to understand the nature of these global and specific influences and their functional significance.

Dissociable effects of manipulations of the chemically defined systems of the reticular core and their possible relationship to frontal cortex function in the rat

Clues about the functions of the monoaminergic and cholinergic pathways have accrued from a number of studies using electrophysiological and neurochemical as well as pharmacological and behavioural methodologies (see Robbins and Everitt *1995*). Our own approach has been to compare the effects of relatively specific neurotoxins to effect changes in each of these systems on performance in common behavioural paradigms. One example is our version of the five-choice reaction time task used to assess attentional performance in rats. We have manipulated different parameters of this task in order to define distinct profiles of deficit following neurochemical lesions. Thus, for example, 6-hydroxydopamine (6-OHDA) lesions of the dorsal noradrenergic pathway, emanating from the locus coeruleus, produce impairments in the accuracy of stimulus detection, but only under certain conditions, in which the stimuli are presented unpredictably in time, or bursts of loud white noise are interpolated to disrupt performance (Carli et al. *1983*). Excitotoxic (Muir et al. *1994*) or immunotoxic (McGaughy et al. *1999*) lesions of the cholinergic nucleus basalis produce deficits in the accuracy of stimulus detection even under baseline conditions (see Everitt and Robbins *1997*). By contrast, profound depletion of mesolimbic dopamine (Cole and Robbins *1989*) and forebrain serotonin (Harrison et al. *1997*) mainly serve to affect the general vigour (speed and probability) of responding without affecting accuracy, and mesostriatal dopamine loss again only leads to significant deficits in accuracy under certain conditions (Baunez and Robbins *1999*). Whilst it requires evidence from other, independent procedures to begin to make firm conclusions about the psychological nature of these deficits, the fact that they are distinct is consistent with the notions that these neurochemical systems are all implicated in the efficient performance of this task, and that they modulate performance in different ways. The functions of the chemical ascending systems are often referred to as *neuromodulatory*: the term 'neuromodulation' here is taken to mean the enhancement, reduction, prolongation or curtailment of information processing by activity within these systems, often with only their minor participation in the computations of the neural networks they innervate. The ascending systems appear to effect different forms of neuromodulation, which interact in complex ways. This is consistent with previous theorizing that unitary theories of arousal have become outmoded (e.g. Robbins *1984*), and must be replaced by more detailed specifications of the roles of these systems.

To what extent the effects of the rather gross manipulations of subcortical neurotransmitter function actually depend on the altered neuromodulation of processes occurring in the prefrontal cortex remains unclear. It is, however, the case that the effects of the basal forebrain cholinergic lesions do somewhat resemble those following excitotoxic lesions of the prefrontal cortex, and also that the effects of forebrain 5-HT depletion to increase premature or 'impulsive' responding are matched by similar excitotoxic lesions of the anterior cingulate cortex (Muir et al. *1996*). Finally, the effects of catecholamine depletion in the prefrontal cortex on the five-choice task are largely manifest as impaired accuracy under conditions of temporal unpredictability - resembling therefore the effects of depletion of catecholamines from the cerebral cortex (Robbins et al. *1998a*). Thus, some of the effects of neurochemical lesions of the ascending monoaminergic and cholinergic systems might serve to alter the neuromodulation of functions of the prefrontal cortex. What is less clear is how prefrontal cortical manipulations regulate these systems, although there is evidence for example that they influence each of the ascending dopamine (Roberts et al. *1994*; Wilkinson et al. *1997*; Dalley et al. *1999*: see Moore et al. *1999* for a review), noradrenaline (Arnsten and Goldman-Rakic *1984*; Jodo et al. *1998*) and serotonin (Hajos et al. *1998*) systems.

