Enhanced or Impaired Cognitive Function in Parkinson's Disease as a Function of Dopaminergic Medication and Task Demands

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We investigated how dopamine (DA) systems contribute to cognitive performance in the domain of learning and attentional flexibility by examining effects of withdrawing DA-ergic medication in patients with Parkinson's disease (PD). Medication remediated impairments in switching between two tasks, thought to depend on circuitry connecting the dorsolateral prefrontal cortex and the posterior parietal cortex to the dorsal caudate nucleus, which is profoundly DA-depleted in PD. By contrast, the same medication impaired probabilistic reversal learning that implicates orbitofrontal cortex–ventral striatal circuitry, which is relatively spared of DA loss in PD. Hence, DA-ergic medication improves or impairs cognitive performance depending on the nature of the task and the basal level of DA function in underlying cortico-striatal circuitry.

Introduction

The mesocorticolimbic dopamine (DA) system is known to play a role in cognitive processes of working memory (Brozoski *et al.*, 1979; Goldman-Rakic, 1992; Castner *et al.*, 2000) and reward-based learning (Hollerman and Schultz, 1998; Schultz *et al.*, 2000). Recent evidence from animal studies suggests a complex, 'inverted U' function, whereby excessive, as well as insufficient DA D1 receptor stimulation in the prefrontal cortex (PFC) impairs working memory (Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997; Arnsten, 1998). Some psychopharmacological studies in human volunteers have additionally shown differential effects of administration of DA agents depending on baseline levels of performance (Kimberg *et al.*, 1997; Mattay *et al.*, 2000; Mehta *et al.*, 2000). However, direct evidence within subjects for dose-dependent effects of DA on cognition, that is both improvement and impairment, comes exclusively from animal studies (Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997; Arnsten, 1998), partly because of the lack of selective compounds suitable for administering to human volunteers.

A different approach to addressing the role of DA in human cognition is investigating disorders that implicate the DA system. Parkinson's disease (PD), associated with nigrostriatal and mesocorticolimbic DA depletion, is accompanied by subtle cognitive impairments even in the early stages, resembling those seen in frontal lobe patients (Taylor *et al.*, 1986; Owen *et al.*, 1995). Although medication with L-Dopa, a precursor affecting primarily levels of DA (Maruyama *et al.*, 1996), ameliorates the motor symptoms in PD, effects of such medication on cognitive functioning are more complex: deleterious, as well as beneficial effects of L-Dopa have been reported (Gotham *et al.*, 1988; Kulisevsky, 1996, 2000; Swainson *et al.*, 2000). For example, Gotham *et al.* observed beneficial effects of L-Dopa on alternating fluency, but detrimental effects on conditional associative learning. They speculated that L-Dopa doses necessary to remedy the DA lack in the putamen may 'overdose' any area where DA regions are relatively intact, such as for example the PFC (Gotham *et al.*, 1988). However, the relationship between their tasks and the supposed dissociable underlying neuronal circuitry is unclear. Moreover, there was no significant difference when the 'on' and 'off' patients were compared directly, but only when the two groups were compared separately with controls.

At the time of Gotham *et al.*'s study (Gotham *et al.*, 1988), clear evidence for an imbalance in different brain regions in PD was not yet available. More recently, studies have shown that, in early PD, DA depletion is restricted to the putamen and the dorsal caudate nucleus, only later progressing to more ventral parts of the striatum and the mesocorticolimbic DA system (Kish *et al.*, 1988; Agid *et al.*, 1993). These different parts of the striatum are connected to dissociable cortical areas in relatively segregated cortico-striatal circuits (Rosvold, 1972; Alexander *et al.*, 1986) and accumulating evidence indicates that there is functional differentiation between these circuits (Dias *et al.*, 1996).

Swainson *et al.* (Swainson *et al.*, 2000) used tasks that have been differentially associated with such dissociable cortico-striatal circuitry, among others a spatial recognition memory task and two reversal learning tasks. Whereas spatial recognition memory has been associated with dorsolateral prefrontal areas (Owen *et al.*, 1996), reversal learning has been linked to ventral striatal-orbitofrontal areas in both monkeys (Divac *et al.*, 1967; Jones and Mishkin, 1972; Dias *et al.*, 1996) and humans (Rolls, 1999). Their results indicated that non-medicated PD patients, although impaired on a spatial recognition task, performed significantly better on tasks of reversal learning than medicated PD patients. It was suggested that medication doses sufficient to restore DA function in the worst affected region (the dorsal striatum) could be excessive for less affected systems (i.e. functions subserved by the ventral striatum). Thus, these findings were consistent with the 'overdose' hypothesis. However, the medicated patients in this study were clinically more severely disabled than the non-medicated patients, which forms an alternative explanation of the impairment in the medicated and more severely affected PD patients. Therefore, direct evidence for DA-dependent impairments and improvements within the same human subjects has not yet been provided.

