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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.

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.