The role of prefrontal dopamine in working memory and other cognitive functions in rats and monkeys

There is also considerable evidence that manipulations of prefrontal dopamine systems have seemingly specific effects on working memory processes. This evidence begins with the work of Brozoski et al. (*1979*), who showed convincingly that 6-OHDA lesions of the prefrontal cortex of macaques impaired their accuracy of performance on a delayed response type test. These deficits could be remediated by dopaminergic agents, indicating that they were mediated largely by dopamine. The evidence was extended and refined further by later demonstrations that iontophoretic applications of dopamine (DA) D1 receptor antagonists to the principal sulcus of the PFC produced similarly specific impairments in performance in delayed saccade tasks. However, since these seminal observations, further behavioural and electrophysiological evidence has shown that the relationship between working memory function and dopaminergic mechanisms of the PFC is far from simple. Thus, for example, Williams and Goldman-Rakic (*1995*) have shown that low doses of DA receptor antagonists sharpen the firing patterns of prefrontal cortical 'memory' cells, predicting that this might lead to behavioural improvements rather than deficits. A number of studies in the rat have suggested that high levels of prefrontal cortical DA activity are associated with poorer delayed alternation performance in the rat (Sahakian et al. *1985*; Murphy et al. *1996*; Zahrt et al. *1997*). These results suggest that the relationship between mesofrontal DA function and efficiency of working memory might be characterized by an inverted U-shaped function, with extreme low and high levels of DA activity being associated with impaired performance (Robbins *1985*; Arnsten *1998*; Zahrt et al. *1997*). This relationship begs the question of what the fluctuations in frontal dopamine activity might reflect in terms of normal physiological processes, a clear possibility being the relationship of mesofrontal DA function to increasing levels of 'stress'.

In recent work (Granon et al. *2000*), we have been able to show that intra-PFC infusions of the partial D1 receptor agonist SKF-38393 can improve the accuracy of performance of rats in the five-choice task. However, these effects depended on the baseline levels of performance. In those rats performing at a lower level of performance (around 70% correct), there was an improvement in accuracy, whereas in rats performing at a superior level (80%), though still well below the

maximum, the drug had no effect. The DA D1 receptor antagonist SCH-233890 had opposite effects, impairing performance at the elevated, but not the lower, level of performance. Such effects were not observed with the DA D2 receptor antagonist sulpiride. Several conclusions can be reached. The mesofrontal DA system is clearly implicated in those processes by which performance reaches a high level of accuracy, with the D1 receptor agonist apparently providing the necessary DA receptor activity for reaching the elevated baseline, and the DA receptor antagonist presumably damping such activity in the high performing rats to reduce performance to the lower level. This appears to reflect a clear modulation of attentional performance by dopaminergic activity. However, such modulation may well depend on the nature of the task under study, presumably reflecting its component processes. The clear possibility exists that DA receptor stimulation sufficient to improve performance on the attentional task may actually be detrimental to performance on other tasks, if for example they require different degrees of dopamine activity for optimal performance. There may thus be costs as well as benefits to cognitive performance following treatment with dopaminergic agents. This notion is consistent with the classic Yerkes-Dodson principle suggesting that undemanding, 'easy' tasks are performed optimally at higher levels of 'arousal' than more 'difficult' ones. This hypothesis remains to be tested directly in the present case, although it might predict that the presumably more effortful task of holding a stimulus 'online' once it has been attended to might well be impaired, consistent with the data reviewed above. On the other hand, it is the more difficult attentional task which seems to respond better to effects of agonists or to resist DA receptor blockade, and so the dimension of task difficulty per se may not be the relevant one. Rather, as suggested by Granon et al. (*2000*), the relevant factor may be one of individual differences in rats in their capacity to perform accurately on the five-choice task.

A series of studies that have employed 6-OHDA-induced lesions of the mesolimbic DA system in marmosets also support the notion that different effects may be obtained following such depletion depending on the nature of the task (Table 1). In this case, performance in the spatial delayed response task was compared in two separate experiments with (1) an extra-dimensional shift learning task, modelled after the Wisconsin Card Sort Test used clinically for humans (Roberts et al. *1994*), and (2) a spatial sequencing task in which marmosets had to monitor their generation of a spatial sequence of responses performed on a computerized touch-sensitive screen (Collins et al. *1998*). Each of these tasks is seriously impaired by lesions of the prefrontal cortex itself (Dias et al. *1996a*, *1996b*; Collins et al. *1998*); however, the effect of mesocortical DA depletion varied as a function of the task. In both cases, acquisition of the spatial delayed response task was seriously impaired, consistent with the evidence of Brozoski et al. (*1979*) mentioned above. However, the performance of the spatial sequencing task was unaffected by the mesofrontal DA depletion (Collins et al. *1998*), and performance of the extra-dimensional shift task was actually apparently facilitated (Roberts et al. *1994*). A parsimonious conclusion is that the frontal DA deletion had the effect of placing the animal into a state that is detrimental to spatial delayed response performance but at the same time beneficial to the demands of making an extra-dimensional shift (in which the animal has to cease responding to one perceptual dimension that characterizes a complex object and to respond instead to another one that has previously been irrelevant). It is possible that a change in attentional lability, or distractibility, might explain the pattern of results. The effects of enhanced dopamine activity in the prefrontal cortex may make the animal focus more effectively on the stimuli currently controlling performance. This would also help to explain the beneficial effects of D1 agonists in the divided attentional task in rats (Granon et al. *2000*).

