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Chemistry of the adaptive mind

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A failure to adapt to novel or changing environmental demands is a core feature of a wide variety of neuropsychiatric disorders as well as the normal states of stress and fatigue. We review the neurochemistry of cognitive control, which has been associated primarily with the prefrontal cortex. Many drugs affect the functioning of the prefrontal cortex, but the direction and extent of drug effects vary across individuals and tasks. Apparently paradoxical effects are often observed, where the same medication causes both cognitive enhancement as well as cognitive side effects. We review neurobiological research that is beginning to elucidate the nature of these contrasting effects and the factors underlying the large variability across individuals and behaviours. The work has considerable implications for the understanding of and treatment development for abnormalities such as Parkinson's disease, attention deficit hyperactivity disorder and drug addiction.

Keywords: dopamine; prefrontal cortex; drugs; cognitive enhancing effects; side effects

1. Introduction

The ability to adapt to our constantly changing environment requires the suppression of irrelevant behaviour and the selection of newly appropriate behaviour. Such adaptive behaviour necessitates a flexible mind, which maintains and updates currently relevant information and exerts top-down control over the perception of incoming information and the execution of outgoing behaviour. This cognitive control is most commonly associated with the anterior pole of the brain, the prefrontal cortex (PFC) (Fuster 1989; Miller & Cohen 2001; Chao & Knight 1995). The PFC is highly sensitive to its neurochemical environment, which is not surprising given diffuse ascending inputs from the major neurochemical systems of dopamine (DA), noradrenaline (NA), serotonin (5-HT) and acetylcholine (Robbins 2000). These neurotransmitters are of fundamental importance to the aetiology of neuropsychiatric abnormalities such as Parkinson's disease, attention deficit hyperactivity disorder (ADHD) and drug addiction. A core deficit in many of these disorders is the failure to regulate behaviour in response to changing environmental demands, leading to inflexibility, impulsivity and/or compulsivity. Drug-induced failures of mental processing occur

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not only in neurochemical disorders or after extended drug abuse. Prolonged or severe periods of stress and fatigue also lead the mind to be inflexible or unfocused. Accumulating evidence from research with monkeys has revealed that one particular family of neurotransmitters, the catecholamines (DA and NA), plays an important role in these normal states (Arnsten 1998). A better understanding of the neurochemistry of prefrontal function will advance not only the treatment development for and understanding of the abnormal mind but also that of the usually adaptive, but at times inflexible, unfocused healthy mind.

2. Chaos in the chemistry of mind?

Stress is not always disadvantageous. A limited amount of stress can improve performance, at least in some people on some tasks. These variable effects of stress are paralleled by apparently paradoxical effects of drug administration. One example of such a paradox concerns the stimulating effects of drugs like methylphenidate (Ritalin) and amphetamine that potentiate neurotransmission of DA and NA. While they are generally thought to stimulate behaviour, they certainly do not stimulate all behaviours (Dews 1958). In fact, in children with (and without) ADHD, the drugs have calming effects on hyperactivity (Rapoport *et al.* 1980). By contrast, stimulant drugs increase activity in adults (Rapoport *et al.* 1980) and help fatigued or sleep-deprived people by energizing behaviour (Koelega 1993). Moreover, while methylphenidate and other DA-enhancing drugs can impair attention and cognition in high-functioning healthy volunteers (Kimberg *et al.* 1997; Elliott *et al.* 1997; Mehta *et al.* 2004*a*), they can improve complex cognition in children with ADHD and patients with traumatic brain injury (McDowell *et al.* 1998; Kempton *et al.* 1999). Increases in vigilance in response to stimulant drugs are not restricted to the fatigued (Koelega 1993) and, conversely, decreases in hyperactivity and improvements in cognition are not restricted to children with ADHD (Rapoport *et al.* 1980). At first sight, the behavioural effects of many drugs appear unpredictable.

However, the relationship between neurotransmission and behaviour is clearly not random. Wilder (1957, 1962) first observed that (the intensity and direction of) drug effects on blood pressure and pulse rate depend on the pre-experimental level of the function tested ('law of initial value'). Discoveries that methamphetamine in pigeons *reduced high* rates of responding but *increased low* rates of responding led to the notion that drug effects on motor activity can also be predicted partly from the initial state of the system (Dews 1958). The wide variety of factors affecting the initial state of 'the system' is now beginning to be elucidated. In this paper we highlight the following points. First, drugs act on neurochemical systems with optimal levels of (neurotransmitter) activity, where too much as well as too little activity impairs behaviour. Second, different behaviours implicate separate brain systems and the optimal range of neurotransmission varies from system to system. Finally, there is large individual variation in the basal level of activity in the various systems, which may arise from genetic predispositions. While appreciating that PFC function implicates other neurotransmitters, we have focused on the role of DA, primarily because PFC function appears particularly sensitive to modulation by DA.

