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Differential Regulation of Fronto-Executive Function by the Monoamines and Acetylcholine

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The prefrontal cortex (PFC) is innervated by the monoamines, dopamine (DA), noradrenaline (NA), and serotonin, as well as acetylcholine, and the marked influence of these neurochemical systems on prefrontal working memory processes has been widely described. However, their potentially, differential contribution to prefrontal functioning is less well understood. This paper reviews evidence to support the hypothesis that these neurochemical systems recruit distinct fronto-executive operations. Direct comparison of the effects of manipulations of these neuromodulators within PFC on performance of an attentional set-shifting paradigm reveals their differential contribution to distinct task stages. Depletion of prefrontal serotonin selectively disrupts reversal learning but not attentional set formation or set shifting. In contrast, depletion of prefrontal DA disrupts set formation but not reversal learning. NA depletion on the other hand specifically impairs set-shifting, whereas its effects on reversal learning remain unclear. Finally, depletion of prefrontal acetylcholine has no effect on either set formation or set shifting but impairs serial reversal learning. Because these neurochemical systems are known to represent distinct states of stress, arousal, attention, and affect, it is postulated that they augment the different types of executive operation that are recruited and performed within these states via a synergistic interaction with the PFC.

Keywords: acetylcholine, cognition, dopamine, noradrenaline, prefrontal cortex, senatonium

Introduction

A seminal study by Brozoski et al. (1979) showed a relatively selective role for prefrontal dopamine (DA) as distinct from other prefrontal monoamines, that is, noradrenaline (NA) and serotonin, in spatial working memory. Further work has elucidated this specific contribution of DA to working memory functions at the psychological (Floresco and Phillips 2001; Chudasama and Robbins 2004), anatomical (Goldman-Rakic et al. 1989; Smiley et al. 1992; Smiley and Goldman-Rakic 1993), cellular (Sawaguchi et al. 1990; Sawaguchi and Goldman-Rakic 1991; Williams GV and Goldman-Rakic 1995), and molecular (i.e. receptor) levels of analysis (Sawaguchi and Goldman-Rakic 1991). Thus, there is considerable evidence for a special role for DA D1, but not D2 receptors in spatial working memory, based on evidence using iontophoresis or intracerebral drug infusion (see Floresco and Magyar 2006 for a review of this literature). Overall there is consensus that spatial working memory function depends upon an optimal level of DA function within the prefrontal cortex (PFC) (Williams GV and Goldman-Rakic 1995; Arnsten 1997; Zahrt et al. 1997; Floresco and Phillips 2001).

However, DA is just one of a number of neuromodulators present in the PFC. The other monoamines, NA and serotonin (5-HT, 5-hydroxytryptamine), as well as acetylcholine, are also widely distributed throughout the PFC (Goldman-Rakic et al. 1990; Mrzljak et al. 1993; Williams SM and Goldman-Rakic 1993; Jakab and Goldman-Rakic 1998; Muly et al. 1998). In this paper we will show that prefrontal control processes are differentially regulated by these specific neuromodulators. It will be argued that, in keeping with the involvement of these neuromodulators in stress, arousal, and mood, as well as reward processes and attention, that activity in these systems may be understood as representing these different states, acting to augment the different types of executive operation that are recruited and performed within these states.

DA and Attentional Selection

Working memory is not the only prefrontal function to be modulated by DA, there being evidence in the rat of additional involvement in processes of attentional selection (Granon et al. 2000; Chudasama and Robbins 2004). Particular insight into the role of DA in attentional selection has come from studies in marmosets investigating the effects of 6-hydroxydopamine (6-OHDA)–induced depletions of prefrontal DA on the ability to develop an attentional set. When performing a task, animals learn to attend to the sensory features and motor responses that are relevant to that task and to ignore those features and responses that are irrelevant. When certain features and responses retain their relevance across tasks then an "attentional set" can develop which biases perception and responses accordingly, allowing for an increased speed of learning new tasks as long as those features and responses that make up the "attentional set" remain relevant. It is important to recognize that attentional selection here is not at the level of specific, concrete stimuli but at the level of higher-order rules, such that features that are common to an array of stimuli are abstracted to form a feature dimension.

The development of such attentional sets has been demonstrated in marmosets performing a series of visual discriminations involving stimuli composed of 2 abstract dimensions, shapes, and lines. Exemplars from one of the dimensions (e.g., shapes 1 and 2) can be paired with one or other of the exemplars from the other dimension (e.g., lines 1 and 2) to form bidimensional compound stimuli (see Fig. 1*a*). Only one exemplar from one of the dimensions is associated with reward (e.g., shape 1) and animals have to learn always to select the compound stimulus that includes that exemplar regardless of which of the exemplars from the other dimension (e.g., line 1 or 2) it is paired with. Over a series of novel discriminations (commonly known as intradimensional shifts, IDS) in which the exemplar that is associated with reward is always from the same dimension, for example, shapes, animals learn to attend to

"shapes" and ignore "lines." This development of an attentional set is usually reflected in an increase in the speed of learning across the series of novel discriminations. However, the clearest demonstration is in the subsequently poor performance on a discrimination in which an exemplar from the previously irrelevant dimension, and currently ignored dimension, for example lines, becomes associated with reward (commonly known as an extradimensional shift, EDS). Intact marmosets show the expected improved performance across a series of discriminations involving IDSs and likewise show impaired performance on a subsequent discrimination requiring an EDS. In contrast, unlike controls, marmosets with global prefrontal DA depletion fail to show improved performance across a series of IDSs (Fig. 1*a*, Crofts et al. 2001) and, as a result, can show enhanced performance when required to perform an EDS (Fig. 1*b*, Roberts et al. 1994), presumably as a consequence of not having learned to ignore the previously irrelevant, but currently, relevant dimension. That these lesioned monkeys are failing to ignore the irrelevant dimension is further supported by the finding that their performance is more susceptible to distraction than controls (Crofts et al. 2001). Having learned to select an examplar from the relevant dimension, lesioned marmosets were impaired at continuing to select this exemplar if the exemplars from the irrelevant dimension were replaced with novel exemplars (Fig. 1*c*). Thus, without DA in the PFC the marmosets had difficulty attending to the relevant features of the task and ignoring the irrelevant features, consequently failing to develop an "attentional" set.