In the current study we intended to test more directly whether the imbalance of DA in different segregated functional cortico-striatal circuitries (Alexander *et al.*, 1986) in PD underlies dissociable effects of L-Dopa on different cognitive tasks (Gotham *et al.*, 1988; Swainson *et al.*, 2000). To this end, we examined the effects of DA-ergic withdrawal on the functioning of differentially depleted areas in patients with PD, by studying three tasks of learning and cognitive flexibility that have been reliably associated with dissociable cortico-striatal circuits. We predicted that, whereas L-Dopa doses would remedy regions suffering from DA depletion, such as the putamen, the dorsal caudate nucleus and thereby its connections to the dorsolateral prefrontal cortex, it may 'overdose' relatively spared regions, such as the ventral caudate nucleus, the nucleus accumbens and

thereby its connections to the orbitofrontal cortex. This 'DA overdose hypothesis' is consistent with the above-mentioned findings of detrimental effects on cognition of both excessive and insufficient DA levels in animals (Arnsten, 1998) and also with a Yerkes–Dodson account of effects of arousal on cognitive performance (Eysenck, 1982).

The following tasks were used. The 'probabilistic reversal learning paradigm', the same task as was used by Swainson *et al*. (Swainson *et al*., 2000) measured the capacity to alter behaviour with changing reinforcement contingencies. Such stimulus–reward shifting is impaired by lesions of the orbitofrontal cortex (OFC) and the ventral striatum circuitry in both monkeys (Divac *et al*., 1967; Dias *et al*., 1996; Rolls, 1999) and humans (Rolls, 1999). The 'intra-/extra-dimensional shift (ID/ED) paradigm' measured extra-dimensional (ED) set shifting, i.e. the ability to alter behaviour according to changes in dimensional relevance of stimuli, and controlled for set formation and set maintenance abilities within the same task. Impairments in this form of higher-level attentional control have been associated with lesions of the monkey lateral PFC (Dias *et al*., 1996), with DL-PFC-striatal damage in human diseases such as PD and Huntington's disease (Downes *et al*., 1989; Lawrence *et al*., 1999) and recent brain imaging studies revealed significant activation in the DL-PFC during ED shifting (Rogers *et al*., 2000; Nagahama *et al*., 2001). Previous attempts to clarify the effect of L-Dopa on ED shifting were inconclusive because of a confounding effect on discrimination learning (in a relatively small number of severely disabled PD patients) (Lange *et al*., 1992). To avoid such confounding problems of new learning in the ID/ED paradigm, we employed a task-set switching paradigm which requires shifting between well-established stimulus–response mappings (see Fig. 1*a*). Several brain imaging studies have shown that performance of task-set switching is accompanied by activity in the DL-PFC and the posterior parietal cortex (PPC), both thought to be connected to the dorsal striatum in so-called 'cortico-striatal' loops (Meyer *et al*., 1998; MacDonald *et al*., 2000; Sohn *et al*., 2000). Thus, whereas reversal learning has been associated with OFC-ventral striatal circuitry, extra-dimensional shifting and task-set switching have been related to DL-PFC/PPC-dorsal striatal circuitry.

We predicted that DA-ergic medication in PD patients would produce beneficial effects on ED set shifting and task-set switching, but detrimental effects on probabilistic reversal learning.

Materials and methods

Subjects

These studies were approved by the Cambridge Local Research Ethics committee and all subjects gave informed consent.

Patients

Twenty-nine PD patients participated in the study. All patients presented to a general neurology clinic and were diagnosed by a consultant neurologist (R.A.B.) as having idiopathic PD according to UK PDS brain bank criteria. Patients with a significant medical history not related directly to their PD (e.g. stroke, head injury, clinical dementia or depression) were not referred for the study. Patients who scored 24 or lower on the Mini Mental State Examination (MMSE) (Folstein *et al*., 1975) were excluded. The severity of clinical symptoms was assessed according to the Hoehn and Yahr, five-point rating scale (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease (44-point) Rating Scale (UPDRS) (Fahn *et al*., 1987). Hoehn and Yahr ratings ranged between I and III. All 29 patients included in the study were receiving daily L-Dopa preparations, DA receptor agonists and/or selegiline (monoamine activity enhancer), all were stable on their medication doses for at least 3 months and responding well. Patients receiving additional medication likely to confound interpretation of the findings were excluded as far as possible. Moreover, exclusion of the three patients taking such medication (anticholinergics) did not affect the statistical significance of our findings. Fifteen out of the 29 patients were asked to abstain from their medication the night before the assessment was scheduled to take place, at least 18 h prior to the experiment. Fourteen out of the 29 patients were taking their medication as normal. Other clinical details are summarized in Table 1.