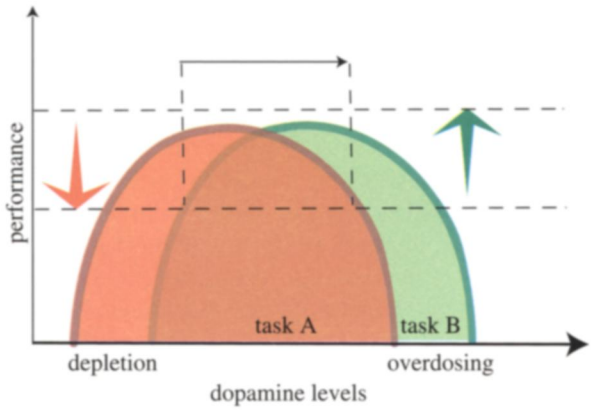

Figure 1. The relationship between cognitive performance and DA levels follows an 'inverted U-shaped' function, where both too little and too much DA impairs performance. How likely it is that a drug will cause beneficial or detrimental effects depends partly on basal DA levels. A single ⋂ curve is insufficient to predict performance: some tasks benefit from extra DA (green), while performance on other tasks is disrupted by extra DA (red). The black arrow represents the DA-enhancing effect of a hypothetical drug, leading to a beneficial effect on task B (green), but a detrimental effect on task A (red).

3. Prediction from initial conditions

The finding that the effects of stimulants depend on basal activity in the undrugged state (Dews 1958) led to the suggestion that the efficiency of stimulant treatment in ADHD is a function of motor activity in the undrugged state rather than the existence of discrete pathology (Robbins & Sahakian 1979). Indeed, stimulants are more effective in reducing hyperactivity in people with high basal levels of activity than in people with lower basal levels of activity (Rapoport *et al.* 1980; Teicher *et al.* 2003). Lyon & Robbins (1975) proposed that differences in cognitive function might underlie the rate-dependent effects observed on locomotor activity. According to this view, stimulation of catecholaminergic transmission reduces high rates of responding by progressively increasing the frequency of multiple, concurrent behaviours. This increases competition between behaviours, leading to a progressively narrow selection of the most prepotent behaviours and eventually to stereotypical, perseverative and *over-focused* behaviour. Large increases in catecholamine levels would induce impairments on certain (but not all) cognitive tasks, particularly those requiring attentional flexibility.

Findings from Granon *et al.* (2000) have shown that drug effects on cognitive function also depend on initial conditions. These authors administered a DA D1 receptor *agonist* (i.e. a compound that acts on the D1 receptor to produce similar effects to natural DA) and observed enhanced performance on a task of attention in rats with poor performance in the undrugged state, but not in rats with good performance. Conversely, a DA D1 receptor *antagonist* (i.e. a compound that blocks a receptor thereby preventing an agonist from eliciting a physiological response) impaired performance only in rats with high (but not low) basal performance levels. Similarly, in humans, administration of a DA D2 receptor agonist (bromocriptine) enhanced complex cognitive functioning in subjects with low basal memory capacity, but, conversely, impaired performance in subjects with high basal memory capacity

(Kimberg *et al.* 1997). In a different study, memory effects of methylphenidate in healthy volunteers correlated with the basal performance on that memory task in the undrugged state (Mehta *et al.* 2000), so that greater improvement was observed in subjects with lower basal memory capacity. Thus, effects of dopaminergic drugs on cognitive function can, at least partly, be predicted from initial conditions in both animals and humans. An important clinical implication is that, while low levels of performance due to psychopathology are likely to be remedied by drug therapy, conversely, the same drugs worsen already-optimized performance in healthy people. Accumulating research now indicates that the differences in basal activity of the system might reflect quantitative variations in neurotransmitter function (Mattay *et al.* 2003; Phillips *et al.* 2004).

4. The optimal state of mind

Too little DA is sub-optimal for several cognitive functions, including working memory, which is defined as the ability to maintain and update currently relevant information 'in mind' during a short delay (Baddeley 1992). A classical working memory test is the delayed response task, in which subjects are presented with a stimulus that is followed by a delay, during which maintenance of the stimulus and its protection against interference are required. In 1979, a landmark study by Brozoski *et al.* revealed that DA and NA depletion in the PFC caused severe working memory impairment in monkeys (Brozoski *et al.* 1979). Subsequent work in both animals and humans has substantiated the necessity of DA for working memory (Sawaguchi *et al.* 1990; Luciana *et al.* 1992) as well as other cognitive functions such as future planning and cognitive flexibility (Elliott *et al.* 1997; Rogers *et al.* 1999).

