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# Slowing of high-speed memory scanning in Parkinson's disease is related to the severity of parkinsonian motor symptoms

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**Summary.** High-speed memory scanning (Sternberg paradigm) was tested in a collective of 20 parkinsonian patients (10 newly diagnosed, untreated patients, duration of the disease 0.5–3.8, mean 1.5 years; 10 levodopa-treated patients, duration of the disease 4.2 to 11, mean 7.6 years). The levodopa-treated patients stopped taking levodopa before the test. There was a tendency towards retarded memory scanning in the patients' collective compared with 20 healthy controls with similar ages and verbal IQs ($p = 0.076$, Mann-Whitney U test). The mental slowing correlated significantly with bradykinesia and the sum-score of the Columbia University Parkinson Rating Scale ($p = 0.021$ and 0.019; Spearman rank correlation). Kruskal-Wallis ANOVA revealed a significant mental slowing in the subgroup of patients with Parkinson's disease for >4 years compared with the newly diagnosed patients and the controls ($H = 8.54$; $p = 0.019$ and 0.006, Mann-Whitney U test). The findings suggest a mental slowing in Parkinson's disease, which is associated with the progression of parkinsonian motor symptoms and not with depression.

**Keywords:** High-speed memory scanning, Parkinson's disease, parkinsonian motor symptoms, levodopa treatment, depression, bradyphrenia.

## Introduction

In 1922, F. Naville published a neuropsychological study of a patient with postencephalitic parkinsonism (Naville, 1922). The author found a retardation of the patient in "complex" intellectual tasks and coined the term bradyphrenia for the observed neuropsychological deficit.

It was not until the late seventies that neurosciences took renewed interest in the speed of central neural processes in basal ganglia disorders. In 1980, Wilson and coworkers reexamined the concept of bradyphrenia in patients with

Parkinson's disease and found a retardation of high-speed memory scanning in patients older than 64 years (Wilson et al., 1980). Several studies presented evidence that the speed of discrimination processes in choice reaction time paradigms is normal in parkinsonian patients (Evarts et al., 1981; Bloxham et al., 1984; Girotti et al., 1986; Brown and Marsden, 1986; Mayeux et al., 1987; Hietanen and Teräväinen, 1988; Pullman et al., 1988). In patients with advanced Parkinson's disease, cognitive impairments were found to correlate with a prolongation of the latencies for the P-200 and P-300 components of the auditory event-related potentials (Hansch et al., 1982). In newly diagnosed parkinsonian patients, the "matching time" in the digit symbol substitution test was shown to correlate with the severity of parkinsonian symptoms and depression (Rogers et al., 1987). Patients with advanced Parkinson's disease were found to exhibit a slowing in the identification of superimposed images of objects correlating with the severity of parkinsonian motor symptoms (Pillon et al., 1989).

It is a matter of discussion, whether or not a slowing of central neural processes is associated with Parkinson's disease. In the studies published so far, parkinsonian patients were tested at various stages of the disease and the tests were of variable intellectual complexity. Some of the tests did not clearly differentiate cognitive and motor latencies. Little is known about the relationship of clinical variables with the speed of purely cognitive processes in Parkinson's disease.

The aim of the present study was to determine the speed of central neural processes in early and advanced stages of Parkinson's disease and to correlate the results with clinical parameters. The high-speed memory scanning paradigm of Sternberg was used (Sternberg, 1966) measuring latencies of purely cognitive processes (Sternberg, 1966, 1975; for review).

## Subjects and methods

The parkinsonian patients were selected according to the following criteria:

The histories of the patients were free of neuropsychiatric disorder and illness except for Parkinson's disease. The patients exhibited mild to moderate, asymmetric tremor, rigidity and akinesia, walking difficulties with shortening of the steps and shuffle, reduced arm swings and parkinsonian vegetative symptoms. Clinical diagnosis of Parkinson's disease was established independently by two neurologists. Included into the study were newly diagnosed patients before treatment and levodopa-treated patients being followed at the movement disorder clinic of the Innsbruck University Hospital at regular (one to six months) intervals. Detailed clinical records were available. Newly diagnosed patients were followed for several months after the study to confirm the clinical diagnosis. The included patients were not demented (DSM III criteria for dementia; American Psychiatric Association, 1980) and there was no clinical evidence of depression.

