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Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease

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ABSTRACT

It is still unclear, whether patients with Parkinson's disease (PD) are impaired in the incidental learning of different motor sequences in short succession, although such a deficit might greatly impact their daily life. The aim of this study was thus to clarify the relation between disease parameters of PD and incidental motor learning of two different sequences in short succession. Results revealed that the PD patients were able to acquire two sequences in short succession but needed more time than healthy subjects. However, both the severity of axial manifestations, as assessed on a subsection of the Unified Parkinson's Disease Rating Scale III (UPDRS III) and the Hoehn and Yahr score, and the levodopa-equivalent dose (LED) were negatively correlated with the sequence learning performance. These findings indicate that, although PD patients are able to learn two sequences in short succession, they need more time and their overall sequence learning performance is strongly correlated with the stage of disease.

1. Introduction

The acquisition and optimization of movement sequences required, for example, for driving a car or brushing one's teeth is essential in daily life. It has been suggested that such action sequences are arranged into subsequences (Sakai, Kitaguchi, & Hikosaka, 2003). Progression through these subsequences might occur by a switching operation, by which, as one subsequence is completed, the representation of this sequence is inhibited and the next one activated (Hayes, Davidson, Keele, & Rafal, 1998).

In PD patients, both sequence learning and switching between different tasks has been shown to be impaired (Cools, Barker, Sahakian, & Robbins, 2001; Woodward, Bub, & Hunter, 2002). A progressive degeneration of nigrostriatal and, to a lesser extent, of mesocortical dopaminergic neurons is the main pathological feature of PD and leads to a lack of dopamine in the basal ganglia and the prefrontal cortex. This dopaminergic deficit causes not only the classical motor manifestations resting tremor, bradykinesia, rigidity, and postural instability (Grahn, Parkinson, & Owen, 2009) but also other deficits, such as in reinforcement learning, planning, sequence learning and set-switching (Carbon et al., 2003; Moustafa, Sherman, & Frank, 2008). Set-switching refers to the changing from one set of rules that guides behavior to another set and is often investigated with the "Wisconsin Card Sorting Task" (Eling, Derckx, & Maes, 2008; Hayes et al., 1998). However, Cools, van den Bercken, Horstink, van Spaendonck, and Berger (1984) found evidence for set-switching deficits in PD patients not only in sorting compound stimuli as in the Wisconsin Card Sorting Task, but also in the domain of verbal fluency and motor sequencing. Accordingly, Robertson and Flowers (1990) noted that PD patients made substantially more errors than control subjects when they had to switch between motor sequences.

On the other hand, findings regarding motor sequence learning in PD are mixed, with some studies showing profound impairment in PD patients (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000), and others showing only minor impairment (Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993; Sommer, Grafman, Clark, & Hallett, 1999), or none (Smith, Siegert, & McDowall, 2001). This suggests that PD patients can still learn sequences, but less efficiently than normal. It remains unclear, however, which pathophysiological factors influence the sequence learning performance of PD patients. Although it has been suggested that learning performance in PD may be related to the stage of disease, clear evidence for this association is still missing. For example, Muslimovic, Post, Speelman, and Schmand (2007) found a significant, but only weak correlation between the degree of axial disorders and implicit learning impairment by using a one-tailed Spearman's rho test. Moreover, patients with a higher Hoehn and Yahr stage of disease score showed only a trend towards worse sequence learning (Muslimovic et al., 2007).

Furthermore, in the learning paradigms of Hayes et al. (1998) and Robertson and Flowers (1990) the motor sequences were prelearned and subjects were aware of the sequence switching.

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Similarly, in common set-switching tasks such as the Wisconsin Card Sorting Task the subjects try intentionally to identify the rule for stimulus classification even though the set-switching usually occurs unbeknownst to the subjects. In contrast, it is unclear whether PD patients reveal also deficits in switching between two different motor sequences, when they learn these sequences incidentally and are not aware of the sequence switching (Grahn et al., 2009; Hayes et al., 1998; Woodward et al., 2002). Such a deficit in incidental sequence switching might have a great impact on motor function of PD patients in daily life, where many learning processes occur unconsciously and frequent switching between different action sequences is required.

The aim of this study was thus to clarify the relationship between disease parameters and motor sequence learning in PD and to test whether learning of two different motor sequences in short succession is impaired. By using the same task as in the present study, we have recently shown that healthy subjects can implicitly learn two motor sequences in short succession without significant interference between the sequences (Stephan, Meier, Orosz, Cattapan-Ludewig, & Kaelin-Lang, 2009). We hypothesized that PD patients show more impairment than healthy subjects in learning two sequences in short succession, and that their sequence learning performance correlates with the stage of disease.

2. Methods

2.1. Subjects

Thirty-nine patients with PD and 39 age-matched healthy subjects (HS) participated in the present study. The characteristics of the patient and healthy groups are listed in Table 1. The patients were recruited from the Movement Disorders Center at the Department of Neurology and diagnosed according to the criteria of the UK PD Society Brain Bank (Hughes, Daniel, Kilford, & Lees, 1992). Exclusion criteria were global cognitive deterioration, as indicated by a score below 24 on the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and an overall attention deficit, as indicated by a score below four on the Forward Digit Span Test (Von Aster, Neubauer, & Horn, 2006). No patient had to be excluded. The study was approved by the local ethics committee, and each subject gave written informed consent.

