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Lack of Selective Vulnerability to Anticholinergic Induced Cognitive Impairment in Early Parkinson's Disease

L. SCHELOSKY[1], TH. BENKE[2] and W. POEWE[1]

[1] *Department of Neurology, UKRV, Spandauer Damm 130, Berlin 19, Germany*
[2] *University Hospital for Neurology, 6020 Innsbruck, Anichstr. 35, Austria*

Correspondence: W. Poewe, Department of Neurology, UKRV, Spandauer Damm 130, 1000 Berlin 19, Germany

Thirteen patients with idiopathic Parkinson's disease of recent onset (mean age 63·2 years) and a group of 10 young healthy volunteers (mean age 26·1 years) underwent a series of neuropsychological tests for assessment of memory, learning ability and mental processing speed before and during treatment with trihexyphenidyl. Retesting after anticholinergic exposure (mean of 2 weeks for patients and 1 week for controls) revealed in young healthy controls the same pattern and magnitude of decline in memory function as in Parkinson patients. Non-demented subjects with Parkinson's disease of recent onset thus do not seem to be selectively vulnerable to cognitive side-effects of anticholinergic treatment.

Introduction

The prevalence of dementia in Parkinson's disease has been estimated to be around 20%, twice the figure given for the general population (Gibb, 1989). Possible substrates include concomitant Alzheimer pathology, cell loss in the nucleus basalis of Meynert and diffuse cortical Lewy body degeneration (Hakim *et al.*, 1979; Whitehouse *et al.*, 1988; Gibb *et al.*, 1988). Neurochemically both Alzheimer type cortical degeneration and neuronal loss in the nucleus basalis are associated with frontal cholinergic deficiency, and even without clinical signs of cognitive impairment a loss of parameters of cholinergic activity can be found in the cortex of subjects with Parkinson's disease (Perry *et al.*, 1985). Parkinson patients have therefore been claimed to be particularly susceptible to anticholinergic induced cognitive impairment (Dubois *et al.*, 1987). Several studies have demonstrated mild to moderate memory loss in patients receiving anticholinergics as add-on treatment with levodopa (Sadeh *et al.*, 1982; Miller *et al.*, 1987). There are however few studies of the effects of anticholinergic therapy on specific cognitive domaines in early Parkinson's disease (Koller, 1984). The present study was performed to investigate the effects of trihexyphenidyl on memory and mental processing speed in patients with Parkinson's disease of recent onset, the majority of whom had not received previous antiparkinson treatment, and to compare this with effects of anticholinergics in a group of young healthy controls.

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Subjects and Methods

Thirteen patients with idiopathic Parkinson's disease were included in the study: eight had not been previously treated (*de novo* patients) and trihexyphenidyl was chosen as primary monotherapy; five were on oral levodopa and/or dopamine agonists and the test drug was added because of insufficient control of tremor. Treatment was started at daily doses of 3 mg with increments of 1 mg every 3 days up to a total daily dose of 6 mg.

To exclude patients with signs of dementia full scale IQ was measured at baseline by use of verbal and performance subtests of the HAWIE, a German equivalent of the Wechsler Adult Intelligence Scale. Patient characteristics are summarized in Table 1. Neuropsychological assessment was performed at baseline and after 2–4 weeks of trihexyphenidyl treatment at a dose of 6 mg/d. Test procedures were designed to assess functions of memory, learning ability and cognitive processing speed and included the following:

Memory

Verbal memory was tested by means of a German version of the Wechsler Memory Scale (WMS) (information, orientation, logical memory, digit span, associate learning). Figural memory was assessed by the use of the Benton Visual Retention Test (immediate reproduction of geometric items). Short term memory assessment comprised Knox cubes and Corsi block tapping (version according to Milner 1971, see Lezak, 1983).