These findings provide empirical support for the computational models of prefrontal function proposed by Cohen and Durstewitz (Cohen and Servan-Schreiber 1993; Braver and Cohen 2000; Durstewitz et al. 2000). Their models suggest that DA plays a role in stabilizing representations within the PFC as well as gating relevant and irrelevant information into the PFC; effects hypothesized to depend upon tonic and phasic DA, respectively. Clearly these effects of DA could contribute equally to the holding of information "on-line," as occurs in tests of working memory, as well as to the active attention to stimuli in the external world, required in tests of attentional selection. From these models it might be expected that, depending upon the exact state of the DA system, not only will deficits in developing an attentional set be seen but also, under certain circumstances, deficits in disengaging would be observed, resulting in impairments in shifting an attentional set.

Further understanding of the modulatory role of DA may depend upon pinpointing those regions of the PFC in which the effects of attentional set formation and shifting are mediated. Indeed, a similar region of ventrolateral PFC to that associated with rule acquisition (Kowalska et al. 1991; Malkova et al. 2000; Wallis, Anderson, et al. 2001; Wallis, Dias, et al. 2001) has also been associated with rule switching. Thus, lesions of ventrolateral PFC (including areas 12/47 and 45 according to Burman et al. 2006) in marmosets impair EDS performance (Dias et al. 1996b, 1997) and functional neuroimaging studies in humans and monkeys have shown differential activity in posterior regions in and around the inferior frontal sulcus (including areas 12/47 and 45 according to Petrides and Pandya 1994) associated with shifting an attentional set (Konishi et al. 1998; Nagahama et al. 2001; Nakahara et al. 2002; Hampshire and Owen 2006). Moreover, DA has been implicated in task-set shifting in the medial PFC of rats, that region of the rat PFC that has been shown to be necessary for attentional set-shifting

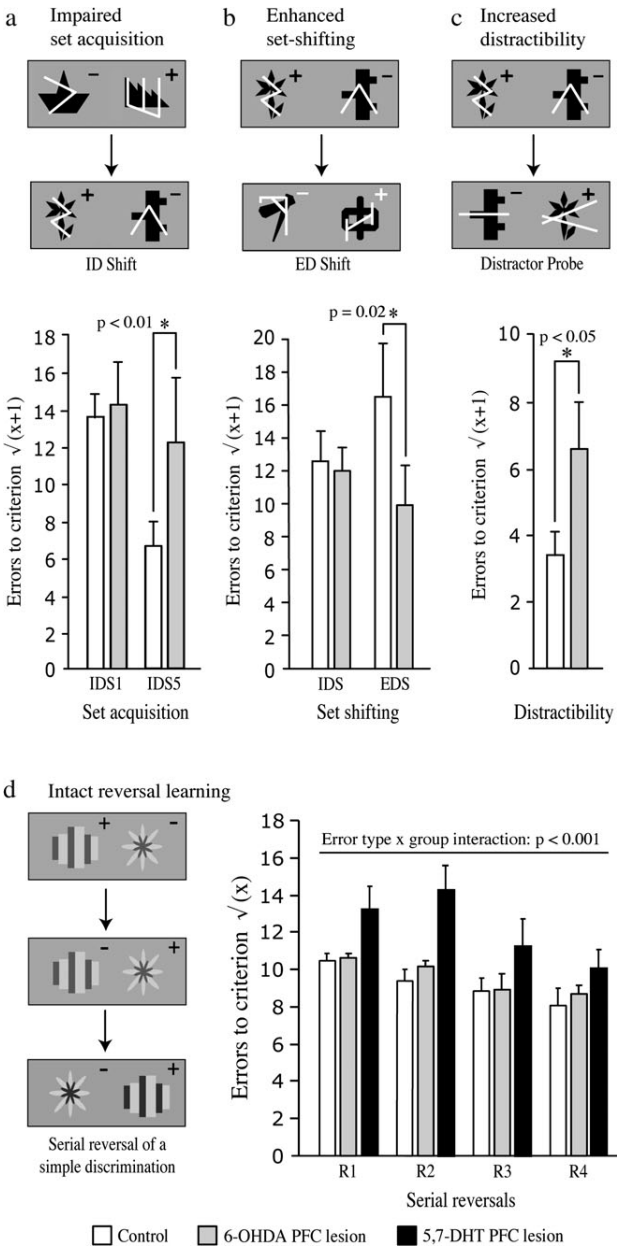

Figure 1. The effects of 6-OHDA induced DA lesions of the marmoset PFC on the acquisition and shifting of attentional sets and on reversal learning. Examples of 2 discriminations in which the same dimension remains relevant, commonly called an IDS, are shown in (*a*). In contrast to controls, the reduction in errors from the first (IDS1) to the last (IDS5) discrimination, reflecting acquisition of an attentional set, is not seen in animals with 6-OHDA lesions of the PFC. Prefrontal 6-OHDA lesioned monkeys do however perform a discrimination requiring a shift of attentional set, that is, EDS, depicted in (*b*), better than controls. Underlying their improved performance on the EDS may be their increased level of distractibility, shown by their increased number of errors on a distractor probe test (*c*), in which the exemplars from the irrelevant dimension of a previously learned discrimination are replaced by novel exemplars. Selective lesions of DA within the OFC have no effect on serial reversals as shown in (*d*), in contrast to 5,7-DHT–induced depletions of 5-HT from the OFC that impair reversal learning (Fig. 2*a*). For comparison purposes all data have been square root transformed. However, where statistical significance between groups is indicated this is based upon the statistical analysis performed on the original data set described in full in the original publications. 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. Control groups all received sham-operated control procedures.

