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ORIGINAL COMMUNICATION

Cognitive complaints in Parkinson's disease: its relationship with objective cognitive decline

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Abstract Cognitive complaint interviews (CCI) have been shown to be useful in the early detection of dementia in elderly people. Surprisingly, CCIs are rarely used in Parkinson's disease (PD), despite a six-fold higher risk of dementia than in healthy subjects. The present study sought to determine whether a structured CCI could detect cognitive decline in PD. A validated CCI was added to the usual clinical interview for 180 PD patients. Objective cognitive status was assessed by the Mattis dementia rating scale score. The CCIs ability to detect cognitive decline in PD patients was determined using a receiver operating characteristic (ROC) curve. 58 (32.22%) patients had a significant, subjective cognitive complaint (CCI score >3). Of these, 48.27% had objective cognitive decline. Objective cognitive decline was significantly more frequent in the patients with subjective cognitive complaint. However, the ROC curve for discriminating between patients with and without objective cognitive deficits as a function of their subjective cognitive complaint had low sensitivity (0.50, 95% CI: 0.36–0.64) and moderate specificity (0.74, 95% CI: 0.69–0.84). Logistic regression incorporating the main demographical and clinical variables showed that the CCI score's discriminant power was improved by adding age and the number of years in education to the predictive model. Objective cognitive decline and dementia are more frequent among PD patients reporting a cognitive complaint than among patients not reporting a complaint. However, the CCI does not enable more accurate screening for PD-associated dementia.

Keywords Dementia · Cognition · Screening procedures · Basal ganglia

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Introduction

Parkinson's disease (PD) is a progressive, degenerative, neurological disorder that is characterized most obviously by its motor manifestations (rest tremor, rigidity, akinesia and postural instability). The condition is also associated with change in cognitive functions—sometimes even very early in the course of the disease [1, 2]. Non-demented PD patients exhibit relatively circumscribed executive deficits and secondary disturbances in several other cognitive domains (e.g., memory and visuospatial abilities). Over the natural course of the disease, cognitive function declines and dementia will affect about 40% of PD patients, with a six-fold greater incidence than in healthy subjects [3]. The decline typically includes difficulties in executive and visuospatial functions, as well as memory deficits [4, 5]. Detecting cognitive decline in PD patients is of importance because dementia increases the health care burden and the frequency of institutionalization and reduces quality of life for both patients and carers [6–8]. Moreover, cholinesterase

inhibitor drugs with demonstrated efficacy in PD-associated dementia are now available [9]. However, given that performing an extensive cognitive assessment takes time and consumes medical resources, there is a need for brief screening procedures in clinical practice. Several cognitive short tests or batteries have been tested for their discriminant power, with mixed results. It has recently been shown that a number of cognitive bedside assessment procedures can screen for cognitive decline in PD more effectively than the mini mental state examination (MMSE) does, since the latter is not very sensitive to executive and visuospatial dysfunction [10–13]. However, the discriminant power of a cognitive complaint interview (CCI) has never been assessed in PD, despite the fact that several studies in the elderly have suggested that cognitive complaints (when recorded using standardized items) may help to predict dementia [14–18]. Hence, we decided to establish whether the CCI might constitute a rapid, easy-to-perform procedure for screening for PD patients with cognitive decline. Even though the dementia in PD has an insidious onset, the condition is often characterized by a worsening in memory deficits (i.e., greater difficulty encoding new information) and executive and attention impairments (with greater distractibility and unusual errors)—the disorders that are targeted specifically by the CCI.

The main aim of the present study was to determine the ability of a validated French-language CCI to detect cognitive decline (as evidenced by an objective measurement of cognitive status) in PD patients. We also sought to determine whether the cognitive profile of PD patients with a subjective cognitive complaint (perhaps suggesting dementia onset) differed from that of patients without such a complaint.

Methods

Patients

One hundred and eighty consecutive patients with probable PD [80 women; mean (SD) age: 62 (10); 11 (3) years of education; 10 (7) years since disease onset; mean (SD) score on the unified Parkinson's disease rating scale (UPDRS) part III: 20.65 (10.4)] participated in the study. Parkinson's disease was defined according to international criteria [19]. All patients were assessed after receiving their usual anti-Parkinsonian medication. None of the patients was suffering from neurological diseases other than PD.

