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Review

Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease

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Abstract

It is well recognised that patients with Parkinson's disease exhibit cognitive deficits, even in the earliest disease stages. Whereas, L-DOPA therapy in early Parkinson's disease is accepted to improve the motor symptoms, the effects on cognitive performance are more complex: both positive and negative effects have been observed. The purpose of the present article is to review the effects of L-DOPA medication in Parkinson's disease on cognitive functions in the broad domains of cognitive flexibility and working memory. The review places the effects in Parkinson's disease within a framework of evidence from studies with healthy human volunteers, rodents and non-human primates as well as computational modeling work. It is suggested that beneficial or detrimental effects of L-DOPA are observed depending on task demands and basal dopamine levels in distinct parts of the striatum. The study of the beneficial and detrimental cognitive effects of L-DOPA in Parkinson's disease has substantial implications for the understanding and treatment development of cognitive abnormalities in Parkinson's disease as well as normal health.

Keywords: Parkinson's disease; Dopamine; L-DOPA; Prefrontal cortex; Ventral striatum; Dorsal striatum; Cognitive flexibility; Stability; Learning; Reward

Contents

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterised primarily by motor symptoms such as tremor, rigidity and bradykinesia. In addition

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to an increased risk for clinical dementia and clinical depression (Brown and Marsden, 1984), non-demented and non-depressed PD patients exhibit subtle cognitive problems, even in the earliest disease stages, which predict incident pathological dementia (Woods and Troster, 2003) and quality of life (Schrag et al., 2000). These cognitive difficulties resemble, but are not identical to those observed in patients with frontal lobe damage and mainly include so-called executive deficits (Brown and Marsden, 1988a; Cooper et al., 1991; Dubois and Pillon, 1997; Lees and Smith, 1983; Owen et al., 1992, 1993; Partiot et al., 1996; Taylor and Saint-Cyr, 1995; Taylor et al., 1986). Whilst medication with L-DOPA (L-3,4-dihydroxyphenylalanine) is well known to improve the motor symptoms, effects on cognitive functions are more complex: both positive as well as negative effects have been observed. In the present article, I put forward the hypothesis that these contrasting effects of L-DOPA reflect the spatio-temporal progression of dopamine (DA) depletion, which, in the earliest disease stages, is most severe in the dorsal striatum and progresses only later to the ventral striatum (Fig. 1) (Bernheimer et al., 1973; Kish et al., 1988). In brief, L-DOPA in early PD may improve certain cognitive functions that are associated with the severely depleted dorsal striatum, whilst at the same time impairing (by 'over-dosing') other cognitive functions, associated with the relatively intact ventral striatum.

The core pathology underlying PD is degeneration of the DA cells in the midbrain, leading to severe DA depletion in the striatum (Dauer and Przedborski, 2003). Accordingly, the motor symptoms and some of the cognitive deficits may be alleviated by replenishment of striatal DA through the oral administration of the DA precursor L-DOPA or synthetic DA receptor agonists (Hornykiewicz, 1974). Surgical treatments including pallidotomy and deep brain stimulation techniques targeting the globus pallidus or the subthalamic nucleus have also been found to improve in particular the motor symptoms of the disease as well as some cognitive functions (e.g. Fukuda et al., 2002; Obeso et al., 2000). The renewed interest in the effects of surgical treatments on cognitive function is not the focus of the present article and the reader is referred to recent reviews (Morrison et al., 2004; Pillon et al., 2003).

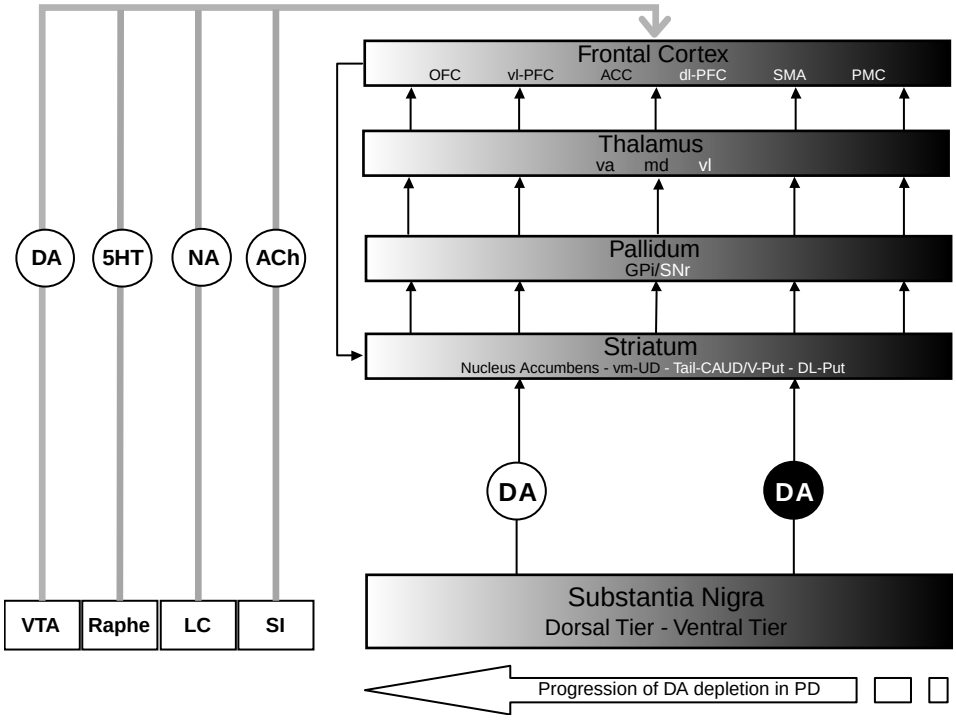

Fig. 1. Schematic to show the chemical neuropathology in PD. PD is characterised by a spatio-temporal progression of dopamine (DA) cell degeneration from the ventral tier to the dorsal tier of the midbrain, which also includes the ventral tegmental area (VTA). The black-to-white shading gradient represents the spatio-temporal progression of pathology from dorsal to ventral fronto-striatal circuitries over the course of the disease. The severely degenerated ventral tier sends DA projections primarily to the dorsal striatum, which projects to relatively restricted portions of the more dorsal and lateral parts of the prefrontal cortex (PFC) (Alexander et al., 1986). The relatively intact dorsal tier sends its DA projections primarily to the ventral striatum, which projects strongly via the output nuclei of the basal ganglia and the thalamus to medial and lateral orbitofrontal cortex (∼ventrolateral and ventromedial PFC). Abbreviations: VTA, ventral tegmental area; DA, dopamine; Raphé, dorsal and medial raphé nuclei; 5-HT, serotonin; LC, locus coeruleus; NA, noradrenaline; SI, substantia innominata; ACh, acetylcholine; vm-CAUD, ventromedial caudate nucleus; Tail-CAUD, tail of the caudate nucleus; V-Put, ventral putamen; DL-Put, dorsolateral putamen; GPi, internal segment of the globus pallidus; SNr, substantia nigra pars reticulata; va, ventral anterior nucleus; md, dorsomedial nucleus; vl, ventrolateral nucleus; OFC, orbitofrontal cortex; vl-PFC, ventrolateral PFC; ACC, anterior cingulate nucleus; dl-PFC, dorsolateral PFC; SMA, supplementary motor area; PMC, premotor cortex.

Most severe in PD is the DA cell loss in the ventrolateral tier of the substantia nigra pars compacta, which projects primarily to the dorsal striatum (i.e. the dorsolateral putamen and the dorsal parts of the caudate nucleus). The dorsal striatum in turn projects predominantly to a selective set of cortical structures, including the motor and premotor cortex, the supplementary motor area as well as the dorsolateral PFC (Fig. 1) (Alexander et al., 1986). Much less affected are cells in the dorsal tier of the midbrain, including the ventral tegmental area (VTA), which project to the ventral striatum (i.e. the ventral putamen, the ventral caudate nucleus and the nucleus accumbens). This part of the striatum is strongly connected to the amygdala, the orbitofrontal cortex (OFC), the anterior cingulate cortex and the inferotemporal cortex (Middleton and Strick, 1996; Selemon and Goldman-Rakic, 1985). Although there may be some degeneration of serotonergic cells in the dorsal raphe nucleus and cholinergic neurons in the substantia innominata (Fig. 1) (Agid et al., 1987; Paulus and Jellinger, 1991) as well as formation of Lewy Bodies (Gibb et al., 1989), these non-dopaminergic abnormalities are thought to develop only in the later stages of the disease, so that pathology is relatively restricted to DA depletion in the dorsal striatum, at least early in the course of the disease (Dauer and Przedborski, 2003; Kish et al., 1988). In the PFC, DA function is relatively unaffected early on (Agid et al., 1987) and may even be upregulated (Kaasinen et al., 2001; Rakshi et al., 1999).

L-DOPA is a widely used and effective treatment for PD and has been shown to benefit certain cognitive functions, although detrimental effects can also develop following L-DOPA therapy. In addition to the occasionally observed severely disabling side effects of psychosis and addiction (Lawrence et al., 2003), the drugs can cause subtle cognitive deficits. At first sight, the effects of L-DOPA appear unpredictable: L-DOPA impairs some, but improves other complex cognitive abilities. However, the relationship between performance and neurotransmission is clearly not random. In the present article I hope to clarify that the apparent unpredictability of the cognitive effects of L-DOPA in PD may be resolved to some extent when the functional and neural heterogeneity of complex cognitive function as well as the disease stage of patients are taken into account.

The procedure most commonly employed to assess effects of L-DOPA in PD is the controlled L-DOPA withdrawal procedure. It requires patients to abstain from their L-DOPA for a period of between 12 and 18 h prior to the neuropsychological assessment. Performance in this OFF state is compared with performance on a separate testing session during which patients take their medication as usual, the ON state. This procedure is less prone to the confounds of differences in disease severity than the alternative procedure in which procedure, performance of de novo, never-medicated patients is compared with performance of the same patients at a later stage after L-DOPA administration or of a different already-treated group.

In most reported medication withdrawal studies, at least some patients also take and withdraw from DA receptor agonists and/or catechol-*O*-methyltransferase (COMT) inhibitors in addition to their L-DOPA, suggesting that the here-reviewed effects may stem partly from withdrawal from these alternative DA enhancers. However, the drug most consistently manipulated in withdrawal studies is L-DOPA and the majority of selected patients are on L-DOPA only, partly because its shorter half-life renders L-DOPA more suitable to the withdrawal procedure than receptor agonists. Therefore, the present review is restricted to discussion of L-DOPA effects in PD. The controlled study of COMT inhibitors and DA receptor agonists, especially those with greater receptor specificity, is an important direction for future research.