A complex 'inverted U-shaped' relationship exists between cognitive performance and DA, whereby excessive as well as insufficient DA levels impair working memory performance (Arnsten 1998; Zahrt *et al.* 1997; Williams & Goldman-Rakic 1995; see also figure 1). For example, using microdialysis in rats, Phillips *et al.* (2004) have shown that poor performance on a difficult (working) memory task (with a long delay) accompanied low *in vivo* DA levels in the PFC, while good performance on an easy task (with a shorter delay) accompanied high levels of PFC DA. Furthermore, a DA D1 receptor agonist improved poor performance on the difficult task, but impaired good performance on the easy task (Floresco & Phillips 2001). Therefore, this study provided direct evidence for the hypothesis that the dependency of drug effects on initial performance reflects differences in basal DA levels. In both monkeys and rats the impairments following DA-enhancing drugs have been characterized as perseverative, such that the animal repeats the previous response inappropriately (Zahrt *et al.* 1997; Druzin *et al.* 2000; Floresco & Phillips 2001).

The principle of 'inverted U-shaped' relationships between DA and cognition is reminiscent of findings reported by Yerkes & Dodson (1908). They observed, in animals, that small increases in stress improved performance on a learning task, but that on the same task large increases of stress impaired performance. Critical for the current paper, (uncontrollable) stress induced large increases in DA release in the PFC (Thierry *et al.* 1976). Furthermore, pre-treatment with DA receptor antagonists prevented stress-induced cognitive impairment (Arnsten 1998). Thus, cognitive impairment following stress results from excessive stimulation of DA receptors in the PFC.

Several authors have criticized the Yerkes–Dodson principle. For example, regression-to-the-mean effects have been suggested to account for the baseline-dependent effects, the independent variable (stress) is ambiguous and limited evidence exists for multiple points on the curve. However, these criticisms of baseline-dependent effects have been discussed and rejected several times previously (see, for example, Robbins & Everitt 1987; Robbins & Sahakian 1979; Teicher *et al.* 2003). The methods of psychopharmacology have enabled better tests of the principle, for example, by variations of dose and the use of control vehicle (or placebo) infusions. Thus, Arnsten (1998) has presented evidence for several points on the 'inverted-U shaped' function. Furthermore, administration of control substances has allowed the quantification and elimination of regression-to-the-mean effects as viable explanations of data such as those obtained by Granon *et al.* (2000). Specifically, if regression-to-the-mean was sufficient to explain the baseline-dependent effect, then placebo treatment should be equally efficacious as stimulant treatment. In fact, the low-performing rats in the Granon *et al.* study never attained the high level of performance under placebo alone. Moreover, Teicher *et al.* (2003) recently used a highly repeatable test procedure and showed that high, but not sub-therapeutic, doses of methylphenidate produced rate-dependent effects on attention significantly greater than what could be attributable to a regression-to-the-mean artefact.

5. Chemical selection of mind set

The findings from Yerkes & Dodson (1908) suggested that the optimum level of stress decreases with increasing task difficulty. Indeed, the detrimental effects of stress (and excessive DA) are particularly apparent on complex PFC functions, while other, perhaps more primitive, functions associated with the amygdala and posterior cortex are improved during stressful periods (Arnsten 1998). Recent work has highlighted that, rather than task difficulty, the particular cognitive demands and their associated neural circuitry may be the critical determinants of where the optimal DA level is set for the task under study.

In marmosets, DA depletion in the PFC impaired performance on a delayed response task with high demands for maintenance of information (Collins *et al.* 1998). Conversely, PFC DA depletion improved performance on attentional set-shifting, requiring the ability to alter behaviour according to changes in dimensional relevance of multidimensional stimuli (figure 2) (Roberts *et al.* 1994). The improved set-shifting was subsequently accounted for by enhanced distractibility during early learning stages of the task, with the result that it was easier to shift when the rule changed (Crofts *et al.* 2001). Enhanced distractibility might well underlie the impairment on the delayed-response task. Thus, there may be different optimum levels of DA for different forms of cognitive processing: whereas certain levels of DA optimize the maintenance of task-relevant representations, other levels of DA optimize the flexible updating of information in the PFC. In humans, administration of the DA D2-receptor agonist bromocriptine to healthy volunteers improved performance on a spatial memory task, but impaired performance on a task of reversal shifting according to changes in reward values (figure 2) (Mehta *et al.* 2001). While spatial memory implicates the more (dorsal) lateral portions of the PFC, reversal learning implicates more ventral portions of the PFC (figure 3*b*) (Jonides *et al.* 1993; Dias *et al.* 1996). These associations with distinct neural systems might be relevant for