The exclusion criteria comprised histories of drug-induced psychiatric symptoms, clinical evidence of cerebrovascular disorder, arterial hypertension and insulin-dependant diabetes, lateral or vertical gaze palsies, preponderance of axial rigidity, dysarthria and postural instability over the remainder of the parkinsonian motor symptoms and clinical evidence of autonomic failure. Excluded were also patients treated with anticholinergic agents and sedative drugs and patients not responding to levodopa therapy.

The control subjects were spouses, siblings, and friends of patients attending the movement disorder clinic and the neurooncology clinic of the Innsbruck University Hospital. The ages of the controls were similar to those of the patients. There was no clinical evidence of a neuropsychiatric disorder and no patient suffered from arterial hypertension.

To minimize potential effects of levodopa on the speed of memory scanning, levodopa treated patients were asked to interrupt the treatment as long as possible before the neuropsychological procedure.

The neuropsychological tests were performed in a quiet, well-illuminated room. At the beginning, the subjects performed the WAIS-subtests "general information" and "similarities" (Wechsler, 1958). The scores obtained in the two tests were converted into verbal IQs, as described elsewhere (Dahl, 1972). After the assessment of the verbal IQ, the subjects performed the high-speed memory scanning test (Sternberg, 1966), as follows:

The subjects faced the monitor of a commodore 128 D personal computer. They kept a "yes"-key in their right and a "no"-key in their left hand. Series ("sets") of two, three, or four different consecutive digits were shown in the center of the monitor. Each digit was presented for two seconds with pauses of two seconds between the digits. After each set, a warning tone announced a target-digit in the center of the monitor. The subjects decided as quickly as possible whether or not the target digit belonged to the memorized set ("yes" or "no"-key). The response latencies and the response categories (yes/no) were recorded. The procedure consisted of nine practice trials and thirty-six test trials divided into four blocks of nine trials. The blocks consisted of each three trials with sets of two, three, and four digits presented in a randomized order. Between the blocks, the subjects were allowed to take a rest. The response latencies (reaction times) include a latency for central neural processing and a motor response time. The time required for the retrieval and the inner serial comparison of the memorized digits with the target digit increases linearly with set-size (Fig. 1.). The motor response latencies do not contribute to the slope of the regression. The slope of the linear regression between the response latencies and the set-sizes indicates the time needed for the comparison of one single digit with a target-digit and was designated as the "mental component".

After the neuropsychological procedure, the patients were rated for the severity of the parkinsonian symptoms (Columbia University Parkinson Rating Scale, CUPRS; Lesser

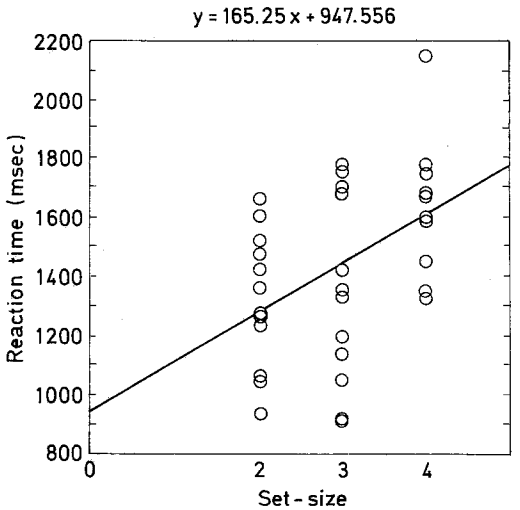


**Fig. 1.** Reaction times (msec; abscisse) for the different set-sizes (ordinate) in a 62-year-old patient suffering from Parkinson's disease for 11 years. Slope of the linear regression = mental component = 165.25 sec. Regression coefficient (r) = 0.466; p = 0.004

et al., 1979) and the stage of the disease (Hoehn and Yahr, 1967). Patients included recently into the study were also rated for depressive symptoms with the Hamilton rating scale for depression (Hamilton, 1967).

