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Switching between abstract rules reflects disease severity but not dopaminergic status in Parkinson's disease

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ABSTRACT

This study sought to disambiguate the impact of Parkinson's disease (PD) on cognitive control as indexed by task set switching, by addressing discrepancies in the literature pertaining to disease severity and paradigm heterogeneity. A task set is governed by a rule that determines how relevant stimuli (stimulus set) map onto specific responses (response set). Task set switching may entail reconfiguration in either or both of these components. Although previous studies have shown that PD patients are impaired at switching between stimuli, in the present study not all patients were impaired at switching entire task sets, that is, both stimulus and response sets: compared with controls, patients with unilateral signs (Hoehn & Yahr Stage I) demonstrated intact switching, even following withdrawal from dopaminergic medication, while bilaterally affected Stage II patients were impaired. The parametric measure of Unified Parkinson's Disease Rating Scale (UPDRS) score predicted increasing switch costs within the patient group. These findings suggest that switching entire task sets may be a function of extrastriatal, possibly non-dopaminergic pathology which increases as the disease progresses.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a complex neurochemical profile in multiple brain regions and neurotransmitter systems. At its earliest stages, pathology is limited to degeneration of dopamine (DA) neurons in the ventrolateral tier of the substantia nigra pars compacta, which project to the putamen and rostrodorsal caudate nucleus in the dorsal striatum (Agid, Ruberg, Dubois, & Pillon, 1987; Kish, Shannak, & Hornykiewicz, 1988). In later stages, ventral striatum including the nucleus accumbens becomes DA-depleted and a parallel mesocortical DA deficit develops, affecting the prefrontal cortex (Dubois & Pillon, 1995), limbic system and hypothalamus. While a major emphasis has been placed on DA neurotransmission, especially in the context of cognitive deficits and medication 'overdose' (Cools, Barker, Sahakian, & Robbins, 2003; Swainson et al., 2000), gradual degeneration of the locus coeruleus, dorsal raphé and cholinergic brainstem nuclei progressively compromise the noradrenergic, serotoninergic and cholinergic systems (Braak et al., 2006; Brooks & Piccini, 2006).

This complex neurodegenerative profile is associated with increasingly severe motor symptoms of tremor, muscular rigidity, bradykinesia and akinesia. Pronounced cognitive deficits are also seen on tasks of executive function sensitive to frontostriatal deficits, such as the Wisconsin Card Sorting Test (WCST), intra and extra-dimensional (ID/ED) shifting, Tower of London (TOL), Odd-Man-Out task and their variants (Bowen, Kamienny, Burns, & Yahr, 1975; Canavan et al., 1990; Channon, Jones, & Stephenson, 1993; Cools, 1984; Downes et al., 1989; Gotham, Brown, & Marsden, 1988; Morris et al., 1988; Owen et al., 1992, 1993; Richards, Cote, & Stern, 1993; Robbins, James, Owen, Lange, et al., 1994; Taylor, Saint-Cyr, & Lang, 1986). However, these tasks comprise multiple cognitive components, including concept formation, hypothesis testing, working memory, and stimulus selection, and deficits reflect impaired functioning on any, or more than one, cognitive process.

In order to elucidate the nature of the parkinsonian cognitive deficit, task set switching investigations have focused on the shifting component of executive function (e.g., Rogers & Monsell, 1995), but have not converged on a robust deficit. Impairments have been reported in terms of inflated switch reaction times (RT) and error rate (Cools, Barker, Sahakian, & Robbins, 2001a, 2001b; Cools et al., 2003; Hayes, Davidson, Keele, & Rafal, 1998; Pollux, 2004; Witt et al., 2006), or switch error rate but not RT (Brown & Marsden, 1988; Pollux & Robertson, 2002). For example, Cools et al. hold that PD switching deficits are a function of 'cross-talk' interference from irrelevant stimuli, and reflect DA dysfunction in

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dorsal corticostriatal loops, since performance is ameliorated by dopaminergic medication (Cools et al., 2001a, 2003). Other studies however fail to find a switching deficit (Fales, Vanek, & Knowlton, 2006; Rogers et al., 1998; Woodward, Bub, & Hunter, 2002). As such, consensus on whether PD causes executive deficits as measured by task set switching, and an accurate characterisation of the role of the basal ganglia, the associated corticostriatal loops and DA within these regions, in executive control, have yet to be realised.

It is proposed here that these discrepancies may stem from (i) paradigm heterogeneity and (ii) the effects of disease severity. In order to compare task set switching paradigms, we address the two major elements of a task set: the stimulus set, which is the mental representation of target stimuli, and the response set, the representation of available responses (Meiran, 2000). The task rule signifies a particular cognitive operation and determines the mapping between stimulus and response set (e.g., the numerical parity rule determines that stimuli '2, 4, 6, 8' map to the 'even' response, '1, 3, 7, 9' map to 'odd'). The reconfiguration in stimulus–response (S–R) mappings after adopting an alternative rule or cognitive operation (e.g., judge whether the number is greater or less than 5) is central to task switching, and may dictate that the same stimuli be associated with different responses (same stimulus set, different response set: e.g., '1' now maps to 'less than 5' instead of 'odd'), or that different stimuli be associated with different responses (different stimulus set, different response set: e.g., 'X' maps to 'consonant'). Hence, the complexity of S–R reconfiguration determines not only the magnitude of the switch cost, but also its cognitive significance and neural basis.

Neuroimaging evidence implicates lateral and posterior prefrontal cortical as well as parietal regions in the process of remapping stimuli and responses (Braver, Reynolds, & Donaldson, 2003; Dreher & Berman, 2002; Dreher, Koechlin, Ali, & Grafman, 2002; Forstmann, Brass, Koch, & von Cramon, 2006; Rushworth, Hadland, Paus, & Sipila, 2002; Wylie, Javitt, & Foxe, 2004; Yeung, Nystrom, Aronson, & Cohen, 2006). These findings are also consistent with neuropsychological evidence of switching deficits in frontal lesion patients (Aron, Monsell, Sahakian, & Robbins, 2004; Mayr, Diedrichsen, Ivry, & Keele, 2006). However, incorporating the PD findings into this framework is hampered by differences in the degree to which switching engenders a switch in cognitive operation and a reconfiguration of *both stimulus and response sets*.

The studies in which switching entails reconfiguration in both stimulus and response sets report intact switching in PD. Combining the Stroop and task switching paradigms, Woodward et al. (2002) found abnormal PD switch costs only in the colour naming (Stroop) condition, which was attentionally the most demanding, but not in the word reading (reverse Stroop) condition, indicative of depleted attentional resources rather than deficient internal (task) control. Importantly, switches in this study entailed changes in both stimulus and response sets, as subjects attended to different aspects of the stimulus and gave a different response on a switch of task. Fales et al. (2006) addressed switching as a function of the recency with which a task set had previously been performed, using letter and digit classification tasks that relied on different cognitive operations and necessitated S–R reconfiguration on a switch. They found no overall PD switching deficits, but, instead, increased error rate limited to those switch trials where the current task had more recently been performed. This finding was interpreted as a specific deficit related to backward inhibition (automatic inhibition of the previously abandoned task set) but not task switching. Notably, that PD group also displayed intact performance on other tasks of executive function such as the WCST and TOL.