Cross-species behavioural homology: comparisons with human studies

There is also evidence for a role for dopamine in human working memory functions; although progress has been beneficial, effects have been shown under certain circumstances of low doses of the DA D2 receptor agonist bromocriptine (Luciana et al. *1992*, *1998*). Follow-up studies have proven rather contradictory in nature, although they all serve to show that DA agonists can have beneficial effects on cognitive performance in certain circumstances. For example, Muller et al. (*1998*) have demonstrated performance-enhancing effects of the mixed D1-D2 agonist pergolide on spatial working memory performance, but no effect of bromocriptine. This result may thus possibly indicate a role for D1 rather than D2 receptors. Kimberg et al. (*1997*) were successful in showing some beneficial effects of bromocriptine on several aspects of executive performance, but only in subjects with low levels of working memory performance, the results being thus reminiscent of those described above for rats in response to DA D1 receptor agonist treatment. In fact, we have observed that bromocriptine can enhance short term spatial memory performance in humans (Mehta et al., unpublished results), and we have also studied in depth the effects of the DA D2 receptor antagonist sulpiride (Mehta et al. *1999*), as outlined below. However, in general we have sought indirect means of assessing the possible role of dopamine in cognitive function, for example by focusing especially on tasks that are known to be sensitive to frontal lobe dysfunction, and also on patient groups with profound dopaminergic dysfunction, as occurs for example in Parkinson's disease. Finally, we have also examined the effects of the stimulant drug methylphenidate (Ritalin), an agent which potentiates catecholaminergic neurotransmission, and which has been used in the treatment of attention deficit and hyperactivity disorder (ADHD).

For cognitive tests we have used those tests from the CANTAB battery that seem especially sensitive to frontal lobe dysfunction, including a test of self-ordered spatial working memory, a test of spatial planning, using a computerized form of the Tower of London task, and the CANTAB 'ID/ED' attentional set-shifting paradigm described above (see Robbins et al. *1998b*). At least two of these tasks (spatial working memory and ID/ED) have clear analogues in the animal literature (see Robbins *1998*). In fact the ID/ED task employs exactly similar stimulus dimensions and exemplars as for the marmoset version (Roberts et al. *1994*). Whether these tasks, despite their obvious superficial similarity across the human and animal versions, do engage similar cognitive processes across species is a debatable point. One way of testing for 'behavioural homology' is to demonstrate that the paradigms show similar qualitative effects when factors of importance to psychological theory are manipulated in parallel across species (e.g. the advantage for IDS performance over EDS performance that has been shown for monkeys as well as humans: Downes et al. *1989*; Robbins *1998*; Weed et al. *1999*). A converging test for behavioural homology is to identify which neural systems are recruited by the tasks in both humans and monkeys. If they too are similar, it would seem reasonable to infer that similar functions are being studied (see Robbins *1998*).

