Neuropsychological abnormalities in first degree relatives of patients with familial Parkinson’s disease

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Abstract

Objective—To investigate the cognitive profile of first degree relatives of patients with familial Parkinson’s disease to determine whether these subjects presented signs of neuropsychological dysfunction compared with healthy controls. Results of recent genetic and neuroimaging studies suggest a genetic contribution to the aetiology of Parkinson’s disease and underline the interest in identifying preclinical signs of the disease.

Methods—A battery of tests evaluating executive function was administered to 41 first degree relatives of patients with well documented familial Parkinson’s disease and 39 healthy controls. A factorial discriminant analysis allowed isolation of a subgroup of 15 first degree relatives who could be considered as impaired compared with the healthy controls. Among these 15 “deviant” relatives, nine performed globally worse than the control subjects on all tasks. The six other subjects had mean or even high scores on all task variables, except on those highly correlated with the discriminant score of the factorial discriminant analysis.

Results and conclusion—Among the first degree relatives of patients with familial Parkinson’s disease, some manifested executive dysfunction comparable with that typically associated with the disease. Such impairment could represent a preclinical form of Parkinson’s disease.

Keywords: Parkinson’s disease; executive function; risk factors

The primary cause of Parkinson’s disease is still unknown. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced parkinsonism suggested that Parkinson’s disease could be induced by some toxic environmental exposures. However, until now, no environmental toxin or protoxin responsible for the disease has been identified. The fact that there are families in which an appreciable number of members of different generations present with typical Parkinson’s disease suggests that Parkinson’s disease could be induced by some toxic environmental exposures. A hypothesis is supported by the detection on chromosome 4 q21-q23 of genetic markers linked with the Parkinson’s disease phenotype in a large kindred with autosomal dominant disease, in whom the mutation of the α-synucleine gene was discovered and the recent mapping of a susceptibility locus for Parkinson’s disease on chromosome 2p13.

Recently, PET studies have shown preclinical abnormalities in unaffected co-twins of patients with Parkinson’s disease and in unaffected members of an Irish family. Piccini et al used 18F dopa PET to estimate the prevalence of subclinical nigrostriatal dysfunction in a series of seven unrelated kindreds in which at least two members were affected by levodopa responsive parkinsonism. They showed abnormally reduced putamen uptake of 18F dopa in 25% of the 32 asymptomatic relatives of parkinsonian patients. They considered that reduced striatal 18F dopa uptake in asymptomatic subjects may indicate subclinical parkinsonism. Besides, three of these relatives who were asymptomatic at the time of 18F dopa PET developed clinical parkinsonism within 7 months, 2 years, and 4 years of their scan. It thus seems that subjects might be subclinically affected by the same morbid processes as clinically affected patients.

Identification by PET of those at risk for developing Parkinson’s disease does not seem to be conceivable on a large scale but it is possible that such impaired nigrostriatal function may also lead to preclinical behavioural signs, more particularly at the cognitive level. Indeed, although there was no abnormality in the caudate uptake of 18F dopa in the relatives of the kindreds examined by Piccini et al., Holthoff et al described modification of the cognitive status in unaffected co-twins of patients with Parkinson’s disease.

The aim of the present study was thus to investigate the cognitive profile of first degree relatives of patients with well documented familial Parkinson’s disease to determine whether these family members present signs of neuropsychological dysfunction compared with normal healthy subjects. In early Parkinson’s disease, cognitive dysfunction is mainly executive. Our hypothesis was that, if signs of cognitive dysfunction emerge, they will affect executive function before other processes related to the progression of the disorders at later stages of the disease. The present investigation thus was mainly concerned with executive function.