The Sternberg tests of twenty patients were evaluable (significant positive linear correlations between the reaction time and set-size). The characteristics and the data of the patients are shown in Table 1.

The collective of patients consisted of ten newly diagnosed and previously untreated cases with a duration of the disease of shorter than four years (6 to 45, mean 18 months) and ten patients suffering from Parkinson's disease for longer than four (4.2 to 11, mean 7.6) years, taking levodopa plus dopa-decarboxylase inhibitor. Characteristics and data of the two subgroups are shown in Table 2. The two subgroups were significantly different as to the duration of the disease, the Hoehn and Yahr score, the sum-score of the CUPRS and bradykinesia (Mann-Whitney U test, Table 2). The Hamilton depression scores determined in the levodopa-treated patients ranged for 1 to 21, mean 9.7 ± 5.9. Eight patients suffered from mild to marked fluctuations in response to levodopa (wearing off, 8 patients; peak-dose dyskinesias, 6 patients; off-period foot dystonia, 4 patients). Nine levodopa-treated patients were free of levodopa for 12 to 51, mean 21 hours, and one, for several weeks before the neuropsychological procedure. One levodopa-treated patients had also been taking bromocriptine (30 mg daily) which was withdrawn 14 hours before the Sternberg test. The withdrawal from levodopa in the patients with Parkinson's disease for more than 4 years resulted in a marked increase of the Hoehn and Yahr scores (from 1.7 ± 0.6 to 3.2 ± 0.4) and the sum-scores of the CUPRS (from 17.4 ± 6.9 to 36.7 ± 6.3).

Cranial CT was normal in 15 patients, showed mild diffuse cortical atrophy in three patients, a (clinically asymptomatic) left parietal infarction in one newly diagnosed patient, and was missing in one patient.

**Table 1.** Characteristics and data of the collectives of patients and controls

| | Collective of patients (N = 20) | Collective of controls (N = 20) | Mann-Whitney U test |
|---|---|---|---|
| Age (years) | 61.6 ± 6.8 | 61.3 ± 6.4 | n.s. |
| Sex (male/female) | 10/10 | 7/13 | |
| Verbal IQ | 101.4 ± 10.2 | 105.9 ± 11.5 | n.s. |
| Duration of the disease (years) | 4.5 ± 3.7 | | |
| Hoehn & Yahr score (0–5) | 2.8 ± 0.6 | | |
| CUPRS sum-score (max. score 100) | 28.8 ± 9.8 | | |
| Tremor score (0–20) | 2.9 ± 2.1 | | |
| Rigidity score (0–20) | 8.1 ± 3.5 | | |
| Bradykinesia score (0–4) | 2.0 ± 1.0 | | |

Means and standard deviations of the means are indicated.

Abbreviations: *CUPRS* Columbia University Parkinson Rating Scale; *n.s.* not significant