An additional group of 50 patients (25 with subjective cognitive complaints and 25 without) underwent an extensive neuropsychological assessment. The two subgroups were strictly matched with regard to age, the number of years in education and the severity of motor symptoms. None of the 50 patients was suffering from depression, according to the DSM-IV criteria. Marsh et al.'s recommendations [20] were used to diagnose depression. The subgroups' demographic and clinical characteristics are shown in Table 1.

Table 1 Demographical and clinical characteristics of PD patients in subgroups with and without cognitive complaints

	WITH complaints	WITHOUT complaints
N (male/female)	25 (13/12)	25 (13/12)
Mean (SD) age (year)	60.5 (8)	61.5 (8)
Years in education (year)	15 (13)	14 (14)
Disease duration (year)	12 (7)	11.5 (5)
UPDRS III score (out of 108)	17.59 (6.75)	16.59 (6.80)
MMSE score (out of 30)	27.16 (2.91)	27.80 (1.98)
MADRS score (out of 60)*	10.77 (4.83)	5.12 (2.88)

* A significant intergroup difference, $p < 0.05$

All participants gave their informed consent to participation in the study.

Cognitive assessment

Cognitive complaints were assessed using a validated, French-language CCI [17, 21], that consists of 10 questions about changes in cognitive function having occurred over the previous 6 months (see Table 2). CCI is rater-administered and does not involve the caregiver. A score over 3 is considered to reflect a complaint [17, 21]. The CCI was administered in addition to the usual clinical interview. The severity of the depressive symptoms was assessed in terms of the score on the Montgomery and Asberg depression rating scale (MADRS) [22].

Overall cognitive status was assessed on the Mattis dementia rating scale (DRS). A cut-off of 130 was used to judge the presence or absence of objective cognitive decline [23–25]. Moreover, in patients with a Mattis DRS score below 130, we applied the DSM-IV criteria for dementia, according to Emre et al.'s recommendations [26] for PD-associated dementia. Forty-two patients met these criteria.

The extensive neuropsychological assessment encompassed a series of tests for detecting cognitive dysfunction in PD patients: the forward and backward digit span test, the French version of the Grober and Buschke 16-item free/cued word learning and recall test [27], according to the procedure described by Pillon et al. [28]; performance was assessed as the total number of words (out of 48) correctly free-recalled and the total number of words (out of 48) correctly remembered after free and cued recall), the Stroop word color test (described in full elsewhere [29];

Table 2 The cognitive complaints interview

	Questions concerning the last 6 months	Response
1	Have you observed a memory change during the last 6 months?	Yes/no
2	During the last 6 months, do you consider that your memory has been worse than the memory of your peers?	Yes/no
3	Do you record less recent events or have you heard your family say 'I have already said so to you'?	Yes/no
4	Do you often forget appointments?	Yes/no
5	Do you often forget where things are left?	Yes/no
6	Do you have more difficulty finding your way in your neighborhood? Have you ever not recognized a route that your family thinks you have already gone?	Yes/no
7	Have you ever forgotten a whole event, even when the family gives you clues, details or pictures of the event?	Yes/no
8	Have you ever encountered difficulty finding particular words (except person names)?	Yes/no
9	Have you reduced your activities (social or leisure's activities, association, papers and invoices) or asked your family to help you because you are afraid you may make a mistake?	Yes/no
10	Have you ever observed mood changes in term of apathy, blunted affect, inertia, loss of volition or interest for activities or persons?	Yes/no

performance was evaluated in terms of an interference index), a letter and number sequencing task corresponding to an oral version of the Trail Making Test (described in full elsewhere [29]; performance was evaluated in terms of an alternation cost index), and a word-generation task (performed over 60 s and under phonemic, semantic and alternating conditions).

Data analysis

The CCI's discriminant power in detecting cognitive decline in PD patients was determined using the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) with a 95% confidence interval.