Methods

Subjects

Diagnosis of Parkinson’s disease was considered as definite when a patient satisfied the criteria of the United Kingdom Parkinson’s Disease Brain Bank (UKPDBB), except for the presence of more than one affected relative. Since 1993, each patient with definite
Table 1  Mean (SD) [range] demographic data of subject groups

<table>
<thead>
<tr>
<th>Subject group:</th>
<th>Sex (M/F)</th>
<th>Age (y)</th>
<th>Education (y)</th>
<th>VIQ - WAIS R</th>
<th>Mattis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relatives</td>
<td>23/18</td>
<td>38.41 (13.82)</td>
<td>105.78 (14.59)</td>
<td>141.41 (2.30)</td>
<td>12.66 (3.21)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>17/22</td>
<td>44.44 (16.51)</td>
<td>109.30 (15.12)</td>
<td>141.90 (1.87)</td>
<td>105.78 (14.59)</td>
</tr>
</tbody>
</table>

Paton’s disease and accompanying family members were interviewed about any occurrence of Parkinson’s disease, Parkinson’s disease-like symptoms, and any other CNS disorder in relatives. Once a secondary case of Parkinson’s disease was found in a family, this affected person was examined when possible by one of us (LD or AD) or a senior neurologist of our group (see acknowledgements), who used UKPDBB criteria to confirm the diagnosis. When this examination was impossible (for example, because of death), Parkinson’s disease was considered as definite when UKPDBB criteria could be retrospectively applied to the data obtained from a neurological report or neurologist interview. Diagnosis of Parkinson’s disease was considered as probable when based on an incomplete medical report or general practitioner interview, or convincing data obtained from relatives. The diagnosis was considered as possible when at least two (three when tremor was present) parkinsonian symptoms from a checklist were present. Such criteria have been used previously, especially in the family in whom the mutation of the a-synucleine gene was discovered. From April 1993 to May 1997, 11 unrelated kindreds identified through presence of one index patient and at least one relative of the first or second degree also presenting with Parkinson’s disease were randomly selected. Forty three relatives (24 men, 19 women) of these 11 di-
eraled that the purpose of the study was to detect preclinical signs of Parkinson’s disease in relatives of patients with familial disease. They were informed that no result would be fed back. They were invited to come back every 2 years for a longitudinal survey. Informed consent was obtained from all subjects. In both groups, subjects who performed below the 20th percentile of the reference population were excluded as well as those obtaining a verbal intelligence quotient (VIQ) below 85, as assessed by the verbal scale of the WAIS-R. From the initial population, 41 first degree relatives and 39 controls were included in the present study.

The characteristics of both groups of subjects are shown in table 1.

NEUROPSYCHOLOGICAL EXAMINATION

Executive functions were evaluated by the following tests:

Wisconsin card sorting test (WCST)
The modified WCST of Nelson was used. The following scores were calculated: the number of categories achieved, the total number of errors, and the percentage of perseverative errors (using Nelson’s version, an error was scored as perseverative if it followed the same category concept as the immediately preceding response).

Sequence generation task (SG)
In 1995, Owen et al described a sequences generation task sensitive to the impairment found in frontal lobe damage and in patients with Parkinson’s disease. A non-computerised version of this task was developed here. All the aspects of the task were in agreement with those developed by Owen et al. Only the recording of response differed. It was inferred that the processes under investigation were the same. A wooden board, on which were four symmetrically disposed identical boxes with a 5 cm × 5 cm bottom face and 2.5 cm in height, was placed in front of the subjects. The subjects were required to generate as many different four box sequences as possible. They were instructed to produce as many sequences as possible without repetition by touching each of the four boxes in turn. A given sequence could start and end with any of the four squares. Every sequence had to include each of the boxes. Subjects were allowed 24 trials. They were not informed that there were 24 possible four box combinations. There was no time limit. Performance was assessed by the total number of different sequences generated within 24 trials, the number of novel sequences before producing the first repetition, and the percentage of perseverative errors. An error (repetition of a sequence already produced) was considered as perseverative if the sequence realised on a trial was the same as those produced at the preceding trial.

Brown-Peterson paradigm (BP)
A dual task paradigm similar to those developed by Brown and Peterson was used. The
primary task was a short term memory retention task: the subject was visually presented a trigram of consonants for 3 seconds and after a delay of retention, he was required to recall the three consonants in exactly the same order as they were presented. To avoid anticipation and learning effects the delay was variable. In the present study, two delay durations were retained—6 and 15 seconds. They were randomly variable among the 15 trials of the task. The task was done in three conditions: control, mild interference, and high interference, which vary depending on the secondary task.