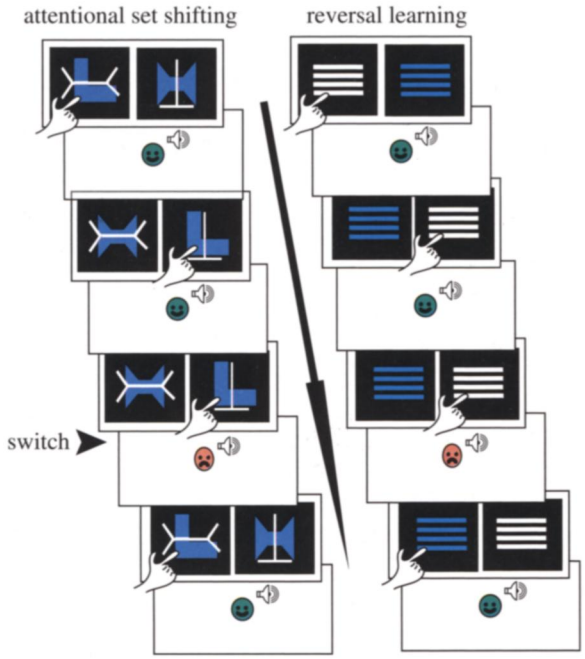

Figure 2. Tasks of cognitive flexibility. Two forms can be distinguished. *Attentional set shifting* requires subjects to shift attention between two dimensions (discrete sets of stimulus features that can be categorized as such) of multidimensional stimuli (akin to 'Wisconsin card sorting test' shifting). In this example (reproduced with permission from Crofts *et al.* (2001)), subjects learn on the basis of feedback (faces and tones) that one of the two blue shapes is correct. The dimension 'white lines' is irrelevant. Subsequently, the dimensional rule changes and subjects have to stop responding according to 'shape' and learn that one of the lines is correct. The dimension 'shape' has become irrelevant. Normal animals (and humans) perform more poorly when shifting between 'shapes' and 'lines' than between different shapes, evidencing the existence of an attentional set at the level of dimensions (Roberts *et al.* 1988). *Reversal learning* requires subjects to learn that one of two stimuli is correct, based on feedback, and subsequently to shift their response from the previously rewarded stimulus to the previously non-rewarded but now correct stimulus.

understanding the differential drug effects on distinct cognitive functions and support the hypothesis that distinct 'inverted U shaped' functions may exist for different neural systems.

Study of the cellular mechanisms underlying the effects of DA receptor stimulation has revealed that stimulation of D1 DA receptors increases evoked responses to signals, but suppresses or leaves unaffected spontaneous background firing, thereby altering the signal-to-noise ratio for inputs onto targets (Foote & Morrison 1987; Servan-Schreiber *et al.* 1990). Specifically, DA receptor stimulation

(i) increases the impact of the NMDA (N-methyl-D-aspartate) component of excitatory synaptic input onto PFC neurons, which is thought to be essential for the maintenance of current PFC activity (Seamans *et al.* 2001*b*);

(ii) reduces calcium currents which convey information from dendrites to cell bodies of pyramidal PFC neurons (Yang & Seamans 1996);

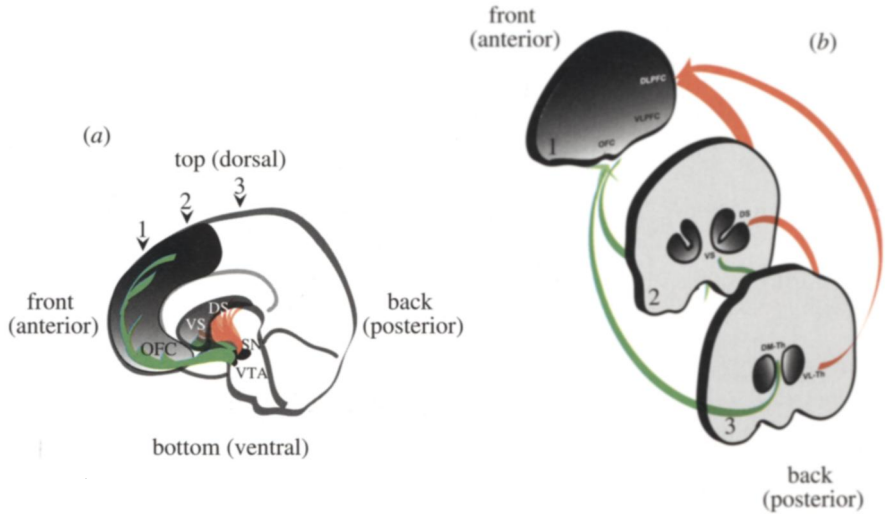

Figure 3. (*a*) Dopamine projections on the medial view of the human brain. Midbrain dopamine-containing cells project from the substantia nigra (SN) primarily to the striatum (red). Cells in the ventral tegmental area (VTA) project to the ventral striatum (VS) and the PFC (green), and other areas. In Parkinson's disease, SN cells projecting to the dorsal striatum (DS) are most vulnerable, while SN and VTA cells projecting to the VS are less vulnerable (Kish *et al.* 1988). As a result (see (*b*)), connections from the VS via the dorsomedial thalamus (DM-Th) to the orbitofrontal cortex (OFC) and ventrolateral PFC (VLPFC) are less affected than connections from the DS via the ventrolateral thalamus (VL-Th) to the dorsolateral PFC (DLPFC) (schematized with black/white gradient). (*b*) Ventral and dorsal fronto-striatal circuits. Three coronal slices through the PFC, striatum and thalamus. Numbering of slices refers to their locations in (*a*). Orientation of brains are shown by high-resolution insets.