(Birrell and Brown 2000). For example, treatment of rats with tolcapone, a pharmacological inhibitor of catechol-*o*-methyltransferase (COMT; an enzyme involved in catecholamine metabolism) has been shown to enhance attentional set-shifting in a rat version of the attentional set-shifting paradigm (Brown and Bowman 2002). In this version of the task rats have to attend to the perceptual dimensions of either odor or touch/vision in order to locate food reward hidden in one of 2 food wells filled with scented material, for example almond scented wood shavings versus peppermint scented tealeaves. Inhibition of COMT resulted in marked elevations in stimulated DA release, but not NA release, within the medial PFC, implicating DA in this effect. Moreover, a polymorphism of a gene controlling COMT, postulated to have a selective effect on PFC DA, has been shown to affect rule shifting on the Wisconsin Card Sort Test (Egan et al. 2001), which is modeled by the EDS procedure in the attentional set-shifting paradigm (Dias et al. 1996a). There is also evidence for DA receptor selective effects on shifting using other, behaviorally less selective, task-set switching paradigms in rats (Ragozzino 2002; Floresco et al. 2006).

Several neurobiological or psychological factors may determine whether DA-ergic manipulations affect the *development* of an attentional set (as seen in the attentional set-shifting studies of marmosets) or specifically affect *attentional set-shifting* (including task-set shifting in rats, Floresco et al. 2006). Neurobiological factors include the overall tone of the DA-ergic system in terms of its phasic and tonic modes of functioning which will differ markedly between studies of 1) 6-OHDA–induced chronic DA depletion (and the resulting compensatory sequelae); 2) acute intra-PFC D1 and D2 selective DA receptor agents (Ragozzino 2002; Floresco et al. 2006); and 3) alterations in COMT (Bilder et al. 2004; Tunbridge et al. 2004). Certainly, the proposal by Seamans and Yang (2004) that overall hypofunction of the prefrontal DA system will cause persistent activity states to be unstable to distractors is consistent with the enhanced distractibility of marmosets with 6-OHDA–induced depletions of prefrontal DA (Crofts et al. 2001). The important psychological factor that may influence the way in which DA modulates attentional set formation and shifting is the potential level of interference between relevant and irrelevant perceptual dimensions. Thus, if competing dimensions are in the same sensory modality, for example, line and shape features of a pattern stimulus, as in the marmoset studies, then it is likely that there is considerably more interference and thus more distraction at set formation stages than if the dimensions are from distinct sensory domains as in studies with rats, for example, visual features and egocentric space (Floresco et al. 2006) or vision/touch and smell (Birrell and Brown 2000). Hence, set formation in marmosets would be more sensitive to DA depletion than that in rats, whereas the opposite may be the case when having to shift set *between*, rather than *within*, sensory modalities. These considerations are relevant to impairments in ID and ED shifting in patients with schizophrenia, tested with the same paradigm as used with marmosets (Pantelis et al. 1999; Jazbec et al. 2006).

The sensitivity of attentional selection processes to DA-ergic manipulations is in marked contrast to the lack of effects of DA-ergic manipulation on processes underlying cognitive flexibility at the level of concrete stimuli, as occurs during reversal learning. In reversal learning, having learned that only one stimulus of a pair, is associated with reward, the subject is required to learn the reverse association, that is, that the previously unrewarded stimulus is rewarded. This capacity for reversal learning has been shown to depend critically on the orbitofrontal cortex (OFC) in humans, monkeys, and rats (Butter 1969; Iversen and Mishkin 1970; Rolls et al. 1994; Dias et al. 1996a; Schoenbaum et al. 2002; Chudasama and Robbins 2003; Fellows and Farah 2003; McAlonan and Brown 2003; Hornak et al. 2004). In many cases, this deficit in reversal learning is perseverative in nature with repetitive responding occurring to the previously rewarded stimulus. Consistent with these findings is the activation of orbitofrontal regions in functional magnetic resonance imaging studies of reversal learning regardless of whether the reward is juice (O'Doherty et al. 2003), happy faces (Kringelbach and Rolls 2003), money (O'Doherty et al. 2001), or a "correct" feedback signal (Hampshire and Owen 2006). The contribution of OFC to cognitive flexibility is highly selective as shown by the finding that the same OFC lesion in marmosets that impairs reversal learning does not disrupt ED shifting (the ability to switch at the level of higher-order rules). Moreover, lesions of the ventrolateral PFC in marmosets that disrupt shifting between higher-order rules, do not disrupt reversing between concrete stimuli (Dias et al. 1996b, 1997). A similar dissociation between these types of shifting deficit has since been seen in a number of patient groups with frontal lobe pathology (Owen et al. 1992; Rahman et al. 1999).