Controls

Previously collected data from age and NART IQ (Nelson, 1982) matched control subjects were used to compare performance of the patients to baseline levels. A group of 27 controls was tested on the task-set switching paradigm, a subset of 20 controls on the ID/ED shift paradigm and a different group of 23 controls was tested on the probabilistic reversal learning paradigm. There was no difference between any of the control

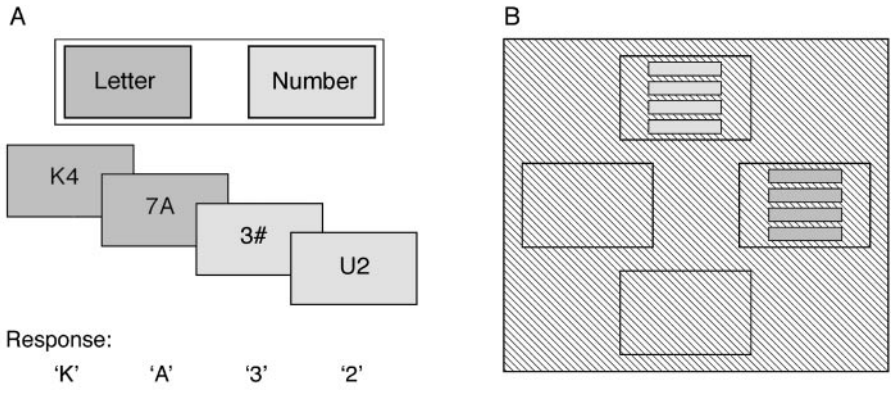

Figure 1. (*a*) The task-set switching paradigm. Cues, stimuli and required responses are shown. The colour of the stimulus-window indicates which task (naming letters or naming digits) has to be performed by the subject. A card with a green and a red rectangle with the words 'letter' and 'number' is placed beneath the computer screen to help subjects remember the colour–task associations. An example of a trial sequence in the 'crosstalk' condition is shown in the middle part of this figure. In this condition, 67% of trials include stimulus attributes associated with the irrelevant task (e.g. 'K4'). On 33% of the trials the irrelevant character is neutral (for example, '3#'). In the 'no-cross-talk' condition (not shown here) none of the stimuli include characters associated with the competing task and irrelevant characters are always non-alphanumeric. The required responses are shown in the bottom part of this figure. In this particular case the colour green is associated with naming letters and the colour red is associated with naming digits. (*b*) The probabilistic reversal paradigm. Four boxes were displayed at the top, the bottom, the left and the right of the screen. In two of the four boxes a red or green 'grating' pattern was displayed and subjects were asked to touch one of these two patterns. Each response was followed by computer feedback, consisting of both an auditory message (a high- or a low-pitch tone) and a visual message (the word 'correct' or 'wrong'). After 40 trials the contingencies were reversed.

Table 1
Clinical characteristics of the two patient groups

	n	L-Dopa dose (mg)	Duration of disease (years)	Hoehn and Yahr rating ('on')	UPDRS ('on')	Hoehn and Yahr (at time of testing)	UPDRS (at time of testing)
PD 'on'	14	482.1 (337.2)	5.7 (4.6)	1.75 (0.7)	25.2 (12.6)	1.78 (0.8)	25.7 (14.8)
PD 'off'	15	416.7 (227.3)	5.0 (3.4)	1.80 (0.6)	29.6 (10.3)	2.17 (0.8)	36.8 (13.8)[a]

Values represent mean (standard deviation). Patients 'on' DA-ergic medication (PD 'on') and patients 'off' medication (PD 'off') were well-matched in terms of L-Dopa dose, duration of disease and disease severity [as measured with the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr rating scale during the 'on' medication state]. Motor symptoms were significantly worsened after withdrawal of medication as measured with the UPDRS at the time of testing.

[a]Significantly different from PD 'on' at the 0.05 level.

groups and the two patient groups in terms of age or premorbid IQ. Other details are summarized in Table 2.

Table 2
Demographic characteristics

	n	NART IQ	Age (years)	Sex ratio (f:m)
PD 'on'	14	115.9 (7.7)	58.2 (7.9)	8:6
PD 'off'	15	115.9 (7.4)	59.0 (7.0)	5:10
CS task-switching	27	116.7 (8.2)	59.4 (9.6)	18:9
CS ID/ED	20	115.8 (8.1)	56.5 (7.9)	15:5[a]
CS reversal	23	113.2 (8.2)	52.4 (14.5)	13:10

Values represent mean (standard deviation). No group differences were found in terms of age or IQ. Abbreviations: PD 'on' = patients with Parkinson's disease 'on' medication; PD 'off' = patients with Parkinson's disease 'off' medication; CS = control subjects; *n* = sample size; NART IQ = premorbid IQ as estimated with the National Adult Reading Test; f:m = female: male.

[a]Significantly different from patients with Parkinson's disease at the 0.05 level. However, this gender difference cannot explain the ED deficit (Downes *et al.*, 1989).

