Motor and cognitive performances of Parkinsonian patients in the on and off phases of the disease

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SUMMARY Twenty-one Parkinsonian patients were tested in on and off phases during chronic levodopa therapy for cognitive function, affective status, and evaluation of motor performance with reaction and movement times. A worsening of mood was observed from the on to the off phase. No variation in cognitive performance was observed from the on to the off phase in spite of evident motor changes. Mood changes during on-off variations may reflect involvement of mesocortical and mesolimbic dopaminergic systems.

Clinical studies of Parkinson's disease have in recent years focused more and more on cognitive features of the disease. On the one hand, several points have been raised, suggesting specific deficits in areas such as memory, language, spatial orientation, and concept formation; on the other hand, the question of a generalised cognitive impairment, at least in some patients, is still being debated.

The relationship between cognitive and motor features of the disease has been the main point of these investigations, bearing with it the question of the functional role of the basal ganglia of humans in cognitive processes. The dramatic evidence of fluctuations of motor symptoms during the on-off phases in Parkinson's disease patients has led some authors to study whether comparable cognitive variations accompany this treatment-induced phenomenon, in the hope of shedding some light on the role that the multisystem dopaminergic disturbance of Parkinson's disease plays in the manifestations of cognitive impairment in that illness.

The present study investigated the changes in motor and cognitive functions and mood that occurred in Parkinson's disease patients presenting the on-off phenomenon. We chose verbal memory, verbal fluency, visuospatial orientation and attention, since these functions have been reported to be affected in Parkinson's disease patients. Standardised measures of clinical status, motor reaction and movement times were also used to compare motor to cognitive performance in our patients.

Methods

Twenty-one non-demented patients (14 males and seven females) with idiopathic Parkinson's disease and 21 controls (13 males and eight females) were examined. The mean age of the patients was 58 ± 8.1 years and mean duration of illness 11 ± 4.8 years, the mean age of the controls was 57.8 ± 7 years.

All the patients were undergoing treatment with levodopa plus peripheral decarboxylase inhibitor. In some, bromocriptine (nine patients) or lisuride (five patients) were also given. All patients were affected by a severe form of the disease and experienced on-off fluctuations. Peak dose dyskinesia were present in 16 patients. Diphasic dyskinesia were evident in three patients; patients showing diphasic dyskinesia experienced at the same time intense anxiety and somatic complaints. The clinical characteristics of the Parkinson's disease patients are reported in table 1. The controls were either relatives of Parkinson's disease patients or patients affected by lumbar disk disease. The examination of the subjects included the following:

(a) Neurological and motor performance assessment

All subjects were given the Duvoisn scale test. Gerlach's rating scale for hyperkinesia was also calculated in the on phase. Objective evaluation of motor performance included a computerised assessment of reaction and movement times. During this each subject had to sit in front of a display screen with seven lights of 5 mm in diameter corresponding to seven touch sensors of 10 mm in diameter arranged under a light source. The distance between lights was 15 cm, so that
the nearest light was 15 cm and the farthest 45 cm away from the central one. Free ocular scanning was allowed. The patient was told to rest his forefinger on the central sensor while the corresponding light was on (ready signal). After two seconds the central light went off (go signal) and a peripheral light appeared in one of the three peripheral positions—on the right side in the case of the patient’s right forefinger and on the left side in the case of the patient’s left forefinger. He then had to move as fast as possible to the corresponding sensor. After two seconds the peripheral light went off and the patient was instructed to move his forefinger back to the central position where the central light was on (ready signal). Two experimental conditions were arranged: in the first the patient already knew before moving which peripheral light was going to be lit (predicted stimulus condition); otherwise peripheral lights were lit according to a random sequence and the patient did not know which one was going to be lit (unpredicted stimulus condition). In the predicted stimulus condition the examiner showed the patient which light was going to be lit any time the position to be reached was changed. When the examiner realised that the patient knew which position he was asked to reach the test was started. In the unpredicted stimulus condition the patient was simply told that both for the right and the left arm any of the peripheral lights was going to be lit and that he was asked to reach the sensor corresponding to the peripheral light that was on. Each sensor was reached 10 times in each condition. Only the mean motor reaction and movement times to reach the position 30 cm away from the central one, adding right plus left performance, are presented here. The session was begun only when it was clear that the subject had clearly understood what he was asked to do. In our setting, motor reaction time was the span of time that elapsed from the moment when the central light was switched off and when contact was lost between the subject’s forefinger and the central sensor. Movement time was the time elapsing from the loss of contact between the subject’s forefinger and the central sensor to when the peripheral sensor was touched. The display screen was connected to a small computer which used a programme to measure both times and to check the time of persistence of the lights. That time was set to 2 s after a preliminary experiment. The programme could also analyse the subject’s responses in terms of errors of position and overlapping of time limits, that is, a reaction time longer than the time of persistence of the peripheral light. These data are not presented here; on the whole, there were very few such errors equally distributed among all positions.