Sensitivity (the probability of obtaining a CCI score over 3 if the patient has objective cognitive decline) and specificity (the probability of obtaining a CCI score below 4 if the patient does not have objective cognitive decline) were also calculated, with a 95% confidence interval.

An item-based analysis was performed using a squared, multiple-regression coefficient.

Logistic regression was then performed in order to identify factors capable of enhancing the accuracy of the decision criteria. The multivariate model's goodness of fit was assessed in terms of the area under the ROC curve and by applying the Hosmer Lemeshow test (also referred to as a calibration test) to determine whether there were differences between the observed and the predicted probabilities of the event.

The multivariate model's validity was assessed using a cross-validation procedure, as follows: for each patient i, a model M-*i* is derived from the sample obtained after elimination of the patient *i*. The cross-validation score (a linear predictor) for *i* is computed from the coefficients of the model M-*i* with the characteristics of the patient *i*. The cross-validation score can be considered as a new covariate. If this covariate is introduced in a logistic regression, the model is considered to be valid if the parameter associated with this new covariate is close to 1 (>0.85).

A multivariate analysis of variance (MANOVA) with "group" (with and without cognitive complaints) as the between-factor was performed on all the parameters in the extensive cognitive assessment. The significance threshold was set at $p < 0.05$.

Results

The CCI results showed that 58 (32.22%) patients had a significant, subjective cognitive complaint (CCI score >3). Of these patients, 28 (48.27%) had objective cognitive decline (Mattis DRS score <130) of whom 26 (44.83%) met the criteria for dementia. Of the 122 patients free of cognitive complaints, 31 (25.41%) had objective cognitive decline of whom 28 (22.95%) met the criteria for dementia. The frequency of objective cognitive decline was significantly higher in patients with a subjective cognitive complaint ($\chi^2 = 11.764$, $p = 0.001$).

Discriminant power of the CCI

Despite significantly different mean scores, the probability density function showed a considerable overlap of the CCI score distributions as a function of the presence or absence of an objective cognitive decline (see Fig. 1).

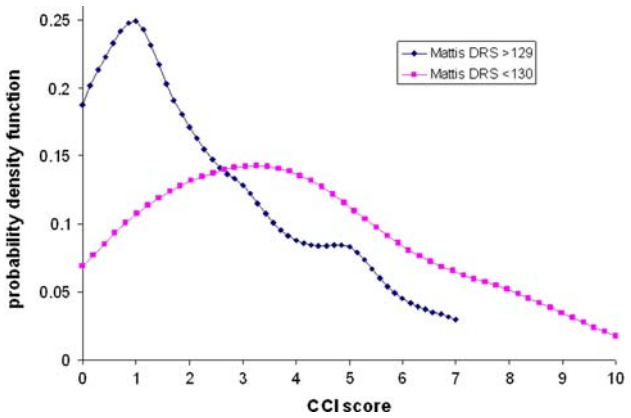

Fig. 1 Probability density function of the cognitive complaint questionnaire (CCI) score in patients with objective cognitive decline (Mattis DRS score <130) and without (Mattis DRS score ≥130)

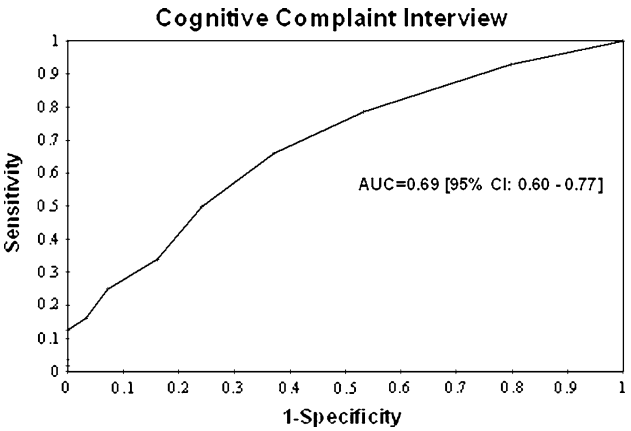

Fig. 2 ROC curve for the CCI score

The ROC curve for discriminating between patients with and without objective cognitive deficits as a function of their cognitive complaint status revealed low sensitivity (0.50, 95% CI: 0.36–0.64) and moderate specificity (0.74, 95% CI: 0.69–0.84) for the CCI's usual cut-off score. As seen in Fig. 2, no other cut-off value was able to yield a better sensitivity/specificity compromise (AUC = 0.69, 95% CI: 0.60–0.77).