Cognitive tasks

Task-set Switching (Rogers et al*., 1998) (see Fig. 1a)*

Subjects were shown a display with a letter and/or number (or vice versa) and required to name the letter or digit as fast as possible without making a mistake. Subjects switched between (A) letter- and (B) digit-naming tasks on every second trial, so that switch and non-switch trials alternated in a predictable way. Thus, the sequence of trials employed was AABBAA and so on, which enabled the measurement of switching (i.e. A to B or B to A) against a baseline of non-switching (i.e. A to A or B to B). The colour of the stimulus window indicated which task was to be performed. Switch costs were calculated by subtracting performance (i.e. reaction times and errors) on non-switch trials from performance on switch trials. Two conditions were distinguished. In the 'cross-talk' condition, both a letter and a number were presented on most trials. Therefore, stimuli primed the previously relevant, but currently distracting task-set and demands on selection mechanisms were increased. In the 'no-cross-talk' condition, the stimulus consisted of attributes, which were associated only with the relevant task (only a letter or only a number was presented).

The task started with a general training session in which the letter- and digit-naming tasks were separately practised. The general training session was followed by the actual experiment, in which the sequence of the 'cross-talk' and 'no-cross-talk' conditions was counterbalanced within the groups. Each experimental condition, consisting of four blocks of 40 trials, was preceded by a practice session, consisting of two blocks of 40 trials. The mapping of the colours green and red with the letter- and the digit-naming tasks was also counterbalanced within the two groups. An IBM-compatible PC was used as a testing machine; a small throat-microphone was used to record reaction times and the program, written in C, was run from real-time MS-DOS to ensure that reaction times (RTs) were measured to millisecond accuracy. Each stimulus consisted of two closely adjacent characters presented side by side. The characters were randomly presented on the left or the right of the stimulus pair. Letters were sampled randomly from the set {G, K, M, P, R, A, E, U}, digits from the set {2, 3, 4, 5, 6, 7, 8, 9} and neutral characters from the set {?, *, %, #}. Each character pair remained on the screen until the subject responded by naming one of the characters. The response–stimulus interval was 1000 ms.

The data were analysed using repeated measures ANOVAs. After exclusion of unreliable trials, RTs were log-transformed to satisfy the assumption of homogeneity of variances. Except for one control subject and two patients 'off' medication, who made between 25 and 36% errors, none of the subjects made >18% errors. Exclusion of the three subjects with many errors did not affect the significance of the RT effects. Proportions of errors were arcsin-transformed (Howell, 1997) ($2\arcsin\sqrt{x}$).

Both the ID/ED shift paradigm and the probabilistic reversal learning paradigm were administered using a Datalux microcomputer with a touch-sensitive screen for recording responses.

Probabilistic Reversal (Lawrence et al*., 1999; Swainson* et al*., 2000) (see Fig. 1b)*

This task was administered using a Datalux 486 microcomputer with a touch-sensitive screen for recording responses.

The task consisted of two stages, starting with a simple probabilistic visual discrimination, in which subjects were required to make a two-alternative forced choice between two colours. The 'correct' stimulus (which was always the first stimulus touched) received an 80:20 ratio of positive:negative feedback and the opposite ratio of reinforcement was given for the 'incorrect' stimulus. After having completed 40 trials of this initial discrimination, the task proceeded to the second, reversal stage in which contingencies were reversed, without warning, so that the previously 'incorrect' colour was now correct and vice versa for the subsequent 40 trials. Although all subjects received a total of 80 trials, a learning criterion of eight consecutive correct trials was imposed for the purposes of analysis.

Main performance measures were failure or success at each stage, mean errors to criterion and mean latencies. Failure/success rates were analysed using the likelihood-ratio method for contingency tables (Robbins, 1977). Subjects failing stage 1 were excluded from subsequent analyses of error rates and latencies at stage 2. They were included when error rates and latencies at stage 1 were analysed. Square-root transformed errors to criterion $[(x + 0.5)^{1/2}]$ were analysed using one-way ANOVAs. However, the assumption of homogenous variances was violated for errors to criterion at stage 2, so this measure was analysed using the non-parametric Mann–Whitney test. In addition, measures of perseveration and maintenance were included. For details of these additional measures the reader is referred elsewhere (Lawrence *et al*., 1999; Swainson *et al*., 2000).

Intra-/extra-dimensional Shift Paradigm (Downes et al*., 1989)*

Like the reversal learning paradigm, the ID/ED task started with a simple discrimination stage in which subjects were asked to touch one of two patterns. Each response was followed by visual and auditory computer feedback. The task proceeded through several stages, with the crucial extra-dimensional shift (EDS) stage requiring a shift in responding from the initially relevant, but now irrelevant, dimension 'shapes' to the previously irrelevant, but now relevant, dimension 'lines'. For a full description of the further stages of the ID/ED shift paradigm the reader is referred elsewhere (Downes *et al*., 1989). Main performance measures were failure or success at each stage and errors to criterion. Failure/success rates were analysed using the likelihood-ratio method for contingency tables (Robbins, 1977). Subjects failing any of the stages were excluded from analysis of subsequent stages.