TABLE 1. *Patient data (n=13)*

Age (years)	63,23 (46–77)
Sex (f:m)	9:4
Years of education	10,38 (8–14)
Full scale IQ	98·5 (92–113)
Duration of illness (years)	2,3 (1–5)
H+Y stage	2,1 (1–3)
UPDRS* motor score (III)	
at baseline	18,72 (8–27)
Treatment details:	
de novo	$n=8$
previously treated	$n=5$
L-Dopa	$n=3$
duration (years)	1·07 (1–5)
dose (mg)	300 (150–400)
dopamine agonists	$n=4$

* UPDRS: Unified Parkinson's Disease Rating Scale

Learning ability was tested using the California Verbal Learning Test (CVLT, German version). After oral presentation of 16 items (familiar nouns from four common categories, one item per second) patients are required to recall immediately as many items as possible. After five repetitive test runs a distractor list of 16 unrelated items is presented and free immediate recall of this list is tested once. Immediately afterwards and after an interval of 20 min subjects are tested for delayed recall of the first list, first without and then with semantic cues. In a final recall task subjects have to identify items of the original test list from a total of 44 presented nouns. For repeated testing two different versions are used (Delis *et al.*, 1986).

Mental processing speed

Mental processing time was assessed by means of a modified version of the Sternberg paradigm measuring high speed memory scanning after visual presentation of sets of digits (Sternberg, 1966; Wilson *et al.*, 1980). A computerized version of a digit symbol substitution task was also employed where subjects were required to respond by the same motor act (pressing of a number key button) both in a simple choice reaction time paradigm (pressing the corresponding button after appearance of a digit between 1 and 4) and in a digit symbol substitution reaction time task (pressing of a digit key button following the appearance of 1 of 4 symbols on a screen, each being associated with a digit 1 to 4 according to a table constantly displayed on top of the screen). Reaction time difference between simple choice reaction task and digit symbol substitution reaction task was taken as a measure of mental processing time (Rogers *et al.*, 1987).

At every test session patients were rated according to the Unified Parkinson's Disease Rating Scale (UPDRS).

Ten young and healthy volunteers (5 females, 5 males; mean age 26·1 [18–19] years; years of education 17·6 [11–20]) agreed to a 1 week's exposure to anticholinergics. They served as controls for effects of trihexyphenidyl on CVLT and mental processing speed as assessed by DSST. IQ testing of controls comprised the WIP, a shortened HAWIE version (full scale IQ 118·3 [111–127]).

Statistical Evaluation

Comparisons were made (1) between baseline test results of patients and controls, (2) between test results of patients at baseline and after 2 to 4 weeks (mean 15·3 days) of stable trihexyphenidyl treatment at a 6 mg/d level, (3) between results of young healthy controls at baseline and after 1 week of stable trihexyphenidyl treatment at 6 mg/d level, and (4) between baseline-retesting differences of patients and controls, using Student's t-test for parametric data and the Wilcoxon signed rank test for nonparametric data.

Results

1. Comparison of baseline CVLT and DSST results of patients and controls

During presentation of CVLT controls learned about four words more than Parkinson patients. Learning speed as displayed by the differences between the single presentations was equal in both groups (mean $p=0{\cdot}51$). In the recall tasks controls again showed a superior performance of four words an average, reflecting their higher baseline learning ability. DSST results of young volunteers showed faster reactions both in simple and choice reaction task, but mental processing speed was equal in both groups ($p=0{\cdot}09$).

2. Changes in cognitive performance of Parkinson patients following trihexyphenidyl

Performance on short term memory tests remained unchanged when compared to baseline values (BVRT, Knox Cubes, Corsi Block Tapping). Sternberg paradigm and the computerized DSST showed no indication of cognitive slowing with anticholinergic treatment. On the WMS only the subtest for associate learning showed significant deterioration over baseline (see Table 2). Learning of word lists as assessed by CVLT was impaired during the drug period (see Fig. 1). Patients learned 2·5 words less on average during the fourth and fifth repetitive test run. Short and long delay free as well as cued recall was also impaired, the number of items produced on the first delayed cued recall being significantly less under anticholinergic