In contrast, the paradigms that highlight PD deficits (Cools et al., 2001a, 2001b, 2003; Witt et al., 2006) were adapted from an earlier study by Rogers et al. (1998), who employed letter and digit naming tasks. Switching in this design required the reconfiguration of stimulus sets only: once the task-relevant stimulus, number or letter, had been selected from the digit-letter compound, the superordinate task set after a switch was still a simple speeded vocalisation of the target's identity; the mappings between stimuli and responses remained unchanged. The PD switching deficit was isolated to the cross-talk condition: the task-relevant stimulus was presented along with a distracter associated with the alternative task set (e.g., '7G'). Compared with the no cross-talk condition (e.g., '7&'), where the distracter was a non-alphanumeric character not associated with either task set (hence easily ignored), the cross-talk manipulation increases the difficulty of switching task sets by increasing the difficulty of selecting the currently appropriate stimulus in the face of interference from the irrelevant character; attentional selection is required to overcome this interference. Pollux (2004) also utilised a paradigm where switching applied to the stimulus only and also found deficits as a function of 'attentional conflict'.

These studies suggest that DA neurotransmission in frontostriatal circuits may only affect stimulus set switching, which is primarily mediated by selective attention, but it remains unclear to what extent striatal DA affects the ability to reconfigure entire task sets, i.e., both stimulus and response sets, which has been associated with frontoparietal function. Hence, we sought to clarify the impact of PD and corticostriatal DA on S–R reconfiguration in a paradigm of switching between tasks governed by abstract rules.

Despite its presumed striatal-cortical progression, which renders PD an informative disease model for studying the roles of different brain regions in executive control, the second issue of disease severity is noteworthy because studies of task switching have grouped together patients ranging widely in disease severity without considering, or taking advantage of, the neuropathological differences between patients at varying stages of disease progression and disability. Disease rating scales take into account the patient's functional status as well as overt motor signs. The Unified Parkinson's Disease Rating Scale (UPDRS) offers a continuous measure of disease severity. In this composite scale, where each item is rated 0 (normal) to 4 (severely affected), the primary focus is on parts II (13-item interview on activities of daily living) and III (14-item motor exam). Conversely, the categorical Hoehn & Yahr staging system (Hoehn & Yahr, 1967) offers a broader classification of patients on the basis of two main criteria: (i) unilateral versus bilateral signs and (ii) balance and gait difficulties. We argue here that disease severity is particularly relevant to investigations into the cognitive impact of a progressive neurodegenerative disease such as PD. As the disease progresses, it not only affects regions like the striatum to an increasing extent, but also encroaches on cortex, particularly in prefrontal and parietal areas. For example, at the earliest disease stage, pathology is generally limited to the substantia nigra and dorsal striatum: a [^{18}F]-6-fluoro-L-dopa PET study showed that in a group of unilaterally affected Stage I patients, dopaminergic underactivity was relatively confined to putamen while caudate DA neurotransmission was normal (Nahmias, Garnett, Firnau, & Lang, 1985). In contrast, the more severe signs later on in the disease, which usually become bilateral and include postural and gait disturbance, reflect more diffuse pathology with greater striatal DA loss (Morrish, Sawle, & Brooks, 1996) as well as probable *prefrontal* cortical dysfunction (for review, see Brooks & Piccini, 2006), parietal cortical abnormalities (Sabatini et al., 2000; Samuel et al., 1997) and serotoninergic and noradrenergic neuron degeneration (Wolters & Braak, 2006). Therefore, disease progression is a critical factor determining the cognitive profile of any given PD patient.

Thus, the present study directly addressed (i) the impact of disease severity and increasing cortical dysfunction on task set switching when this entails switching between abstract rules and S–R reconfiguration, and (ii) the role of striatal DA neurotransmission, or the effects of dopaminergic medication on S–R reconfiguration.

The effects of PD severity on task set switching with S–R reconfiguration were systematically investigated in two ways: first, using the categorical measure of Hoehn & Yahr stage, and specifically focusing on one of the two primary classification parameters, the transition from unilateral to bilateral signs, by comparing the performance of Stage I and Stage II–III patients. Second, by analysing the impact of the parametric and arguably more sensitive measure of total UPDRS score, the summed total of parts II and III (activities of daily living and motor score), obtained on the day of testing, on switching. At the earliest stages, the effects of PD on cognitive control may be said to represent the effects of a relatively limited asymmetric dorsal striatal DA lesion which is most pronounced on the contralateral side of the motor signs; any cortical DA deficits as a function of *subcortical* DA neurotransmission may be limited to the motor cortex, which the compromised putamen projects to. Frontal and prefrontal DA neurotransmission however can be assumed to be relatively normal, given that these cortical areas are reciprocally interconnected to the mostly intact caudate. At later stages, DA dysfunction is primarily a function of two factors: (1) the striatal DA deficit which encompasses the caudate and more ventral regions of the basal ganglia, and which reduces DA neurotransmission in striatocortical loops, and (2) a parallel mesocortical DA deficit. As discussed, noradrenergic and serotoninergic deficits may also become apparent. Thus, while it is impossible to unequivocally rule out frontal pathology as a function of subcortical DA deficits at the earliest disease stage, particularly given patient heterogeneity, it may be possible to assume that this is relatively limited compared to the deficits seen in more severely affected patients, which reflect more direct frontal or other cortical DA abnormality, as well as non-dopaminergic pathology. Since S–R reconfiguration requires intact frontal functioning, more severely affected patients were predicted to exhibit S–R reconfiguration deficits.

We also investigated the role of DA in task set switching. Whilst it has previously been shown that dopaminergic medication ameliorates cross-talk deficits, which we have argued arise from the need to switch stimulus sets, it is unclear whether it would also enhance switching between abstract rules and reconfiguring S–R mappings. The effects of dopaminergic withdrawal in Stage I patients will help clarify the basis of any disease severity findings: (i) if, similarly to switching between stimuli (or stimulus sets), switching between abstract rules (which entails switching both stimulus and response sets) relies on DA neurotransmission in striatal-PFC loops, withdrawal should inflate Stage I switch costs. (ii) If S–R reconfiguration relies on DA neurotransmission at the level of cortex, namely in frontal and parietal areas, then medication should in fact 'overdose' the theoretically intact Stage I cortical DA systems (e.g., Swainson et al., 2000), and reduce switch costs, i.e., *improve* switching, in the 'off' state. Such a finding would also suggest that Stage II S–R reconfiguration deficits reflect frontal DA dysfunction. (iii) If S–R reconfiguration depends on frontoparietal circuitry but not on DA, then the manipulation should have no effects on this type of switching. This would also suggest that deficits seen in more progressed patients likely originate in the non-dopaminergic pathology that emerges as the disease progresses.

In addition to investigating the association between disease severity, striatal DA neurotransmission and switching deficits, an attentional manipulation was undertaken to test a prediction that follows from the cognitive significance assigned to cross-talk deficits. As discussed previously, cross-talk refers to interference between task sets stemming from the nature of the presented stimuli, typically a task-relevant character and a task-irrelevant distracter. Switching to the currently relevant task set requires overcoming interference from the alternative task set which the irrelevant character effectively primes. The mechanism by which this interference is said to be overcome is *attentional selection*, which presumably operates on the compound of task-relevant and task-irrelevant characters, boosting the representation of the relevant one and inhibiting the other. It has been argued that increased attentional selection load is critical in exposing switching deficits in cross-talk studies; in other words, that PD is associated with task set switching deficits when the additional process of attentional selection is required (e.g., Cools et al., 2001a,b; Witt et al., 2006). We tested this hypothesis directly. Switching in a compound stimulus condition (e.g., '7G'), where the compound of target and distracter is associated with both tasks and hence requires *both* attentional selection and S–R reconfiguration, was compared to switching with a single, unitary stimulus (e.g., '7') associated with both tasks which requires S–R reconfiguration but not attentional selection. If attentional selection is indeed a critical cognitive process which necessarily interacts with switching to expose the PD deficit, then switch costs with compound as opposed to unitary stimuli should be greater in PD compared with controls, particularly following dopaminergic withdrawal.