Particularly vulnerable to PD are a set of complex cognitive control mechanisms, often referred to as 'executive functions', which contribute to the continuous orchestration of well-adapted habitual and goal-directed behaviour. Cognitive control mechanisms are generally accepted to comprise two mutually opponent computations: (i) the stable maintenance of cognitive representations, rendering them robust, stable and not easily degradable, even in the face of intervening distractors and (ii) the flexible alteration of these representations in response to changing environmental demands. I have chosen to restrict the review to these processes because they (i) have been examined in experimental animals and computational models, thereby directly guiding hypotheses regarding deficits in PD, (ii) are sensitive to manipulations of DA and (iii) are vulnerable in mild, early-in-the-course PD.

Much of our understanding about the role of DA in cognitive functioning has been elucidated by research with experimental animals, healthy human volunteers or computational modeling work. Therefore, the sections on L-DOPA effects in PD are preceeded by summaries of the progress made from these alternative approaches, culminating in explicit hypotheses regarding impairment in PD. Particular emphasis has been placed on functional differences between the striatum and the PFC (Bilder et al., 2004; Crofts et al., 2001; Frank et al., 2001) as well as those between the dorsal and ventral striatum (Robbins and Everitt, 1992; Voorn et al., 2004). More specifically, I suggest that the complex effects of PD and L-DOPA be understood from the perspective of the hypothesis that the striatum and the PFC play distinct roles in the plasticity and stability of cognitive representations, respectively. In addition, the dorsal and ventral striatum may subserve the plasticity of dissociable abstract, stimulus-response and more concrete, stimulus-outcome associations. Within this framework, the effects of L-DOPA in PD patients are considered. This approach highlights the consistency of behavioural patterns observed in PD patients with studies

with experimental animals, healthy human volunteers and computational modeling work.

2. Effects of dopaminergic drugs depend on individual variation in baseline dopamine function

Research with experimental animals has revealed that there is large individual variation in the extent as well as direction of drug effects. Wilder (1962) first observed that drug effects on blood pressure and pulse rate depended on the pre-experimental level of the function tested (law of initial value). Subsequent discoveries that amphetamine in pigeons reduced high rates of responding but increased low rates of responding led to the notion that drug effects on motor activity can similarly be predicted from the initial state of the system (Dews, 1958, 1977).

More recent work has shown that the cognitive effects of dopaminergic drugs also depend on baseline levels of performance in the control (un-drugged) state (Granon et al., 2000; Kimberg et al., 1997; Mehta et al., 2000, 2004a; Robbins and Sahakian, 1979). For example, administration of a DA receptor agonist (i.e. a compound that acts at the DA receptor to produce similar effects to endogenous DA) to healthy volunteers enhanced cognitive flexibility in subjects with low baseline performance, but by contrast, impaired such functioning in subjects with high baseline performance (Kimberg et al., 1997; Mehta et al., 2000). Neurobiological evidence indicates that this dependence on baseline performance reflects a dependence on baseline DA levels: low levels of DA accompany poor performance, which is generally improved by DA receptor agonists. By contrast, high levels of DA accompany good performance, which is generally impaired by DA receptor agonists (Phillips et al., 2004). Indeed, large doses of DA receptor stimulation in the PFC of rats impair performance on delayed alternation tasks and these detrimental 'over-dose' effects are absent when the animals are pre-treated with DA receptor antagonists, suggesting that both excessive and insufficient DA levels impair performance (Zahrt et al., 1997). Thus, the relationship between DA and performance follows a so-called 'Inverted-U'-shaped function (Arnsten, 1998; Williams and Goldman-Rakic, 1995). Different individuals may have different baseline levels of DA and may therefore exhibit differential sensitivity to the positive and negative effects of dopaminergic drugs.

Strong evidence for the hypothesis that dissociable effects of dopaminergic drugs in different individuals reflect distinct baseline DA levels comes from pharmacogenomics research. Weinberger and colleagues have made use of the Val$^{108/158}$Met-polymorphism in the catechol-*O*-methyltransferase (COMT) gene (Egan et al., 2001; Malhotra et al., 2002; Mattay et al., 2003), by comparing individuals with differential activity of COMT, an enzyme that breaks down DA released in the synaptic gap. COMT activity has little direct effect on DA concentrations in the striatum, where DA is submitted to rapid reuptake mechanisms via the DA transporter (DAT). Because there are fewer DATs on DA terminals in the PFC (Lewis et al., 2001), DA can diffuse out of the synaptic cleft where it is submitted to metabolism by COMT. Therefore, COMT activity and thus the phenotypic expression of the COMT polymorphism is thought to have a greater impact within the PFC. Bilder et al. (2004) proposed to interpret the effects of the COMT polymorphism on DA transmission from the perspective of the 'tonic-phasic' DA theory, put forward by Grace (1991). This theory states that DA in the striatum is regulated by two antagonistic processes: (i) high-amplitude phasic DA release induced by burst firing in DA neurons and (ii) low-level constant tonic DA maintained by baseline DA neuron firing and glutamergic afferents from cortex (Floresco et al., 2003; Grace, 1991). The high-amplitude synaptic DA release induced by bursting is rapidly removed by reuptake via the DAT before escaping the synaptic cleft. Phasic DA is not affected directly by COMT, which is thought to eliminate primarily extracellular DA. Conversely, tonic extrasynaptic DA levels are less influenced by reuptake and consequently are under greater control of metabolism by COMT. Tonic DA levels are proposed to control and thus oppose phasic DA responses via stimulation of highly sensitive autoreceptors on DA terminals, thereby maintaining a steady-state homeostasis.

The valine (Val) allele of the COMT polymorphism has been associated with higher COMT activity than the methionine (Met) allele. According to Bilder et al. (2004), this higher COMT activity would reduce DA in the PFC, which does not contain as many DATs, as well as tonic DA in the striatum, with a consequent increase in phasic DA transmission in the striatum. Thus, individuals homozygous for the Val-allele would exhibit lower extracellular (tonic) DA transmission in the PFC and the striatum, but higher phasic DA transmission in the striatum. Conversely, individuals homozygous for the Met-allele would exhibit higher extracellular DA transmission in the PFC and the striatum, but lower phasic DA transmission in the striatum.

Substantial evidence indicates that those subjects, who are homozygous for the Met-allele (high tonic, low phasic DA), perform significantly better on certain cognitive tasks than subjects with the high-enzyme Val-allele (Egan et al., 2001; Malhotra et al., 2002; Mattay et al., 2003). Moreover, amphetamine (thought to block the reuptake of DA and noradrenaline) improved performance in Val-individuals, whereas it impaired performance in Met-individuals, associated with high PFC DA levels (Mattay et al., 2003). Thus, in short, contrasting effects of dopaminergic drugs between individuals may reflect genetic variation in baseline levels of DA and therefore, in their positioning on a hypothetical 'Inverted-U'-shaped curve.

3. Individual variation in the effects of L-DOPA in Parkinson's disease

In keeping with the above-reviewed literature from studies with experimental animals and healthy human volunteers, there is large variation across individual PD patients in the cognitive response to L-DOPA medication. Controlled L-DOPA withdrawal studies have revealed that medication with L-DOPA can improve cognitive function in some patients but make them worse in others (Gotham et al., 1986). Consistent with the proposal that dissociable effects of dopaminergic drugs in different individuals reflect distinct baseline levels of performance (Kimberg et al., 1997), Gotham et al. (1986) observed a correlation between performance on a conditional associative learning task of patients in their OFF state and the change in performance on the same test after L-DOPA administration. Thus, patients who did well OFF L-DOPA were impaired after the drug, whereas those who did poorly OFF L-DOPA were improved after the drug. Gotham et al. (1988) suggested that L-DOPA doses that are necessary to remedy DA levels in the severely depleted 'motor' brain areas, such as the putamen, may detrimentally 'over-dose' other more 'cognitive' brain areas, such as the PFC or the caudate nucleus, where DA levels remain relatively intact, at least in some patients. Consistent with this so-called 'L-DOPA over-dose' model, they observed a strong correlation between performance and L-DOPA dose: the higher the dose, the more errors were made. The extent of impairment, induced by L-DOPA, would depend on individual variation in DA depletion in these 'cognitive' areas, with greater impairments in patients with less DA loss. The 'L-DOPA over-dose' hypothesis is consistent with the above-reviewed observations from genetic studies and work with experimental animals, which suggest that individual variation in drug effects may reflect individual variation in baseline levels of DA. Moreover, it concurs with the above-mentioned findings of detrimental effects on cognition of both excessive and insufficient DA levels in animals (Arnsten, 1998).

Kulisevsky et al. (Kulisevsky, 2000; Kulisevsky et al., 1996) advocated a different account of individual variation in L-DOPA effects. These authors observed that L-DOPA improved performance on a battery of cognitive tests in de novo (never-medicated) patients (Kulisevsky et al., 1998), but did not affect performance in patients with a stable response to L-DOPA. By contrast, the drug impaired performance on the same task in patients with fluctuating, 'wearing-off' motor responses to the drug. The existence of fluctuations in motor ability in response to L-DOPA was taken as evidence for greater DA cell loss and deficiency of compensatory mechanisms. The selective drug-induced deficit in patients with such fluctuations is consistent with previous observations that 'long range L-DOPA' patients, who had been receiving L-DOPA for 40 months or more, were found to perform more poorly on a set of memory tests than 'short range' patients, who had been receiving L-DOPA for 22 months or less (Halgin et al., 1977). Kulisevsky et al. (1996) interpreted their selective effect to reflect enhanced sensitivity to changes in plasma L-DOPA concentrations, possibly due to reduced storage, reuptake and regulated release mechanisms, and consequent supersensitivity of striatal neurons to DA receptor stimulation (Bedard et al., 1992; Kostrzewa et al., 2005; Gerfen, 2003). The finding that L-DOPA-induced impairment was dependent on hypothetical DA-denervation was related to findings from microdialysis studies with experimental animals showing that L-DOPA increases extracellular DA (hypothetically responsible for detrimental L-DOPA effects) to a greater extent in the DA-depleted striatum than the DA-intact striatum (Abercrombie et al., 1990; Carey et al., 1995; Miller and Abercrombie, 1999). In the current review, this alternative hypothesis is referred to as the 'DA-denervation' model of L-DOPA-induced cognitive deficit.