TABLE 2. *Neuropsycholgical test results of PD patients*

	Baseline	*Under trihexyphenidyl*
WMS		
information	5	5
orientation	5	5
story reproduction	94·2	89·9
associate learning	101·3	89·9*
digit span	100	99·7
Knox cubes	5·5	5·5
CORSI's block tapping	12	11·2
BVRT	10·9	10·23
Reaction times (msec):		
Sternberg motor	1191·1	1124·8
Sternberg cognitive	48·6	42·5
Digit Symbol (no encoding)	991·6	903·9
Digit Symbol (encoding)	1210·8	1170·1

* $p<0{,}03$

treatment ($p < 0{\cdot}05$). Slight but nonsignificant impairment of recognition memory was also evident with a greater number of false positive identifications (2,58 words vs 0·77 at baseline, $p = 0{\cdot}07$) while the total number of correct identifications remained unchanged (14·33 vs 14·69). Intrusions and perseverations remained at the same level at both test sessions (intrusions 2·1 to 3·3, perseverations 4·1 to 3·3).

Anticholinergic treatment lead to significant motor improvement as assessed by the UPDRS (UPDRS motor part values 18·8 at baseline vs 15·8 with anticholinergic treatment, $p < 0{\cdot}05$).

3. Changes in cognitive performance of controls following trihexyphenidyl

Young healthy controls showed no impairment of mental processing speed during drug administration as assessed by DSST (simple choice reaction time 615·8 vs 596·1 msec, digit symbol substitution reaction time 720·2 vs 647·8 msec, p = n.s.), but they developed a significant decrease in words learned in delayed memory tasks of CVLT (see Fig. 2). No changes were evident in perseverations, intrusions and recognition.

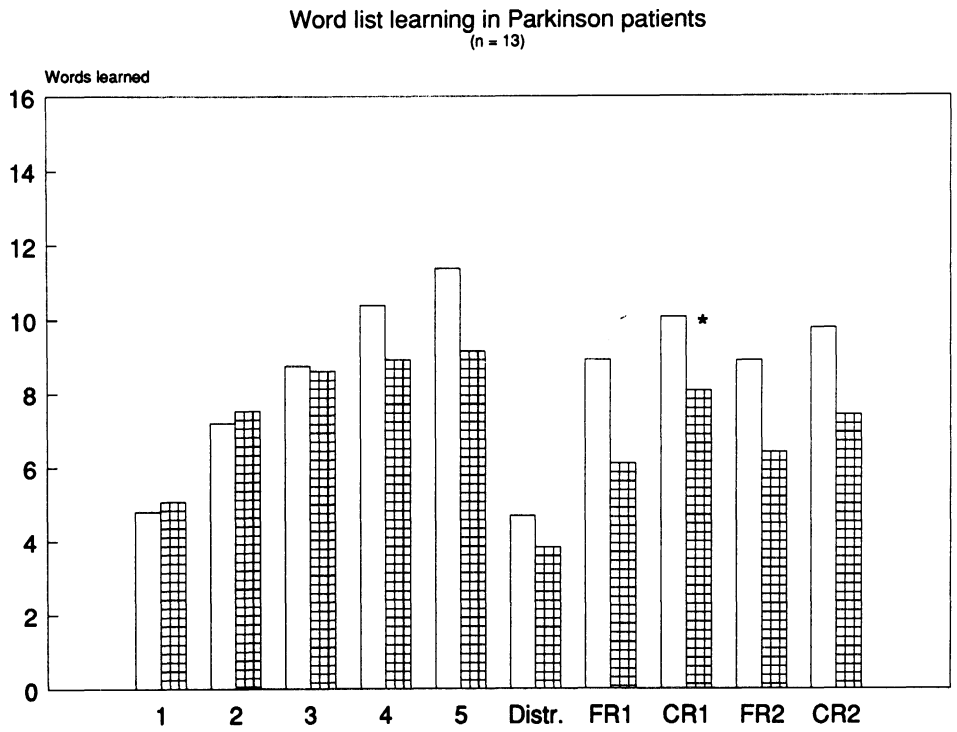
4. Comparison between baseline-retesting differences of patients and controls