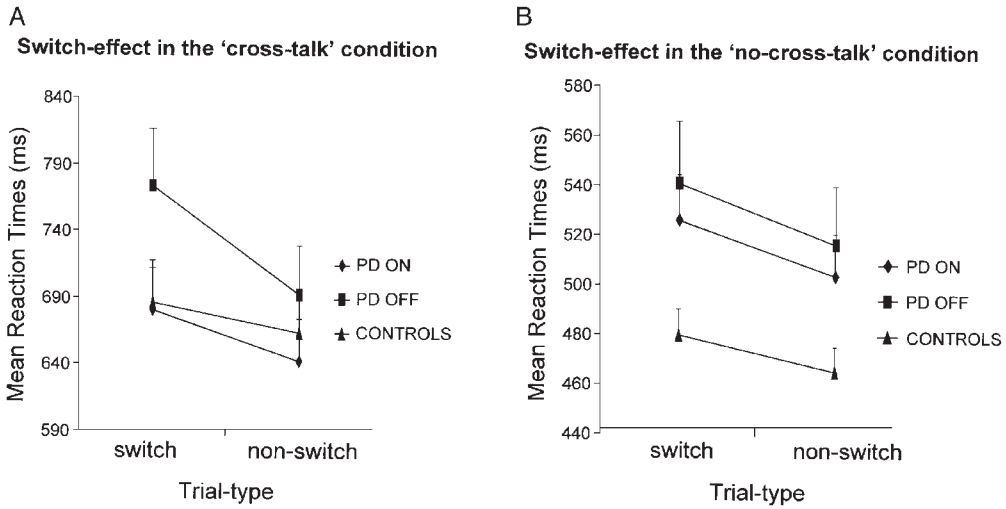

Figure 2. Task-set switching data. Patients 'off' medication exhibited significantly increased switch costs in the 'cross-talk' condition, but not in the 'no-cross-talk' condition [significant group × switch × 'cross-talk' interaction, $F(1,27) = 11.2$, $P = 0.002$]. (*a*) Mean reaction times in the 'crosstalk' condition. Patients exhibited significantly increased switch costs [$F(1,54) = 10.7$, $P = 0.002$] compared with controls. Moreover, patients 'off' medication exhibited increased switch costs compared with patients 'on' medication [$F(1,27) = 13.24$, $P = 0.001$]. (*b*) Mean reaction times in the 'no-cross-talk' condition. There were no significant differences in terms of switch costs between any of the groups.

Results

The Task-set Switching Paradigm (Fig. 1)

Mean RTs for the 'cross-talk' and the 'no-cross-talk' conditions are presented in Figure 2 as a function of trial-type and group. Consistent with our prediction, patients 'off' medication exhibited increased switch costs relative to patients 'on' medication [$F(1,27) = 5.07$, $P = 0.033$]. The three-way interaction of group × switch × 'cross-talk' was highly significant [$F(1,27) = 11.2$, $P = 0.002$] and simple interaction effect analyses showed that the switch × group interaction was significant only in the 'cross-talk' condition [$F(1,27) = 13.24$, $P = 0.001$] and not in the 'no-cross-talk' condition [$F(1,27) = 0.06$, $P = 0.82$]. The 'cross-talk' × switch interaction was significant for patients 'off' medication [$F(1,14) = 32.0$, $P < 0.0001$], but not for patients 'on' medication [$F(1,13) = 1.34$, $P = 0.3$] or controls [$F(1,26) = 0.33$, $P = 0.6$].

PD patients (collapsed over the 'on' and 'off' group) exhibited increased switch costs relative to controls [$F(1,54) = 7.6$, $P = 0.008$]. Although the three-way interaction of group × switch × 'cross-talk' did not quite reach significance [$F(1,54) = 3.3$, $P = 0.078$], simple interaction effect analyses revealed that the group × switch interaction was only present in the 'cross-talk' condition [$F(1,54) = 10.7$, $P = 0.002$] and not in the 'no-cross-talk' condition [$F(1,54) = 0.97$, $P = 0.33$].

There were no group differences in terms of errors.

The increased switch costs in terms of RTs cannot be explained by generalized slowing of cognitive processes because: (i) the deficit was specific to certain conditions of the experiment; (ii) there were no significant differences in terms of overall RT (patients versus controls, $P = 0.13$; patients 'on' versus patients 'off', $P = 0.31$); (iii) the groups also exhibited significantly different proportional switch costs, which were calculated by dividing the actual switch cost by the mean baseline non-switch reaction time for each individual subject. Again, proportional switch costs were increased in the 'cross-talk' condition (patients versus controls, $P = 0.02$; patients 'on' versus patients 'off', $P = 0.005$) and not in the 'no-cross-talk' condition.