At the time of the experiment and clinical assessments, seven patients were not being treated with any dopaminergic drug, because they had only recently received the diagnosis of PD and had not yet begun chronic dopaminergic therapy. Of the remaining patients, seven were being treated with levodopa in fixed combination with a peripheral levodopa decarboxylase inhibitor, four with a dopamine agonist only (1× ropinirol, 2× pramipexol, 1× rotigotine), and 16 with levodopa and a dopamine agonist (8× ropinirol, 5× pramipexole, 3× rotigotine), while five were receiving a combination of levodopa, dopamine agonists, anticholinergic drugs (biperiden hydrochloride) and glutamate antagonists (amantadine). To study the effect of dopaminergic medication on learning performance, the different drugs were pooled in a levodopa-equivalent dose (LED) according to the following conversion algorithm, adapted from Esselink et al. (2004): levodopa × 1 = ropinirol × 16.7 = pramipexol × 100 = rotigotine × 16.7. None of the patients had undergone deep brain stimulation. The severity of motor symptoms was assessed with the UPDRS III (Fahn & Elton, 1987) either immediately before or after the experiment. For more detailed analyses, we determined several subscores of the UPDRS III: (1) *bradykinesia* (finger taps, hand movements, rapid alternating movements of hand, leg agility, body bradykinesia and hypokinesia); (2) *rigidity*; (3) *tremor* (tremor at rest, action or postural tremor of hands); and (4) *axial symptoms* (arising from chair, posture, gait, postural stability). The stage of disease was rated on the Hoehn and Yahr scale (Hoehn & Yahr, 1967). Treatment-related complications were evaluated with the UPDRS IV (historical information relating to the past week, assessed in all but seven untreated patients). Independence in daily living was rated on the Schwab and England Activities of Daily Living (ADL) scale (Schwab & England, 1969). The duration of the disease was defined as the time interval between the occurrence of the first PD symptoms as reported by the patient and the moment of the experiment. Handedness was assessed with the Edinburgh Handedness Inventory Score (Oldfield, 1971).

Each subject was randomly assigned to either a sequence learning task or a random control task. In the PD group, 16 patients performed the random control task, 23 the sequence learning task. In the HS group, 13 subjects performed the random and 26 the sequence task.

Potential demographic and clinical intergroup differences were analysed with independent two-tailed *t*-tests or Mann–Whitney tests for ordinal data. There were no differences in age between PD patients and HS [$t(76) = 1.47$, $p = 0.15$] or between subjects performing the random task and subjects performing the sequence task [HS: $t(37) = -0.05$, $p = 0.96$; PD: $t(37) = 0.29$, $p = 0.78$]. Nor were there any differences between the PD random and the sequence groups in the UPDRS III score [$t(37) = 0.61$, $p = 0.55$], in the UPDRS IV score [$t(30) = 0.94$, $p = 0.36$], in the duration of disease [$t(37) = -1.34$, $p = 0.19$], and in the LED [$t(37) = -1.13$, $p = 0.27$], in the Hoehn and Yahr score [$U = 178.5$, $p = 0.85$], or in the ADL score [$t(37) = 0.53$, $p = 0.60$].

Table 1
Subject characteristics.

Variable	PD *n* = 39	HS *n* = 39
Age (years)	65.0 (9.0) Range: 42–82	61.0 (10.0) Range: 38–77
Sex (F/M)	14/25	23/16
Handedness (R/L/A)	36/3/0	36/2/1
Duration of PD (years)	7.6 (5.0)	
Hoehn and Yahr		
Stage 1:	2	
Stage 1.5:	0	
Stage 2:	25	
Stage 2.5:	3	
Stage 3:	9	
ADL (%)	86.8 (9.9)	
LED (mg/day)	503.1 (510.7)	
UPDRS III	24.0 (10.0)	
UPDRS IV	5.3 (4.1)	

R/L/A, right/left/ambidextrous; PD, Parkinson's disease; ADL, Schwab and England Activities of Daily Living; LED = levodopa-equivalent dose; UPDRS, Unified Parkinson's Disease Rating Scale; HS, healthy subjects; values are M (SD) or N unless otherwise specified.

2.2. Experimental procedure

We used a variant of the classic serial reaction-time task (Nissen & Bullemer, 1987), as previously described in detail (Stephan et al., 2009). Each subject was assigned to either a sequence learning condition or a separate, random control condition. Subjects had to respond with key presses corresponding to flashing-light stimuli appearing on a special Serial Response Box (SRBox, model 200a, Psychology Software Tools Inc., Pittsburgh, PA, USA). This device consists of a row of four lights above four horizontally aligned keys and is controlled by E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA, USA).

The subjects were told to respond as rapidly and as accurately as possible with the more affected hand, which was the non-dominant one in 15 PD patients. The non-dominant hand was used by 7 of 39 HS as well. Each light went out after a correct key press,