In the Kulisevsky et al. (1996) study, the fluctuating patients received higher doses of L-DOPA than the stable patients. Moreover, plasma L-DOPA levels peaked significantly earlier in fluctuating patients than in stable patients. Therefore, it is possible that the disproportionate drug-induced deficit in fluctuating patients relative to stable patients was due to earlier and greater L-DOPA doses rather than greater DA depletion, as predicted by Gotham et al.'s 'L-DOPA over-dose' model (Gotham et al., 1988). Similarly, the few studies that revealed selective cognitive deficits in 'long range L-DOPA' patients or 'poor responders' relative to 'short range L-DOPA' patients or 'good responders' did not actually control for the medication status of the patients and the selective deficits may therefore reflect enhanced disease severity and/or comorbidity rather than drug-induced impairment (Halgin et al., 1977; Taylor et al., 1986). The controversy with regard to individual variation in disease severity and L-DOPA-induced cognitive impairment needs to be resolved in future studies by taking into account these individual differences in DA depletion This may be done either by consideration of disease severity and the nature of the patients' (stable/fluctuating) response to medication (while holding constant L-DOPA doses/time to peak) and/or, preferably by explicitly measuring (endogenous) DA function with positron emission tomography. The two alternative models make contrasting predictions with regard to disease severity/progression of cell loss, so that the 'DA-denervation' model predicts disproportionate L-DOPA-induced impairment in clinically severely affected patients, whilst, by contrast, the 'L-DOPA over-dose' model predicts greater drug-induced deficit in mildly affected patients.

4. Effects of dopaminergic drugs vary as function of task demands and neural circuitry

Work with experimental animals and healthy human volunteers has revealed that a single 'inverted-U-shaped'

relationship between DA levels and performance is insufficient to predict performance on cognitive tasks: certain functions benefit, whilst other functions are disrupted within the same set of subjects by the same drugs. Thus, the direction and extent of dopaminergic drug effects vary not only across individuals, but also across tasks.

This variability across task demands has become particularly apparent on set-shifting and working memory tasks (Fig. 2). One reason for this large variability may stem from the fact that performance on working memory and set-shifting tasks rely differentially on the functionally opposing requirements of cognitive stability and cognitive flexibility. Whilst cognitive stability is exemplified in delayed-response tasks (Fig. 2A), which typically require the subject to hold one of more stimuli 'on-line' across a cue-probe interval, cognitive flexibility is exemplified in attentional set-shifting tasks that measure the ability to shift attention according to changes in the dimensional relevance of stimuli. The test most commonly used to examine attentional set-shifting is the Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948), which requires subjects to sort multi-dimensional cards (with attributes varying in colour, shape and number) according to one of three sorting rules. Following a certain number of consecutively correct responses, the rule is changed and the subject has to discover the new rule by trial and error. The intra-dimensional/extra-dimensional (ID/ED) set-shifting task was designed to decompose the WCST into its constituent elements, and so that it could be presented to experimental animals (Roberts et al., 1988). It enables the relatively separate investigation of the ability (i) to shift attention to the alternate exemplar following a simple stimulus-reward reversal (reversal learning) (Fig. 2C), (ii) to form and maintain an initial attentional set (intra-dimensional shifting; IDS) and finally, (iii) to shift attention between dimensions (extra-dimensional shifting; EDS) (Fig. 2B). At a first simple discrimination stage, subjects are presented with two stimuli (e.g. two shapes), and they have to discover by trial and error which of the two stimuli is correct. Following a number of consecutively correct trials, the task proceeds to the reversal stage, at which point the contingencies are reversed and subjects have to shift attention from one stimulus exemplar to the other. At the third, compound discrimination stage, a second dimension is introduced (e.g. lines), but subjects have to maintain responding to the initially correct dimension (here: shape). At the IDS stage, completely novel exemplars are introduced, but subjects have to maintain attention to the initially correct dimension (here: shape). It is only at the critical EDS stage that subjects have to shift attention from that dimension to the other dimension (here: lines). Thus, whilst delayed-response tasks require primarily cognitive stability, i.e. the ability to maintain a representation across a delay, classic attentional set-shifting tasks such as the WCST and the ID/ED shift task require both cognitive stability and flexibility. Enhanced ability to maintain representations may benefit performance

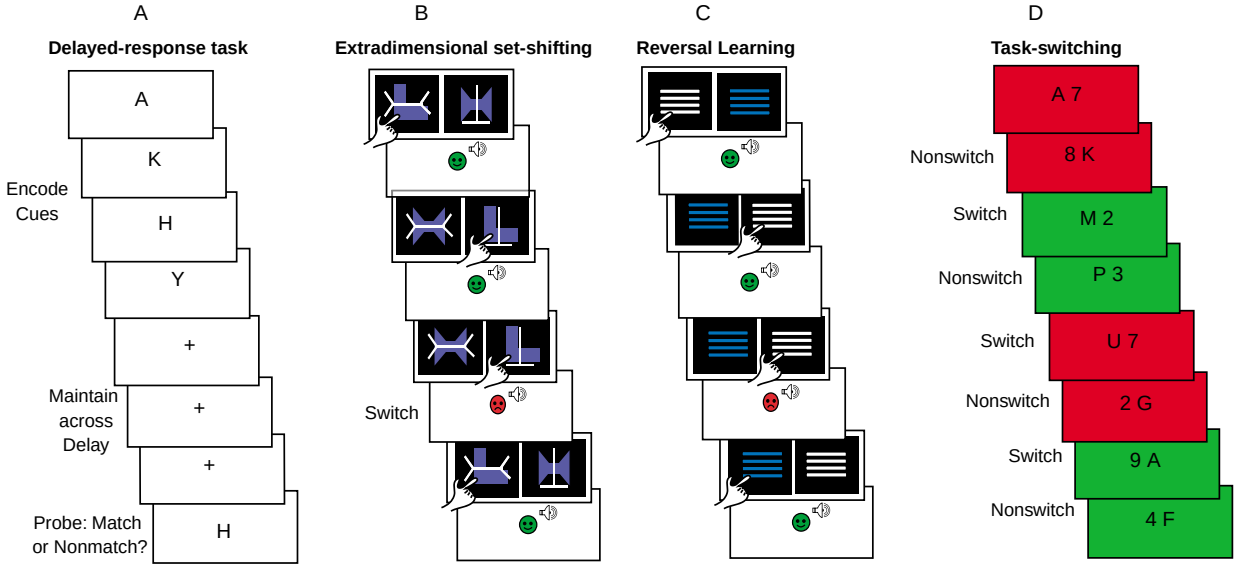

Fig. 2. Examples of tasks measuring cognitive flexibility and cognitive stability. (A) In this example of the delayed-response paradigm, subjects have to encode four cues, which they have to maintain across a delay. After the delay (e.g. 8 s), a probe stimulus is presented and subjects respond according to whether or not it matches one of the cue-stimuli. (B) In this example of extra-dimensional set-shifting, subjects are required to shift attention, on the basis of feedback, from the stimulus dimension 'shape' to the stimulus dimension 'line'. Prior to the switch, the blue L-shaped stimulus is correct, irrespective of the identity of the superimposed white line. After the switch, the horizontal white line is correct, irrespective of the identity of the blue shape. (C) In this example of reversal learning, subjects have to switch from choosing the white grating to the blue grating based on changes in stimulus-outcome values. (D) In this example of task-switching, subjects are required to name the letter or the number, presented in the centre of the screen, depending on the colour of the stimulus window. Switch costs are calculated by subtracting reaction times and error rates on non-switch trials from switch trials.

on delayed-response tasks and the early set-formation and set-maintenance stages of the classic set-shifting tasks, whereas this same ability may disrupt performance on tasks that require cognitive flexibility, i.e. the ability to flexibly alter representations. It is the opponent interaction between cognitive stability on the one hand and cognitive stability on the other hand that is proposed to underlie the existence of some paradoxical effects of dopaminergic drugs on complex cognitive tasks. For example, Mehta et al. (2004b) have shown that administration of the DA receptor antagonist sulpiride impaired set-shifting, whereas it improved working memory maintenance in the face of task-irrelevant distraction. Along similar lines, studies by McDowell et al. (1998) and Kimberg et al. (1997) have revealed a selective sensitivity to modulation by the DA receptor agonist bromocriptine of tasks requiring cognitive flexibility, such as dual-tasking and the WCST, but not simple delayed-response tasks. By contrast, a different study revealed that yet another DA receptor agonist, pergolide, modulated performance on delayed-response tasks, but left unaltered performance on a set-shifting task (Kimberg and D'Esposito, 2003).

It has recently been hypothesised that these apparently paradoxical effects across different tasks may reflect effects on dissociable neural systems with distinct optimal DA levels (Bilder et al., 2004; Cohen et al., 2002; Crofts et al., 2001; Frank et al., 2001). More specifically, while performance on tasks with high demands for cognitive stability may benefit from high DA receptor stimulation in the PFC, tasks with high demands for cognitive flexibility may benefit from high DA receptor stimulation in the striatum. Furthermore, the same high DA levels in the PFC, which are beneficial for the stability of representations, may lead to reduced ability to flexibly alter cognitive representations in response to novel stimuli. Conversely, the high DA levels in the striatum may be beneficial for the flexible alteration of cognitive representations, but at the same time may impair the ability to maintain representations in the face of intervening distractors.

DA receptors are divided into two major receptor families: the D1 and the D2 family receptors. These D1 and D2 receptors are differentially distributed across the PFC and the striatum, respectively, and the distinct DA receptor agonists used in the above-mentioned drug studies in human volunteers are known to differentially modulate these distinct DA D1 and D2 receptors. Consequently, the drugs may have acted at different neural sites: in keeping with that hypothesis, the DA D2 receptor antagonist sulpiride, which modulated flexibility, but not maintenance in the face of task-irrelevant distraction (Mehta et al., 2004b), was recently shown to modulate the striatum (Honey et al., 2003; Mehta et al., 2003). Conversely, the mixed D1/D2 receptor agonist pergolide, which modulated delayed responses but not set shifting (Kimberg and D'Esposito, 2003) may have acted primarily at the level of the PFC.