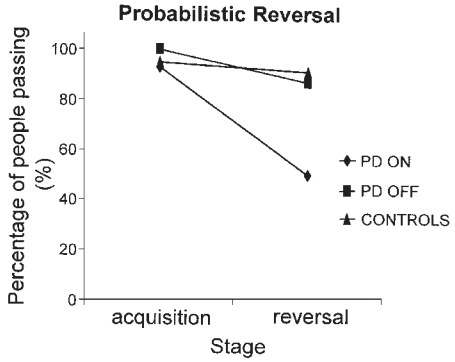

Figure 3. Failure rates on the probabilistic reversal paradigm. At the initial acquisition stage, no patients 'off' medication, one out of 14 patients 'on' medication, and one out of 23 controls failed to reach criterion. In contrast, at the reversal stage six out of 14 patients 'on' medication failed to reach criterion, while only two out of 15 patients 'off' medication and one out of 23 controls failed to reach criterion. The difference between controls and patients was significant (χ^2 (1) = 5.5, $P = 0.02$) and a second orthogonal contrast and inspection of the data show that this difference was due to significantly more patients 'on' medication failing the reversal stage than patients 'off' medication (χ^2 (1) = 3.8, $P = 0.05$) and than controls.

The Probabilistic Reversal Learning Paradigm (Fig. 3)

Almost no subjects failed the initial acquisition stage. Consistent with our prediction, significantly more patients 'on' medication failed the reversal stage than patients 'off' medication (six out of 13 patients 'on' and two out of 15 patients 'off' medication: χ^2 (1) = 3.8, $P = 0.05$). Non-parametric analysis revealed that there was no difference in terms of errors at the acquisition stage [mean values (SEM) for patients 'on', 1.2 (0.6); patients 'off', 1.5 (0.8); controls, 1.1 (0.5)]. However, at the reversal stage both patients 'on' and 'off' medication made significantly more errors than did controls [mean values (SEM) for patients 'on', 12.6 (3.4); patients 'off', 11.1 (3.0); controls, 4.5 (0.9), $P = 0.02$], while there was no difference between patients 'on' and 'off' medication. There was no difference in terms of 'perseverative' errors and error patterns were generally non-perseverative.

The ID/ED Shift Paradigm

Significantly more patients (seven out of 28) failed the crucial

EDS stage than did controls (one out of 20) [χ^2 (1) = 3.8, P = 0.05], but there was no difference between patients 'on' (three out of 13) and 'off' medication (four out of 15) [χ^2 (1) = 0.05, P = 0.83]. Patients made more errors at the EDS stage (but not at other stages) than controls, but this difference was not significant (P = 0.13).

There were no significant correlations between the following selected task measures: the number of errors at the EDS stage from the ID/ED shift paradigm; the number of errors and number of stages completed from the probabilistic reversal learning paradigm; and switch costs from the task-set switching paradigm.

Discussion

This is the first study in humans providing evidence for both beneficial and deleterious effects of DA-ergic medication within the same group of PD patients on cognitive tasks that were selected a priori on the basis of their sensitivity to differentially depleted areas in the parkinsonian brain. Whereas withdrawal of DA-ergic medication in PD patients had a detrimental effect on task-set switching, which is associated with the DL-PFC/PPC-dorsal caudate 'loop', withdrawal had a beneficial effect on probabilistic reversal learning, associated with the OFC-ventral striatal 'loop'. Because the effect of L-Dopa stems mainly from its ability to elevate DA levels (Maruyama *et al.*, 1996) in the striatum (Hornykiewicz, 1974), the observed effects on task-set switching and reversal learning are most likely due to effects of DA in the dorsal and the ventral striatum, respectively, which are known to be connected to different cortical areas, the DL-PFC/PPC and the OFC, via segregated cortico-striatal 'loops' (Alexander *et al.*, 1986). Unlike a previous study (Gotham *et al.*, 1988), this double dissociation was evident when directly comparing patients 'on' and 'off' medication and was predicted a priori by the 'DA overdose hypothesis' (Gotham *et al.*, 1988; Swainson *et al.*, 2000) stating that administration of DA-ergic medication to PD patients may replete DA depleted circuits (including the dorsal striatum), but 'overdose' relatively intact circuits (including the ventral striatum). Our findings are consistent with an 'inverted U' relationship between DA and cognitive functioning (Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997; Arnsten, 1998) (see Fig. 4).

Our results extend previous studies of DA-ergic effect in PD patients on probabilistic reversal learning (Swainson *et al.*, 2000) and task-set switching (Hayes *et al.*, 1998). Previous data from Swainson *et al.* (Swainson *et al.*, 2000), indicating that medicated PD patients performed more poorly than non-medicated PD patients on probabilistic reversal learning, could be explained by either 'DA overdosage' or disease severity. The present study, in which the two patient groups were matched for disease severity, solves this problem and provides strong evidence for a 'DA overdose' effect on probabilistic reversal learning in medicated patients.

Hayes *et al.* (Hayes *et al.*, 1998) reported ameliorative effects of medication on colour–shape switching. However, their results were confounded by changes in baseline non-switch reaction times, which, as they admit, 'present a problem that is difficult to correct for in the on–off manipulation' (Salthouse, 1985). As outlined in the Results section, our findings are unconfounded by generalized slowing of cognitive processes and, therefore, the present study provides much stronger evidence for a beneficial effect of DA-ergic medication on task-set switching.