2. Methods

2.1. Participants

This study was approved by the Peterborough and Fenland Local Research Ethics Committee, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave informed consent prior to participation.

2.1.1. Patients

Twenty-four patients participated in the study. Consent of the patients' GP and consultant neurologist was obtained prior to participation. All patients were recruited from the Cambridge Centre for Brain Repair and were initially diagnosed by a Consultant Neurologist (RAB) as having idiopathic Parkinson's disease based on UK Parkinson's Disease Society (PDS) Brain Bank criteria. They were assessed with the UPDRS (part II: activities of daily living; part III: motor examination) (Fahn, Elton, & Committee, 1987) in the 'on' medication state, and the scores from the two subscales were summed to give a total UPDRS score representing functional status and motor impairment. Exclusion criteria were current psychiatric diagnoses, including depression, colour blindness, surgery for PD, anticholinergic and antidepressant medication, and neurological disease other than idiopathic PD, resulting in the exclusion of one patient due to epilepsy. To assess the effects of disease severity according to Hoehn & Yahr stage, the patients were divided into a Stage I ($N = 13$) and a Stage II ($N = 11$) group based on their rating on the day of testing. The Stage I PD group had a mean (S.D.) Hoehn & Yahr rating of 1.2 (0.5). All Stage I patients were receiving L-dopa (13 patients), combined with DA receptor agonists (7 patients), other DA activity enhancers (4), amantadine (3) and MAO-B-inhibitors (4). One patient was receiving a beta-blocker. The mean (S.D.) Hoehn & Yahr staging of the Stage II group was 2.2 (0.5). All Stage II patients were receiving L-dopa (11 patients), combined with DA receptor agonists (6 patients), other DA activity enhancers (2) and amantadine (3). One patient was receiving a beta-blocker and another patient was receiving a tricyclic antidepressant (discovered upon debriefing). One-way ANOVAs confirmed that, compared with Stage I patients, the Stage II group had a greater total UPDRS score [$F(1, 23) = 49.06$, $P < 0.0001$] and Hoehn & Yahr rating [$F(1, 23) = 23.59$, $P < 0.0001$].

Demographic features are summarised in Table 1a. One-way ANOVAs revealed that the Stage I PD group was matched to controls in terms of age [$P = 0.65$] and premorbid verbal NART IQ [$P = 0.27$], as was the Stage II PD group [age: $P = 0.37$; verbal IQ: $P = 0.48$]. The two PD groups were also matched in terms of age [$P = 0.23$] and verbal IQ [$P = 0.64$]. Compared with controls, the chi-square test with Yates' correction revealed no sex-ratio difference for the Stage I [$P = 0.6$] and Stage II PD group [$P = 0.95$]; there was also no difference between PD groups [$P = 0.79$].

A subset of 11 Stage I PD patients underwent dopaminergic withdrawal: they were tested in the 'on' and 'off' state, after abstaining from all their PD medication for at least 18 h prior to testing. The UPDRS motor scale (part III) (Fahn et al., 1987) was administered in both medication states. Their medication included L-dopa combined with DA receptor agonists (six patients), other DA activity enhancers (five) and MAO-B-inhibitors (two). One patient was receiving a beta-blocker. Demographic features of these Stage I patients are summarised in Table 1b. Similarly to the original Stage I group, this subset was matched to controls in terms of age [$P = 0.6$], verbal IQ [$P = 0.2$] and sex-ratio [$P = 0.89$]. Five patients were tested 'on' first. The two testing sessions were conducted with an intervening period of 3 months, which was deemed long enough to avoid practice or fatigue effects, and short enough to ensure no significant change in disease severity. Hence, their Hoehn & Yahr rating in the 'off' state remained unchanged, but their UPDRS motor score was greater in the 'off' compared with the 'on' state [$t(10) = 3.77$, $P = 0.004$].

Table 1a
Demographic and clinical characteristics of the PD patient groups and controls.

	N	Sex (f:m)	Age (year)	NART	Hoehn & Yahr	UPDRS total (parts II–III)
Stage I PD	13	3:10	62.2 (9.1)	118 (5.6)	1.2 (0.5)	18.8 (5.6)
Stage II PD	11	4:7	66.6 (8.5)	119.2 (3.7)	2.2 (0.5)	38.9 (8.1)
Controls	16	6:10	63.6 (8.3)	120.3 (4.2)	–	–

Data represent mean (standard deviation) values. f:m = female:male; NART = National Adult Reading Test. No significant differences were found.

Table 1b
Demographic and clinical characteristics of Stage I PD patients undergoing dopaminergic withdrawal.

	N	Sex (f:m)	Age (year)	NART	Hoehn & Yahr	UPDRS motor	
						'on'	'off'
Stage I PD	11	3: 8	61.7 (9.9)	117.8 (5.7)	1.05 (0.4)	9.4 (3.5)	19.2 (7.6)

Data represent mean (standard deviation) values. f:m = female:male; NART = National Adult Reading Test. No significant differences compared to controls were found.

Table 2a
Performance of the control, Stage I and Stage II PD groups on the background tests.

Task	Measure	Controls	Stage I PD patients	*P* value	Stage II PD patients	*P* value
FAS letter fluency	Mean no. of words	43.6 (10.5)	44.8 (10.9)	0.76	48 (10.8)	0.3
Pattern recognition	Mean correct	22.1 (1.7)	21.2 (2.2)	0.26	20.2 (2.1)	0.017*
Spatial recognition	Mean correct	16.2 (1.6)	15.8 (2.9)	0.64	16.3 (1.8)	0.9
MMSE	Mean score	28.6 (1.7)	28.2 (1.6)	0.51	28.3 (1.7)	0.67
BDI	Mean score	3.7 (3.5)	8.2 (3.9)	0.003*	7.1 (3)	0.015*

Data represent mean (standard deviation) values; MMSE = Mini Mental State Examination; BDI = Beck Depression Inventory. Letter fluency, pattern and spatial recognition, MMSE and BDI data for 16 controls, 13 Stage I and 11 Stage II PD patients.

* $P < 0.05$ Stage I PD patient group difference compared with the matched control group.

2.1.2. Controls

Sixteen healthy volunteers were recruited to match the patients in terms of age, sex-ratio and premorbid verbal IQ, which was estimated using the National Adult Reading Test (NART; Nelson, 1982).

Depression was assessed by administration of the BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and dementia using the MMSE (Folstein, Folstein, & McHugh, 1975). The FAS verbal fluency task (Benton, 1968) and the pattern (PRM) and spatial (SRM) recognition memory tasks from the CANTAB test battery (Cambridge Cognition plc Cambridge, UK; Robbins, James, Owen, Sahakian, et al., 1994) were given to assess background neuropsychological profile. PRM tests visual pattern recognition memory in the context of a 2-alternative forced choice discrimination, and consists of an initial presentation phase and a subsequent recognition phase. SRM is a 2-alternative forced choice discrimination test of spatial recognition memory in which subjects are initially presented with different screen locations and subsequently required to recognise these. Data were analysed using one-way ANOVAs and are presented in Tables 2a and 2b.

None of the patients scored less than 24 out of 30 on the MMSE (cut-off score for clinical dementia) and in neither group was the mean BDI score at a level indicative of a depressive illness. Although both PD groups had a greater BDI score than controls, reflecting inflated scores on the somatic items, this was still within normal range. Overall, the neuropsychological profile of the PD groups was consistent with the mild impairment pattern seen in previous studies of non-demented PD patients (Owen et al., 1992; Sahakian et al., 1988).