(iii) increases the excitability of inhibitory GABA-ergic inter-neurons, thereby attenuating the strength of further excitatory input (Seamans *et al.* 2001*a*).

These cellular mechanisms lead to a 'quelling' of activity in all but the most strongly active cell assemblies and would result in a single strengthened working memory representation, resistant to subsequent inputs. Conversely, *supra-optimal* levels of DA receptor stimulation might lead to an abolition of calcium currents (Yang & Seamans 1996) and, consequently, perseveration might be observed, presumably because of a lack of new input to the PFC necessary to update currently active representations.

Computational models have contributed to the progress made in understanding the role of DA in PFC functioning (Cohen *et al.* 2002; Braver & Cohen 2000; Durstewitz *et al.* 1999). For example, early connectionist modelling by Servan-Schreiber *et al.* (1990) simulated system level function and performance on cognitive tasks by modelling DA-induced increases in the signal-to-noise ratio of neuronal activity (Foote & Morrison 1987) as a change in the slope of a sigmoidally shaped input-output function of PFC units. Models by Durstewitz *et al.* (1999) have simulated detailed biophysics of the above-mentioned and additional cellular processes, and have demonstrated that (simulated) enhanced DA increases the stability of PFC representations by increasing the resistance to susceptibility from distractors. In keeping with empirical data (Sawaguchi *et al.* 1990; Muller *et al.* 1998), the various models focus on the effects of long-acting (tonic) DA D1-receptor stimulation (see also Dreher *et al.* 2002).

More recent computational work has emphasized the role of short-latency, spike-dependent (phasic as opposed to tonic) DA responses in updating PFC representations. DA neurons are well known to exhibit transient (phasic) burst responses to salient stimuli, which predict upcoming rewards (Schultz 2002). Braver & Cohen (2000) have hypothesized that these DA bursts signal the need for updating of PFC representations, by *gating* afferent input at the precise time of its presentation. The phasic and tonic modes of DA action were recently proposed to be antagonistic (Grace 1995), to be mediated by the DA D2 and D1 receptors, respectively, and to serve the opposing computations of updating versus maintenance of PFC representations (Cohen *et al.* 2002). Unlike D1-receptor activation, D2-receptor activation decreases NMDA-mediated excitatory PFC input as well as interneuron excitability (Seamans *et al.* 2001*a*; Cohen *et al.* 2002). Thus, low D2-receptor stimulation and high tonic (PFC) DA action at D1 receptors would result in enhanced maintenance but impaired updating, while high D2- and low D1-receptor stimulation would lead to flexible but unstable representations easily degradable by intervening distractors (Cohen *et al.* 2002). D2 receptors, unlike D1 receptors, are more abundant in the striatum than the PFC (Camps *et al.* 1989) and thus the striatum may be well suited to serve the gating mechanisms that updates PFC representations.

Observations from studies with marmosets are consistent with this proposal (Crofts *et al.* 2001). In contrast to the increased distractibility and the maintenance impairment in the attentional set-shifting paradigm observed following 6-OHDA lesions of the PFC (see above), DA lesions from the striatum in marmosets induced a greater focusing on the relevant perceptual dimension during the maintenance of an attentional set within the same paradigm (Crofts *et al.* 2001). Animals with striatal DA lesions were significantly less distractible than control monkeys. These opposing effects of striatal and frontal 6-OHDA lesions underline the possible competition and co-ordination between the PFC and the striatum (Pycock *et al.* 1980).

The hypothesis that D2-receptor stimulation is important for updating while antagonizing maintenance is also corroborated by findings from Mehta *et al.* (2004*a*), who showed that the DA D2-receptor antagonist sulpiride (shown to modulate brain activity in the striatum (Mehta *et al.* 2003)) improved performance on a delayed response task that required the maintenance of information in the face of task-irrelevant distraction, but by contrast, impaired performance on task switching.

In summary, particularly sensitive to the detrimental effects of excessive DA receptor stimulation in the PFC are somewhat complex cognitive tasks, which require attentional flexibility. Conversely, such high PFC DA levels may optimize tasks with high demands for updating. The perseverative, over-focused nature of the impairments induced by excessive DA stimulation in the PFC as well as by striatal DA depletion and the distractibility observed following PFC DA depletion can be accounted for by computational models, which suggest that action at D2 receptors subserves attentional flexibility, while action at D1 receptors facilitates attentional focusing and maintenance.