Each of the three tasks has been employed in functional neuroimaging studies in normal volunteers using positron emission tomography (PET) to index changes in regional cerebral blood flow (Baker et al. *1996*; Owen et al. *1996a*, *1996b*). The self-ordered spatial working memory task produces activations in both the ventrolateral and dorsolateral prefrontal cortex (Owen et al. *1996a*). This pattern may be consistent with Petrides' (*1996*) two-stage model which proposes that the function of holding memories 'online' depends on the ventrolateral prefrontal cortex, whereas the task of monitoring choices (for example, the strategy by which they are sequenced and their association with reinforcement) may recruit additional dorsolateral

prefrontal activation. The pattern of activation is quite similar for the Tower of London test of planning, which also, however, exhibited considerable parieto-occipital activation. However, this similarity is consistent with evidence of psychometric associations between the two tasks (Robbins *1996*). The Tower of London task was also shown to activate the caudate nucleus upon a later analysis (Elliott et al. *1997b*). Finally, the attentional set-shifting task, in a modified form in which three (rather than the usual two) perceptual dimensions were employed, produced significant changes in regional cerebral blood flow in the right dorsolateral prefrontal cortex and the left frontal pole for the extra-dimensional shift compared with the intra-dimensional shift control condition (Rogers et al. *2000*).

Effects of dopaminergic agents on tests sensitive to frontal lobe dysfunction in humans

In the absence of very specific DA receptor agonists for use in human subjects, it has proven necessary, but productive, to investigate the dopaminergic modulation of cognitive function by relatively indirect means, including patient groups such as Parkinson's disease, as well as examining effects of less specific agents in healthy volunteers. Comparison of patients with Parkinson's disease at various stages of the disease, including the early-in-the-course, never previously medicated condition, provides some clues. For example, the extra-dimensional set-shifting deficit seen early in the disease in unmedicated patients seems less severe later in the course when patients have been stabilized on medication (Downes et al. *1989*). A similar picture is evident for the one-touch Tower of London task (Owen et al. *1995a*). On the other hand, severely affected patients, later in the course of the disease, seem to lose the beneficial effects of medication (Owen et al. *1992*, *1995a*).

The critical study is to withdraw L-dopa in a controlled, but double-blind manner. This has been done by Lange et al. (*1992*), but only for relatively severely affected Parkinson's disease patients. The results were quite clear cut in showing selective deficits in the tests sensitive to frontal lobe dysfunction, but no effect on visual recognition memory or visuospatial paired associate learning tasks. Unfortunately, the effects for the extra-dimensional set shifting task were ambiguous, as the deficit under placebo was so profound for the earlier discriminations in the series that it precluded a meaningful analysis of the effects of L-dopa withdrawal on extra-dimensional shifting itself. The results are consistent with other clinical studies of the effects of L-dopa medication. For example, Growdon et al. (*1998*), in a longitudinal clinical study of a large number of patients, concluded that medication had no major effect on cognitive function, but that it improved performance on certain tests of executive function that would be sensitive to frontal lobe dysfunction. What is not yet apparent is at which neural locus dopaminergic agents might exert their effects on cognition, as it is difficult, on present evidence, to distinguish between possible targets in the striatum or the prefrontal cortex.

Some converging evidence has come from a recent study of the effects of the dopamine D2 receptor antagonist sulpiride in normal healthy volunteers, which showed that the drug generally simulated the pattern of cognitive deficits seen in Parkinson's disease, including impairments in certain forms of spatial working memory, attentional set-shifting and planning, though not visual recognition memory (Mehta et al. *1999*). As dopamine D2 receptors greatly predominate in the striatum as compared with the prefrontal cortex, it can be assumed that the effects probably reflect an action within the former structure, rather than a modulation of prefrontal cortex. The possibility of effects via D1 receptors in Parkinson's disease, possibly at the level of the prefrontal cortex, can, however, not be excluded.

In order to test the possibility of improvements in aspects of cognitive function sensitive to frontal lobe lesions, following treatment with compounds that might modulate function in the prefrontal cortex via catecholamine receptors, we have resorted to testing the effects of the psychomotor stimulant drug methylphenidate, which is much used in the treatment of ADHD, but potentiates noradrenergic as well as dopaminergic transmission. An acute dose of methylphenidate (40 mg p.o.) produced significant improvements in the self-ordered spatial working memory task as well as in spatial span, and in two forms of the Tower of London planning task, when compared with placebo in a double-blind crossover design (Elliott et al. *1997b*). The performance-enhancing effects were generally seen on the first session, but the significance of this selectivity is not yet totally clear. It might, for example, simply reflect a less sensitive baseline on session 2 for exhibiting drug-induced improvement because of practice effects carrying over from session one. On the other hand, some aspects of performance appeared to worsen after methylphenidate on session 2. This was mainly evident for the easier form of the Tower of London planning task, where subjects produce the actual move sequences. Performance was faster in terms of more rapid initiation times, but less accurate after methylphenidate. These results were interpreted in terms of a model which suggests that performance on this task might reflect a balance between cortical and striatal function, with methylphenidate affecting the neuromodulation (by dopamine and noradrenaline) of the cortical monitoring of performance accuracy and also, via effects on striatal dopamine, the speed and vigour of performance. This pattern of results emphasizes the costs, as well as the benefits, inherent in the effects of catecholaminergic agents.