The Stage I subgroup undergoing dopaminergic withdrawal exhibited the same normal MMSE score [$P = 0.77$]. Their BDI score was inflated relative to controls [$F(1, 26) = 12.58$, $P = 0.002$] but within the normal range. Furthermore, this subgroup exhibited an otherwise intact neuropsychological profile and medication withdrawal did not affect these measures (see Table 2b). They were unimpaired relative to controls on the fluency task in both the 'on' [$P = 0.87$] and 'off' states [$P = 0.42$], as well as on PRM ['on': $P = 0.44$; 'off': $P = 0.83$] and SRM ['on': $P = 0.54$; 'off': $P = 0.82$].

2.2. Task set switching procedure

2.2.1. Compound stimulus condition

Each stimulus consisted of two characters presented side by side, a number (1–9, except 5 and 0) and a letter from the subset A, E, I, U, F, C, T, X. On each trial, the task-relevant stimulus and task-irrelevant distracter were counterbalanced across conditions, and the distracter was presented randomly to the left or right of the target to prevent subjects from adopting a constant search strategy. Preserving one of the design constraints of the Rogers et al. (1998) paradigm, the current design contained no stimulus repetitions. Task A required the subject to judge the letter as a vowel or consonant, and task B required the subject to judge the number as higher or lower than 5, as fast as possible and without making a mistake. These tasks were selected because (a) they were relatively easy and based on well-learnt associations, (b) enabled responding with a short vocalisation for ease of triggering the voice key, and (c) responses mapped directly to judgment outcome ('high/low', 'odd/even' and 'vowel/consonant') to avoid loading response selection mechanisms. The tasks employed in the different stimulus conditions were piloted to ensure that they were comparable in terms of difficulty or dominance, in order to control for asymmetrical switch costs (Allport, Styles, & Hsieh, 1994; Allport & Wylie, 2000), which is important in PD given findings of reduced task set inertia (Pollux & Robertson, 2002). The task sequence followed the alternating runs procedure of AABB, so that subjects switched between two vowel/consonant- and two high/low-judgments on every second trial. Because the Rogers et al. (1998) paradigm contained no stimulus repetitions and responding to the target consisted of vocalising its identity, it also contained no response repetitions. In the current design though, if the response on a repeat trial (i.e., every second trial) always switched compared with that on a switch trial (i.e., every trial preceding the repeat), subjects could adopt a constant response strategy of switching to the alternative response, without performing the task at hand. Thus, the probability of a response repetition was implemented at approx. 40% (this should ideally be 50%, but its implementation was dictated by design constraints pertaining to stimulus and distracter alternation). Salient spatial cueing was

Table 2b
Performance of the Stage I patients 'on' and 'off' medication on the background tests.

	FAS letter fluency	Pattern recognition	Spatial recognition	MMSE	BDI
Stage I PD				28.4 (1.6)	8.8 (3.9)
'on'	44.3 (11.5)	21.5 (2.3)	16.6 (2.1)		
'off'	40.4 (9)	21.9 (1.9)	16 (2.6)		
P value	0.13	0.36	0.11		

Data represent mean (standard deviation) values. MMSE = Mini Mental State Examination; BDI = Beck Depression Inventory. Letter fluency, pattern and spatial recognition, MMSE and BDI data for 11 Stage I patients 'on' and 'off' dopaminergic medication. There were no significant differences between the 'on' and 'off' states on any of these measures.

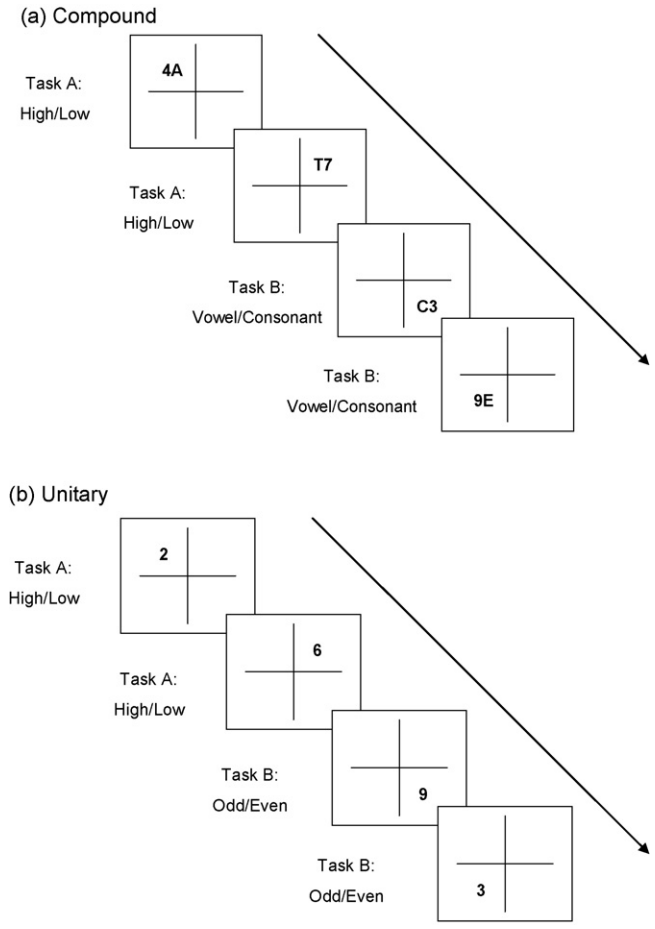

Fig. 1. (a) is an example of a trial-sequence in the compound condition, in which stimuli included task-irrelevant characters. (b) is an example of a trial sequence in the unitary condition, where there were no task-irrelevant characters.

employed, in the form of stimulus position in a 2 × 2 grid (Rogers & Monsell, 1995). The task mapping within the grid was counterbalanced within groups. Since preparation has been shown to mask, or abolish, parkinsonian switching deficits (Cools et al., 2003) and reduce sensitivity to frontal activation (Wylie et al., 2004), a short (300 ms) response to stimulus interval (RSI) duration was utilised in order to maximise design sensitivity. No feedback was given. In the compound stimulus condition, successful performance required selection of the currently appropriate character in the face of interference from the irrelevant one, and then applying the currently relevant judgment or rule (Fig. 1(a)).

2.2.2. Unitary stimulus condition

The unitary stimulus condition differed in the following respects: (i) *stimulus type*: subjects were presented with a single digit on the screen which was a number between 1 and 9, except 5 and 0; and (ii) *task*: task A required judging the number as odd or even, and task B required judging the number as higher or lower than 5. Accurate performance in this condition did not require filtering out distracters. The RSI, cues, absence of feedback, and stimulus and response repetition constraints were identical to those in the compound condition (Fig. 1(b)).

2.2.3. Design

The task started with a training session in which subjects practised switching between judging letters as vowels and consonants, and numbers as higher or lower than 5, and judging them as odd or even. This consisted of one 24-trial block, with compound and with unitary stimuli. The experiment proper comprised a total of 640 trials. The compound and unitary stimulus conditions each comprised eight blocks of 40 trials administered in two sessions with a short break. When a block was completed, the reminder instructions and the word "Ready" were displayed on the screen until the experimenter pressed the space bar. Each session comprised half the blocks of each experimental condition, and the sequence of the compound and unitary stimulus blocks was counterbalanced within and across subjects.

2.2.4. Apparatus and stimuli

A Paceblade SlimBook P120 Centrino 12.1 in. XGA Panel was used as a testing machine and the task was programmed in Visual Basic and run using the Whisker control system (Cardinal & Aitken, 2001) to ensure that responses were measured to millisecond accuracy. A purpose-built voice-key, which was constructed at the Department of Experimental Psychology, University of Cambridge, was used to record reaction times. Errors were scored manually by the experimenter.

Table 3a
Effects of PD severity on mean RT and error rate as a function of stimulus type and switch.