4.1. Dopamine in the prefrontal cortex drives cognitive stability

In keeping with this proposal, evidence indicates that stimulation of DA D1 receptors in the PFC alters the firing of neurons specifically engaged during the delay of delayed-response tasks (Sawaguchi et al., 1990; Wang and Goldman-Rakic, 2004; Williams and Goldman-Rakic, 1995) (Fig. 2A). Computational modeling work by Durstewitz et al. (2000) have simulated cellular effects of DA D1 receptor stimulation in the PFC (Seamans et al., 2001a,b), and have demonstrated that enhanced DA D1 receptor stimulation can increase the stability of PFC representations by increasing the resistance to susceptibility from distractors.

Models simulating the effects of DA on the maintenance of cognitive representations have generally focused on the effects of long-acting stimulation of DA D1 receptors (Cohen et al., 2002; Dreher et al., 2002; Durstewitz et al., 2000), as opposed to DA D2 receptors, and this is in keeping with recent neurophysiological evidence showing that DA agents acting at D1 but not D2 receptors modulate delay-related neuronal activity (Wang and Goldman-Rakic, 2004).

4.2. Dopamine in the striatum drives cognitive plasticity

Cohen and colleagues have suggested a complementary cognitive role for stimulation of D2 receptors, which are more abundant in the striatum than the PFC (Camps et al., 1990). Specifically, these authors have highlighted a role for phasic DA burst responses from midbrain DA neurons in the flexible adaptation of cognitive representations maintained by the PFC. Whilst phasic DA can stimulate intra-/postsynaptic D2 receptors, it has been argued to be inactivated rapidly via uptake by the DAT before it can escape the synaptic cleft (Floresco et al., 2003). Therefore, it is less likely to exert effects at D1 receptors, thought to be located mostly extrasynaptically at greater diffusional distances (Smiley et al., 1994). Stimulation of D2 receptors by phasic DA was proposed to drive plasticity by signaling the 'reward prediction error'. This term was borrowed from formal learning theory (Mackintosh, 1975; Waelti et al., 2001), according to which learning occurs only when there is discrepancy between an expected and an actual reinforcer. This discrepancy has been termed the 'reward prediction error' (Schultz and Dickinson, 2000). A positive reward prediction error occurs when a stimulus is followed unexpectedly by reward, thereby promoting new associative learning (and thus, adaptation of current representations). A negative reward prediction error occurs when a reinforcer is omitted following a stimulus which was previously associated with that reinforcer, thereby leading to extinction of the learned association (and again, adaptation of current representations). Neurophysiological studies have revealed that midbrain DA neurons signal the reward prediction error and display phasic deviations from their tonic firing rate, when a monkey is presented with an unpredicted reward or

with unpredicted reward-associated stimuli (Schultz, 2000). Furthermore, DA neuronal firing is depressed when an expected reward is omitted. Thus, phasic changes in DA signal the behavioural significance of newly relevant environmental events (Hollerman and Schultz, 1998) and may drive plasticity of existing representations.

It has been suggested that this phasic DA activity, stimulating primarily D2 receptors, may serve the mechanism by which the system updates as well as learns when to update PFC representations, which guide behaviour according to current predictions of rewards and/or goals (Braver and Cohen, 2000; Cohen et al., 2002). Adaptation of current representations occurs specifically following the presentation of newly relevant, unexpected environmental events or the omission of expected reward and thus, phasic DA responses (or dips) may reflect the need to alter current behavioural or cognitive representation in response to changes in certain goal or reward states (Horvitz, 2000; Redgrave et al., 1999).

D2 receptors, unlike D1 receptors, are more abundant in the basal ganglia than the PFC and accordingly, the basal ganglia might be well suited to serve the learning and gating mechanism for updating PFC representations. This is consistent with a model proposed by Frank et al. (2001), in which the PFC exhibits robust maintenance, while the basal ganglia serves a dynamic gating mechanism that learns when to update frontal representations in a task-relevant manner.

Support for this hypothesis was obtained by Nolan et al. (2004), who revealed that participants who were homozygous for the Met-allele of the COMT genotype, associated with increased PFC DA levels but reduced striatal phasic DA (Bilder et al., 2004), showed better acquisition of an imitation rule (in their words, increased cognitive stability) but greater costs when flexible alternation was required (impaired cognitive flexibility) relative to Val–Val participants. Further support comes from studies with marmosets by Roberts and colleagues (Collins et al., 1998, 2000; Crofts et al., 2001; Roberts et al., 1994). DA depletion in the PFC of marmosets impaired performance on a delayed-response task with high demands for maintenance of information (Fig. 2A), whilst actually improving extra-dimensional shifting on the ID/ED set-shifting task (Fig. 2B) (Collins et al., 1998; Roberts et al., 1994). Animals with PFC DA depletion made fewer errors than controls at the EDS stage of the task (Roberts et al., 1994). A follow-up study revealed that this improved performance on attentional set-shifting may have been due to a disruption in performance at the earlier set formation and maintenance (IDS) stages of the task (Crofts et al., 2001). The lesioned animals' performance was subject to increased susceptibility to distraction from variation in task-irrelevant information, which induced an apparent increased flexibility when shifting to that now newly relevant dimension. Such a failure to maintain task-relevant information in the face of distraction may well have caused the impairment on the delayed-response task (Collins et al., 1998).

Follow-up studies with marmosets have revealed that DA lesions of the striatum have effects opposite to those following DA lesions of the PFC (Crofts et al., 2001). Thus, in contrast to DA lesions of the PFC, DA lesions from the caudate nucleus in marmosets induced a greater focusing on the relevant dimension during the maintenance of an attentional set at the IDS stage of the same ID/ED paradigm. These animals with striatal DA lesions were significantly less distractible by variation in the irrelevant dimension than control monkeys, leading to the animals' responding being controlled more strongly by the currently relevant stimulus (Crofts et al., 2001). Consistent with such an overly stable attentional set following striatal DA depletion, a separate study revealed a specific impairment following 6-OHDA lesions of the caudate nucleus in marmosets in the shifting to a previously learned attentional set, although an initial EDS to a novel, not yet well-established set was unaffected (Collins et al., 2000). These findings mirror the enhanced flexibility and impaired stability reported by Nolan et al. (2004) in Val/Val individuals with presumed low PFC DA levels.

In sum, these data support the hypothesis that PFC DA optimises performance on tasks of stable maintenance, whilst striatal DA drives cognitive flexibility and suggest that distinct cognitive processes have different optimal levels of DA. It follows that the effects of dopaminergic drugs may depend on the particular task demand under study and baseline DA levels in underlying frontal versus striatal systems.

4.3. Dopamine drives stability and plasticity of multiple representations

The firing characteristics of DA neurons do not appear to differ greatly between their dorsal and ventral striatal projection sites (Schultz, 2000). However, accumulating evidence indicates that dopaminergic modulation of these respective striatal sites and their cortical connections (Fig. 1) may contribute to the adaptation of dissociable representations (Cardinal et al., 2002; O'Reilly et al., 2002).

There are currently two competing hypotheses with regard to the types of representations subserved by dorsal versus ventral frontostriatal circuitry. The first states that mechanisms of cognitive flexibility are organized according to different levels of abstraction. This proposal is largely based on a lesion study in marmosets, which revealed that lesions of the lateral PFC (which is connected strongly to the dorsal striatum) disrupted ED set-shifting between abstract stimulus dimensions, while lesions of the ventral OFC (which is connected strongly to the ventral striatum) disrupted reversal learning between concrete stimulus exemplars (Dias et al., 1996). Consequently, Roberts and Wallis (2000) have proposed that the lateral PFC is involved in the control of abstract rules, whereas the OFC is involved

in the control of concrete rules. On the basis of the same data, O'Reilly et al. (2002) have hypothesized that abstract dimensional information is encoded in dorsolateral PFC, whereas specific featural information is encoded in OFC. Three recent functional imaging studies compared attentional shifting between concrete stimulus exemplars with attentional shifting between abstract dimensions or task-rules (Cools et al., 2004; Nagahama et al., 2001; Rogers et al., 2000) and provided partial support for the hypothesis that frontostriatal mechanisms of cognitive control may be organised according to distinct levels of abstraction. Specifically, both Rogers et al. (2000) and Nagahama et al. (2001) revealed greater activity in dorsolateral PFC, which is connected strongly to the dorsal striatum, during ED shifting than reversal learning. Moreover, both Rogers et al. (2000) and Cools et al. (2004) revealed greater activity in the ventral striatum during shifting between concrete objects/reversal learning than shifting between abstract rules/dimensions. Human functional imaging studies of object alternation that have shown selective neural activity in OFC further support the proposal that control of concrete exemplars is subserved by ventral frontostriatal circuitry (Zald et al., 2002).

An alternative hypothesis derives mainly from work with rodents, but also human functional imaging studies, and indicates distinct roles for the dorsal striatum and the ventral striatum in stimulus-response and stimulus-outcome associations, respectively (Voorn et al., 2004). The learning and adaptation of stimulus-response (S-R) 'habits' has been associated with the dorsolateral striatum (Featherstone and McDonald, 2004; Jog et al., 1999; McDonald and White, 1993; Reading et al., 1991; Yin et al., 2004). Conversely, DA projections from the VTA to the nucleus accumbens as well as the strongly connected anterior cingulate cortex have been suggested to mediate Pavlovian (stimulus-outcome; S-O) associative processes and to direct both approach and instrumental (response-outcome; R-O) behaviour (Brown and Braver, 2005; Cador et al., 1991; Cardinal et al., 2002; Robbins et al., 1989; Taylor and Robbins, 1984; Wyvell and Berridge, 2000). The anterior cingulate cortex is thought to generate the feedback-evoked error-related negativity (ERN), an electrophysiological brain potential compellingly attributed to the arrival of a negative reward prediction error signal in medial PFC signaling a valence-sensitive updating-process during learning (Holroyd and Coles, 2002; Nieuwenhuis et al., 2004). The dissociable functions of the dorsal and ventral striatum are upheld by neuroimaging studies in humans (Knutson et al., 2001; McClure et al., 2003; O'Doherty et al., 2003b, 2004; Pagnoni et al., 2002). Thus, O'Doherty et al. (2004) showed that functional imaging responses in human ventral striatum correlated significantly with the reward prediction error, mentioned above, in a Pavlovian conditioning experiment with pleasant taste rewards. Conversely, the response in the dorsal striatum correlated with the reward prediction error during instrumental conditioning where rewards depended on the response (see also Tricomi et al., 2004).