6. An overdosed mind

Much understanding of the functional role of striatal DA comes from the study of patients with Parkinson's disease (PD), characterized primarily by a severe DA depletion in the striatum (figure 3*a*). PD patients exhibit impairments on tests of cognitive

flexibility and working memory that differ subtly from those observed in patients with frontal lobe lesions (Owen *et al.* 1993). Evidence from neuropsychological studies indicates that the deficits observed on learning and working memory tasks could be at least partly accounted for by a problem with flexible shifting between certain strategies (see, for example, Sarazin *et al.* 2002; Shohamy *et al.* 2004). Performance deficits on attentional set-shifting tasks appear related to overly rigid, over-focused attention, consistent with evidence from studies with marmosets (Gauntlett-Gilbert *et al.* 1999; Crofts *et al.* 2001). Such exaggerated selective attention in subjects with predominantly striatal DA depletion contrasts with observations that subjects with primarily PFC DA depletion exhibit instability rather than inflexibility (see below and Nolan *et al.* (2004)).

Dopaminergic replacement therapy (e.g. L-Dopa) remedies some of these cognitive impairments (Lange *et al.* 1992). However, like DA-enhancing drugs in healthy volunteers, L-Dopa may cause detrimental effects on other cognitive functions (Gotham *et al.* 1988). As outlined below, we argue that a spatio-temporal progression of DA depletion in PD is at the core of the opposing effects of L-Dopa on distinct cognitive tasks, by leading to differential basal DA levels in dissociable neural systems (figure 3*b*).

The primary pathology, early in the disease, is relatively restricted to the dorsal parts of the striatum and progresses later to the ventral parts of the striatum (Kish *et al.* 1988). The dorsal and ventral striatum are strongly connected to, respectively, the dorsal and the ventral parts of the PFC in relatively segregated fronto-striatal circuits (figure 3*b*) (Alexander *et al.* 1986). Gotham *et al.* (1988) proposed that medication doses necessary to ameliorate the DA lack in severely depleted brain areas may 'overdose' any area where DA levels are relatively normal. Evidence for this hypothesis came from a study by Swainson *et al.* (2000), who showed that, relative to never-medicated patients, medicated patients were impaired on 'affective' reversal shifting when reward values changed, which has been associated with the ventral striatum and the ventral PFC (Divac *et al.* 1967; Iversen & Mishkin 1970; Dias *et al.* 1996; Cools *et al.* 2002*a*; Fellows & Farah 2003). The deficits in reversal learning correlated with the medication dose. Additional support for this 'overdose' hypothesis was obtained from studies employing controlled L-Dopa-withdrawal procedures, in which patients with mild disability were asked to abstain from their L-Dopa for at least 18 h prior to the assessment, while they took their medication as usual on another occasion. Patients were tested on different cognitive tasks, associated with distinct fronto-striatal circuitry (Cools *et al.* 2001, 2003). Medication withdrawal had contrasting effects on these tasks. Patients 'on' medication performed significantly better than patients 'off' medication on a task-switching paradigm, which measures rapid switching between two well-learnt tasks: letter naming and number naming (Rogers *et al.* 1998). Functional imaging studies and studies with patients have revealed that task switching is associated with the lateral PFC (Sohn *et al.* 2000; Aron *et al.* 2004). This area is strongly connected to the dorsolateral striatum (Alexander *et al.* 1986), which is severely depleted in PD. The beneficial effect of medication on task switching was hypothesized to result from a remediation of DA levels in severely depleted fronto-striatal circuitry. In contrast, patients 'on' medication performed more poorly than patients 'off' medication on reversal shifting according to changes in reward values, associated with ventral fronto-striatal circuitry. This detrimental effect of L-Dopa was presumed to reflect 'overdosing' of DA

levels in relatively intact brain regions. A second withdrawal study revealed that L-Dopa induced abnormally fast (impulsive) responses when placing bets in a gambling task, which has also been associated with the ventral PFC (Rogers *et al.* 1999). By contrast, the same L-Dopa medication alleviated the task-switching deficit as previous (Cools *et al.* 2003). Together, these results suggest that L-Dopa can improve or impair mental flexibility as a function of task demands, as predicted by the Yerkes–Dodson principle. However, the improved tasks were not easier than the impaired tasks. Rather than differences in task difficulty, differences in basal DA levels in dissociable (dorsal versus ventral) neural systems may account for the contrasting effects of DA.