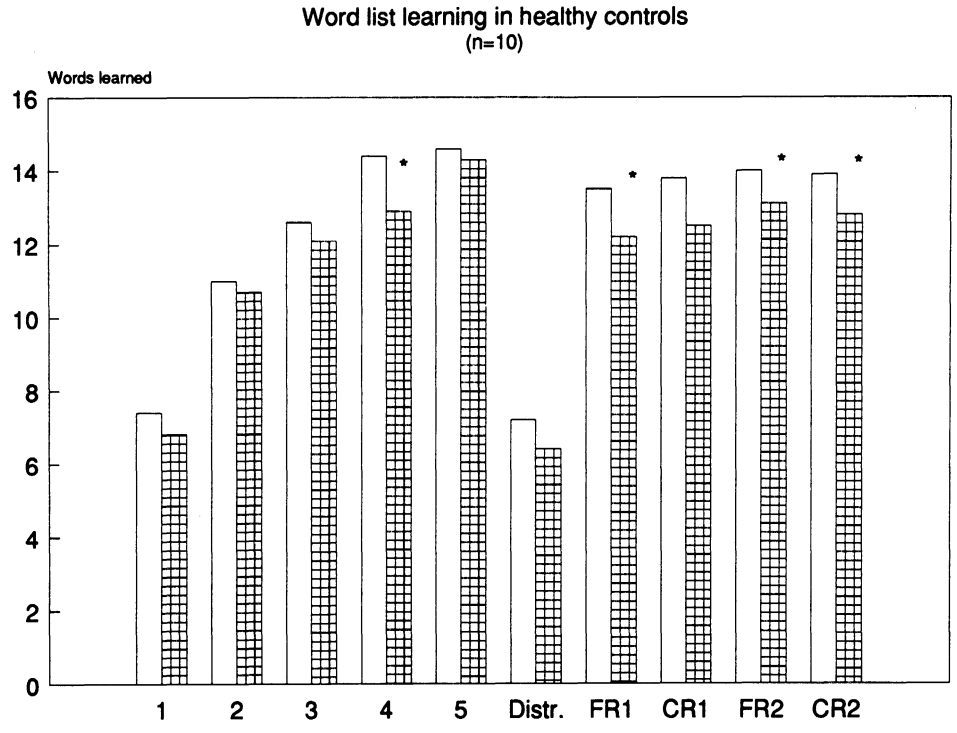
Amounts of words achieved in repetitive presentations of word lists, in free and cued recall during drug phase and DSST results were subtracted from respective baseline values in both groups, differences reflecting the change of memory function or cognitive processing speed in anticholinergic treatment. In both groups these differences were equal (CVLT: mean $p = 0{\cdot}45$; choice reaction time task of DSST: $p = 0{\cdot}7$; mental processing time: $p = 0{\cdot}3$) with the exception of the fifth CVLT presentation ($p = 0{\cdot}04$) and the simple reaction task of DSST ($p = 0{\cdot}01$).

Discussion

At baseline patients did not exhibit signs of global cognitive impairment or dementia as assessed by the HAWIE. Learning ability in CVLT was better in the young healthy volunteers which might be a function of age and not of disease as McEvoy found similar results in a comparison of young and old healthy volunteers (McEvoy *et al.*, 1987). Controls showed a higher reaction speed in DSST probably due to a better motor ability, because both simple and choice reaction tasks are affected to a similar extent. Mental processing time at baseline showed no significant difference between the two groups.