Despite reversal learning being dependent upon the PFC, the cognitive processes that underlie it are not dependent upon DA-ergic modulation of the PFC. Global prefrontal DA depletion disrupted attentional selection but did not affect the reversal of a visual discrimination (Roberts et al. 1994). A similar dissociation has been seen in humans treated with methylphenidate (Rogers et al. 1999). More recently, DA depletion restricted to the OFC, induced by local infusions of 6-OHDA, was also found to be without effect on serial reversal performance of marmosets (Fig. 1*d*, Clarke et al. 2006). Thus, the ability to detect a change in the contingencies between a stimulus and reward, to respond to punishment, and to use such error and punishment cues to direct responding away from the previously rewarded stimulus and toward the previously unrewarded stimulus are not dependent upon orbitofrontal DA. However, certain aspects of orbitofrontal processing are DA dependent. For example, 6-OHDA–induced DA depletion within OFC disrupts the evaluation of reward magnitude and delay in a temporal discounting task in rats (Kheramin et al. 2004) and DA utilization in the OFC, as measured by levels of 3,4-dihydroxy-phenylocetic acid, is increased in rats performing a temporal reward discounting task (Winstanley et al. 2006). Moreover, intra-OFC infusions of DA D1 and D2 receptor antagonists decrease the breakpoint on a progressive ratio schedule, that is, the point at which a rat will not increase responding further to obtain food reward, implicating DA in the translation of incentive motivation into action (Cetin et al. 2004).

The original emphasis of a role for PFC DA in working memory has been substantiated by the results of several studies reviewed above, including our own in the marmoset (Collins et al. 1998). However, the question has been whether effects of DA on attentional set formation and shifting can be accommodated within a working memory explanation. Our own hypothesis is to suggest the converse relationship between deficits in working memory and attentional set formation, specifically that both arise from a failure of attentional selection. This is also consistent with our observations that spatial working memory deficits resulting from prefrontal DA depletion in marmosets

depend critically upon the presence of distracting stimuli in the delay interval (Collins et al. 1998). We think this hypothesis is also consistent with the notion that PFC DA D1 receptors are implicated in the stabilization of representations (Durstewitz et al. 2000) which leads to their protection under conditions of distraction. The importance of the PFC in guiding behavior by representations of discriminative stimuli, rather than the stimuli themselves, was highlighted by Goldman-Rakic (1987), but although her hypothesis emphasized the importance of the PFC in representational memory, it is clear that the PFC and its DA input are also involved in representing knowledge in contexts which require little or no working memory.

NA and Attentional Set-Shifting

There is burgeoning evidence that the noadrenergic (NA) system, specifically the coeruleo-cortical NA projections to diverse forebrain sites, including the neocortical mantle and the hippocampus, is implicated in attentional set-shifting. There is already substantial evidence that manipulations of the NA system affect working memory functions in nonhuman primates in a way perhaps similar to the effects of DA neuromodulation (reviewed in Arnsten and Robbins 2002). Parallel investigations have also suggested a role for central, particularly prefrontal, NA in attentional functioning based on electrophysiological studies in monkeys (Aston-Jones and Cohen 2005), and studies in rats of the effects of profound cortical depletion of NA (Carli et al. 1983; Cole and Robbins 1992; Milstein et al. 2006).

An early literature described effects of central NA manipulations on task set switching in the rat after lesions of the dorsal noradrenergic ascending bundle (DNAB) or systemic drug treatments, but due to a mixture of conflicting results and interpretations, as well as procedural confounds, it is somewhat confused (Mason and Lin 1980; Devauges and Sara 1990; Rowe et al. 1996). Consequently, it has been of considerable interest to examine effects of manipulations of NA function on the acquisition and shifting of attentional sets and reversal learning with some novel pharmacological agents on the rat version of the attentional set-shifting paradigm when rule shifting and reversal learning are completely independent (Birrell and Brown 2000). Converging new evidence suggests a selective effect of prefrontal NA manipulations on attentional set shifting. First, Lapiz and Morilak (2006) have shown that atipamezole, an α-2-adrenergic autoreceptor antagonist, improves set shifting when injected systemically, and that its effects are blocked by intramedial PFC infusions of a postsynaptic α-1 receptor antagonist, but not by intra-PFC infusions of a β-1, or β-2 receptor antagonist. A similar improvement in set-shifting has also been described by Lapiz et al. (forthcoming) following a regimen of subchronic treatment with the NA-reuptake blocker desipramine leading to an upregulation of medial prefrontal NA (as confirmed with microdialysis). Second, DNAB lesions using 6-OHDA produce substantial depletions of cortical NA and selectively impair set shifting (Tait et al., unpublished findings). This effect in rats is probably mediated by the PFC as infusions of the anti-dopamine β-hydroylase saporin into the medial PFC impair set shifting (Eichenbaum et al. 2003). It is of interest that agents affecting noradrenergic transmission such as methylphenidate (Rogers et al. 1999), and more particularly clonidine and idazoxan (especially when combined, Middleton et al. 1999) all selectively affect attentional set-shifting in human volunteers, although more detailed investigation is necessary.