**Table 2.** Characteristics and data of the two parkinsonian subgroups

| | Newly diagnosed patients N = 10 | Patients with duration of the disease of > 4 years N = 10 | Mann-Whitney U test |
|---|---|---|---|
| Age (years) | 63.6 ± 7.8 | 59.6 ± 5.3 | n.s. |
| Sex (male/female) | 3/7 | 7/3 | |
| Duration of the disease (years) | 1.5 ± 1.2 | 7.6 ± 2.5 | p = 0.001 |
| Hoehn and Yahr score (0–5) | 2.3 ± 0.5 | 3.2 ± 0.4 | p = 0.001 |
| CUPRS sum-score (max. 100) | 21.0 ± 5.2 | 36.7 ± 6.3 | p = 0.005 |
| Tremor score (0–20) | 2.7 ± 1.6 | 3.1 ± 2.7 | n.s. |
| Rigidity score (0–20) | 7.3 ± 3.3 | 9.1 ± 3.8 | n.s. |
| Bradykinesia score (0–4) | 1.4 ± 0.8 | 2.7 ± 0.8 | p = 0.006 |
| Duration of levodopa treatment (months) | | 62.4 ± 39.7 | |
| Cumulative levodopa dosage (g) | | 1,091.5 ± 808 | |
| Mean daily levodopa dosage (mg) | | 484.1 ± 175.2 | |
| Last daily levodopa dosage (mg) | | 820 ± 471 | |

Means and standard deviations of the means are indicated.
Abbreviations see Table 1

Twenty healthy subjects served as normal controls (Table 1). In eighteen control subjects, the ages differed by maximally one year, in two controls, by two and three years from the ages of the patients. The ages were, thus, similar in the patients' and the controls' group (Table 1; $Z = -0.231$, $p = 0.818$; Mann-Whitney U test). The verbal IQs were also not different (Table 1; $Z = -1.065$, $p = 0.287$; Mann-Whitney U test).

The parkinsonian patients and the controls were compared to one another for the response latencies and the mental components in the Sternberg test (Mann-Whitney U test). In the patients' collective, the mental components were correlated with age, verbal IQ, duration of the disease, the scores of the CUPRS items tremor, rigidity, bradykinesia, the sum of the scores of all items of the CUPRS and the Hoehn and Yahr Score (Spearman rank correlation). In the controls, the mental components were correlated with age and verbal IQ (Spearman rank correlation). The collectives of patients and controls were compared to one another for the numbers of false responses (Mann-Whitney U test). Finally, the newly diagnosed patients, the patients with advanced Parkinson's disease and the controls were compared for mental components, ages and verbal IQs (Kruskal-Wallis ANOVA and Mann-Whitney U test).

## Results

The response times and the mental components of the parkinsonian patients and the controls are shown in Table 3. There were no differences between the patients and the controls as to the individual mean response latencies for sets of two, three and four digits (Z-scores = −0.923, −0.923, −1.337; p-values 0.356, 0.356, 0.181; Mann-Whitney U test).

Two-way ANOVA of the effects of set-size (2,3 or 4 digits) and diagnosis (controls versus patients) on the variations of the individual response latencies showed a significant effect of set-size (F-value 3.119, $p = 0.048$) and no effect of the diagnosis on the variations of the response latencies (F-value 1.128, $p = 0.291$). There was no set-size x diagnosis interaction (F-value 0.49, $p = 0.614$).

The mental components were mildly albeit insignificantly prolonged in the collective of parkinsonian patients compared with the controls ($Z = -1.772$, $p = 0.076$; Mann-Whitney U test). In the patients' group, mental component correlated significantly with bradykinesia ($Z = 2.301$, $p = 0.021$) and the sum of all scores of the CUPRS ($Z = 2.347$, $p = 0.019$; Spearman rank correlation). A trend to a significant positive correlation was shown between mental component and duration of the disease ($Z = 1.75$, $p = 0.075$). The correlation coefficients of the mental component with age, verbal IQ, tremor, rigidity, and the

**Table 3.** Reaction times for the three different set-sizes and mental components (slope of the linear regression between reaction time and set-size) in the collectives of parkinsonian patients and controls

| | Collective of patients N = 20 | Collective of controls N = 20 | Mann-Whitney U test |
|---|---|---|---|
| Response latency Set-size 2 digits (msec) | 995.6 ± 353.4 | 883.4 ± 180.7 | n.s. |
| Response latency Set-size 3 digits (msec) | 1,054.3 ± 344.9 | 935.9 ± 184.1 | n.s. |
| Response latency Set-size 4 digits (msec) | 1,197.7 ± 430.2 | 1,000.2 ± 215.6 | n.s. |
| Mental Component (msec) | 102.5 ± 52.7 | 73.6 ± 23.7 | n.s (p = 0.076) |

Means and standard deviations of the means of the reaction times indicated. Abbreviation see Table 1

Hoehn and Yahr score were not significant ($Z = -0.801$, 0.291, 0.797, 0.33, 1.621; $p = 0.423$, 0.771, 0.425, 0.741, 0.105).

