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Cognitive and motor effects of dopaminergic medication withdrawal in Parkinson's disease

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Abstract

Aims: Recent evidence points towards dissociable effects of dopaminergic medication on motor function and cognitive function mediated by different fronto-striatal neural circuits. This study aimed to clarify the role of dopaminergic medication in spatial working memory, and reinforcement-based associative learning in relation to clinical changes in motor function in early Parkinson's disease (PD). *Method:* We tested 14 patients with mild to moderate PD on and off dopaminergic medication, on a spatial delayed-response working memory task, and on spatial and non-spatial (visual) trial-and-error learning tasks based on reinforcement, carefully matched for motor requirements. In addition, we explored relationships between the effects of withdrawal on motor symptom expression and performance on the cognitive tasks. *Results:* Withdrawal from dopaminergic medication significantly exacerbated motor symptoms. This was related to spatial learning, but not visual learning, or delayed response accuracy. Moreover, medication withdrawal led to dissociable effects of response latency on the spatial learning and spatial delayed response tasks, with patients becoming faster after spatial learning, but relatively slower on the delayed response task. These changes in response latency were unrelated to motor symptom impairment. *Conclusion:* Our findings suggest dissociable effects of dopamine medication withdrawal on cognitive processes putatively mediated by dorsal and ventral striatal regions.

Keywords: Parkinson's disease; Dopamine; Working memory; Reinforcement learning; L-Dopa

1. Introduction

Parkinson's disease (PD) is characterised primarily by nigrostriatal dopaminergic degeneration and is associated with motor and cognitive dysfunction (Bowen, Kamienny, Burns, & Yahr, 1975; Lees & Smith, 1983; Taylor, Saint-Cyr, & Lang, 1986, 1990; Kish, Shannak, & Hornykiewicz, 1998; Pillon, Deweer, & Agid, 1993; Swainson et al., 2000; see Nieoullon, 2002 for review). Although additional neurotransmitter systems are involved, such as the noradrenergic (Zweig, Cardillo, Cohen, Giere, & Herdeen, 1993), serotonergic (Jellinger & Paulus, 1992) and cholinergic systems (Price, Whitehouse, & Struble, 1986), dopaminergic medication may theoretically improve some of the cognitive impairments seen in PD.

The neuropsychological profile observed in PD patients has been suggested to resemble that seen in patients with circumscribed frontal-lobe damage (Owen, James, Leigh, Summers, Quinn, Marsden, & Robbins, 1992; Owen, Roberts, Hodges, Summers, & Polkey, Robbins, 1993; Owen, Sahakian, Hodges, Summers, Polkey, & Robbins, 1995; Taylor et al., 1986, 1990; Marié, Barré, Dupuy, Viader, Defer, & Baron, 1999; see Kulisevsky, 2000 for review). For example, performance on tests of working memory has been shown to be impaired in PD (Lange, Robbins, Marsden, James, Owen, & Paul, 1992; Kulisevsky, Avila, Barbanoj, Antonijoan, Berthier, & Gironel, 1996; Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990; Bublak, Muller, Gron, Reuter, & von Cramon, 1990; Postle et al., 1997b). However, not all studies in unmedicated patients have been able to confirm this (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Owen et al., 1992; Owen, Iddon, Hodges, Summers, & Robbins, 1997). In order to help clarify the role of dopaminergic medication in spatial working memory performance in PD, we have tested the effect of withdrawal from dopaminergic medication on a simple spatial delayed response task, similar to that used by Luciana, Depue, Arbisi, & Leon, 1992 and Luciana and Collins (1997) in healthy volunteers, based on tasks used with experimental animals.

The role of dopamine (DA) in motivation and reinforcement-based learning has also been demonstrated in experimental animals (Young, Ahier, Upton, Joseph, & Gray, 1998; Schultz, Tremblay, & Hollerman, 1998; Tremblay & Schultz, 1999; reviewed by Martin-Solech, Leenders, Chevalley, Missimer, Kunig, Magyar, Mino, & Schultz,