	Compound		Unitary	
	RT (ms)	Errors (%)	RT (ms)	Errors (%)
Stage I PD patients				
Repeat	992.4 (66.3)	0.31 (0.08)	820.4 (52.4)	0.24 (0.04)
Switch	1229.6 (102.9)	0.36 (0.08)	1128.6 (96.4)	0.39 (0.07)
Switch cost	237.2 (45.6)	0.05 (0.05)	308.1 (51.5)	0.15 (0.08)
Stage II PD patients				
Repeat	1179.2 (131.5)	0.26 (0.08)	912.1 (71.6)	0.32 (0.07)
Switch	1515.1 (137.2)	0.31 (0.05)	1283 (104.6)	0.42 (0.11)
Switch cost	335.9 (46.6)	0.05 (0.05)	370.9 (52.5)	0.1 (0.09)
Controls				
Repeat	957.4 (32.3)	0.26 (0.08)	775.2 (22.1)	0.24 (0.06)
Switch	775.2 (49.4)	0.31 (0.05)	1006.1 (33.8)	0.35 (0.06)
Switch cost	199.6 (26.5)	0.07 (0.06)	231 (22.6)	0.11 (0.05)

Data represent mean (S.E.M.) values.

2.2.5. Data analysis

The first two trials of a block and all trials deemed unreliable due to voice key errors or irrelevant subject vocalisations were excluded from the analysis proper, and analysed separately for group differences. Reaction time (RT) on trials where an error had occurred, and the following trial, and RTs shorter than 300 ms were also excluded from the RT analysis. RTs were subjected to means trimming to exclude all datapoints lying beyond 2.5 S.D. from the mean for that condition. Error rates were arcsin-transformed, as the variance was proportional to the mean (Howell, 1997), although the data presented in Tables 3a and 3b represent raw values. Greenhouse–Geisser corrections were applied in those cases where the assumption of covariance was violated. Fisher's LSD tests were additionally performed as post hoc tests.

3. Results

The mean RT and proportions of errors of the Stage I and Stage II PD group were compared with the control data in a repeated measures ANOVA, with stimulus type (compound versus unitary) and switching (repeat versus switch) as the within subject factors and group (PD Stage I versus PD Stage II versus control) as the between subjects factor. Subsequent repeated measures ANOVAs were carried out with the between subjects factor assuming two levels (PD Stage I versus control; PD versus control) to directly contrast Stage I and Stage II PD performance to controls. The effect of disease severity was addressed in two ways: first, using the categorical variable of Hoehn & Yahr stage and using a similar repeated measures ANOVA with the between subjects factor assuming two levels (PD Stage I versus Stage II), and second, using a continuous measure of disease severity, UPDRS total score, which was used as a covariate in the repeated measures within subject ANOVA. Regression analyses

Table 3b
Effect of dopaminergic medication withdrawal on mean RT and error rate as a function of stimulus type and switch.

	Compound		Unitary	
	RT (ms)	Errors (%)	RT (ms)	Errors (%)
Stage I PD patients 'on'				
Repeat	975.5 (75.8)	0.32 (0.1)	810.3 (60.3)	0.21 (0.05)
Switch	1222.9 (119.3)	0.32 (0.9)	1127.1 (108.2)	0.4 (0.09)
Switch cost	247.4 (52.8)	0.001 (0.003)	316.8 (55.7)	0.19 (0.1)
Stage I PD patients 'off'				
Repeat	974.8 (86.7)	0.24 (0.06)	819.9 (53.9)	0.2 (0.06)
Switch	1224.7 (125)	0.36 (0.1)	1119.6 (104.8)	0.35 (0.12)
Switch cost	249.9 (60.1)	0.12 (0.08)	299.7 (61)	0.15 (0.1)

Data represent mean (S.E.M.) values.

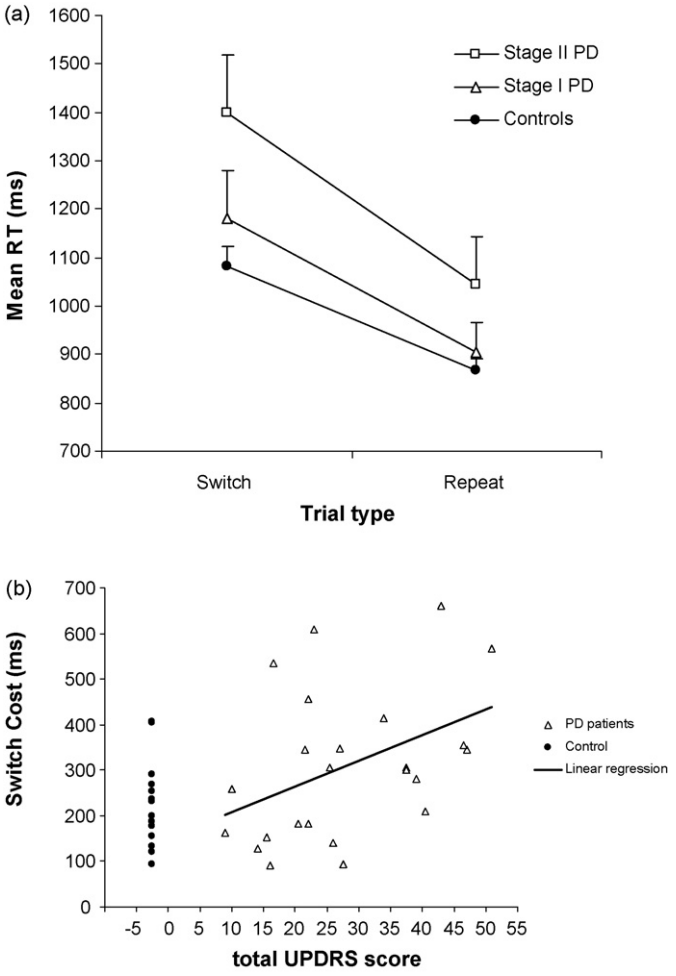

Fig. 2. (a) Mean (S.E.M.) reaction times (in ms) of Stage I and Stage II PD patients and matched controls obtained in the task set switching procedure are shown as a function of trial type (*X* axis). PD patients at Stage II (blank squares), with bilateral motor signs, but not Stage I, with unilateral signs (blank triangles), exhibited elevated switch cost relative to controls (filled circles), seen in the slope of the difference between Switch and Repeat RT. Error bars represent standard errors. (b) Individual switch costs (in ms) for the PD group as a whole (triangles) plotted against total UPDRS score (parts II and III). Control switch costs presented leftmost (filled circles). Graph represents the linear increase in PD switch cost as a function of increasing total UPDRS score, a more sensitive predictor of cognitive impairment within the patient group.

were carried out to further address the effect of the UPDRS total score on switch costs.

3.1. Effects of disease severity

3.1.1. RT data

3.1.1.1. Effect of Hoehn & Yahr stage. Data for RT as a function of switch and stimulus type, and switch costs for the Stage I and Stage II PD groups and controls are presented in Table 3a and Fig. 2(a). There was a marginally significant main effect of group on RT [$F(2, 37) = 3.14$, $P = 0.055$], indicating overall differences between the three groups and there were switch cost differences [switch × group: $F(2, 37) = 3.25$, $P = 0.05$]. There was neither clear evidence that attentional selection demands impacted differentially on overall performance across groups [stimulus type × group: $F(2, 37) = 2.14$, $P = 0.13$], nor were there selection-induced switching differences [switch × stimulus type × group: $F(2, 37) = 0.76$, $P = 0.47$]. These effects are decomposed below.

