

Learning sequence movements in a homogenous sample of patients with Parkinson's disease

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Abstract

We investigated the acquisition of sequence movements in Parkinson's disease (PD) by means of the serial reaction time (SRT) task. To this end, we used a sample of PD patients that fell within the same stage of the disease. Sixteen PD patients and 16 age-, sex- and education-matched control subjects performed the SRT task with a first-order conditional (FOC) sequence and with a second-order conditional (SOC) sequence. The results showed that the group of PD patients could be divided into two distinct subgroups: a fast PD patient subgroup ($n = 11$) and a slow PD patient subgroup ($n = 5$). FOC and SOC sequence learning in faster PD patients proved to be highly comparable to the group of controls. In contrast, learning of FOC and SOC sequences was severely impaired in slower PD patients. Since slow PD patients also scored lower on measures of cognitive functioning than faster PD patients, we assume that the deficits in SRT learning of the former reflect some more general cognitive impairment. This indicates that SRT performance can provide additional information about the cognitive abilities of PD patients, and accordingly may contribute to disease screening.

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Parkinson's disease (PD) is a movement disorder that is characterized by a general loss of motor control, resulting in primary symptoms of tremor, rigidity, postural instability and bradykinesia (e.g. Tarsy, 2005). The disease is caused by the degeneration of the dopamine-producing cells in the substantia nigra, which leads to the dysfunction of the basal ganglia (e.g. Riederer, Gerlach, & Foley, 2002). As the basal ganglia structures are assumed to play a central role in the acquisition of skills in general and learning of sequence movements in particular (e.g. Gabrieli, 1995), many studies have been conducted with PD patients in order to get more insight in the processes underlying the acquisition of sequential behaviour.

In the present study, learning of sequence movements in PD patients is investigated by means of the serial reaction time (SRT) task, developed by Nissen and Bullemer (1987). In a typical

SRT task, participants respond as quickly as possible to a stimulus presented in one of four horizontal locations. Responses are made by pressing a key that is assigned to the spatial position of the stimulus. Unbeknown to the participants, the location of the stimulus follows a repeating sequence. Typical results are that reaction times (RTs) decrease progressively over training, and increase significantly when the sequence of locations turns to a random order. The increase in RT with the insertion of the random sequence is ascribed to the acquisition of sequence-specific knowledge.

As participants' execution of sequence movements is in response to a sequence of perceived objects, both motor and perceptual components contribute to sequence learning (e.g. Deroost & Soetens, *in press*; Deroost & Soetens, 2006; Goschke, 1998; Koch & Hoffmann, 2000; Mayr, 1996; Remillard, 2003). However, ample research has demonstrated that knowledge acquired during sequence learning is predominantly motor in nature (e.g. Deroost & Soetens, *in press*; Nattkemper & Prinz, 1997; Willingham, 1999; Willingham, Nissen, & Bullemer, 1989), so that the SRT task can be considered as an appropriate tool to investigate learning of sequence movements.

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To gain insight in the brain structures involved in sequence learning, many studies have addressed SRT learning in PD patients, leading, however, to mixed results. Whereas some authors found severe sequence learning deficits in PD patients as compared to healthy controls (e.g. Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998), other studies only found relatively minor impairment (e.g. Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993) or even reported intact sequence learning (e.g. Smith, Siegert, & McDowall, 2000).

A possible explanation for these inconsistent findings is that the studies cited above used PD patients that differed with respect to the severity of the disease, as measured by the Hoehn and Yahr (1967) scale. Even within a single study, patients classified as being in different stages of the Hoehn and Yahr scale are included. This makes general interpretation of the SRT results problematic, as it seems likely that differences in learning performance are related to the degree of the severity of the disease. If the basal ganglia truly play a central role in the acquisition of sequence movements, SRT learning should become more impaired as the disease progresses. In order to enhance the comparison of SRT performance across PD patients, we used a homogeneous patient sample, in the present study: only patients with a moderate degree of severity of PD were included. All PD patients were classified as being in Stage 3 of the Hoehn and Yahr scale (early impairment of equilibrium, along with significant slowing of body movements).