Enhanced DA neurotransmission potentiates the mechanism that contributes to the new learning of these representations. Injection of DA receptor agonists and amphetamine into the caudate nucleus of rats enhanced S-R habit learning (Packard and White, 1991), whereas augmentation of DA function within the amygdala and nucleus accumbens enhanced S-O learning (Harmer and Phillips, 1999; Hitchcott et al., 1997; van der Kooy et al., 1983). Ito and colleagues have shown that, in rats, the presentation of predicted conditioned stimuli, contingent upon certain responses and therefore assisting in the formation of habitual behaviour, induced DA release in the dorsal striatum (Ito et al., 2002). By contrast, the non-contingent presentation of unpredicted conditioned stimuli, associated with cocaine induced DA release in the nucleus accumbens (Ito et al., 2000).

In sum, different parts of the basal ganglia contribute to the adaptation of distinct abstract and/or S-R versus concrete and/or S-O representations. Furthermore, evidence implicates potentiated subcortical DA transmission in increased expression of these processes.

5. Variation in the effects of L-DOPA in PD as a function of task demands and neural circuitry

In keeping with evidence from studies with experimental animals, healthy human volunteers and computational modeling work, there is large variation in the cognitive effects of L-DOPA in PD as a function of task demands. For example, longitudinal and cross-sectional studies, which have compared de novo, never-treated patients with mild patients ON L-DOPA, have revealed significant impairments in de novo patients relative to medicated patients on tasks of attentional set-shifting (Bowen et al., 1975; Downes et al., 1989), working memory, cognitive sequencing (Cooper et al., 1992; Growdon et al., 1998) and spatial delayed memory (Swainson et al., 2000) with the greatest L-DOPA-induced improvements on tasks that were impaired most in the untreated patients (Cooper et al., 1992). By contrast, de novo patients have been observed to perform significantly better than medicated patients on probabilistic and concurrent reversal learning tasks (Swainson et al., 2000). These studies have generally found that performance was unaltered by L-DOPA on tasks of verbal memory, recognition memory and visuospatial skills (Cooper et al., 1992; Taylor et al., 1986; Whittington et al., 2000).

Controlled L-DOPA withdrawal studies have revealed beneficial effects of L-DOPA on self-ordered searching in spatial working memory, Tower of London planning, compound discrimination learning (Lange et al., 1992), dual-tasking (Fournet et al., 2000; Malapani et al., 1994), task-switching (Cools et al., 2001a, 2003; Hayes et al., 1998),

conditional associative learning (Mollion et al., 2003), feedback-based sequence learning (Shohamy et al., 2005), reordering of information within working memory (Lewis et al., 2001), *n*-back working memory (Costa et al., 2003), verbal fluency (Gotham et al., 1988) and verbal delayed memory (Mohr et al., 1987). By contrast, detrimental effects of L-DOPA have been observed on memory scanning rate in the classic Sternberg task (Poewe et al., 1991), self-ordered pointing, conditional associative learning (Gotham et al., 1986, 1988), probabilistic reversal learning (Cools et al., 2001a), extinction learning (Czernecki et al., 2002), betting strategies in a gambling task (Cools et al., 2003) and the WCST (Kulisevsky et al., 1996).

As is the case in experimental animals and healthy human volunteers, the variability across task demands has become particularly apparent on complex cognitive tasks that require cognitive flexibility and/or stability. In the present article, it is proposed that integration of these contrasting effects in PD with the above-described models may help resolve some of the apparent paradoxes seen in PD, as well as direct more clearly future experiments. To briefly summarise the above-presented models, cognitive stability is thought to benefit from increases in PFC DA transmission and reductions in phasic striatal DA transmission. By contrast, cognitive flexibility is thought to benefit from potentiated phasic striatal DA transmission and reduced DA transmission in the PFC. Furthermore, much research indicates that dorsal and ventral frontostriatal circuits contribute to the control (i.e. stability and flexibility) of distinct types of representations.

PD is characterized primarily by DA depletion in the dorsal striatum, whilst, at least in the early stages, DA function in the ventral striatum and also the PFC is relatively intact or even upregulated. The effect of L-DOPA stems mainly from its ability to elevate DA levels (Maruyama et al., 1996) in the striatum (Hornykiewicz, 1974; Lloyd et al., 1975). In fact, administration of L-DOPA to rodents generates 50–60 times more extracellular DA in the striatum than in the PFC (Carey et al., 1995). The behavioural effects of L-DOPA do not correlate with the changes in tonic, extracellular DA levels in the striatum, but have been suggested to reflect increases in spike-dependent (phasic) DA release (Harden and Grace, 1995). It seems reasonable to speculate that PD disrupts phasic DA release in the striatum (Frank et al., 2004), for example, by sensitisation (i.e. the process by which repeated stimulation of neurotransmitter receptors results in progressive enhancement of responsiveness) of somatodendritic autoreceptors (Hollerman and Grace, 1990) and that L-DOPA enhances phasic DA cell burst firing, for example, by desensitising autoreceptors (Harden and Grace, 1995).

Integration of these findings with the above-mentioned models leads to the following three predictions: (i) L-DOPA affects primarily tasks with high demands for cognitive plasticity (by modulation of phasic DA cell burst responses), (ii) L-DOPA leaves unaffected tasks with high demands for cognitive stability (associated with PFC DA), and (iii) L-DOPA improves plasticity of representations associated with the dorsal striatum, but detrimentally 'over-doses' plasticity of representations associated with the ventral striatum.

5.1. Hypothesis (i): L-DOPA in PD modulates cognitive plasticity

In keeping with the hypothesised role for striatal DA in cognitive plasticity/flexibility, a large number of studies have revealed attentional- and task-set shifting deficits in PD (Beatty and Monson, 1990; Bowen et al., 1975; Brown and Marsden, 1988c; Caltarigone et al., 1989; Canavan et al., 1989; Cools et al., 1984; Cooper et al., 1991; Dimitrov et al., 1999; Inzelberg et al., 2001; Lees and Smith, 1983; Owen et al., 1992, 1993; Paolo et al., 1995; Taylor et al., 1986; Van Spaendonck et al., 1995). Strong support for a selective set-shifting impairment (i.e. not confounded by other difficulties with working memory, learning or general cognitive slowing) comes from studies that have employed the task-switching paradigm (Fig. 2D) (Cools et al., 2001a,b, 2003; Hayes et al., 1998; Meiran et al., 2004; Pollux, 2004; Pollux and Robertson, 2002; Woodward et al., 2002). In this paradigm, the acquisition of task-sets is well learnt beforehand and switches are externally cued. The paradigm requires subjects to switch continuously between two tasks A and B and the sequence of trials (e.g. AABBAA and so on) enables the measurement of switching against a baseline of non-switching (Rogers and Monsell, 1995). The critical measure, the switch cost, is calculated by subtracting performance on non-switch trials from that on switch trials. Using such a paradigm, we have shown that mild PD patients exhibited significantly enhanced switch costs, compared with matched control subjects (Cools et al., 2001b). Moreover, the deficit was specific to certain 'cross-talk' conditions, in which stimuli primed both the relevant and the irrelevant task and thus loaded highly on selection mechanisms (replicated by Pollux, 2004 and Ravizza and Ciranni, 2002). This finding resolved contrasting results from two previous studies on task-switching in PD (Hayes et al., 1998; Rogers et al., 1998). In subsequent studies, the task-switching deficit was shown to depend on the medication status of the patients: patients OFF medication exhibited a significantly greater switching deficit than patients ON medication who performed as well as control participants (Cools et al., 2001a, 2003; Hayes et al., 1998). These findings concur with the above-described models that striatal DA depletion leads to cognitive inflexibility, which is remediated following L-DOPA therapy.

In order to compare the performance profile of PD patients more directly with that seen in animals with striatal DA depletion, researchers have employed the ID/ED set-shifting paradigm (Fig. 2B) to assess both cognitive stability (set maintenance) and flexibility (set-shifting). Whilst

several studies have revealed a specific deficit at the EDS stage of the ID/ED shifting task in mild PD patients (Cools et al., 2001a,b; Downes et al., 1989; Gauntlett-Gilbert et al., 1999), it is now clear that this EDS deficit does not depend on the L-DOPA medication status of patients (Bedard et al., 1998; Cools et al., 2001a; Gotham et al., 1988; Lewis et al., 2005; Owen et al., 1993). The lack of modulation by L-DOPA in PD of ED shifting to a novel attentional set concurs with the observation that marmosets with striatal DA lesions performed as well as sham marmosets at a first ED shift to a novel stimulus dimension (Collins et al., 2000). In the marmosets with striatal DA depletion, a set-shifting deficit emerged only when the marmosets had to shift back to the already well-established attentional set at a second EDS stage. Thus, striatal DA depletion appears to affect attentional set-shifting only when shifting to very well-established attentional sets. One explanation of the shifting-back impairment could be that shifting deficits surface only when the newly relevant (to-be-shifted to) set has to be actively suppressed at pre-shift. Indeed, the animals' responding was controlled more strongly by the currently relevant stimulus at the pre-shift stages, indicative of such excessive suppression of task-irrelevant information following DA depletion. A shift to a well-learnt set may be more sensitive to excessive suppression of irrelevant information and deficient activation of newly relevant information. This hypothesis is consistent with the observation that L-DOPA in PD benefits task-switching between well-established task-sets, but leaves unaltered attentional shifting to a novel attentional set (Cools et al., 2001a).

Two subsequent task-switching studies have manipulated the dominance of task-sets, and thereby the need to suppress and maintain them at pre-switch (non-switch) trials (Pollux and Robertson, 2002; Woodward et al., 2002). If anything, these patients found it easier to overcome previously exerted suppression and exhibited reduced set-maintenance, rather than excessive suppression of the previous set (see also Flowers and Robertson, 1985). Thus, switch costs in PD patients were enhanced rather than reduced when patients switched from a well-established task to a difficult (i.e. not well-established) task. In addition, Pollux and Robertson (2002) observed that switch costs were reduced rather than enhanced when patients had to switch from difficult to easy (i.e. well-established) task-sets. Note that the 'excessive maintenance' hypothesis would have predicted the opposite pattern of results, namely greater difficulty with switching to easy, well-established tasks. Unfortunately, both these studies failed to take the medication status of patients into account, so that it is impossible to draw conclusions regarding the L-DOPA-dependency of these effects.