3.1.1.1.1. Stage I PD patients versus controls. The Stage I PD group RT was overall no different to controls [$F(1, 27) = 0.77$, $P = 0.38$] and these patients did not exhibit switch cost deficits [switch × group: $F(1, 27) = 1.31$, $P = 0.26$]; the 58 ms switch cost difference between Stage I PD patients (mean = 273, S.E.M. = 172) and controls (mean = 215, S.E.M. = 93) was not significant ($P = 0.27$). No Stage I deficits were seen as a function of attentional selection overall [stimulus type × group: $F(1, 27) = 0.98$, $P = 0.33$] and simple effects analyses revealed normal Stage I switch costs irrespective of stimulus type [compound: $F(1, 27) = 0.55$, $P = 0.46$; unitary: $F(1, 25) = 2.16$, $P = 0.15$].

3.1.1.1.2. Stage II PD patients versus controls. Stage II PD patients were overall slower than controls despite being 'on' medication [$F(1, 25) = 6.77$, $P = 0.015$]. As predicted, the switch × group interaction was significant [$F(1, 25) = 8.83$, $P = 0.006$], and post hoc *t*-tests confirmed that the 138 ms switch cost difference between Stage II patients and controls (mean = 353, S.E.M. = 149) was significant ($P = 0.015$). There was no evidence of deficits with compound versus unitary stimuli for this PD group compared with controls [stimulus type × group: $F(1, 25) = 1.83$, $P = 0.19$]. Simple effects analyses confirmed that Stage II patients had greater switch costs than controls with both stimulus types [switch × group: compound: $F(1, 25) = 7.45$, $P = 0.01$; unitary: $F(1, 25) = 7.51$, $P = 0.01$].

3.1.1.1.3. Stage I PD versus Stage II PD patients. There was no overall RT difference between the two groups [$F(1, 22) = 1.94$, $P = 0.18$]. Notably, the switch × group interaction was absent [$F(1, 22) = 1.48$, $P = 0.24$], and the 81 ms switch cost difference between the two groups did not reach significance ($P = 0.16$). There was no clear evidence that patient performance differed as a function of attentional selection [stimulus type × group: $F(1, 22) = 2.78$, $P = 0.11$]. Simple effects analyses on this non-significant trend did not reveal a significant switch × group interaction indicative of differential switching deficits with compound [switch × group: $F(1, 22) = 2.27$, $P = 0.15$] or unitary [switch × group: $F(1, 22) = 0.72$, $P = 0.4$] stimuli.

3.1.1.2. Effect of UPDRS score. In this analysis, PD differences as a function of the parametric measure of total UPDRS score were addressed. There was a trend for an overall significant effect of the UPDRS covariate [$F(1, 22) = 4.03$, $P = 0.06$], indicating that RT increased with increasing total UPDRS score. Notably, there was a significant switch × UPDRS score interaction [$F(1, 22) = 4.72$, $P = 0.04$], indicating that within the PD group as a whole, switch costs also increased with increasing score. There were neither severity-dependent deficits with compound as opposed to unitary stimuli [stimulus type × UPDRS: $F(1, 22) = 2.72$, $P = 0.11$], nor was the switch × stimulus type × UPDRS interaction significant [$F(1, 22) = 1.01$, $P = 0.32$]. A linear regression analysis revealed that total UPDRS score was a significant predictor of switch cost magnitude ($\beta = 0.425$, $P = 0.04$); the regression line is shown in Fig. 2(b). Further regression analyses were performed to confirm the specificity of the UPDRS effect to switching in particular, since there was a trend for UPDRS score to predict mean RT ($\beta = 0.39$, $P = 0.057$). Critically, UPDRS score predicted Switch RT ($\beta = 0.42$, $P = 0.04$) but not Repeat RT ($\beta = 0.34$, $P > 0.1$).

3.1.2. Error data

3.1.2.1. Effect of Hoehn & Yahr stage. Proportions of errors as a function of switch and stimulus type, and error switch costs for the Stage I and Stage II PD groups and controls are presented in Table 3a. There were no group differences in overall error rate [effect of group: $F(2, 37) = 0.12$, $P = 0.89$], or as a function of stimulus type [stimulus type × group: $F(2, 37) = 0.16$, $P = 0.85$], switch [switch × group: $F(2, 37) = 0.2$, $P = 0.82$], or error switch cost as a function of stimulus type (switch × stimulus type × group: $F(2, 37) = 0.61$, $P = 0.55$].

3.1.2.2. Effect of UPDRS score. The effect of total UPDRS score on error rate was not significant [$F(1, 22) = 1.76$, $P = 0.2$], and

error switch cost did not increase as a function of UPDRS score [switch × UPDRS score: $F(1, 22) = 0.17$, $P = 0.67$]. There was no severity-dependent error increase with compound as opposed to unitary stimuli [stimulus type × UPDRS: $F(1, 22) = 1.7$, $P = 0.21$], and the switch × stimulus type × UPDRS score interaction was not significant [$F(1, 22) = 0.03$, $P = 0.87$].

3.2. Effects of dopaminergic medication withdrawal

To assess the effects of medication withdrawal in the Stage I patient subgroup, the mean RT and proportion of errors from the 'on' and the 'off' sessions were analysed using a within subject repeated measures ANOVA, with three within subject factors: medication status ('on' versus 'off'), stimulus type (compound versus unitary) and switch (repeat versus switch). Additionally, the mean RT and proportion of errors for the Stage I 'off' session were also compared with control data in a repeated measures ANOVA with stimulus type and switch as the within subject factors, and group (PD 'off' versus controls) as the between subjects factor.

3.2.1. RT data

3.2.1.1. Patients 'on' versus 'off' dopaminergic medication. RT data as a function of switch and stimulus type, and switch costs for the Stage I PD group in the 'on' and 'off' medication state are presented in Table 3b. Overall, patients did not respond faster in the 'on' than in the 'off' state [main effect of medication: $F(1, 10) = 0.001$, $P = 0.97$]. Critically, patients exhibited similar switch costs 'on' and 'off' medication [switch × medication: $F(1, 10) = 0.055$, $P = 0.82$] (see Fig. 3) and the 7 ms switch cost difference between the 'on' (mean = 282 ms, S.E.M. = 53.6) and 'off' states (mean = 274.8 ms, S.E.M. = 59.9) was not significant ($P = 0.82$). Withdrawal did not affect overall performance differentially as a function of attentional selection [stimulus type × medication: $F(1, 10) = 0.001$, $P = 0.97$], or switching as a function of selection [switch × stimulus type × medication: $F(1, 10) = 0.98$, $P = 0.34$].

3.2.1.2. Patients 'off' versus controls. Stage I PD patients in the 'off' state responded as fast as controls [$F(1, 25) = 0.534$, $P = 0.47$] and did not exhibit switching deficits [switch × group: $F(1, 25) = 1.1$, $P = 0.3$]. Compared with controls, they did not exhibit differences in overall performance as a function of attentional selection [stimulus type × group: $F(1, 25) = 0.95$, $P = 0.34$] or switching deficits with compound as opposed to unitary stimuli [switch × stimulus type × group: $F(1, 25) = 0.56$, $P = 0.46$].

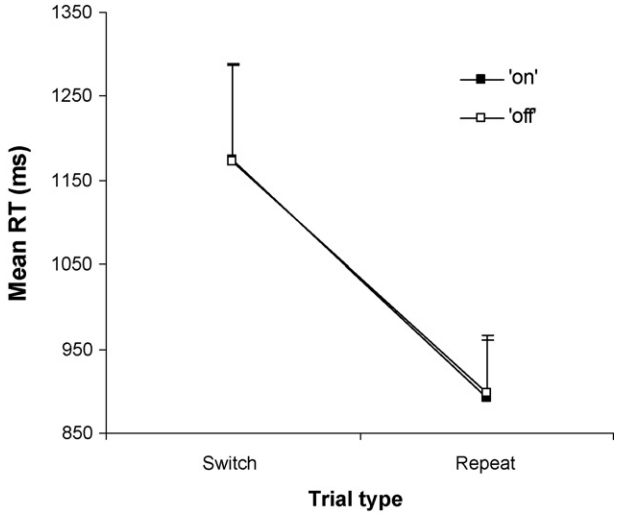

Fig. 3. Mean (S.E.M.) reaction times (in ms) of the Stage I PD patients in the medicated ('on') and withdrawn ('off') state obtained in the task set switching procedure are shown as a function of trial type (*X* axis). Note the complete lack of effect of dopaminergic medication withdrawal on switch cost, seen in the slope of the difference between Switch and Repeat reaction time, in the 'off' (blank squares) compared to the 'on' state (filled squares). Error bars represent standard errors.