In the control condition, the delay of retention was free and it could then be hypothesised that the subject could use the phonological loop of working memory to maintain the consonants.

In the mild interference condition, the delay of retention was occupied by a secondary task. In this condition, the secondary task consisted of one by one forward counting from a number given by the examiner.

In the high interference condition, the secondary task consisted of a three by three backwards counting task from a number given by the examiner.

In each condition, performance was assessed by the number of trigrams correctly restituted in the correct order (score on 15) and the number of consonants recalled in correct position (score on 45).

Motor dynamic sequences (MDS)
This task was based on the neuropsychological investigation of Luria.32 After the description and demonstration by the examiner of a movement, the subject was instructed to perform it with no time limit.

In the present study, the task comprised three parts:

(a) Simple movements:
- Touch the fingers in turn with the thumb while counting them. This movement was performed with both hands together
- Bring together, then separate the fingers of both hands and repeat.
- Bring together, then separate the fingers of both hands and clench the hands.
Each movement correctly achieved scored 5.
(b) Dynamic organisation:
- Both hands palm down, alternatively clench and extend opposite hands. This movement was repeated five times
- Open hands, right hand palm up, left hand palm down, and alternate five times.
- Right hand open palm up, left hand closed palm down, and alternate five times.
Each sequence correctly achieved was scored 5.
(c) Rhythms:
- The subject was instructed to put his index fingers on the table and:
  - Tap twice with right hand, once with left hand, and repeat five times
  - Tap twice with right hand, once with left hand, three times with right hand, twice with left hand, and repeat five times.

Word fluency test (WF)29
Subjects were instructed to name, in 1 minute, as many words as they could beginning with the letter “L”, then with “M”, and then alternatively with “P” and “R”. People’s names and proper nouns were not permitted; nor were words from the same root.

In each part of the task, performance was assessed by the number of different words named in 1 minute and the percentage of perseverative namings.

Visual discrimination test (VD)30
The 15 objects test is a complex test of visual discrimination elaborated to assess the executive component of perception. It consists of a figure (7.5 x 10 cm) composed of embedded images of 15 familiar objects. Subjects were instructed to name, as fast as possible, each of the objects in the figure, with a maximum time of 120 seconds. The responses were recorded on tape. According to the instructions of Pillon et al., performance was assessed by the time needed to identify the first 12 objects.

The same sequence of tasks was adopted for each subject.

STATISTICAL ANALYSIS
All statistical analysis was performed with SAS software31 (SAS Institute Inc, Cary, NC, USA). p Values<0.05 were considered statistically significant. The assumption of normality was assessed using the Shapiro-Wilk test.

In a first step, the two groups of subjects were compared for each task variable. These comparisons were performed using the unpaired Wilcoxon rank sum test because the normality assumption was violated in at least one group or the variables had less than six distinct values.

In a second step, a factorial discriminant analysis was performed. This procedure provides a linear combination of the task variables (the discriminant score) that has the highest possible multiple correlation ($R^2$) with the groups. $R^2$ is the ratio of the between group variation and the total variation. Discriminant score is a new non-observed variable that best shows the differences between the groups. The relations between discriminant score and the neuropsychological variables were assessed by Spearman correlation coefficients.

Results
Table 2 presents, for each group, the median, mean, and range obtained for each score.

As shown in table 2, these bivariate analyses did not allow isolation of a set of variables differentiating the two subject groups, as the distributions of only one variable (the dynamic organisation part of the motor dynamic sequences task) were significantly different (p=0.03). A multivariate analysis was then conducted.
The results of the factorial discriminant analysis showed a relatively moderate quality of discrimination with a square correlation ratio $R^2 = 0.42$. However, our aim was not to completely separate both populations but to look for those, among the first degree relatives, whose cognitive profile could be considered different from those of the healthy controls.