In sum, it is clear that PD patients exhibit impairment on tasks measuring cognitive plasticity. Consistent with the above prediction, L-DOPA alleviates this cognitive inflexibility, but the beneficial effects of L-DOPA appear restricted to shifting to well-learnt attentional or task-sets. There is controversy with regard to the origin of the switching deficit and some work suggests that it may reflect excessive maintenance of the previously relevant task-set in the face of distraction, while other studies indicate reduced maintenance of those previous task-sets (Pollux and Robertson, 2002). Future studies should take the medication status of patients into account when attempting to address this issue, as modeling work and research with marmosets suggests that too little and too much striatal DA may have contrasting effects of the ability to maintain a set in the face of distraction (Crofts et al., 2001).

5.2. Hypothesis (ii): L-DOPA in PD does not modulate cognitive stability

Cognitive stability is exemplified in 'working memory tasks' and PD is well known to affect 'working memory'. Moreover, L-DOPA medication has been repeatedly found to alleviate the 'working memory deficit' (Costa et al., 2003; Fournet et al., 2000; Lange et al., 1992; Malapani et al., 1994; Mollion et al., 2003). Does this mean that we must reject the hypothesis that L-DOPA leaves unchanged performance on tasks with high demands for cognitive stability? No. The simplest definition of working memory is the ability to 'keep events 'in mind' for short periods of time' This has been studied most commonly with delayed-response tasks (Goldman-Rakic, 1990) and has been associated with persistent neural activity in PFC. However, during cue-probe intervals (Curtis and D'Esposito, 2003) most authors now recognize that these working memory tasks require multiple processes, including the flexible updating of currently relevant information (Braver and Cohen, 2000; Cohen et al., 2002; Curtis and D'Esposito, 2003; Goldman-Rakic, 1995). It has become clear that the requirement simply to hold spatial information 'on line' over a delay per se may not be critical to the impairment seen in PD patients on working memory tasks. The impairment on working memory tasks may rather reflect difficulty with flexibly altering representations of information in mind.

In keeping with this hypothesis, mild PD patients perform as well as healthy control subjects on simple span tasks, which require subjects simply to remember sequences of spatial locations or objects (Owen et al., 1992). This intact performance on span tasks contrasts markedly with severely impaired performance on working memory tasks that require the flexible modification and updating of information within memory, such as the spatial self-ordered search task and the Tower of London planning task, or other tasks in which performance benefits from the use of particular reorganisational strategies, such as the California Verbal Learning Test (Buytenhuijs et al., 1994; Gabrieli et al., 1996; Lewis et al., 2003a; Morris et al., 1988; Owen et al., 1992, 1995; Pillon et al., 1998; Stebbins et al., 1999). A number of recent studies have provided more direct evidence for the 'inflexible' nature of the L-DOPA-dependent working memory deficit. For example, in a study by Lewis et al.

(2003a) subjects were required simply to maintain four letters and subsequently either to retrieve the letters in the order that they were presented or alternatively, to flexibly reorder the letters according to some specified rule. A subgroup of mild PD patients exhibited a disproportionate deficit in the flexible reordering of verbal information whereas the simple maintenance and the retrieval of that information were intact (Lewis et al., 2003a). The observation that the reordering condition in the same paradigm activated selectively the caudate nucleus in a parallel functional imaging study in healthy volunteers (Lewis et al., 2004) is consistent with the hypothesis that the reordering deficit in PD reflects depletion at the level of the striatum. Gilbert et al. (2005) and Lewis et al. (2005) recently replicated the selective reordering deficit in mild PD patients. Moreover, it was shown to be L-DOPA-dependent: patients were found to perform significantly more poorly on the reordering condition when they were OFF L-DOPA compared with their ON L-DOPA state. The L-DOPA effect was significantly greater for reordering than for simple maintenance and retrieval processes, further supporting the hypothesis that the requirement to flexibly alter representations is more sensitive to L-DOPA modulation than the need to maintain information (Lewis et al., 2005). A different working memory study in PD revealed that L-DOPA alleviated impairment in the ability to perform two span-tasks simultaneously, whereas performance on single span tasks was not affected by the medication status (Fournet et al., 2000). Similar L-DOPA-induced improvements on dual tasks were observed by Malapani et al. (1994), while Costa et al. (2003) revealed L-DOPA-improvement on a set of *n*-back working memory tasks also thought to rely heavily on the flexible updating in working memory. In further support of the hypothesis that PD does not affect the maintenance of information, Ketcham et al. (2003) showed that a deficit on the pointing version of the spatial span task (measured in millimeter accuracy) in mild PD patients was not qualified by changes in memory load, such as delay or familiarity manipulations. Their data also suggest that storage capacity is intact in PD, which concurs with many previous studies employing classical span measures (Bradley et al., 1989; Cooper et al., 1991; Dalrymple-Alford et al., 1994). Interestingly, a recent study by Foltynie et al. (2004) revealed that in 288 PD patients, the COMT Met-allele, associated with increased PFC but reduced striatal phasic DA, predicted poor performance on the Tower of London planning task, which loads particularly highly on the need to update representations within working memory.

Together, these findings support the hypothesis that the DA-dependent deficit on working memory tasks in PD patients reflects difficulties with the plasticity rather than the maintenance of working memory representations, associated with striatal rather than PFC DA depletion. However, the conclusion that L-DOPA does not affect cognitive stability in working memory should be considered preliminary, mainly because most conditions measuring cognitive stability in working memory are inherently easier and therefore possibly less sensitive than other experimental conditions, including those measuring cognitive flexibility. Future research should employ more sensitive tasks to test the hypothesis that L-DOPA in mild PD leaves unaltered cognitive stability (associated with the PFC DA system), while at the same time improving the plasticity of representations in working memory (associated with the striatal phasic DA system). Good candidates for such sensitive tasks could be paradigms measuring the ability to maintain representations across a delay in the face of distracting stimuli (e.g. Miller et al., 1996).

5.3. Hypothesis (iii): L-DOPA improves dorsal, but impairs ventral striatal function: the 'L-DOPA over-dose' model

The above-reviewed studies have demonstrated that tasks with high demands for cognitive flexibility are particularly sensitive to PD and L-DOPA treatment. This dependency of cognitive flexibility on optimal DA levels is broadly consistent with both animal studies and work with healthy volunteers. However, the direction of the effects of L-DOPA treatment in PD on cognitive flexibility is less clear: both detrimental as well as beneficial effects have been observed (Cools et al., 2001a, 2003; Kulisevsky et al., 1996). Two alternative, mutually exclusive hypotheses have been raised to account for the impairing effects of L-DOPA on cognitive functions. The first 'DA-denervation' hypothesis was outlined above and states that the effects of L-DOPA are 'neuropsychologically' non-specific but depend solely on the progression of DA cell loss. Specifically, it was predicted that beneficial effects of L-DOPA are seen only in de novo patients, in whom cell loss is relatively minor. Patients with fluctuating response to L-DOPA with relatively severe DA loss would exhibit selective vulnerability to L-DOPA-induced cognitive impairment, possibly due to receptor supersensitivity, relative to stable responders, who were predicted to be insensitive to manipulations of L-DOPA.

The alternative 'L-DOPA over-dose' hypothesis was raised initially by Gotham et al. (1986, 1988), extended more recently by Swainson et al. (2000), Cools et al. (2001a, 2003), Frank (2005) and Frank et al. (2004). Gotham et al. (1986) observed that performance on word fluency tasks was impaired in patients OFF, but not ON medication. By contrast, performance on a self-ordered pointing task and an associative conditional learning task was impaired in patients ON, but not OFF medication. These authors hypothesized that L-DOPA doses necessary to remedy the DA lack in severely depleted brain areas, such as the putamen, would detrimentally 'over-dose' relatively intact brain areas, such as the PFC and caudate nucleus. Poewe et al. (1991) observed a performance pattern that was similar to that observed by Gotham et al.: mild PD patients OFF medication exhibited impaired motor speed, but more efficient memory scanning on the classic Sternberg memory

task than patients ON their medication. These authors also attributed the detrimental effect of L-DOPA to an 'over-dosing' of the PFC. However, clear reference to intact versus depleted regions in relation to their tasks was not possible in the Gotham et al. and Poewe et al. studies. From subsequent work, it has become clear that PD is characterized by selective DA depletion in the dorsal striatum, whereas DA levels in the ventral striatum are relatively intact, at least in the early stages of the disease (Kish et al., 1988). On the basis of this evidence and the hypothesis suggested by Gotham et al. (1988), it was predicted that L-DOPA doses necessary to remedy performance on tasks associated with the dorsal striatum, may impair performance on tasks associated with the ventral striatum (Cools et al., 2001a; Swainson et al., 2000).

Swainson et al. (2000) used tasks that have been differentially associated with these dissociable parts of the striatum, a spatial delayed memory task and two reversal learning tasks. Whereas, spatial delayed memory has been associated with the dorsal striatum and connected dorsolateral PFC (Levy et al., 1997), reversal learning has been linked to the ventral striatum in both monkeys (Divac et al., 1967; Stern and Passingham, 1995) and humans (Cools et al., 2002a). Their results indicated that de novo PD patients, although impaired on a spatial delayed memory task, performed significantly better on tasks of reversal learning than medicated PD patients. These findings were consistent with the 'L-DOPA over-dose' model. However, the medicated patients in this study were clinically more severely disabled than the non-medicated patients, thereby confounding the effect with disease severity. We assessed more directly whether the imbalance of DA in different parts of the striatum in PD underlies dissociable effects of L-DOPA on different cognitive tasks. To this end, we examined the effects of controlled L-DOPA withdrawal on the functioning of differentially areas in patients with PD, by studying two tasks of cognitive flexibility reliably associated with dissociable striatal areas (Cools et al., 2001a). We predicted that, whereas L-DOPA doses would remedy the severely depleted dorsal striatum, it may 'over-dose' relatively spared regions, such as the ventral striatum. Note that the 'DA-denervation' model would predict the opposite pattern of results, with greater L-DOPA-induced impairment on tasks associated with the DA-denervated dorsal striatum than on tasks associated with the DA-intact ventral striatum.