Serotonin and a Specific Form of Cognitive Flexibility

In contrast to the catecholamines, far less is known of the role of 5-HT in prefrontal processing. Like DA, 5-HT can affect working memory function (Goldman-Rakic 1999) and within dorsolateral PFC 5-HT2A and 5-HT3 receptors have been located on the same pyramidal neurons as DA receptors, except that in contrast to DA receptors they are found on the proximal dendrites rather than in the spines. However, unlike DA, 5-HT has a marked influence on reversal learning. Large depletions of 5-HT throughout the PFC (induced by 5,7-dihydroxytryptamine [5,7-DHT] infusions, Clarke et al. 2004, 2005) as well as more restricted lesions targeting the OFC (Clarke et al. 2006) have resulted in impaired discrimination reversal performance (Fig. 2*a*) despite intact performance of a discrimination learned prior to surgery and intact acquisition of a novel visual discrimination (Fig. 2*b*). The deficit is characterized by a marked perseveration, the lesioned monkeys displaying repetitive responding to the previously rewarded stimulus across a number of sessions despite the continued failure to get reward. Moreover, the deficit is present whether animals have been performing a series of reversals of a simple pattern discrimination (Clarke et al. 2004) or reversing a compound discrimination immediately after a shift of attentional set (Clarke et al. 2005). However, the deficit is abolished if the previously correct stimulus is no longer present at the time of the reversal and the subject has to choose instead between a novel stimulus and the previously unrewarded, but currently rewarded stimulus (Fig. 2*c*, Clarke et al. 2006). Intact performance on this version of reversal learning rules out any explanation of the deficit in terms of a failure to learn to respond to a previously unrewarded stimulus (learned avoidance). It suggests, instead, that the deficit in reversal learning is due to a failure to cease responding to the previously rewarded stimulus. Consistent with this is the finding that the reversal deficit is still present if, at the time of the reversal, the previously unrewarded stimulus is replaced with a novel stimulus and the animal has to choose the novel stimulus and inhibit responding to the previously rewarded stimulus (Fig. 2*c*). A similar stimulus bound behavior is seen in marmosets with 5,7-DHT–induced depletions of prefrontal 5-HT during acquisition of the detour reaching task (Fig. 2*d*). Although lesioned monkeys, like controls, can learn to make a detour reach around a transparent barrier in order to gain access to food reward that is located immediately behind the barrier, nevertheless, during acquisition the lesioned animals made many more reaches along their line of sight, directly into the barrier, to retrieve the visible reward compared with controls (Walker et al. 2006).

The specificity of this deficit is shown by the intact performance of marmosets with prefrontal 5-HT depletion in shifting an attentional set from one perceptual dimension of a compound stimulus to another (Fig. 2*e*, Clarke et al. 2005), an ability dependent not on OFC but on ventrolateral PFC in marmosets (Dias et al. 1996b, 1997). Moreover, we have also failed to find in preliminary studies an effect of prefrontal 5-HT depletion in marmosets on the performance of a spatial sequencing task (Walker et al. 2005), a task previously shown to be disrupted by global lesions of the PFC (Collins et al. 1998) and which recent evidence would suggest is particularly dependent upon ventrolateral PFC (Walker et al. 2005). These dissociable effects of 5-HT on functions differentially dependent upon OFC and lateral PFC may suggest differential sensitivity of