3.2.2. Error data

3.2.2.1. Patients 'on' versus 'off'. Proportions of errors as a function of switch and stimulus type, and error switch costs for patients in the 'on' and 'off' states are presented in Table 3b. Overall, withdrawal had no effect on patients' overall error rate [effect of medication: $F(1, 10) = 0.13$, $P = 0.73$], switching [switch × medication: $F(1, 10) = 0.02$, $P = 0.89$], and performance as a function of attentional selection demands [stimulus type × medication: $F(1, 10) = 0.51$, $P = 0.49$]. The switch × stimulus type × medication interaction was also not significant [$F(1, 10) = 3.18$, $P = 0.11$]. Probing this non-significant trend further revealed no switch cost differences between the 'on' and 'off' states with compound [$t(10) = 1.47$, $P = 0.17$] or unitary stimuli [$t(10) = 1.16$, $P = 0.27$].

3.2.2.2. Patients 'off' versus controls. Patients in the 'off' state did not differ from controls in terms of overall error rates [$F(1, 25) = 0.3$, $P = 0.59$], or as a function of stimulus type [stimulus type × group: $F(1, 25) = 0.38$, $P = 0.54$]. There were no differences in error switch costs between patients 'off' and controls [switch × group: $F(1, 25) = 0.67$, $P = 0.42$], and their error switch costs across stimulus conditions also did not differ [switch × stimulus type × group: $F(1, 25) = 0.68$, $P = 0.42$].

3.3. Group differences in excluded unreliable trials

Overall, trials excluded due to irrelevant vocalisations as a proportion of the total number of trials per data set was low, ranging between 16 and 45 trials per dataset (2–7%). More trials were excluded from the PD datasets compared with controls [$F(1, 38) = 4.81$, $P = 0.03$] and there was a near significant effect of group (Stage I PD, Stage II PD, controls) [$F(2, 37) = 3.13$, $P = 0.056$]. Post hoc comparisons revealed there were more unreliable trials for the Stage II group compared with controls ($P = 0.018$) (Stage II PD: mean = 45, S.E.M. = 15; controls: mean = 16, S.E.M. = 3), but not compared with the Stage I group ($P = 0.24$) (Stage I PD: mean = 31, S.E.M. = 5) who also did not differ from controls ($P = 0.2$). The dopaminergic withdrawal procedure had no effect on the number of unreliable trials [$t(10) = 0.2$, $P = 0.8$] ('on': mean = 29, S.E.M. = 6; 'off': mean = 30, S.E.M. = 7).

In summary, the RT analyses revealed that compared with controls, Stage II but not Stage I PD patients were impaired at switching between well-learnt judgments entailing S–R reconfiguration. While the two patient groups did not differ, the continuous measure of total UPDRS score predicted switch cost magnitude within the patient group as a whole. There was no evidence that the requirement to apply attentional selection to a compound stimulus increased PD switch costs. Dopaminergic withdrawal in the Stage I subgroup had no effect on switch cost magnitude, and no differential withdrawal effects were observed as a function of stimulus type.

4. Discussion

This study is the first to demonstrate that disease severity is a predictor of executive deficits in PD as indexed by task set switching involving S–R reconfiguration. This finding is deemed to be a pure measure of dynamic behavioural reorganisation according to abstract but well-learnt contingencies, uncontaminated by learning, use of feedback, concept formation, hypothesis testing and working memory demands. While the categorical distinction of Hoehn & Yahr stage was not sensitive to switch cost differences

between a unilaterally (Stage I) and a bilaterally (Stage II) affected patient group, the parametric measure of total UPDRS score predicted increasing switch costs, consistently with the progressive nature of a neurodegenerative disease such as PD. Furthermore, the switch cost inflation exhibited by Stage II PD patients compared with controls cannot be explained in terms of overall differences in cognitive functioning: in agreement with previous findings (Owen et al., 1992; Sahakian et al., 1988), they were only impaired on visual pattern recognition memory, possibly reflecting cholinergic disturbance in temporal cortex (Aigner & Mishkin, 1986; Winters & Bussey, 2005), but showed normal performance on tests of spatial memory and verbal fluency.

Stage I and Stage II patients were specifically selected for this investigation to avoid confounding factors such as general cognitive and physical deterioration linked to early fatigue, which obscure interpretations of executive performance. Medication was well controlled by virtue of strict pharmacotherapeutic criteria which excluded anticholinergics and antidepressants and included only L-dopa and DA receptor agonists (one patient was also receiving a beta-blocker). The patients displayed significantly elevated BDI scores compared with controls, and this could be a cause for concern given the prevalence of depression in PD, and its association with increasing disease severity and cognitive deterioration on tests of frontal function (Mayeux, Stern, Rosen, & Leventhal, 1981; Remy, Doder, Lees, Turjanski, & Brooks, 2005; Silberman et al., 2007). However, their elevated scores were within the normal range and most likely reflect inflation due to the somatic items of the questionnaire which are affected as part of the physical symptoms of PD.

Previous studies have shown that the interpretability and significance of PD patient performance depends critically on the specific characteristics of any given patient sample, including age (Aarsland, Tandberg, Larsen, & Cummings, 1996), gender distribution (Kaasinen et al., 2001), predominant motor symptom type (Zetusky, Jankovic, & Pirozzolo, 1985), laterality (Cheesman et al., 2005; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007) and subtype (Graham & Sagar, 1999; Lewis, Foltynie, et al., 2005) which may be linked to particular genetic polymorphisms (Foltynie, Sawcer, Brayne, & Barker, 2002; Williams-Gray, Hampshire, Barker, & Owen, 2008). While the effects of disease severity have been previously addressed (Owen et al., 1992, 1993), the present study is the first to relate severity-dependent task switching deficits to a parametric disease measure, namely total UPDRS score, although Hoehn & Yahr stage was not sensitive to differences between patients. This may reflect lack of power due to the relatively small patient groups employed in this study. On the other hand, the progressive nature of the disease may explain the greater sensitivity of this parametric disease measure to switch cost variation in the patient group. Arguably, the parametric UPDRS score may be more ecologically valid than the categorical Hoehn & Yahr distinction.

The pharmacological manipulation carried out in the Stage I patient group neither compromised nor improved executive function: patients' switching aptitude in the hypodopaminergic state did not differ from that in the dopaminergically replete state. This null effect does not reflect unsuccessful withdrawal. Following abstinence from medication, Stage I patients exhibited motoric deterioration in the form of increased tremor and slowness of movement, and decline in movement coordination and motor sequencing in limbs on their affected side, which was statistically confirmed by comparison of the UPDRS motor scores in the 'on' and 'off' states. Session order was counterbalanced, so practice effects between 'on' and 'off' sessions can also be ruled out as a confounding factor. Critically, the null effect of dopaminergic withdrawal on task switching in the current sample of 11 patients is unlikely to reflect lack of power. Previously, Cools et al. (2003) carried out dopaminergic withdrawal in a group of 12 patients performing a cross-talk switching paradigm and were able to demonstrate a 76% switch cost increase from the 'on' to the 'off' state. Furthermore, a seminal and highly cited L-dopa withdrawal study was carried out by Lange et al. (1992) within a sample of 10 PD patients, and demonstrated specific effects of withdrawal on frontostriatal DA-mediated tasks of spatial working memory, TOL, and intra-dimensional set shifting (IDS), but not on DA-independent pattern and spatial recognition memory and visual conditional associative learning.