The following tasks were used. The 'probabilistic reversal learning paradigm', the same task as was used by Swainson et al. (2000) measured the capacity to alter behaviour with changing reinforcement contingencies. It required subjects to learn by trial and error which of two abstract visual patterns was correct. The task was probabilistic, so that there was a 80:20 ratio of positive:-negative feedback for the correct pattern and vice versa for the incorrect pattern. The initial acquisition stage was followed by a reversal stage in which the contingencies were suddenly reversed (Fig. 2C). As described above, such adaptation of stimulus exemplar-outcome associations has been associated with the ventral striatum and direct evidence for a key role of the ventral striatum in reversal learning comes from studies with monkeys (Annett et al., 1989; Divac et al., 1967; Stern and Passingham, 1995; Taghzouti et al., 1985) as well as human volunteers (Cools et al., 2002a, 2005). We also employed a task-switching paradigm, which required shifting between well-established abstract stimulus-response mappings (Fig. 2D). As reviewed above the adaptation of abstract stimulus-response rules has been associated with the dorsal striatum. Indeed, human functional imaging studies have revealed significant activation in the (dorso)lateral PFC as well as the dorsal striatum during task-switching (Brass et al., 2003; Meyer et al., 1998; Sohn et al., 2000), but in ventral PFC and ventral striatum during reversal learning (Cools et al., 2002a; Kringelbach and Rolls, 2003; O'Doherty et al., 2001, 2003a). Moreover, selective deficits on reversal learning tasks have been observed following lesions of the ventral PFC, both in humans and animals (Dias et al., 1996; Fellows and Farah, 2003; Hornak et al., 2004; Iversen and Mishkin, 1970; Jones and Mishkin, 1972).

Consistent with the 'L-DOPA over-dose'model, but not the 'DA-denervation' model, withdrawal of L-DOPA in PD patients impaired task-switching, associated with the dorsal striatum and connected lateral PFC structures, whereas withdrawal improved probabilistic reversal learning, associated with the ventral striatum (and connected structures) (Cools et al., 2001a). The effects were observed within the same patients and, consequently, cannot be explained by general changes in affect, arousal or motor symptoms. This also precludes Kulisevsky's proposal that the nature of the DA-ergic effect depends on the response to medication (Kulisevsky, 2000; Kulisevsky et al., 1996, 1998), an argument that is strengthened by the fact that the patient groups were well-matched for disease duration and all patients responded well to their medication. Rather, the results suggested that L-DOPA effects on cognition are task-specific and, in PD, dependent on the underlying neural substrates of the tasks (Fig. 3).

The suggestion that the L-DOPA-induced impairment on probabilistic reversal learning was a result of selective modulation of the ventral striatum (as opposed to the dorsal striatum and the ventral PFC) was recently confirmed by an event-related fMRI study in patients with mild PD (Cools et al., 2005). In this study, PD patients were scanned both ON and OFF their L-DOPA during the performance of a modified, serial version of the above probabilistic reversal learning paradigm (Cools et al., 2002a; Evers et al., 2005). Preliminary results revealed that L-DOPA abolished neural activity in the nucleus accumbens, but not the dorsal striatum or PFC, specifically during reversal learning. Thus, patients exhibited significant fMRI responses in the nucleus accumbens at the time of reversal (relative to baseline non-reversal trials) when they were OFF their L-DOPA, and this

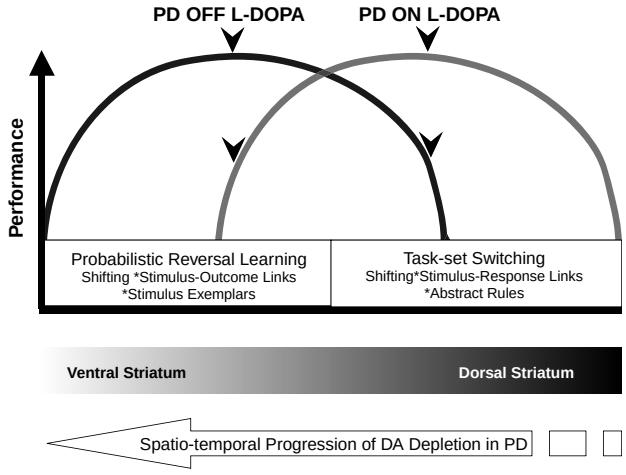

Fig. 3. Schematic of the 'L-DOPA over-dose' hypothesis in PD. See Cools et al. (2001a) for more details. The top left arrow pointing towards the top of the left (black) 'Inverted-U-shaped' curve refers to the finding that performance on the probabilistic reversal learning task, associated with the ventral striatum, is intact in patients OFF medication (PD OFF L-DOPA). The lower left arrow pointing towards the lower left half of the right (grey) 'Inverted-U-shaped' curve refers to the finding that performance on task-set switching, associated with the dorsal striatum, is impaired in the same patients OFF medication. It is hypothesised that this dissociation reflects the finding that the dopamine levels are depleted to a greater extent in the dorsal striatum compared with the ventral striatum, as shown in the bottom half of the figure. The top right arrow pointing to the top of the right (grey) 'Inverted-U-shaped' curve refers to the finding that performance is remedied on the task-switching paradigm, associated with the dorsal striatum, in patients ON medication (PD ON L-DOPA). The lower right arrow pointing to the lower right half of the left curve refers to the finding that performance is impaired, hypothetically 'over-dosed', on the probabilistic reversal learning task, associated with the ventral striatum.

reversal-related activity was at a very similar neural locus as that observed in young healthy volunteers during the same paradigm (Cools et al., 2002a). However, this reversal-related activity was abolished in the same patients when they were ON their L-DOPA.

There are a number of differences between the task-switching and probabilistic reversal learning paradigm that could account for the dissociable effects of L-DOPA. One possibility is that the double dissociation reflects the hypothetically hierarchical nature of cognitive flexibility mechanisms. Thus, task-switching requires the adaptation of abstract representations or rules applicable to multiple stimulus exemplars, whereas reversal learning requires the adaptation of associations with concrete stimulus exemplars. A considerable literature indicates that dorso-lateral frontostriatal circuitry subserves the control of abstract rule representations, whereas ventral frontostriatal circuitry may subserve that of concrete feature representations. Alternatively, the double dissociation may reflect the fact that the task-switching procedure required the adaptation of well-established stimulus-response mappings, while the reversal learning paradigm required the adaptation of stimulus-outcome mappings. The exact computational determinants of the contrasting effects of L-DOPA should be assessed in future studies.

Independent findings from other studies further strengthen the 'L-DOPA over-dose' hypothesis: administration of DA receptor agonists to healthy human volunteers, as well as animals with intact ventral striatum has been shown to impair reversal-learning performance (Jentsch et al., 2002; Mehta et al., 2001; Ridley et al., 1981; Smith et al., 1999). Czernecki et al. (2002) revealed that L-DOPA in PD patients also impaired performance on a test measuring extinction of a stimulus-reward contingency, although they failed to replicate the detrimental effect on reversal learning using a less sensitive deterministic reversal-learning task. A more recent study, employing a within-subjects design, replicated the beneficial effect of medication on task-switching, and also furthermore revealed that the detrimental 'over-dose' effect of L-DOPA extended to a decision-making task (the Cambridge gamble task; Rogers et al., 1999), which has also been associated with functioning of ventral frontostriatal circuitry (Cools et al., 2003; Rogers et al., 1999). Specifically, patients ON medication adopted a more impulsive betting strategy when placing bets, reflecting their confidence in the accuracy of their decision, than patients OFF medication. This increased impulsivity may reflect fundamental abnormalities in reward mechanisms as seen in delay aversion and may parallel the L-DOPA-induced impairment on the reversal-learning task. It may be noted that further progression of the disease leading to more extensive DA loss also in the ventral striatum is predicted to reverse the 'over-dose' effects into beneficial effects even on motivational reward-related mechanisms.

5.4. Pharmacological and functional mechanisms of over-stimulation by L-DOPA in PD

The 'over-dose' account of the contrasting medication effects is consistent with theorising regarding an 'Inverted-U'-shaped relationship between DA levels and cognitive performance, even though the precise mechanism by which L-DOPA elevates DA levels in the intact striatum is as yet unclear (Harden and Grace, 1995; Miller and Abercrombie, 1999).

After exogenous L-DOPA has penetrated the blood–brain barrier, it is converted to DA by decarboxylase, which is present both within and outside DA neurons. The L-DOPA-induced increase in extracellular DA is greater in the DA-denervated than the DA-intact striatum (Abercrombie et al., 1990; Carey et al., 1995; Kostrzewa et al., 2005; Miller and Abercrombie, 1999). This relatively larger increase in the DA-denervated striatum may reflect reduced efficiency of DA reuptake mechanisms or diminished capacity to transform L-DOPA to DA in nerve terminals (Abercrombie et al., 1990; Carey et al., 1995; Miller and Abercrombie, 1999). While increased extracellular DA in the DA-denervated striatum (converted

from L-DOPA by extracellular decarboxylase/non-dopaminergic mechanisms) can stimulate pre- and postsynaptic receptors independent of nerve impulses, L-DOPA in the DA-intact striatum is submitted to normal nerve turnover and may participate in intraneural metabolism and stimulate impulse-dependent phasic DA transmission (Miller and Abercrombie, 1999). Repeated L-DOPA was shown to increase the proportion of spontaneously active midbrain DA neurons, and was therefore hypothesised to increase spike-dependent, phasic DA release (Harden and Grace, 1995). In keeping with the hypothesis that L-DOPA modulates behaviour by changing spike-dependent, phasic DA cell bursting rather than tonic DA transmission in the striatum, there is no correlation between L-DOPA induced behavioural changes and the striatal extrasynaptic, tonic DA pool as measured with in vivo microdialysis (Harden and Grace, 1995). It was argued that autoreceptor desensitization might facilitate the effects of L-DOPA on DA cell spiking, thereby leading to the beneficial effects of L-DOPA. These beneficial effects, however, may occur at the expense of stability in the system, so that the same desensitisation may prevent normal autoreceptor inhibitory feedback regulation of excessive tonic, extraneuronal DA levels (Harden and Grace, 1995; Kostrzewa et al., 2005). In addition, L-DOPA may induce over-expression of D2-family D3 receptors in the nucleus accumbens (Bordet et al., 1997), strongly implicated in the detrimental effects of dopaminergic over-stimulation. Although it is recognised that these studies do not speak directly to the here-presented hypothesised selectivity of the 'over-dose' effect to intact striatal areas, the data do suggest that the detrimental effects of L-DOPA on functioning associated with the DA-intact ventral striatum may reflect phasic, though not tonic DA transmission. Abnormally increased phasic DA activity in the ventral striatum may hypothetically, via uncalibrated reward-prediction signals (Schultz and Dickinson, 2000), lead to over-expression and loss of plasticity of previous stimulus-reward associations following contingency reversal and thereby to the observed L-DOPA-induced reversal learning impairment.