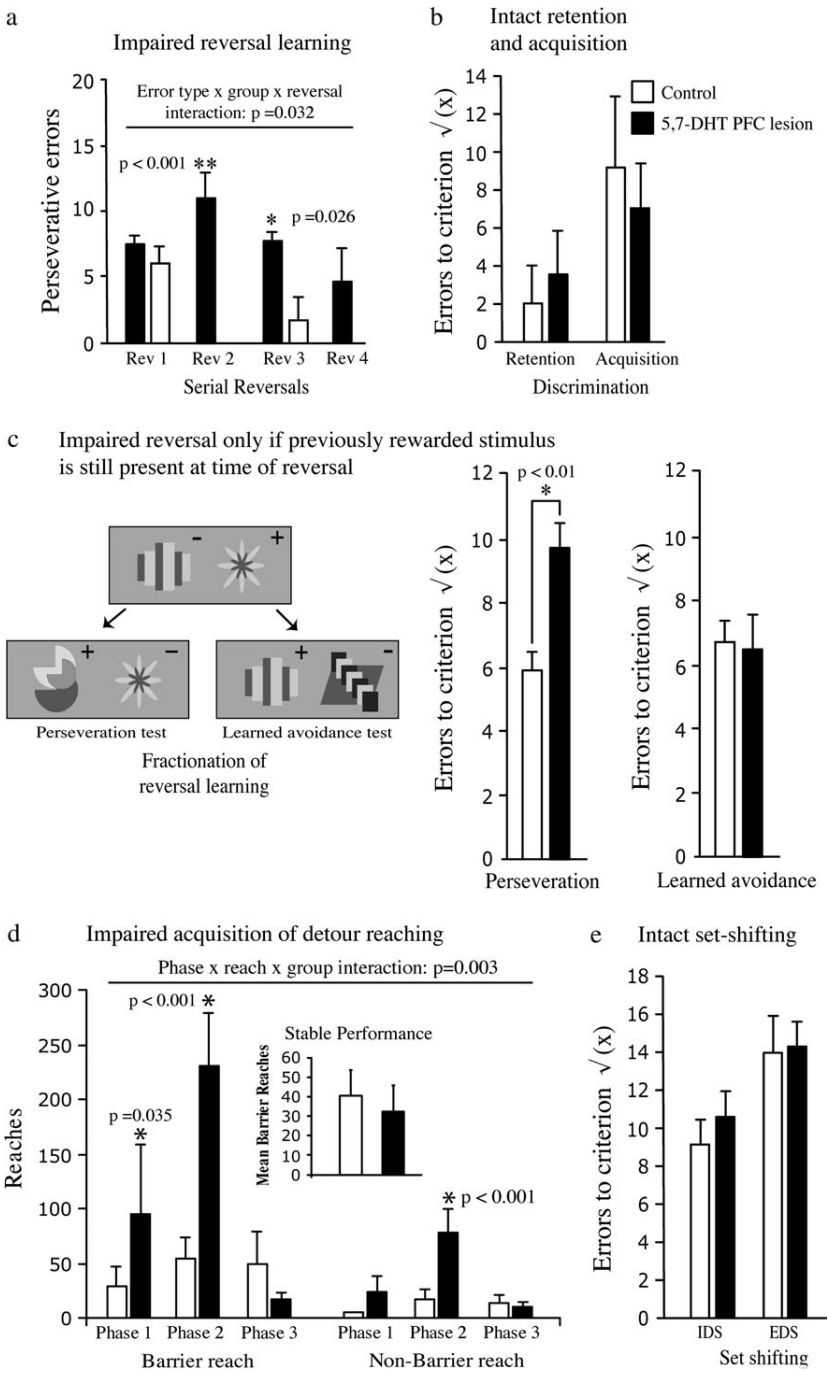

Figure 2. The effects of 5,7-DHT–induced depletions of 5-HT from marmoset PFC on reversal learning, detour reaching, and the maintenance and shifting of attentional sets. Animals with 5,7-DHT lesions of the PFC made more errors than controls before reaching criterion across a series of reversals, the errors being primarily perseverative in nature, as shown in (*a*). In contrast, their performance on the retention of a discrimination learned immediately prior to surgery and on acquisition of a novel discrimination learned postsurgery was intact, as shown in (*b*), The deficit in reversal learning was dependent upon the presence of the previously rewarded stimulus (perseveration test) at the time of the reversal, as shown in (*c*). In contrast, reversal performance was intact if the previously rewarded stimulus was replaced by a novel stimulus (learned avoidance test), also shown in (*c*). 5,7-DHT lesioned monkeys are also impaired at inhibiting a prepotent response tendency to reach for food reward as measured by their increased number of barrier reaches to the closed side of the box in the detour reaching task, shown in (*d*). Here, phases 1 and 2 represent different stages of acquisition and phase 3, stable performance. In contrast, their performance on the maintenance and shifting of an attentional set, shown in (*e*), is equivalent to controls. For comparison purposes, the data have been square root transformed. However, where statistical significance between groups is indicated this is based upon the statistical analysis performed on the original data set described in full in the original publications. The "+" and "−" signs in (*c*) indicate whether the stimuli were associated with reward or not. Control groups all received sham-operated control procedures.

these prefrontal regions to 5-HT modulation. Thus, the distribution of 5-HT and its receptors does exhibit regional and laminar selectivity (Pazos et al. 1987; Audet et al. 1989; Goldman-Rakic et al. 1990; Gebhard et al. 1995). Nevertheless, 5-HT receptors are found throughout dorsolateral and ventrolateral regions of PFC and as described earlier, 5-HT has been shown to

modulate the delay firing of monkey pyramidal cells engaged in the spatial delayed response task. Thus, the differential effects of 5-HT on prefrontal functioning more likely reflect the differential sensitivity of specific control processes to 5-HT modulation.

Disruption of a number of mechanisms may be responsible for the perseverative, inflexible behavior associated with prefrontal 5-HT depletion including a failure in error detection, altered responsiveness to punishment or loss of reward and a deficit in inhibitory control. Indeed there is evidence to implicate 5-HT in all of these functions (Deakin 1991; Murphy et al. 2002; Evers et al. 2005). Further investigations should seek to specify the specific mechanism dependent on 5-HT for rapid response reversal and the role of distinct types of 5-HT receptors within the OFC.

Acetylcholine (ACh) and Serial Reversal Learning

The functions of the basal forebrain cholinergic systems projecting to the cortex have been subject to intense scrutiny, with proposed roles in learning, working memory, and attention (Everitt and Robbins 1997; Sarter and Bruno 1997; Hasselmo and McGaughy 2004). In terms of the attentional set-shifting paradigm the balance of evidence suggests intriguingly that cortical ACh manipulations selectively affect reversal learning dependent on the OFC. An initial study examined the effects of N-methyl-d-aspantate (NMDA)-induced excitotoxic lesions of the nucleus basalis of Meynert (nbM) in marmosets (Roberts et al. 1990). This lesion led to reductions immediately post-surgery in excess of 70% in cortical acetyltransferase throughout the PFC, (although reductions in cortical choline acetyltransferase activity had declined to around 30% by the end of the study, 1 year later). There was relative sparing of the globus pallidus which is much more difficult to achieve in rats because of the proximity of this structure to the cholinergic neurons of the nucleus basalis in that species. The marmosets had been trained on a visual discrimination task prior to surgery and the major deficit was in performance of the visual discrimination over a series of reversals. This serial reversal learning impairment was characterized by a tendency on the first reversal to make perseverative errors, as well as a failure to improve over successive reversals (Fig. 3*a*). New discrimination learning was only impaired if tested soon after surgery. In a second study, the maintenance of an attentional set and the shifting of attentional sets were shown to be insensitive to such nbM lesions (Fig. 3*b*) although reversal learning, as before, was disrupted (Roberts et al. 1992). The results were discussed in terms of the close anatomical relationships between the OFC and the nbM in marmosets. A definitive conclusion that ACh contributes to reversal learning is not possible, because of the possibility of incidental damage to other noncholinergic neurons in the nbM. A follow-up study by Fine et al. (1997) investigated the effects of the cholinergically selective immunotoxin, IgG saporin, infused into the marmoset nbM and showed no significant effects on serial reversal learning, but such deficits were unmasked by concomitant treatment with scopolamine.