Methylphenidate also has striking, mixed effects on performance of a difficult version of the ID/ED attentional set-shift task, with three perceptual dimensions. Rogers et al. (*1999a*) have shown that methylphenidate, while tending to impair performance at the intradimensional shift (IDS) stage, actually reduces errors made at the extra-dimensional shift (EDS) stage - and generally lengthens response latencies. The most obvious interpretation of this pattern of results, which generally mirrors the effects of the D2 receptor antagonist sulpiride, described above, is that Ritalin increases distractibility, possibly both at the level of attending to the perceptual dimensions in the compound stimuli - and also to extra-task stimuli, thus accounting for the lengthier latencies. The results are of considerable interest for the studies reviewed above in non-human primates in the context of the improvements in performance produced by Ritalin on tests such as the self-ordered spatial working memory task. In those studies (Roberts et al. *1994*), impaired spatial delayed response was accompanied by enhanced extra-dimensional shift learning. Presumably, it can be concluded that methylphenidate is not simply mimicking the effects of the altered cortical/striatal balance in dopaminergic activity that accompanies mesofrontal dopamine loss (cf. Roberts et al. *1994*).

Another example of mixed effects of dopaminergic drugs on cognitive function comes from certain effects of dopamine agonist therapy in Parkinson's disease (L-dopa, bromocriptine and pergolide) (Swainson et al. *2000*). These authors reported results that could be construed as showing a deficit in the learning of a difficult, probabilistic reversal task, following dopaminergic therapy in patients with Parkinson's disease whose spatial working memory function, according to certain measures, was enhanced under drug treatment. The deficits in reversal learning were significantly correlated with the dose of the mixed D1/D2 agonist pergolide for these patients. The results are reminiscent of an earlier study of L-dopa withdrawal, in which Gotham et al. (*1988*) found that certain tests sensitive to frontal lobe dysfunction were improved following L-dopa, whereas others were impaired. Those authors speculated that the dopaminergic therapy repleted certain corticostriatal circuits (notably the putamen) but effectively 'overdosed' others (e.g. the caudate nucleus) that had been less affected by the

disease. Swainson et al. (*2000*) make a parallel suggestion that the ventral striatum might be more selectively implicated in reversal learning (for which there is some evidence in humans (Rogers et al. *2000*), and so this circuitry, which is also relatively spared in the early stages of Parkinson's disease, would be relatively more susceptible to possible 'overdosing' effects of medication. Regardless of the actual neural mechanisms involved, these data do again demonstrate the varied effect of dopaminergic medication on cognitive function, while also showing how a Yerkes-Dodson-like function might reflect the engagement of circuitries with variably impaired neuromodulation, rather than simple effects on tasks with absolute and variable levels of difficulty. Task difficulty for patients will vary according to which systems are likely to be intact, rather than as a function of intrinsic 'task-difficulty'.

Effects of manipulation of brain serotonin (5-HT) on tests sensitive to frontal lobe dysfunction in humans

Investigation of the role of central serotonin receptors in cognition in humans is also handicapped by a lack of suitably selective agents. Grasby et al. (*1992*) have shown that buspirone, a rather non-specific 5-HT_{1A} agonist, impairs verbal learning in a functional neuroimaging context, the deficit correlating with changes in regional cerebral blood flow in the posterior neocortex. Another popular method has been the tryptophan depletion technique. By giving food-deprived humans or rats a diet deficient in the amino acid tryptophan, it is possible to produce a transient depletion of the indoleamine 5-HT, and presumably deficient serotoninergic activity, because tryptophan is a necessary precursor of 5-HT synthesized in the brain (Young et al. *1985*).