Finally, the present study provides stronger evidence for contrasting effects of DA-ergic medication than previous studies, because the effects were observed within the same group of patients tested 'off' medication 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 progression of the disease and the response to medication (Kulisevsky, 1996, 2000), an argument that is strengthened by the fact that our

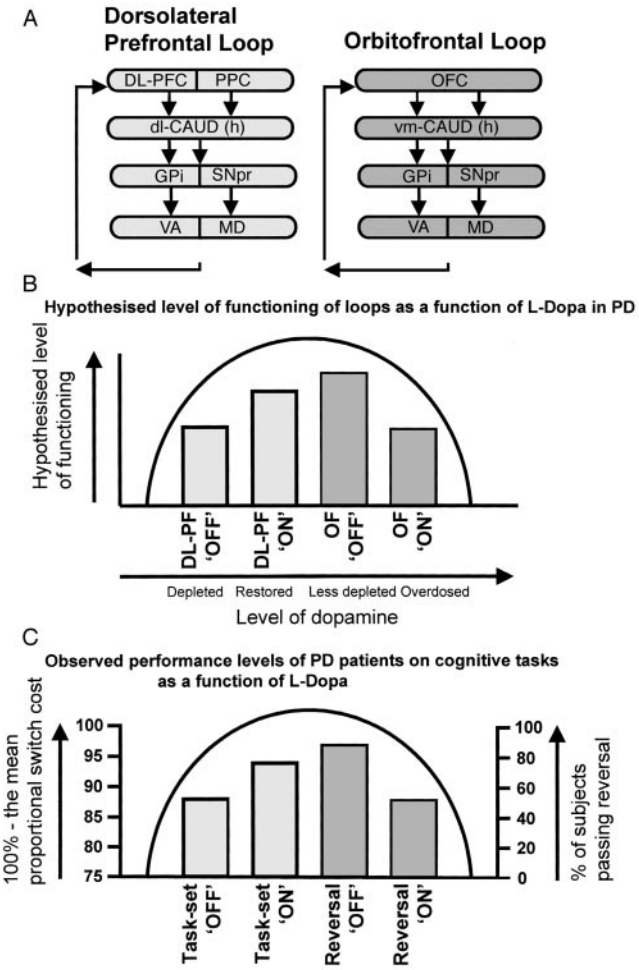

Figure 4. The DA 'overdose' hypothesis, which states that the administration of DA to PD patients may replete DA-depleted regions, such as the dorsal, rostral head of the caudate nucleus and the putamen (not shown), but may 'overdose' relatively intact regions, such as the ventral striatum. (*a*) The dorsal and the ventral striatum are connected to different cortical regions (the dorsolateral prefrontal cortex, the posterior parietal cortex and the orbitofrontal cortex, respectively) in segregated cortico-striatal circuits. Abbreviations: DL-PFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex; OFC = orbitofrontal cortex; CAUD = caudate nucleus; h = head; dl = dorsolateral; vm = ventromedial; GPi = globus pallidus, internal segment; SNpr = substantia nigra, pars reticulata, VA = ventral anterior thalamic nucleus; MD = medial dorsal thalamic nucleus. This hypothesis is shown schematically in (*b*) DA levels are depleted in the dorsolateral prefrontal/posterior parietal loop in patients 'off' medication (DL-PF 'OFF'). DA-ergic medication may partially restore these levels (DL-PF 'ON'). DA levels are less depleted in the orbitofrontal loop in patients 'off' medication (OF 'OFF') and may be 'overdosed' by the administration of medication (OF 'ON'). (*c*) Data from the present study are consistent with this hypothesis. Patients 'off' medication were significantly impaired compared with patients 'on' medication on task-set switching, thought to rely on the DL-PF 'loop'. However, patients 'off' medication performed significantly better than patients 'on' medication on probabilistic reversal learning, thought to rely on the OF 'loop'. Note that we have plotted performance levels for task-set switching as inverse proportional switch costs (see Results section for calculation of the proportional switch cost) in order to emphasize the compatibility of our data with the 'inverted U' shape relationship between DA and cognition that has been shown in experimental animals (Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997; Arnsten, 1998).

patient groups were well-matched for disease duration and all patients reponded well to their medication. Rather, our results suggest that DA-ergic effects on cognition are task-specific and, in PD, depend on the underlying neural substrates of the tasks.

On the probabilistic reversal learning task, although performing significantly better in terms of failure rates than patients 'on' medication, patients 'off' medication made more errors than controls. This result can be reconciled with the finding that there is some degree of DA loss in the ventral striatum and the mesocorticolimbic pathway (Agid *et al*., 1993). DA loss in these areas, however, is less severe than DA loss in the putamen and the more dorsal striatum (Kish *et al*., 1988), at least in the early stages of the disease. Medication doses necessary to remedy DA loss in the more severely affected areas may 'overdose' less severely depleted areas, thereby leading to an impairment in patients 'on' medication compared with patients 'off' medication. It is predicted that further progression of the disease, known to be accompanied by more extensive DA loss in the ventral striatum, would lead to an abolition of this 'overdose' effect 'on' L-Dopa and even to a remediation of this deficit.