The median value of discriminant score was 27.4 (mean=27.6, range 25.7–29.4) in the first degree relatives and 25.9 (mean=25.9, range 23.9–27.5) in the healthy controls. The projection of the persons of both groups on the discriminant score, as represented in the figure, clearly showed two populations among the first degree relatives.

By examining this projection, a threshold (discriminant score=28) could be identified. When the discriminant score was below this threshold, the healthy controls and the relatives populations overlapped. When the discriminant score was higher than this threshold, there were no more healthy controls but a group all from the population of first degree relatives. Examination of the correlations between the observed variables and the discriminant score allowed identification of some variables which best explained such typology. They were: the score on the dynamic organisation part of the motor dynamic sequences task (Spearman correlation coefficient $r = -0.44$), the “L” fluency ($r = -0.34$), and the percentage of “L” ($r = 0.33$) and “M” perseverative namings ($r = 0.33$). The better the scores on the dynamic organisation part of the motor dynamic sequences and the higher the “L” fluency, the higher was the probability for a person to belong to the healthy controls and the “non-deviant” first degree relatives. The higher the percentage of “L” and “M” perseverative namings, the higher was the probability for a person to belong to the deviant first degree relatives.

Other variables were also correlated with the discriminant score. However, they were less useful for separating the two populations. A stepwise discriminant analysis was performed to simplify the discriminant score by removing some variables. The square correlation ratio of this analysis was low. This was not surprising because the bivariate analyses could only isolate one variable and the factorial discriminant analysis failed to completely separate both populations. Consequently, all variables were used for the following analyses.

To explain the observed typology, the performances of the two groups as shown by the factorial discriminant analysis were examined. To standardise the scores on each variable, the raw scores were converted to $z$ scores (raw score−mean/SD), on the basis of the scores from the healthy control group. This was done in such a way that positive scores always indicated performance better than the control mean. The sum of these $z$ scores was computed to obtain a global executive score. This global executive score included all tests except the Mattis dementia rating scale and the VIQ.
which served as exclusion criteria and did not provide an evaluation of the executive function. This method of analysis gives equal weight to each component of the summary score. Similar methods of data reduction and analysis have been reported by other authors.33,34 In the healthy control group, the normality assumption of the global executive score was not rejected (Shapiro-Wilk test, p=0.55). Consequently, those whose global executive score was 2 SD below the mean score of the healthy control group were identified as impaired persons. By this procedure, eight first degree relatives were isolated. Among them, five were identified as “deviant” by factorial discriminant analysis. The three others were just at the limit of the cut off threshold. An analysis of the individual scores of these subjects disclosed that they performed globally worse than the other subjects on all task variables. However, the factorial discriminant analysis also considered as deviant 11 other people. Among them, four were comparable with the previous subjects. Although their global executive score was not below 2 SD of the mean score of the healthy control population, they performed globally at a lower level on all task variables. The seven other subjects cannot be considered as impaired on the basis of their global executive score. The analysis of their individual scores showed that all of them, except one, presented a particular cognitive profile. All had mean or even high scores on all task variables, except on those highly correlated with the discriminant score. All had low performance on the dynamic organisation part of the motor dynamic sequences, low “L” fluency, and made more “L” and “M” perseverative namings. One subject showed a different profile: he only made more perseverative namings on the “M” word fluency test. Thus, according to the factorial discriminant analysis, among the 41 first degree relatives, 15 could be considered as cognitively deviant. Among them, nine presented with a global executive impairment. The six others only showed a limited executive dysfunction.

**Discussion**

The present study showed that among first degree relatives of patients with Parkinson's disease, some manifest executive dysfunction comparable with that typically associated with early Parkinson's disease. Such impairment cannot be related to global cognitive deterioration. Indeed, all the subjects who performed below the 20th percentile of the reference population on the Mattis dementia rating scale32 and whose VIQ was below 85 were excluded from the present study. Moreover, examination of table 1 clearly shows that most of the included subjects performed largely above these exclusion criteria. In addition, as the same criteria were applied to healthy controls, if the cognitive impairment shown by the subjects was related to a global cognitive deterioration, controls could also be discriminated by the factorial discriminant analysis. Now, the discriminant score showed a clear limit between the healthy controls and the deviant first degree relatives.