7. Localizing drug effects

One approach to assessing more directly in humans at which neural locus DA exerts its effects on cognition is to combine psychopharmacology with functional brain imaging. Two recent datasets revealed that medication withdrawal in PD patients increased brain activity in the dorsolateral PFC during working memory performance (Cools *et al.* 2002*b*; Mattay *et al.* 2002). In both studies, the increase in brain activity following withdrawal correlated with impairment in performance. This correlation strengthened the hypothesis that the alleviating effect of DA in PD involves circuitry connecting to the dorsolateral PFC. Medication withdrawal induced the opposite effect, i.e. decreased brain activity in other areas during sensori-motor control tasks. The findings in PD patients are consistent with a pharmacological imaging study in healthy volunteers (Mehta *et al.* 2000), which revealed that *improvements* in working memory, following methylphenidate, co-occurred with *reductions* in blood flow in the dorsolateral PFC. Other brain regions that were activated by the task were not affected by the drug. These findings have been interpreted to reflect a DA-induced increase in 'efficiency' (or signal-to-noise ratio) of neuronal response within the PFC (Foote & Morrison 1987) such that better performance requires less recruitment of PFC or reflects enhanced focusing of PFC neuronal activity.

We have also assessed the neural mechanisms underlying performance on reversal learning, which was impaired following L-Dopa in PD patients as well as bromocriptine in healthy volunteers (Mehta *et al.* 2001). Consistent with studies in animals and humans with frontal lobe damage (Divac *et al.* 1967; Dias *et al.* 1996; Fellows & Farah 2003), reversal learning activated the ventral PFC and the ventral striatum (Cools *et al.* 2002*a*). Preliminary data from a pharmacological functional magnetic resonance imaging (fMRI) study using the same task revealed that dopaminergic medication exerts its effect on reversal learning via modulation of the ventrolateral PFC (Clark *et al.* 2004). In this study, healthy volunteers were scanned on three occasions after intake of one of the following drugs: methylphenidate, the DA D2-receptor antagonist sulpiride or placebo. The pharmacological opponents sulpiride and methylphenidate reduced the BOLD signal during reversal learning in the left ventrolateral PFC to similar extent. While the reversal learning task activated both left and right PFC, the drug only modulated the left PFC and the effects were specific to reversal learning such that the drugs left unaffected the BOLD response during a visual control task. Although methylphenidate and sulpiride did not impair reversal learning in this study (presumably due to extensive practice leading to a ceiling effect), together with behavioural studies, the data suggest that, in the ventrolateral

PFC, *reductions* in brain activity might be associated with a *worsening*, rather than an improvement of performance. A positive correlation between DA-induced performance change on tasks of cognitive flexibility and change in PFC activity has indeed previously been reported (Daniel *et al.* 1991). Clearly, this hypothesis contrasts with the 'efficiency' hypothesis outlined above. This controversy will be addressed below.

8. Individual differences in brain chemistry

Strong evidence for the notion that dissociable effects of dopaminergic drugs in different people depend on distinct basal levels of DA comes from pharmacogenomics research. This approach makes use of the $Val^{108/158}$Met-polymorphism in the catechol-*O*-methyltransferase (COMT) gene, by comparing people with differential activity of COMT, an enzyme that breaks down DA released into the synaptic gap. The polymorphism is thought to have regionally selective effects on the PFC as opposed to for example the striatum (Diamond *et al.* 2004). While the Met-allele is associated with low COMT activity (presumably high PFC DA function), the Val-allele is associated with high COMT activity (presumably low PFC DA function). Substantial evidence indicates that subjects with the low-enzyme Met-allele perform significantly better on tasks of cognitive flexibility and working memory than subjects with the high-enzyme Val-allele (Egan *et al.* 2001; Diamond *et al.* 2004). Nolan *et al.* (2004) recently observed that patients with schizophrenia, homozygous for the Met polymorphism for the COMT gene, showed better acquisition of an imitation rule (in their words, increased cognitive stability) but greater costs when flexible alteration was required (in their words, impaired cognitive flexibility) relative to patients, homozygous for the Val polymorphism. Performance of heterozygotes was intermediate. These findings concur with findings from studies with marmosets (Crofts *et al.* 2001) and theorizing by Cohen *et al.* (2002) that high levels of tonic DA within the PFC allow representations in the PFC to be stabilized and maintained, but not effectively updated, while low levels of (tonic) PFC DA would 'degrade' representations and leave updating and switching intact or over-reactive.