A related proposal was put forward by Lawrence et al. (2003), who suggested that the 'DA dysregulation syndrome (DDS)' or apparent addiction to L-DOPA seen in some PD patients may be due to L-DOPA-induced motivational potentiation of stimulus-outcome associations or aberrant attribution of incentive salience to the drugs (subserved by excessive mesolimbic DA). This DDS is characterised by the compulsive intake of excessive medication doses and may result in stereotypy, impulsivity, pathological gambling and euphoria, symptoms which are similar to those observed in psychostimulant addicts. Both the selective reversal-learning impairment and the increased impulsivity following L-DOPA medication in PD patients (Cools et al., 2001a, 2003) may well also reflect over-expression of (Pavlovian) motivational, reward-related influences on behaviour.

Frank (Frank, 2005; Frank et al., 2004) recently provided a more detailed mechanistic account of the medication 'over-dose' effects. Following work from Schultz and colleagues (Schultz and Dickinson, 2000), these authors proposed that positive feedback leads to phasic DA bursts, and negative feedback to phasic DA dips. These DA bursts and dips would subsequently modify synaptic plasticity to facilitate and suppress cortical activity associated with the current response, respectively. PD was modeled as a reduction of the phasic and tonic levels of DA, whereas, conversely, the medicated PD state was assumed to enhance the tonic levels of DA, thereby preventing the phasic dips from being effective. Thus, PD would impair the 'go' learning from positive feedback, normally induced by phasic DA bursts, whilst an 'over-dose' of dopaminergic medication in ventral striatum would impair the 'no-go' learning from negative feedback, normally induced by phasic DA dips. The authors were able to simulate performance of PD patients on the probabilistic weather prediction task (Knowlton et al., 1996) as well as the detrimental effect of L-DOPA medication on the probabilistic reversal-learning task (Cools et al., 2001a; Frank, 2005). In addition, the model was able to account partially for newly acquired data on two paradigms that explicitly tested the prediction that PD patients OFF medication would display not only impaired 'go' learning from positive feedback, but also enhanced 'no-go' learning from negative feedback. Conversely, PD patients ON medication would display not only impaired 'no-go' learning from negative feedback, but also enhanced 'go' learning from positive feedback (Frank et al., 2004). The empirical data from two trial-and-error learning tasks partly supported these predictions: patients OFF medication exhibited enhanced learning from negative feedback, thus they displayed a persistent bias in favor of 'no-go' learning, whilst patients ON medication exhibited enhanced 'go' learning from positive feedback. These data certainly provides a challenge for future experiments.

The hypothesis that L-DOPA specifically impairs 'no-go' learning from negative feedback is consistent with data from Charbonneau et al. (1996) who observed a deficit in mild medicated PD patients on an instrumental (R-O) avoidance task, in which subjects had to learn to make a motor response in order to avoid an aversive stimulus (money loss). Furthermore, the earlier-mentioned feedback-based ERN, thought to reflect a negative reinforcement prediction error in the anterior cingulate cortex, was reduced in PD patients ON medication (Falkenstein et al., 2001), but unaffected in patients OFF medication (Holroyd et al., 2002), also suggesting reduced negative feedback-related processing following L-DOPA. Clearly, there are parallels between this proposal and the suggestion made above that excessive mesolimbic DA levels induce aberrant reward-related influences on behaviour. According to Frank, over-expressed reward-related 'go' influences would coexist with reduced

impact of punishment-related 'no-go' signals in patients ON medication.

Over-expressed reward-related learning mechanisms following L-DOPA may be of therapeutic benefit to patients in the form of enhanced reliance on salient, visual (reward) cues during the performance of motor or complex cognitive tasks (Brown and Marsden, 1988b; Praamstra et al., 1998). However, they may also contribute to the impulsive and compulsive behaviours observed in certain patients, particularly when aberrant reward-related learning is combined with hypothetical under-expression of punishment-related processing or 'myopia for future (losses)' (Bechara et al., 2002; Frank et al., 2004).

6. Conclusion

The present article has placed the cognitive deficits in mild PD within a framework of evidence from studies with human volunteers, rodents and non-human primates and computational modeling work. These studies have highlighted the neural heterogeneity of cognitive function, emphasising in particular the computationally opposing roles of the striatum and the PFC as well as the functional distinctions between dorsal and ventral striatum. More specifically, striatal DA is suggested to subserve the flexible updating of representations whereas prefrontal DA is implicated in the stable maintenance of representations. The computation by which DA acts across both dorsal and ventral frontostriatal systems is thought to be relatively non-specific. However, modulation of these distinct neural circuitries by DA may affect dissociable 'ventral' and 'dorsal' representations.

The cognitive profile of PD follows the spatio-temporal progression of DA depletion. In the early stages, PD is characterised primarily by severe DA depletion in the dorsal striatum. The ventral striatum is relatively intact. Accordingly, the cognitive deficits in mild PD patients are relatively restricted to functioning associated with the dorsal striatum: patients exhibit impaired adaptation of well-established (abstract) S-R mappings and reduced updating within working memory. It is proposed that these deficits may reflect disruption of a common updating mechanism subserved by phasic DA transmission in the striatum. L-DOPA, which is known to act primarily at the level of the striatum, may alleviate this cognitive inflexibility by remediating phasic DA transmission within the dorsal striatum. L-DOPA has much smaller effects on the PFC DA system, which is depleted to a lesser extent in early PD. Accordingly, L-DOPA in PD leaves unaffected performance on purely mnemonic tasks measuring the simple, though robust maintenance of information.

The L-DOPA dose that alleviates the inability to switch between well-learnt S-R mappings may impair a different form of cognitive plasticity, associated with the relatively intact ventral striatum. Thus, the L-DOPA dose that releases the patient from cognitive inflexibility and that potentiates a healthy 'go' or updating bias in dorsal striatum-dependent behaviour (Frank et al., 2004), may impair ventral striatal function, by enhancing reward-related 'go'-like biases and reducing healthy punishment-induced 'no-go'-like control of inappropriate prepotent tendencies. This 'L-DOPA over-dose' model may be distinguished from the alternative 'DA denervation' hypothesis, which states that detrimental effects of L-DOPA are 'neuropsychologically' non-specific, but which could be attributed to DA-denervation in more severely affected individuals.

7. Future directions

Future research should continue to tease apart the factors of task demands (by using paradigms expressly designed to test the here-presented hypotheses), variation in DA levels (e.g. as a function of disease severity and/or allelic variation in the COMT Val^{158}Met polymorphism) and medication status in mild PD patients. L-DOPA withdrawal experiments should be conducted in both mild and more severely affected PD patients, thus resolving the present controversy between the 'DA-denervation' model and 'L-DOPA over-dose' model.

It is recognised that the here-presented hypotheses are preliminary, particularly given the existence of strong frontostriatal connections (Alexander et al., 1986) and the resulting difficulty to tease apart completely the striatal and prefrontal origin of cognitive deficits in PD. Indeed, it has been argued that PD patients may exhibit frontal-lobe like deficits, as a consequence of abnormal outflow from the striatum, which alters the expression of PFC function (Owen et al., 1998). Neuroimaging studies in PD patients may shed further light on the locus of pathology that causes the cognitive impairments observed. Performance on a variety of cognitive tasks has been found to correlate positively with the extent of [^{18}F]-6-fluorodopa uptake, DAT activity and DA D2 receptor availability in the striatum in PD patients (Berger et al., 2004; Bruck et al., 2001; Marie et al., 1999; Muller et al., 2000), although positive correlations with prefrontal DA have also been observed (Rinne et al., 2000). Only very few studies have examined the effects of L-DOPA in PD on brain activity during the performance of complex cognitive tasks (Cools et al., 2002b; Mattay et al., 2002) and the interpretation of brain activation profiles is complicated by the potentially confounding factors of indirect effects, such as performance differences between groups as well as vascular changes induced by L-DOPA or disease pathology. Whereas, several studies in PD have revealed selective functional abnormalities in the striatum (Cools et al., 2005; Dagher et al., 2001; Owen et al., 1998), other studies in PD patients (in which L-DOPA status was not controlled) have shown altered brain activity during cognitive performance across broad frontostriatal circuitry (Dagher et al., 2001; Goerendt et al., 2004; Grossman et al., 2001; Lewis et al., 2003b; Monchi et al., 2004; Owen et al., 1998; Rowe et al.,

2002; Thiel et al., 2003). The reader is referred to recent reviews on neuroimaging studies in PD for more information (Brooks, 2003; Carbon and Marie, 2003; Owen, 2004).

The present article has focused on the nigrostriatal DA depletion, the predominant pathology in PD. Non-dopaminergic forms of pathology, including noradrenergic, serotonergic and cholinergic deafferentiation of the cortex and cortical Lewy bodies may play a significant role in some of the cognitive deficits, particularly at later stages of the disease (Bedard et al., 1998; Riekkinen et al., 1998; Van Spaendonck et al., 1993). L-DOPA affects all catecholamines including noradrenaline, which may also alter cognitive functioning (Arnsten, 1998; Coull, 1994). In addition, L-DOPA reduces the serotonin (5-HT) concentration in the brain (Batholini et al., 1968; Everett and Borcherding, 1970; Kostrzewa et al., 2005), and the opponent interaction between DA and 5-HT (Millan et al., 1998) may be significant for the precise balance between reward- versus punishment-related processing (Daw et al., 2002). It is thus recognised that L-DOPA may impair certain functioning via alternative mechanisms such as reduction of 5-HT transmission and indeed, the L-DOPA-induced impairments on reversal learning and gambling tasks resemble deficits observed following depletion of 5-HT (Clarke et al., 2004) and tryptophan, the 5-HT precursor (Park et al., 1994).

However, there are also significant differences between the effects of 5-HT depletion, noradrenaline administration and elevation of DA by L-DOPA (Robbins, 2000). Moreover, despite its additional effects on 5-HT and NA transmission, L-DOPA in PD patients elevates primarily DA levels (Maruyama et al., 1996) in the striatum (Hornykiewicz, 1974), and the most severe, although not exclusive pathology in the early stages of the disease is depletion of DA from the dorsal striatum. Therefore, the here-described effects of PD and L-DOPA medication on cognitive function are most likely due to direct effects of DA in the striatum.

Nevertheless, examination of the effects of alternate drugs, such as partial DA D3 receptor agonists (which behave as agonists or antagonists in vivo depending on the response considered (Pilla et al., 1999)) or serotonin receptor agonists (Nicholson and Brotchie, 2002) that may maximise the positive, and minimize the negative effects of L-DOPA is an additional important direction for future work.

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