In the collective of the controls, the mental component did not correlate with age ($Z = 1.435$, $p = 0.151$) and there was a trend to a correlation of mental component with the verbal IQ ($Z = 1.865$, $p = 0.062$; Spearman rank correlation).

The numbers of incorrect responses of the individual subjects ("yes" instead of "no" responses and vice versa) ranged between 0 and 7 in the patients' and the controls' collectives and there were no statistical differences between the two groups ($Z = -0.496$, $p = 0.620$; Mann-Whitney U test).

Age and verbal IQs were not different in the two subgroups of parkinsonian patients and the controls ($H = 1.635$ and 4.034, $p = 0.442$ and 0.133; Kruskal-Wallis ANOVA). The mental component was, however, significantly slower in the subgroup of patients with a duration of the disease of more than 4 years as compared to the newly diagnosed patients and the controls ($H = 8.542$; Kruskal-Wallis ANOVA; $Z = -2.343$ and $-2.75$, $p = 0.019$ and 0.006; Mann-Whitney U test). There was no difference as to the mental component between the newly diagnosed patients and the controls ($Z = -0.151$, $p = 0.879$). The slowing of the mental component in the group of patients with advanced Parkinson's disease did not correlate with the Hamilton depression score ($Z = 1.394$, $p = 0.163$). There was also no correlation of the mental components with the duration ($Z = 0.236$, $p = 0.814$), the cumulative dosage ($Z = 0.636$, $p = 0.636$) and the mean daily dosage of levodopa ($Z = 1.691$, $p = 0.090$; Spearman rank correlation).

## Discussion

The Sternberg test has been used in a variety of neuropsychiatric disorders including Parkinson's disease (Sternberg, 1975, for review; Wilson et al., 1980; Rafal et al., 1984; Hart and Kwentus, 1987; Bitschnau, 1989; Poewe et al., 1989). It has been demonstrated that the latencies for the "yes" and the "no"-responses are similar (for review see Sternberg, 1975; Wilson et al., 1980; Bitschnau, 1989) and need not to be evaluated seperately. The intellectual functions tested in the Sternberg paradigm include stimulus encoding, serial comparison of the target-digit with the memorized digits, binary decisions, the translation of the decisions into the response organization and the shift to a new set of digits (Sternberg, 1966, 1975; Bitschnau, 1989).

Acute and chronic application of levodopa (Horvath and Meares, 1974; Botez and Barbeau, 1975; Bowen et al., 1975; Riklan et al, 1976; Halgin et al., 1977; Delis et al., 1982; Brown et al., 1984; Rafal et al., 1984; Gotham et al., 1986, 1988; Huber et al., 1987; Mohr et al., 1987; Pullman et al., 1988; Starkstein et al., 1989) may have an effect on the speed and the quality of cognitive processes. Patients previously treated with levodopa were, therefore, tested in "off"-states after withdrawal of levodopa. Impairment of attention, severe ak-

inesia and tremor, somatic discomfort (e.g. pain in "off"-periods) and on-off fluctuations during the procedure contribute to variations of the response latencies and, thus, to insignificant linear correlations of the reaction times with the set-sizes. Four patients in "off"-phases failed to perform the test correctly and were, therefore, not included into the study.