Functional imaging studies have shown that there is a relationship between the Val/Met polymorphism and brain activity in the dorsolateral PFC. During working memory tasks subjects with the low-enzyme Met-allele (presumably high DA levels) exhibit less task-related brain activity than subjects with the high-enzyme Val-allele (presumably low DA levels) (Egan *et al.* 2001; Mattay *et al.* 2003). Furthermore, recent work has revealed that dextroamphetamine reduced activity in the dorsolateral PFC during working memory performance in the Val–Val subjects (with high basal PFC activity), but conversely, enhanced PFC activity in the Met–Met subjects (with low basal PFC activity) (Mattay *et al.* 2003). These results were interpreted in terms of contrasting effects of DA on the 'efficiency' of PFC functioning during working memory. Drug administration to subjects with low basal DA levels (the Val–Val subjects) increased 'efficiency' in the dorsolateral PFC during working memory performance, presumably by shifting DA levels from the lower end of an 'inverted U-shaped' curve to a more optimal range on the 'inverted U-shaped' curve. In contrast, drug administration to subjects with high basal DA levels (the Met–Met subjects) impaired 'efficiency' in the dorsolateral PFC, presumably by shifting DA levels to supra-optimal levels on the 'inverted U-shaped' curve. Overall, these data suggest

that individual variations in the response to dopaminergic drugs depend partly on genetic variations in the COMT polymorphism, via affecting basal levels of DA.

There is controversy with regard to the relationship between performance changes and changes in PFC brain activity. On the one hand, adequate performance on tasks with high demands for cognitive flexibility appears associated with increased PFC brain activity, with greater activity presumably leading to greater flexibility or 'top-down control' over other regions (Daniel *et al.* 1991; Bishop *et al.* 2004; Clark *et al.* 2004; Mattay *et al.* 1996). On the other hand, adequate performance on tasks that emphasize the need for maintenance of information within working memory appear associated with decreased brain activity in the PFC, with reduced activity presumably leading to greater 'efficiency' and enhanced focusing of input from other brain regions to the PFC (Mehta *et al.* 2000; Cools *et al.* 2002*b*; Mattay *et al.* 2002; 2003; Rypma & D'Esposito 2000). A somewhat speculative suggestion is that a reduction of brain activity by DA, via focusing of neuronal activity in distinct dorsal and ventral PFC areas has contrasting effects on different tasks. Thus, DA-induced reductions in the dorsolateral PFC might enhance working memory performance, but reductions in the ventrolateral PFC might impair performance on tasks requiring cognitive flexibility, such as reversal learning (Daniel *et al.* 1991; Mattay *et al.* 1996; Clark *et al.* 2004). It is difficult to judge the plausibility of this hypothesis, partly because many studies that reveal drug-induced changes in brain activity do not reveal concurrent behavioural changes. While the precise interpretation of pharmacological fMRI data will clearly benefit from further advances in the understanding of the physiology underlying the BOLD signal, the existing data have contributed substantially by putting forward some, admittedly speculative, hypotheses that might challenge future research.

9. Conclusion

Behavioural adaptation to our changing environment requires our minds to be focused and flexible at the same time. The paradoxical cognitive functions of (i) persistent 'on-line' maintenance of information and (ii) flexible updating in response to novel task-relevant information are highly dependent on precisely balanced neurotransmission within the PFC and the basal ganglia and may be subserved by antagonistic modes of tonic versus phasic DA function. Many drugs can affect the functioning of the PFC, but the direction and extent of drug effects vary widely across individuals and tasks. The effects on cognitive control appear partly predictable from performance in the undrugged state, which may reflect quantitative variation in neurotransmitter function. Different cognitive functions are subserved by dissociable neural systems, which have distinct neurochemical needs, and consequently, the same drugs can have both cognitive enhancing effects and cognitive side effects. The likelihood of the side effects depends on the task under study and basal levels of DA in distinct neural circuitry, which are subject to great individual variation. Elucidating the differential drug effects at distinct loci within the PFC and basal ganglia will have substantial implication for the development of targeted pharmaco-therapies for neurochemical disorders such as ADHD, PD and drug addiction. An important direction for future research is the precise definition in both cognitive and neural terms of the detrimental 'overdose' effects of excessive DA levels. It will enhance our understanding of the likelihood that drugs will be cognitive

enhancing or cognitive impairing. Moreover, it will have considerable implication for understanding why and how certain disorders, such as schizophrenia, anxiety and post-traumatic stress disorder, are exacerbated by stress.

While we have focused on the role of DA, extensive research indicates that NA is also critical for working memory (Arnsten 1998) and both focused and flexible responding and Aston-Jones *et al.* (1999) have invoked constructs similar to the 'inverted-U-shaped' function for NA function. Like DA, NA enhances the signal-to-noise ratio of target systems, but as opposed to DA, phasic NA appears critical for focused attention, while tonic NA may subserve flexibility with excessive levels of tonic NA leading to distractibility (Aston-Jones *et al.* 1999). Furthermore, PFC function is affected by manipulation of the 5-HT system. While all these systems provide diffuse projections to large parts of the PFC and clearly interact to orchestrate integrated behaviour, comparison of relatively specific neurochemical manipulations on common cognitive paradigms has revealed differential implication in distinct mental functions (Robbins 2000). Clearly, a second important direction of future research is identification of the differential functional roles of the distinct ascending neurochemical systems. Precisely how and why these systems are different should be the primary aim of future work.

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