An early study of the effects of tryptophan depletion on cognitive function in humans found that there was rather little effect on many tests sensitive to frontal lobe dysfunction. For example, performance on the Tower of London test of planning and self-ordered spatial working memory were both unaffected (Park et al. *1994*), in marked contrast to the effects of the catecholaminergic agents sulpiride, methylphenidate and also the noradrenergic agents clonidine and idazoxan (Middleton et al. *1999*). Learning of the paired associates task was retarded, an interesting parallel to the effects seen on verbal learning by Grasby et al. (*1992*). The paired associates learning deficit may have been due to actions of 5-HT in posterior cortical memory circuits, for example in the parietal or temporal lobe, although the task is also sensitive to frontal cortical damage (Owen et al. *1995b*).

The low tryptophan treatment did impair performance on the CANTAB attentional set-shifting paradigm, although the effects were more evident at the extra-dimensional reversal stage than the extra-dimensional shift condition, which immediately precedes it. Reversal learning is another example of shift learning in which the discriminative stimuli remain the same, but identity of the reinforced stimulus (or 'object') is switched. Thus the subject has to desist responding to the previously reinforced stimulus and begin responding to the previously non-reinforced stimulus in order to gain reward. The capacity to show reversal can be partialled into two main components: the ability to inhibit responding to the previously reinforced stimulus; and the ability to learn which stimulus is now rewarded. Marmosets with lesions of the lateral and orbitofrontal cortex exhibit differential impairments on reversal learning as compared with extra-dimensional shift learning. Animals with lateral lesions are impaired in the extra-dimensional shift learning task, whereas those with the orbitofrontal lesions are impaired specifically at extra-dimensional reversal learning (Dias et al. *1996a*). This result can be characterized as a double dissociation of effects of prefrontal lesions on two forms of shift learning - shift learning at the level of single

stimuli or objects, and learning at the more abstract level of entire stimulus dimensions. Given the strong anatomical connections of the orbitofrontal cortex with limbic structures such as the anterior cingulate and the amygdala, it is perhaps not surprising that the orbitofrontal lesion should impair the specific stimulus-reward learning required in reversal. Further evidence for a specific role of the orbitofrontal cortex in reversal learning comes from human studies. Rolls et al. (*1994*) have found that patients with closed head injuries producing brain damage that includes the orbitofrontal cortex are impaired in forms of reversal learning. Rahman et al. (*1999*) have recently shown using the CANTAB suite of visual discriminations that includes reversal learning, as well as extra-dimensional set shifting, that patients with dementia of the frontotemporal type (where the initial neurodegeneration affects the orbitofrontal cortex) have greater problems with the reversal, rather than the non-reversal, stages of the task. Consequently, it appears that there may be functional commonalities between the effects of orbitofrontal lesions and procedures affecting 5-HT function in humans.

In order to test further the hypothesis that reductions in central 5-HT may selectively impair reversal learning, Rogers et al. (*1999a*) used the same, three-dimensional discrimination learning and shifting paradigm as was employed to test the effects of methylphenidate. It was anticipated that this more difficult form of the two-dimensional version of the task might lead to more clear-cut findings than were apparent in the Park et al. study, where effects appeared to be limited largely to the first session in a crossover design. Significantly, the results of Park et al. (*1994*) were extended and confirmed, reversal learning being much more impaired than non-reversal learning at several of the stages of the task - contrasting also with the effects of both methylphenidate (described above) and clonidine (Rogers et al. *1999a*).