The finding that task-set switching, but not ED shifting, was affected by withdrawal of medication suggests that striatal DA is more important for switching between well-learned stimulus–response mappings than for shifting to a 'yet-to-be-established' attentional set. This hypothesis is supported by a recently shown impairment in re-engaging a well-established attentional set in monkeys with 6-OHDA-induced DA loss in the caudate nucleus (Collins *et al*., 2000). Psychopharmacological studies in healthy volunteers (Elliott *et al*., 1997; Mehta *et al*., 1999; Rogers *et al*., 1999) and studies on PD patients (Downes *et al*., 1989; Lange *et al*., 1992; Owen *et al*., 1992) have only provided ambiguous or conflicting results on the role of DA in ED shifting. It is possible that deficits at the ED shift stage in PD patients may be caused by disruption of other ascending neurotransmitter systems, that also degenerate in PD, such as noradrenaline (NA), acetylcholine or serotonin (Agid *et al*., 1987), but which are not primarily reinstated by L-Dopa (Maruyama *et al*., 1996). A role for NA in ED shifting is plausible given the recent observation of a specific deficit at the EDS stage following the administration of clonidine (an NA agonist) and idazoxan (an NA antagonist) to healthy volunteers (Middleton *et al*., 1999) and is consistent with recent theories about the function of the coeruleal-cortical NA pathway (Usher *et al*., 1999).

The finding that the effect of DA-ergic withdrawal in the task-set switching paradigm was specific to the 'cross-talk' condition, in which demands for selection mechanisms were increased by the presence of stimuli that primed the competing task-set, is consistent with a proposed 'gating' or 'focusing' role for DA (Gerfen, 1992; Cohen and Servan-Schreiber, 1993; Schultz *et al*., 1995). Braver and Cohen (Braver and Cohen, 2000) suggested that DA modulates the access of relevant and irrelevant information to active memory mechanisms subserved by the prefrontal cortex. This 'gating' function may provide a mechanism by which DA-ergic medication in our PD patients affects task-set switching, associated with lateral prefrontal-parietal cortex networks (Meyer *et al*., 1998; MacDonald *et al*., 2000; Sohn *et al*., 2000).

The observed deleterious effect of medication on the probabilistic reversal learning task was specific to the reversal stage and performance at the initial acquisition stage was intact in all groups. However, because the correct stimulus at the acquisition stage was always the first colour chosen by the subject, the conclusion that reversal learning (involving the inhibition of previously relevant responses) is more specifically sensitive to DA modulation than probabilistic discrimination learning must be drawn with caution. Indeed, it is conceivable that reversal learning is essentially a difficult learning situation following a rule change (Swainson *et al*., 2000) and, consistently, the DA system has been implicated in such reward-related learning and PD patients have previously been shown to be impaired on probabilistic learning (Knowlton *et al*., 1996). For example, on the basis of electrophysiological data Schultz and colleagues (Hollerman and Schultz, 1998; Schultz *et al*., 2000) proposed a role for the precise timing of the short-latency, burst responses of DA neurons in guiding reward-based learning. These DA responses have been shown to be important for signalling deviations from learned predictions of reward, which is crucial in reversal learning. Repeated L-Dopa was recently shown to increase spike-dependent, phasic DA release in 6-OHDA-lesioned rats (Harden and Grace, 1995). Abnormally increased phasic DA activity in OFC-ventral striatal circuitry may hypothetically, via such uncalibrated 'error-prediction' signals (Schultz *et al*., 2000), lead to over-sensitivity to 'probabilistic' error-feedback following contingency reversal. Although it was not possible in the current study actually to acquire *in vivo* measurements of DA at the receptors, this hypothesis is consistent with the observed random pattern of errors (as distinct from simple perseveration). Further support for a special sensitivity of probabilistic reversal learning to DA overdosing is provided by a recent study by Mehta *et al*. (Mehta *et al*., 2001), who showed that, in young healthy volunteers, the D2 agonist bromocriptine impairs performance on the same probabilistic reversal task, while improving performance on a spatial memory span task.

Conclusion

In conclusion, DA-ergic medication improves or impairs cognitive performance depending on the nature of the task and the basal level of DA function in underlying cortico-striatal circuitry. The dual cognitive enhancing and impairing effects of DA-ergic medication in these PD patients may serve as a model for understanding how DA-ergic modulation of normal cognitive function in healthy human subjects (Kimberg *et al*., 1997) may occur in different states such as fatigue (e.g. vigilance decrement) (Koelega, 1993) and stress (Arnsten, 1998).

Notes

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