An item-based multiple-regression analysis showed that over 90% of the variance was explained by 6 of the 10 questions. However, consideration of these items did not improve the questionnaire's discriminant power (AUC = 0.72, 95% CI: 0.63–0.80).

The logistic regression analysis incorporating the main demographical and clinical variables (i.e., age, number of years in education, disease duration, severity of motor symptoms and severity of the anxious-depressive symptoms) showed that it was possible to significantly enhance the CCI's discriminant power by adding in two items of demographic information: age and number of years in education. Thereafter, the AUC was 0.84 (95% CI: 0.78–0.90, see Fig. 3), with a good calibration result (Hosmer Lemeshow test: $p = 0.41$). The cross-validation covariate was associated with a coefficient value of 0.89 (i.e., close to 1). The composite score calculated from the logistic regression equation enabled determination of the risk of objective cognitive decline according to the patient's age, number of years in education and severity of the cognitive complaint, as follows: $-5.40 + 0.098 \times$ age $- 0.27 \times$ number of years in education $+0.38 \times$ CCI score. For example, in a 70-year-old subject with 8 years in education and a CCI score of 5, the probability of objective cognitive decline was 0.77.

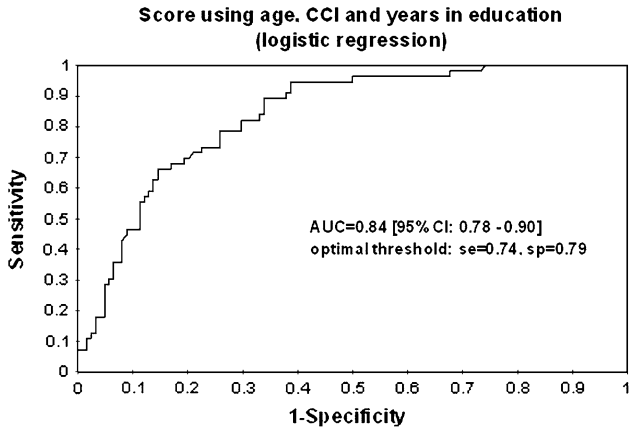

Fig. 3 ROC curve for the composite score using age, CCI score and number of years in education

Comparisons of subgroups with and without cognitive complaints

The mean (SD) results for the cognitive assessment in both patient subgroups are shown in Table 3.

The MANOVA did not reveal any significant group effect (Wilks' lambda, $F_{(14,36)} = 1.91$, $p = 0.059$). The two groups did not differ in terms of any of the cognitive assessment's parameters.

Discussion

The present results show that objective cognitive decline and dementia are more frequent among PD patients reporting a cognitive complaint than among those not reporting such a complaint. However, use of the CCI score does not facilitate screening for PD-associated dementia. Indeed, for PD patients with a significant cognitive complaint, the proportion of patients with and without objective cognitive decline was quite similar—leading to very low sensitivity in a CCI-based test. Moreover, the CCI's

Table 3 Mean (SD) results of the cognitive assessment in PD patients with and without subjective cognitive complaints