The present study presents evidence that the speed of high-speed memory scanning is slowed in patients with advanced Parkinson's disease compared with newly diagnosed parkinsonian patients and normal control subjects. In newly diagnosed parkinsonian patients, the speed of memory scanning is not different from that of normal controls. These findings correspond to results published elsewhere (Bitschnau, 1989). There were no differences between the patients and the controls in the present study for the variations of the response latencies suggesting that the slowing of memory scanning in the parkinsonian patients was not due to larger variations of the response latencies as compared to the controls. There were also no differences for the number of incorrect responses between the groups, which is in accordance with results published elsewhere (Wilson et al., 1980; Bitschnau, 1989).

The question arises, which clinical characteristics are associated with a slowing of central processing, in particular with high-speed memory scanning in Parkinson's disease:

In the present study, the retardation in memory scanning correlated significantly with the severity of the motor symptoms. These findings are in accordance with the results of other studies showing a relationship of the slowing of central neural processes with the severity of motor symptoms (Hansch et al., 1982; Rogers et al., 1987; Pullman et al., 1988; Pillon et al., 1989).

A trend to a correlation was found between the mental slowing and the duration of Parkinson's disease, which was not the case in an other study (Pillon et al., 1989). No correlation was found between the mental slowing and age. This finding contrasts to the findings of a study revealing a slowing in memory scanning only in parkinsonian patients older than 64 years (Wilson et al., 1980). Another study found a correlation of age with the slowing of patients in the discrimination of superimposed pictures (Pillon et al., 1989).

It has so far not been discussed in the literature, whether or not there is a relationship between the speed of central neural processes and duration, cumulative dosage and mean daily dosage of levodopa treatment. In the present study, duration of levodopa treatment, cumulative levodopa dosage and mean daily levodopa dosage did not correlate with the speed of high-speed memory scanning suggesting that chronic levodopa treatment did not exert a significant effect on the speed of high-speed memory scanning in the tested subjects. However, this finding needs to be verified in larger series of patients.

The mental slowing observed in the present study is not related to depression. It was observed only in the group of patients with advanced Parkinson's disease, where the Hamilton depression scores were normal (range 1 to 14) in all except one patient (21). It was also demonstrated elsewhere that memory scanning is not affected by depression (Hart et al., 1987).

The association of parkinsonian motor symptoms, in particular bradykinesia, with a retardation of latencies for purely cognitive neural processes has so far been demonstrated in only one study (Pullman et al., 1988). The findings of the present study correspond to the concept of bradyphrenia as described by Naville (Naville, 1922). Naville found a slowing of his postencephalitic patient in "complex" and not in "simple" intellectual functions (Naville, 1922). Studies employing "simple" cognitive tests, in particular choice reaction time tests in Parkinson's disease, have failed to demonstrate a slowing of central neural processes in parkinsonian patients (Evarts et al., 1981; Bloxham et al., 1984; Girotti et al., 1986; Brown and Marsden, 1986; Mayeux et al., 1987; Hietanen and Teräväinen, 1988; Pullman et al., 1988), whereas "complex" tests revealed a mental slowing in Parkinson's disease (Wilson et al., 1980; Rogers et al., 1986; Pillon et al., 1989). It is likely that "simple" neuropsychologic tests are not sensitive enough to detect a retardation of intellectual functions in parkinsonian patients.

A slowing of memory scanning was previously found in aphasics, Korsakoff patients, and patients with Friedreich's ataxia (Sternberg, 1975; Wilson et al., 1980, for review; Hart and Kwentus, 1987). A slowing in high-speed memory scanning is, thus, not specific for Parkinson's disease. The pathophysiological mechanisms underlying bradyphrenia remain obscure. The mental slowing in Parkinson's disease might be related to the loss of cerebral dopamine (Pullman et al., 1988). Bradyphrenia, however, was shown to be resistent to levodopa so that also non-dopaminergic lesions may underly bradyphrenia (Rafal et al., 1984; Pillon et al., 1989). The pathophysiological mechanisms causing bradyphrenia need, thus, to be clarified in further investigations.

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