The issue has been addressed more recently by several studies in the rat. Thus, Tait and Brown (unpublished manuscript, personal communication) have shown that 192-IgG saporin infusions into the rat basal forebrain did not impair performance at any stage of the odor/texture discrimination variant of the attentional set-shifting paradigm for rats, including reversal learning. However, a complementary experiment employing a spatial serial reversal paradigm in an operant

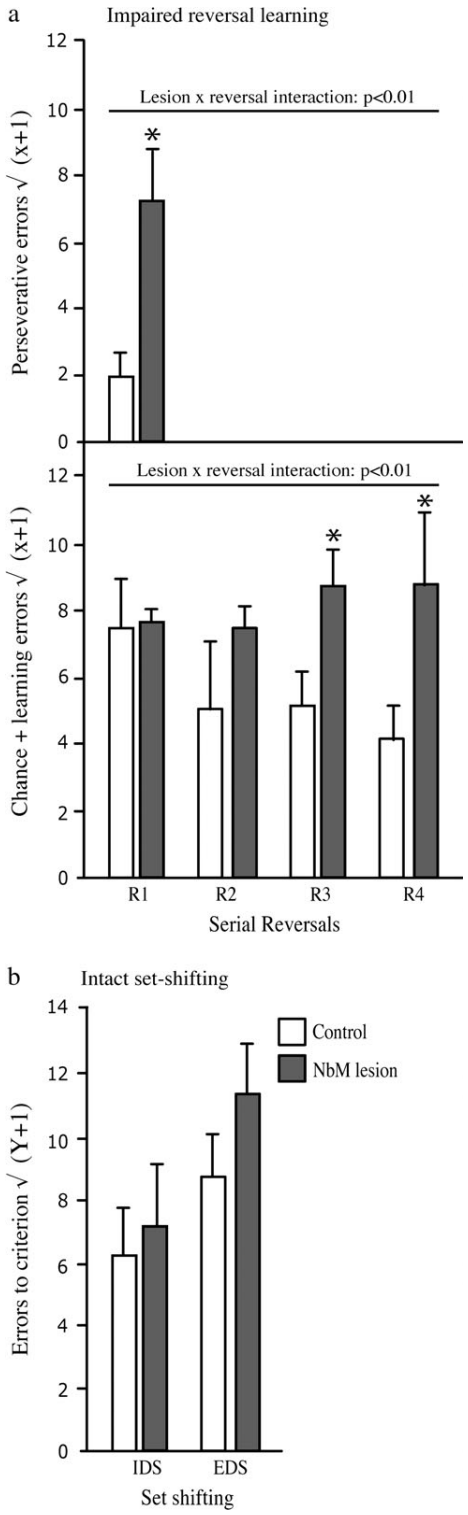

Figure 3. The effects of excitotoxic lesions of the nbM on the maintenance and shifting of attentional sets and reversal learning in marmosets. Lesions of the nbM impaired reversal learning, resulting in an increase in perseverative errors on the first reversal and a failure to show an improvement in performance across a series of reversals, as shown in (*a*). Such lesions had no effect on the number of errors to reach criterion on a discrimination requiring maintenance of an attentional set (IDS) or shifting of an attentional set (EDS), as shown in (*b*).

chamber did find that infusions of 192-IgG saporin into the rat basal forebrain selectively impaired serial reversal while leaving performance on the first reversal intact (Cabrera et al. 2006). A further study by McGaughy et al. (personal communication) using the odor/texture attentional set-shifting paradigm investigated the effects of 192-IgG saporin infused directly into the rat lateral OFC. They found that these selective cholinergic lesions had no effect on initial acquisition of the discriminations, or on initial reversal learning or set shifting, but impaired serial reversal learning selectively for odor-related learning. These findings contrast with those following nonselective lesions of the rat OFC which are not selective for modality and also impair initial reversal learning (McAlonan and Brown 2003) suggesting that the cholinergic innervation has quite specific functions. Thus, it does appear that manipulations of the cholinergic innervation of the OFC can produce quite selective impairments of serial reversal learning that generalize across modalities. An earlier study with 192-IgG saporin infused into the medial PFC (Eichenbaum et al. 2003) had no effects on any aspect of the attentional set-shifting paradigm (in agreement with the earlier finding in marmosets using a less selective lesioning protocol) suggesting that the effects of ACh manipulations of the PFC were limited to reversal learning. If serial reversal learning, but not the first reversal, is dependent upon prefrontal acetylcholine then this would give support for the speculative proposal that acetylcholine is involved in "expected uncertainty" (Yu and Dayan 2005), because, across a series of reversals, animals learn to predict a change in the response contingencies.

Overall, the available evidence suggests that ACh in the OFC is implicated in aspects of reversal learning. Although cholinergic treatments also apparently affect set-shifting (Chen et al. 2004), their site of action is unclear and may include posterior parietal cortex (Fox et al. 2003).

Summary and Conclusions

The differential contributions of the monoamines and acetylcholine to specific aspects of fronto-executive processing have been reviewed. Performance on the various stages of an attentional set-shifting paradigm, designed to measure the ability of humans and other animals alike, to develop and maintain higher-order attentional sets, shift attentional sets, and reverse responding between concrete stimuli based upon changing reward contingencies, has been shown to be differentially affected by manipulations of these neuromodulators (See Table 1 and Fig. 4). Direct comparison of the effects of the catecholamine neurotoxin, 6-OHDA and the 5-HT neurotoxin, 5,7-DHT infused into the PFC of a new world primate, the common marmoset, has implicated prefrontal 5-HT in reversal learning but not in developing or shifting an attentional set. In contrast, prefrontal DA has been implicated in attentional set formation but not reversal learning. A similar dissociation between the effects of DA and 5-HT manipulation has been reported in volunteers using the human analog of the attentional set-shifting paradigm. Prefrontal NA, on the other hand, has been implicated specifically in the shifting of an attentional set in studies using the odor-texture version of the attentional set-shifting paradigm devised for rats. Although prefrontal acetylcholine does not appear to contribute to higher-order attentional selection or shifting of an attentional set, it may play a role in reversal learning.