Tests	WITH complaints	WITHOUT complaints
Mattis DRS score (out of 144)	135.12 (5.07)	135.92 (5.77)
Forward digit span	5.15 (0.92)	5.00 (0.87)
Backward digit span	3.65 (0.69)	3.36 (0.86)
Gröber and Buschke 16-item recall test		
Free recall (out of 48)	29.04 (5.86)	28.08 (7.39)
Free + cued recall (out of 48)	46.69 (1.46)	46.18 (2.54)
Stroop word/color test (interference index)	0.83 (0.39)	1.11 (0.81)
Letter/number sequencing (alternation cost)	3.39 (1.77)	3.61 (1.99)
Word-generation task (60 s)		
Letter "P"	13.15 (4.51)	14.28 (6.05)
"Animals" category	15.85 (6.04)	17.76 (5.90)
Alternating "T"/"V"	9.54 (2.76)	12.04 (3.09)

discriminant power was not improved by varying the cut-off score and an item-based analysis did not enable identification of a selection of items that improved the discrimination. Nevertheless, our results suggest that one way to improve the CCI's ability to detect PD patients with dementia is to use age and the number of years in education as additional information. Although the validity of this predictive logistic equation has yet to be assessed on an independent series of patients, cross-validation yielded satisfactory results.

A further objective of this study was to investigate any cognitive profile differences between PD patients with and without cognitive complaints. An extensive neuropsychological assessment of two strictly matched patient subgroups revealed that whatever the cognitive domain, PD patients with significant cognitive complaints performed as well as those without complaints. The only difference between the groups was a significantly higher MADRS score for the patients with cognitive complaints, than in patients without complaints (see Table 1). Although none of the study patients met the DSM-IV criteria for depression (since depression was an exclusion criterion), anxious-depressive symptoms were more severe and/or more numerous in patients with complaints. This suggests that patients with complaints had more concerns about their situation in general and their cognitive status in particular and were thus, more likely to complain than the others. This hypothesis is in line with the results reported by Rouch et al. [30] in non-institutionalized, elderly individuals.

Overall, our present results do not support the use of a CCI as a rapid, easy-to-use instrument for helping detect cognitive decline in PD patients. However, a number of study limitations must be considered. Firstly, the CCI we used was initially designed for elderly subjects in general and has mainly been used for the detection of mild cognitive impairment and Alzheimer's disease (AD) in memory clinic outpatients. It was initially designed to detect the cognitive difficulties typically associated with AD (forgetting whole events, anomia, orientation difficulties, lack of interest, etc.). Consequently, the CCI does not feature items that are specific for PD-associated cognitive difficulties, such as executive dysfunction. It is possible that the addition of more PD-specific items could increase the CCI's discriminant power. This also highlights the specificity of PD-associated dementia which is mainly characterized by impaired attention and executive and visuospatial functions [3]. Secondly, the cognitive complaints dealt with here were only patient-rated and an informant's opinion was not incorporated in the evaluation. Hence, it is possible that some of the patients with objective cognitive decline were not aware of their difficulties and, as a result, did not complain. This eventuality may have reduced the CCI's sensitivity. Comparing the patient's opinion with a reliable opinion from a caregiver could also help enhance the procedure's discriminant power. Thirdly, all the study patients had suffered from PD for several years (10 years, on average). It is thus, very likely that they had already been experiencing cognitive symptoms for a long while and were thus, perhaps less sensitive to recent changes in their cognitive status. This possibility may also explain the low rate of complaints among those with objective cognitive decline. Lastly, the present study's cross-sectional design may also induce bias. Indeed, some of the patients with objective cognitive decline and/or dementia had suffered from these conditions for more than 6 months; however, the CCI only deals with changes having occurred over the previous 6 months. It is thus, possible that some patients reported no change but were well aware of their difficulties. A longitudinal design would provide more information on changes over time and could help determine more precisely the CCI's ability to detect cognitive changes heralding dementia in PD.

Overall, our results suggest that due to its specificity, PD-associated dementia has effects on the reporting of

cognitive complaints that differ clearly from those usually associated with AD and thus, needs to be detected by using specific signs of cognitive and behavioral change.

In conclusion, although subjective cognitive complaints are related to objective cognitive decline in PD patients, the CCI does not have adequate clinimetric properties for detecting dementia in PD patients. Our present results underline the difficulty of rapid screening for cognitive decline in PD and highlight the need to develop new instruments which take account of the condition's specific features, incorporate a caregiver opinion and assess recent changes in the patient's activities of daily living.

Conflicts of interest statement The authors report no conflicts of interest.

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