(b) Psychometric assessment
All patients were given the following tests. (1) Benton visual orientation line test (form V for the off phase and form H for the on phase),21 (2) the Set-test modified as follows. Each patient was asked to recall as many words as he could for each of the four semantic categories in 30 s; the same categories were used in the on and off phase for Parkinson’s disease patients.22 (3) A short tale memory test from the Randt memory test; two different forms with the same number of words were used for Parkinson’s disease patients.23 (4) Rene Zazzo’s attention test;24 25 the page of the test was composed of 40 lines, each consisting of 25 signs for a total of 1000 signs of eight different categories (□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ }
corresponded to the number of the two signs crossed in 2 min. The inaccuracy of the crosses was calculated as the ratio between the total number of errors (omission + additions) and the number to be crossed plus the number of additions. (5) Brief Psychiatric Rating Scale (BPRS)26, a partial score was calculated taking into account item nos. 2, 4, 6, 9, 12, 15, 16. Other items were judged to be unsuitable for Parkinson's disease patients. Parkinson's disease patients were evaluated twice in two sessions on different days, within one week, once when on and once when off. Eleven patients were assessed first in the on phase, and 10 patients were assessed first in the off phase, according to a random sequence. Controls were assessed only once. The mean test results of Parkinson's disease patients and controls were analysed with Student's t test, adjusting for age and education level. The comparison between patients and controls was done taking into consideration only those patients whose on testing was the first assessment to avoid possible practice effects when the on testing was the second examination. Tests results of parkinsonian patients in the on-off phases were compared with Student's t test for paired data.

Results

Patients significantly differed from controls in verbal fluency, Rene Zazzo's test speed and inaccuracy and in movement times (table 2). A significant worsening of motor parameters was evident when patients passed from the on to the off phase, except for motor reaction time (table 3). No significant variation in cognitive performance was observed between on and off phases. A significant change in the psychiatric rating score was evident (table 3). The analysis of single items of their scores showed a change in the depressive mood score in 15 patients, in the anxiety score in 12, and in the tension score in six. The thought disorganisation score changed in two patients, and the strange content of thought score in one patient; the hallucination score did not change in any patient.

Discussion

The small number of Parkinson's disease patients compared with controls does not allow definite conclusion concerning the impairment of Parkinson's disease patients in specific cognitive functions. However, in a study of a larger population of Parkinson's disease patients done at our laboratory and whose preliminary results have been presented elsewhere we observed a definite impairment of patients in Rene Zazzo's attention test and in reaction times to predicted and unpredicted stimuli in agreement with that already reported on reaction times of Parkinson's disease patients.18 27–29

Some tests in the present study did significantly discriminate between patients and controls but no test changed between the on and the off phase in spite of the dramatic motor changes. These results, showing that there was no cognitive variation from the on to the off phase, are in agreement with those of Brown et al.17 who attributed the minor cognitive changes they observed from the on to the off phase to the more relevant changes in affect/arousal and did not confirm the variation in verbal fluency and memory of the single care report of Delis et al.16 In accordance with Brown et al.17 is our observation of a worsening of affective status in the off phase. It is noteworthy that the changes in the psychiatric rating total score could be accounted for almost entirely by the changes in depressive mood and anxiety scores. Although an obvious reactive change may occur in the passage from a state of relative well-being to one of almost helpless immobility, the observation of intense and paroxysmal change in mood in three patients of our series all of them showing prominent dophasic dyskinesia, may suggest a true dopaminergic dysfunction of mesolimbic systems30 31 and not a reactive affective change. Such intense mood swings were also
described in detail by Hardie et al.\textsuperscript{32} in their patients with diphasic dyskinesia.

It is indisputable that the on-off phenomenon is a change in the patient's motor status. In fact, a significant lengthening of movement time was observed in the off phase, thus confirming the efficacy of levodopa to ameliorate programming and execution of ballistic movements.\textsuperscript{33,34} Recent clinical observations\textsuperscript{17,32} stressed a variation in mental status too from the on to the off phase; that clinical phenomenon presumably reflects a change of mesocortical and mesolimbic dopaminergic systems function. Why such a change expresses itself mainly as a modification of affective status and not in a variation of cognitive functions remains unsettled and leaves the question of the role of dopaminergic systems in intellectual processes in Parkinson's disease still unanswered.

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