In order further to test the hypothesis that the serotoninergic manipulation might be affecting functions controlled by the orbitofrontal cortex to a greater extent than those of the dorsolateral prefrontal cortex, we have also compared the effects of the catecholaminergic agent methylphenidate with those of tryptophan depletion on performance in another paradigm that we have showed to be sensitive to orbitofrontal dysfunction. This task is modelled after the 'gambling task' sensitive to orbitofrontal damage in humans reported by Bechara et al. (*1998*) and is described in greater detail in a recent paper (Rogers et al. *1999b*). Briefly, subjects are required to make probabilistic decisions and then assign proportions of their previously earned reward to those decisions. This decision-making task is also sensitive to damage of the orbitofrontal cortex, whether produced by lesions (Rogers et al. *1999b*) or by neurodegeneration (Rahman et al. *1999*). Importantly, in the present context, tryptophan depletion produced effects on performance which mimicked some of those produced by orbitofrontal lesions (Rogers et al. *1999b*). On the other hand, the same dose (40 mg p.o.) of methylphenidate previously shown to affect many of the other tasks described above that depended on dorsolateral prefrontal cortical functioning had no effects on the decision-making task. Given the relative lack of effect of tryptophan depletion on performance on the spatial working memory task and the Tower of London planning task, in relation to its significant effects on reversal learning and the decision-making task - and the opposite effects on these of the indirectly acting catecholaminergic agonist methylphenidate, we appear to have provided evidence, summarized in Table 2, for a double dissociation of effects on tasks controlled by different sectors of the prefrontal cortex.

Synthesis and implications

We have reviewed the effects of manipulations of the main monoaminergic systems in the context of frontal lobe functions in rats, monkeys and humans. The main points to have emerged are as follows:

1. Drugs or manipulations affecting the central catecholamine (noradrenergic and dopaminergic) systems specifically affect certain tasks sensitive to frontostriatal dysfunction.
2. Performance on such tasks can be improved or impaired in experimental animals, healthy human volunteers, or patients, for example with Parkinson's disease, depending on such factors as the dose of drug, level of baseline performance, and individual differences.
3. An especially important factor is probably the nature of the task under study. This may in turn depend on the neural circuitry that underlies different tasks: those exhibiting improvement following catecholamine agonists appear to be more dependent for example on the dorsolateral rather than the orbitofrontal cortex.
4. Manipulations of other neurotransmitter systems, for example, serotonin (and also acetylcholine; see Roberts et al. *1992*) appear to affect tasks mediated by rather different frontal circuitry that includes the orbitofrontal rather than the dorsolateral prefrontal cortex.
5. The implication is that the different chemically defined systems of the reticular core do have different functions. This conclusion is apparent from the effects of gross manipulations to the different systems in a common task requiring attentional processing, as in the case of the studies of the five-choice task in the rat, but also when more local manipulations are made into these systems projecting into a common terminal field, in this case the prefrontal cortex.

From the perspective purely of neurochemical anatomy, these conclusions may perhaps be surprising, as there is very little evidence of major differences in the pattern of innervation of different regions within the prefrontal cortex for any of the four main systems considered. Further research is required to explain this apparent mismatch between function and anatomy: there is apparently much more specificity than at first would have appeared likely from the details of the neurobiological organization of the monoamine systems.

The results have many theoretical and clinical implications. In the latter case, we can begin to make predictions about which types of function are likely to respond to pharmaceutical treatment in different disorders. We can also make more precise conclusions about the types of function that are vulnerable to malfunction in particular neurotransmitter systems, for example, serotoninergic abnormalities in depression. Finally, we can speculate about the adaptive significance of the types of functional relationships we have seen between neurotransmitter function and behaviour, in terms of the natural influences that affect the functioning of these chemically identified systems. Most of them have been implicated in such general functions as stress and arousal, although little is known about the precise pattern or sequence of changes of state in these systems. However, it is evident that a single inverted U-shaped Yerkes-Dodson-like function is inadequate to account for all of these effects. The different states in which the fluctuating levels of neurotransmitter activity place the prefrontal neuronal circuitry would seem to allow a much greater flexibility in facilitating those sets of 'cognitive control processes' most adaptive to the situation at hand, for example, working memory, response inhibition, response sequencing, and 'somatic marking'. The current working hypothesis is therefore:

That chemically selective neuromodulation of executive functioning can serve to optimize performance of certain types of task or operations, but not others, related to the adaptive imperative to engage processing that is appropriate to both the current environmental setting (including the presence of stressors) and the internal state (e.g. fluctuations in mood and arousal).

What now has to be determined, however, is a greater understanding of what constitutes these optimal allocations of resources and how they are facilitated by the neuromodulatory systems we have investigated.

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