An alternative hypothesis is that the typology found could be explained by age. Such an argument can also clearly be discarded. Indeed, among those considered as deviant by factorial discriminant analysis, age varied between 24 and 64 years (mean 40.76 (SD 14.32), range 24–64). This subgroup was then representative of the initial sample. Moreover, as first degree relatives and healthy controls were matched for age and education, if age was an explanatory factor the factorial discriminant analysis could also discriminate healthy subjects as deviant. This was not the case.

The discriminated people thus manifested specific cognitive impairment in tasks evaluating executive function. Such impairment has largely been considered as reflecting dysfunction of the striatofrontal system.25–36 It can then be suggested that, although they are clinically normal, some people considered as being at risk for developing Parkinsonism, already present dysfunction of the processes depending on the striatofrontal loop. As the impairment found typically resembles those seen in Parkinson's disease, even early in the course of the disease,11–15,25,36 can such cognitive signs indicate preclinical parkinsonism? The discriminated persons were distributed into two categories: nine subjects who manifested a generalised dysexecutive syndrome and performed below the healthy controls on all tasks and six subjects who manifested poor performance only on some particular tasks. In the first category, given the diversity of the tasks administered, it can be argued that the impairment concerns most of the cognitive operations dependent on executive function and might correspond to a preclinical stage of the disease. These people represent 22% of the initial sample. This proportion is then very close to that described by Piccini et al11 when measuring striatal 18F dopa uptake. In the second category, consideration of the processes involved in the impaired tasks showed that all required abilities to alternate between categories of response. Moreover, this shifting was not dependent on an external signal but required internal control. It can then be argued that the supervisory attentional system of the model of attentional control of Norman and Shallice41 is largely involved in such tasks. It can then in turn be hypothesised that the subjects of the second category presented some “fragility” of their supervisory attentional system involving impairment in a limited number of tasks highly dependent on the supervisory attentional system. As the impaired tasks also required complex motor production, an alternative explanation of the findings could be that these subjects present a breakdown in motor and articulatory processes. This would be in agreement with the results of Puccini et al showing reduced putaminal 18F dopa uptake in subjects at risk of developing Parkinson's disease.15 However, the predictive value of such impairment has to be determined by a longitudinal survey of these subjects. Indeed, the duration of the preclinical period of Parkinson's disease is variable. On the basis of extrapolation of pathological and PET data, it...
was estimated to vary from 3 to 5 years to 40 to 50 years. Moreover, the high interpatient variability in the clinical rate of progression of the disease further enhances the variability of the preclinical phase. Among the 15 deviant first degree relatives, none had actually developed Parkinson's disease and four presented minimal motor signs at clinical examination. Unilateral mild slowing or reduction in amplitude of finger taps was found in two of them and slight rigidity activated by mirror movement was found in the two others. The two people with unilateral mild slowing or reduction in amplitude of finger taps belong to the second category of deviant subjects, although the two others belong to the category of globally impaired subjects. It is then possible that both categories of people identified here represent different rates of evolution of the preclinical period. However, the relevance of finding executive dysfunction in clinically normal subjects still has to be determined, as has the predictive value of the association of isolated motor signs and executive dysfunction. The present study thus shows that cognitive impairment without obvious motor disturbances could represent a preclinical form of Parkinson's disease in relatives of patients with familial disease. The nigrostriatal dysfunction shown by PET can then induce a dyselective syndrome before the identification of motor signs. A longitudinal survey of these first degree relatives of patients with Parkinson's disease is in progress to ascertain the predictive value of these cognitive changes. Moreover, the discovery of cognitive dysfunction in first degree relatives of some patients with apparently sporadic Parkinson's disease is interesting. Indeed, the evidence of neuropsychological abnormalities close to those found here could then be interpreted as a phenotypic variant of the disease, demonstrating that familial Parkinson's disease is more frequent than usually estimated.

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