Another factor that could contribute to the heterogeneity of results of SRT studies, involving PD patients, concerns the statistical structure of the sequences. As demonstrated repeatedly, a sequence can contain many kinds of information, which all have a specific influence on SRT performance (e.g. Cohen, Ivry, & Keele, 1990; Reed & Johnson, 1994). In a sequence containing first-order associations (called first-order conditional sequence or FOC sequence; Reed & Johnson, 1994), an upcoming target position can be predicted by the previous position. For instance, in the FOC sequence used in the present study, 132342134142 (with the numbers 1–4 denoting the leftmost, left, right and rightmost target position), Position 1 is two times more likely to be followed by Position 3 than by Position 4, but never by Position 2 (repetitions are excluded). In contrast, learning a sequence composed of second-order conditionals (called second-order conditional sequence or SOC sequence) requires knowledge of the previous two positions in order to predict the next position, as the previous position alone provides insufficient information. For instance, for the presently used SOC sequence, 121342314324, Position 1 is equally often followed by Positions 2–4. However, since each pair of target positions has only one unique successor in the sequence, knowing the previous two Positions 1–2 facilitates prediction of the upcoming Position 1.

Because SOC sequences are built up of more complex, higher-order associations, SOC sequence learning tends to be reduced as compared to FOC sequence learning in normal populations (e.g. Deroost & Soetens, *in press*; Reed & Johnson, 1994; Remillard & Clark, 2001; Soetens, Melis, & Notebaert,

2004). However, if statistical structure affects learning in PD patients in a similar way, then differences in statistical structure of the sequential material may to some extent account for the conflicting findings in sequence learning studies with PD patients. Unfortunately, previous research with PD patients that attempted to control for statistical structure of the sequences has yielded mixed results. For instance, Kelly, Jahanshahi, and Dirnberger (2004) compared PD patients and healthy control subjects on learning of hybrid and ambiguous sequences (Cohen et al., 1990). Whereas ambiguous sequences are composed entirely of second-order conditionals, hybrid sequences contain a mixture of first- and second-order conditionals. The results showed that, in concurrence with tone-counting, PD patients and controls performed the SRT task equally well with hybrid sequences, but ambiguous sequence learning was absent in both groups. The authors concluded that hybrid and ambiguous sequence learning are differentially affected by attentional load, imposed by the tone-counting task, but that, nevertheless, sequence learning of first-order conditionals is preserved in PD patients.

This observation is in disagreement with the results reported by Smith and McDowall (2004), who used a verbal version of the SRT task to overcome patients' motor deficits. In this study, a group of PD patients and control participants performed the SRT task with both a FOC sequence and a SOC sequence. The results showed that PD patients demonstrated learning of both the FOC and SOC sequence. However, as compared to the group of controls, learning of both sequences was less pronounced in PD patients. This indicates that PD patients are impaired in the acquisition of both first- and second-order conditionals, at least on the verbal SRT task.

In the present study, we compared FOC and SOC sequence learning effects in PD patients by using the standard motor version of the SRT task. After all, it is possible that the results obtained by Kelly et al. differ from those of Smith and McDowall because in the latter study a verbal version of the SRT task was used. By controlling for statistical structure, in combination with a homogeneous sample of PD patients, we tried to surmount a number of important difficulties that complicate the interpretation of SRT data in PD patients.

1. Method

1.1. Participants

Sixteen patients with PD and 16 healthy control subjects, matched for age, sex and education, participated in the study. All subjects had normal to corrected-to-normal vision and participated as volunteers with informed consent in accordance with the Ethics Committee of the Vrije Universiteit Brussel (VUB). Both groups consisted of 10 women and six men. The average age of the control group was 65.9 years (S.D. = 6.04 years), ranging from 55 to 74 years. For the PD group, the average age was 66.6 years (S.D. = 5.73 years), range 55–72 years. The control group's average years of education amounted to 12.3 years (S.D. = 1.88 years), whereas the patients' average years of education amounted to 12.6 years (S.D. = 2.53 years).

All PD patients were classified as being in Stage 3 of the Hoehn and Yahr scale (moderate impairment: early impairment of equilibrium, along with significant slowing of body movements). The time since diagnosis ranged from 4 to 22 years, with an average of 11.5 years (S.D. = 5.13 years). At the time of testing, all patients were in the on-phase of anti-Parkinsonian medication.

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