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2001), implicating the ventral striatum, which connects the 'limbic' and prefrontal cortex via the orbitofrontal and anterior cingulate circuits (Alexander, DeLong, & Strick, 1986). To the best of our knowledge, no studies have assessed the effects of medication withdrawal on reinforcement-based learning tasks in patients with PD. However, some authors assessing associative learning in PD patients have observed no change following medication withdrawal (Lange et al., 1992), while others have reported that such learning is improved (Gotham, Brown, & Marsden, 1998). The ventral striatum includes the nucleus accumbens, and DA projections to this area are relatively spared at early stages of PD progression (Broussolle, Dentresangle, & Landais, 1999; Holthoff-Detto, Kessler, & Herholz, 1997; Kish et al., 1988). It has been suggested that 'overdosing' of ventral striatal regions by dopaminergic agents may lead to some cognitive deficits seen when patients are on medication (Cools, Barker, Sahakian, & Robbins, 2001; Cools, Stefanova, Barker, Robbins, & Owen, 2002, 2003; Gotham et al., 1988; Swainson et al., 2000). Therefore, if motivation and reinforcement learning are partly mediated by dopaminergic transmission in the ventral striatum (Young et al., 1998), medication withdrawal may, theoretically be beneficial to reinforcement learning by 'normalising' DA levels in the ventral striatum.

Dopaminergic medication may also have differential effects on spatial and non-spatial processing, with spatial memory tasks being more sensitive to the effects of medication (Cools et al., 2002; Kulisevsky et al., 1996; Lange et al., 1992; Postle, Locascio, Corkin, & Growdon, 1997a; Postle, Jonides, Smith, Corkin, & Growdon, 1997b; Owen et al., 1997;), although such a distinction has not always been found (e.g. Mollion, Ventre-Dominey, Dominey, & Broussolle, 2003). We have therefore, tested the effects of withdrawal from medication on performance in two trial-and-error associative learning tests based on reinforcement, carefully matched for motor requirements and utilising both spatial and non-spatial (visual) stimuli.

While the cognitive effects of medication may prove to be important in patient management, clinical efficacy is currently rated primarily on the cardinal motor symptoms of PD presentation. In this study, in addition to examining the effect of medication withdrawal on cognitive performance we have examined possible relationships between changes in motor and cognitive function in PD. Two assessments of motor function were included, one clinical rating scale and one simple computer-based movement-timing test. It was hypothesised that medication withdrawal would lead to dissociable effects of cognitive performance: measures sensitive to 'dorsal striatal' function such as working memory would be associated with changes in motor symptom presentation, whereas aspects of reinforcement-based learning would be improved after medication withdrawal, unrelated to clinical improvement.

2. Materials and methods

2.1. Participants

Fourteen patients (eight female) with mild to moderate idiopathic PD, aged from 54 to 76 years (mean 66.6, S.D. 6.6), were seen on two occasions, separated by a minimum of 1 week. On one occasion patients omitted their morning dopaminergic tablets (specifically L-dopa, dopamine agonists and amantadine; patients treated with selegiline were asked not to discontinue this medication and no patients were taking anticholinergic medications), thus withdrawing from medication for a minimum of 15 h. Longer withdrawal times may have exaggerated the difference between the 'on' and 'off' states, and therefore, this design may be considered conservative. However, this 'practically defined off-state' design was more acceptable to patients and allowed for comparison with other studies. Patients were seen at the same time of day on both occasions and the order of testing 'on' and 'off' medication was counter-balanced across the group.

All patients were diagnosed by a neurologist as having idiopathic PD according to UK PDS Brain Bank criteria (Gibb and Lees, 1988). Exclusion criteria were clinical depression, clinical evidence of other neurological disease, psychosis and possible dementia, assessed clinically and using the mini mental state examination for PD (MMP; Mahieux, Michelet, Manifacier, Boller, Fermanian, & Guillard, 1995). Only volunteers scoring above 24 on the MMP were included in the study (mean score 28.4 $\pm$ 1.2). Predicted premorbid verbal IQ was tested using the national adult reading test (NART; Nelson & Willison, 1991).

The severity of motor symptoms was rated immediately following cognitive testing during both 'on' and 'off' medication states (by ALW) using part three of the Unified PD Rating Scale (motor score, UPDRS; Fahn, Elton, & members of the UPDRS Development Committee, 1987) and by the Hoehn–Yahr scale (Hoehn & Yahr, 1967). Patients with more severe forms of PD, including motor complications such as freezing, falling or dyskinesia, were not recruited since the effects of the disease upon cognitive function are known to depend on severity and motor complications as well medication status (Jankovic, McDermott, & Cater, 1990; Owen et al., 1997; Swainson et al., 2000). Hoehn–Yahr ratings thus ranged from 1.5 to 3 in both the 'on' and 'off' states. The mean duration of the disease was 6.7 ($\pm$2.3) years. Table 1 lists patient clinical and demographic details.

Fifteen age and NART IQ matched control participants were tested on one occasion in identical conditions to the patients. Controls were screened for neurological, psychiatric and substance abuse history by interview with a neurologist, and also given the MMP with the same inclusion threshold as the patients (>24).

All participants gave written informed consent and the study was approved by the local research ethics committee.