The fact that PD patients at Stage I, presumably representing the effects of a relatively unilateral striatal DA depletion, displayed intact task switching compared with controls even in the hypodopaminergic state demonstrates at the very least that dopaminergic medication did not mask or ameliorate any switching deficits. However, it also suggests that this type of switching, which entails switches in both stimulus and response sets and S–R reconfiguration, may be relatively independent of striatal DA neurotransmission, as opposed to task switching limited to the stimulus set level. This has at least some implications for the neurochemical and neural origin of the switching deficit seen as a function of increasing UPDRS score which may well be unrelated to a DA deficit. The fact that a DA manipulation had no impact on higher order switching performance in a group of Stage I PD patients suggests that the impairment observed despite medication in more severely affected PD patients is unlikely to have been mediated by a deficit in striatal DA, but may depend on non-dopaminergic, extrastriatal pathology. Whilst dopaminergic medication is capable of ameliorating some of the cognitive deficits in Stage II PD patients (see e.g., Lange et al., 1992), this effect may not extend to S–R reconfiguration in the context of switching between abstract rules.

In theoretical terms, this study may serve to highlight a distinction between higher and lower order switching. Higher order switches refer to situations where both stimulus and response sets are switched because the overall task rule changes (i.e., from judging a letter as a vowel/consonant, to judging a number as higher or lower than 5). In lower order switches on the other hand, such as those in the Cools et al. studies, the same operation (target vocalisation) is applied to different stimuli, so that only the stimulus sets change (i.e., switching from vocalising the letter in the display to vocalising the number). While it is impossible to conclude unequivocally that this type of higher order switching does not depend on DA on the basis of this negative behavioural effect, it does at least raise the possibility that not all forms of switching rely on corticostriatal DA neurotransmission: unlike switching attention between stimuli, S–R reconfiguration which occurs when switching between abstract rules may be similar to extra-dimensional shifting in the context of the ID/ED paradigm (Robbins, 2007). The anatomical and neurochemical substrates of shifts in this task depend on the order of the shift within a rule hierarchy. At the lowest level, reversal shifts (RS) require switches in responding to the previously non-reinforced exemplar within the same category, and serotoninergic OFC input appears critical for this (Clarke, Dalley, Crofts, Robbins, & Roberts, 2004). Intra-dimensional shifts (IDS) reflect the formation of attentional set (continued responding to particular stimulus dimensions), and has been associated with PFC DA neurotransmission (Crofts et al., 2001; see also, Williams-Gray et al., 2008). Extra-dimensional shifting (EDS) does not pertain either to a specific exemplar (as in RS), or a new set of exemplars (IDS), but instead to a higher order rule altogether. Despite paradigm differences (the higher order rule is well-learnt in task switching but in EDS it is acquired on the basis of feedback), EDS also loads on frontal and parietal regions (Hampshire & Owen, 2006), appears sensitive to NA depletion in the rat (Tait et al., 2007), is impaired by PD and, similarly to the present task set switching findings, is unaffected by DA manipulations (Cools et al., 2001a; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen et al., 1992; Slabosz et al., 2006). On the other hand, DA appears to be a common neurochemical denominator of lower order shifts. Switching attention between stimuli in the dis-

play, or a low-level switch of attention to a different stimulus (from numbers to letters) in the context of the same higher order task rule (verbalise target), as in the Rogers et al. (1998) design subsequently employed by Cools et al., may be similar to IDS, where new targets must be selected but the higher order modality dictating attentional set (lines) remains unchanged.

Taken together, the current findings on PD severity and dopaminergic withdrawal suggest that the switching impairment seen with increasing disease severity may originate extrastriatally, most likely as a consequence of PFC and parietal dysfunction, as implicated by neuroimaging investigations in healthy volunteers (e.g., Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Liston, Matalon, Hare, Davidson, & Casey, 2006; Sohn, Ursu, Anderson, Stenger, & Carter, 2000) and studies on the effects of cortical lesions on task set switching with S–R reconfiguration (e.g., Aron et al., 2004; Mayr et al., 2006). Its neurochemical basis may lie in the noradrenergic deficits which emerge even at the earliest disease stages, e.g., arising from locus coeruleus degeneration (Braak et al., 2003; Del Tredici, Rub, De Vos, Bohl, & Braak, 2002), if, as argued previously, switching between abstract rules is indeed similar to EDS, which is also present in medication-naïve mildly affected PD patients. The current findings suggest that switching entire task sets, i.e., switching between different rules and applying different judgments to different stimuli, may be sensitive to extrastriatal, cortical deficits in PD, which are relatively independent of the dorsal frontostriatal 'loop' implicated in simpler, lower level switches where subjects only switch attention between stimuli (Cools et al., 2001a, 2003).

An unforeseen aspect of the present results concerns the impact of stimulus-induced cross-talk interference with compound stimuli. The compound and unitary stimulus conditions were designed to equate the degree to which stimuli afforded interference at the task set level, since stimuli in both conditions invoked both task sets, but differed in the degree to which they required attentional selection, necessary with compound but not unitary stimuli; the manipulation was designed to control for task set interference and thus isolate the effects of attentional selection. Contrary to formulations positing that conditions invoking attentional selection highlight parkinsonian task set inflexibility, the concrete presence of a stimulus within the display was not associated with elevated switch costs in the presence of concrete cross-talk in either medicated PD patients or the dopaminergically withdrawn Stage I subgroup. Therefore, this finding appears inconsistent with the hypothesis that the physical presence of distracting stimuli would highlight parkinsonian switching deficits; instead, PD switching deficits at least in the current design, stemmed from deficient S–R reconfiguration, since the additional selection manipulation had no impact on PD switch costs. The current finding also suggests that the original cross-talk deficit may not necessarily reflect the deficient product of two cognitive processes in PD, i.e., task set switching and attentional selection that mediates switching between stimuli, but only the latter. We have theorised here that the cross-talk paradigm does not engender S–R reconfiguration, but instead may also be conceived as a paradigm of switching attention between stimuli; hence, attentional selection may not merely be a factor which affects switching between task sets in that design, but the attentional process itself may be *what the cross-talk deficit measures*, directly reflecting the operation of attentional selection mechanisms on physical stimuli in the environment, a function which has previously been attributed to the basal ganglia (e.g., Redgrave, Prescott, & Gurney, 1999). Future studies should address PD task set switching deficits as a function of stimulus set overlap across task sets.

Beyond theoretical and clinical implications for parkinsonian cognition, the present findings inform theories concerning the role of the basal ganglia in executive control. Previous findings of DA-dependent cross-talk deficits in PD patients emerged from switching paradigms entailing attentional changes pertaining to stimulus selection, rather than entire task sets. Thus, while flexibility at the stimulus level is associated with striatal DA neurotransmission, the present findings of intact S–R reconfiguration at Stage I PD irrespective of medication state and PD switch cost inflations which are a function of increasing disease severity, suggest that DA neurotransmission in the basal ganglia may not be essential to behavioural flexibility at the level of abstract rules. Instead, this type of higher order control may be undertaken at the level of the cortex, presumably in prefrontal and parietal networks (Brass et al., 2003; Braver et al., 2003). Thus, the findings presented here suggest that the neurodegenerative profile associated with the earliest stages of PD may offer a promising disease model for dissociating behavioural flexibility and cognitive control at the level of lower order stimulus selection and higher order abstract rules.

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