When patients were under sufficient anticholinergic treatment to induce motor improvement as assessed by the UPDRS, significant changes in delayed recall of CVLT and associate learning of WMS became evident. The observed changes were opposite to what would be expected with





FIGS. 1 and 2. Word list learning as assessed by means of CVLT. 1–5: learning during five repetitive presentations. Distr.: Learning of distractor list.FR1/CR1: free/cued recall of first list immediately after distractor list, FR2/CR2: free/cued recall of first list after 20 min. Open bars: pretreatment phase; hatched bars: treatment phase. $*p < 0{\cdot}05$.

repeated administration of the CVLT or WMS where learning effects should normally improve performance. Other tests of this study addressing mainly short term memory functions revealed no change following trihexyphenidyl therapy. There was also no indication for altered cognitive processing speed. The change in simple reaction time of patients but not of controls most probably reflects the improvement of Parkinson symptoms during drug treatment. Anticholinergic exposure in a group of healthy volunteers also led to long term memory impairment of similar magnitude, despite their significantly younger age.

Corresponding effects of cholinergic blockade on memory function in healthy individuals of different age have been previously demonstrated in a number of studies (see Kopelman, 1986 for a review). Anticholinergic exposure consistently produced deficits in long-term memory functions but failed to induce short term memory impairment both in young and elderly individuals (Crow *et al.*, 1973; Drachman, 1977; Broks *et al.*, 1988). Assessing the effects of trihexyphenidyl on different memory functions, time estimation and mood status in an elderly (mean age 66 years) control population McEvoy *et al.* found a significant decline in free recall of word lists and recognition. Similarly to the present study probands exhibited more false positive identifications in recognition during drug application and the authors discussed a lowering of sensitivity in discrimination between targets and distractors by trihexyphenidyl (McEvoy *et al.*, 1987).

Anticholinergic treatment of patients with Parkinson's disease has likewise been shown to affect long-term memory performance. The patients studied by Sadeh and coworkers presented a significant deterioration in delayed but not in immediate digit span during add-on treatment with trihexyphenidyl (Sadeh *et al.*, 1982), while Miller and colleagues found a correlation between verbal memory decline and benzhexol intake in a group of PD patients with disease duration over 3 years and various drug treatment (Miller *et al.*, 1987). Koller assessed a group of patients in early stages of Parkinson's disease (mean duration of disease 2·8 years) with different memory tasks and showed a decline of long term memory functions during treatment with trihexyphenidyl (Koller, 1984).

These cognitive side-effects of anticholinergic drugs are supposed to be due to a blockade of subcortico-frontal cholinergic systems. In Parkinson's disease these systems are involved in the degenerative process. Post-mortem findings have displayed decline of Ach and CAT activity in cerebral cortex as well as loss of cholinergic neurons in nucleus basalis Meynert (see above). Clinical experimental findings of Dubois (Dubois *et al.*, 1987) indicated an increased susceptibility of Parkinson patients towards subthreshold doses of scopolamine resulting in an impaired handling of new information under time pressure

On the other hand the broad variance of memory tests applied in different studies of anticholinergic effects in Parkinson patients and young and elderly controls alike resulted in a nearly uniform decline of acquisition of new material into long term memory. The present results in patients and young controls are in accordance with such findings. Therefore the cognitive

changes of the Parkinson patients as assessed during anticholinergic treatment in this and other studies (Sadeh *et al.*, 1982; Koller, 1984) do not necessarily imply a specific vulnerability of cholinergic systems in such patients. Alternatively cholinergic dysfunction in non-demented patients with Parkinson's disease of recent onset as tested in the present study may not yet have reached a critical threshold for such increased susceptibility to anticholinergic induced cognitive decline to become evident. Indeed several neurobiochemical studies of brains of subgroups of parkinsonian patients showed no (Perry *et al.*, 1983) or only mild signs of cholinergic deficiency in non-demented patients (Perry *et al.*, 1985; Dubois *et al.*, 1983) whereas in later stages of the disease there is good evidence for a rapid decline of cholinergic parameters (Perry *et al.*, 1985; Arendt *et al.*, 1983; Hakim *et al.*, 1979; Whitehouse *et al.*, 1988; Whitehouse *et al.*, 1983).

Clinically relevant anticholinergic induced cognitive impairment might therefore be restricted to patients with more advanced degrees of cholinergic basal forebrain and/or cortical degeneration, while intellectually unimpaired patients with disease of recent onset behave in a fashion similar to healthy individuals, at least over short treatment periods.

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