Together, these findings 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. The goal of future studies must be to define the specific contexts in which these neuromodulatory systems are acting to bias prefrontal processing. Of central importance to our understanding of the functions of these neuromodulatory systems is their top-down regulation by the very system that they themselves modulate, the fronto-executive system. For example, the ascending 5-HT system receives descending inputs from the medial PFC of the rat that signal stressor controllability. Without this signal, controllable stress, like uncontrollable stress causes dysregulation of the 5-HT system. Similar control principles may thus apply to NA (Amat et al 2005; Arnsten and Goldman-Rakic 1984; Jodo et al. 1998), DA, and acetylcholine (Gaykema et al. 1991) as the PFC also sends descending projections to each of these modulatory systems, although possibly from different regions of PFC. For example, the fact that the midbrain DA neurons are responsive to reward contingencies (Mirenowicz and Schultz 1994; Hollerman and Schultz 1998) suggests that the relevant

Table 1
Effects of monoaminergic and cholinergic manipulations of PFC on attentional set formation (IDS) or shifting (EDS), and reversal learning in animals.

Experimental procedure	CNS location and neurotransmitter	Animal species	Attentional set-shifting task	Reversal	Reference
Intra-PFC 6-OHDA infusions	Global PFC DA depletions	Marmoset	Enhanced set-shifting	No effect	Roberts et al. 1994
Intra-PFC 6-OHDA infusions	Global PFC DA depletions	Marmoset	Impaired acquisition of an attentional set	—	Crofts et al. 2001
Peripheral injection of tolcapone, a COMT inhibitor	Elevations in stimulated DA release in medial PFC	Rat	Enhanced set-shifting	No effect	Tunbridge et al. 2004
Intra-OFC 6-OHDA infusions	OFC DA depletions	Marmoset	—	No effect	Clarke et al. 2006
Peripheral injection of atipamezole, an α-2-adrenergic autoreceptor antagonist	Global increase in NA (behavioral effects blocked by intramedial PFC in-fusions of α-1 postsynaptic receptor antagonist)	Rat	Enhanced set-shifting	No effect	Lapiz and Morilak 2006
Subchronic peripheral treatment with the NA-reuptake blocker, desipramine	Elevations in NA in medial PFC	Rat	Enhanced set-shifting	No effect	Lapiz et al. forthcoming
Intra-medial PFC infusions of anti-DBH saporin	NA depletions in medial PFC	Rat	Impaired set-shifting	No effect	Eichenbaum et al. 2003
DNAB lesions using 6-OHDA	Cortical and subcortical NA depletions	Rat	Impaired set-shifting	No effect	Tait et al., unpublished findings
Intra-PFC 5,7 DHT infusions	Global PFC 5-HT depletions	Marmoset	No effect	Impaired reversal	Clarke et al. 2005
Intra-OFC 5,7-DHT infusions	OFC and ventrolateral 5-HT depletions	Marmoset	—	Impaired reversal	Clarke et al. 2006
NMDA-induced excitotoxic lesions of the NBM	Global PFC depletions of acetylcholine	Marmoset	No effect	Impaired reversal	Roberts et al. 1992
192-IgG saporin infusions in medial PFC	Medial PFC reductions in acetylcholine	Rat	No effect	No effect	Eichenbaum et al. 2003

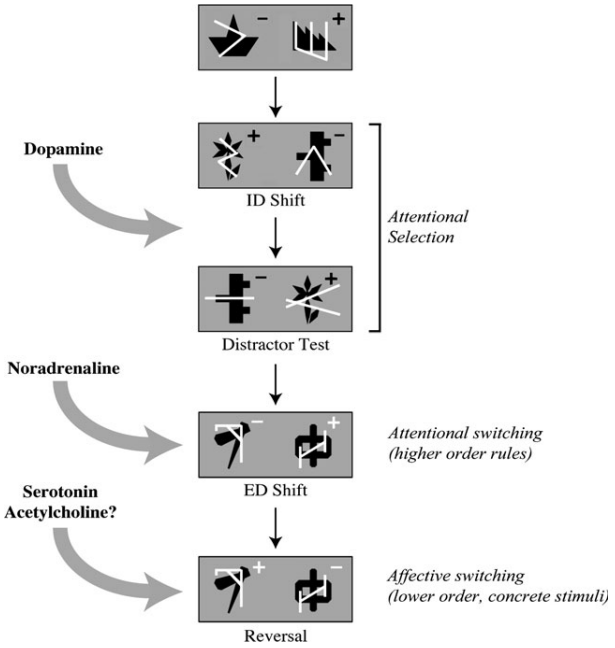

Figure 4. Differential regulation of the executive control processes (shown in italics) underlying the attentional set-shifting paradigm by DA, 5-HT, NA, and acetylcholine.

associative information may derive from processing within such limbic structures as the OFC (and the amygdala). Moreover, sensitization of the response to repeated doses of stimulant drugs depends on the influence of descending input from the PFC onto the midbrain DA neurons. NA too receives input from the PFC, both from the medial PFC and OFC (Aston-Jones and Cohen 2005), whereas the basal forebrain neurons receive inputs from the OFC (Mesulam and Mufson 1984), although the role of the PFC in modulating these latter systems is unknown.

The differential modulation of fronto-executive function by these discrete neurochemical systems highlights a degree of specificity for these "nonspecific" neuromodulatory pathways which has hitherto been underestimated. These systems interact within the PFC at the level of single pyramidal neurons but also at the level of functional modules in order to optimize overall executive control. They represent distinct arousal, attentional, and affective states and, as can be seen from the findings reviewed in this article, recruit different executive operations, for example holding information 'on-line, updating, maintaining vigilance, and response inhibition. Consistent with this is the recent finding that chronic stress in rats that causes a retraction of dendritic arbors in the medial PFC, but not lateral OFC, selectively impairs attentional set-shifting but not reversal learning (Liston et al. 2006). Top-down control by the PFC may be providing the basis of this functional differentiation; hence these neurochemical systems are recruited by the very system that they themselves are modulating and it is postulated that this interaction is essential for overall cognitive plasticity.

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