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ORIGINAL COMMUNICATION

Subjective cognitive decline and progression to dementia in Parkinson's disease: a long-term follow-up study

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Abstract

Introduction Increasing evidence suggests that subjective cognitive decline is associated with Alzheimer's disease pathology and with an increased risk for future dementia development. However, the clinical value of subjective cognitive decline in Parkinson's disease (PD-SCD) is unclear. The aim of the present work was to characterize PD-SCD and its progression to dementia.

Methods Forty-three PD patients and twenty normal controls were evaluated with a neuropsychological protocol. Patients were classified as PD-SCD and PD with mild cognitive impairment (PD-MCI). Follow-up assessment was conducted to a mean of 7.5 years after the baseline.

Results Thirteen patients were diagnosed with PD-SCD (30.2%) and 22 patients were classified as PD-MCI (51.2%) at the baseline. Difficulties in language (60.5%) and memory (51.5%) were the most frequent cognitive complaints. PD-MCI showed alterations in processing speed, executive functions, visuospatial skills, memory and language. No significant differences were found between normal controls and PD-SCD in any of the neuropsychological measures. Conversion to clinically diagnosed dementia during the follow-up was 50% in PD-MCI, 33.3% in PD-SCD and 14.3% in patients without subjective cognitive complaints. Discriminant function analyses and logistic regression analyses revealed that language domain and, especially memory domain are good predictors of dementia.

Conclusions The present investigation is the first to conduct a long-term follow-up study of PD-SCD and its relationship with the development of dementia. The results provide relevant data about the characterization of SCD in PD patients and show that PD-SCD is a risk factor for progression to dementia.

Keywords Mild cognitive impairment · Dementia · Neuropsychological assessment · Memory · Follow-up study · Risk factor

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor signs and non-motor symptoms. Mild cognitive impairment is common in non-demented PD patients (PD-MCI), even in the early stages of the disease [1], and is considered as a risk factor for the development of dementia (PDD) [2–4]. The prevalence of PDD increases from 28% after 5 years of evolution to 80% after 20 years of the disease [5].

Subjective cognitive decline (SCD) is very common in the elderly and has gained attention as a predictor of dementia in recent years. Increasing evidence suggests that this subjectively experienced decline is associated with an increased likelihood of biomarker abnormalities consistent with Alzheimer's disease (AD) pathology and with an increased risk for future cognitive decline and AD dementia [6–8].

Subjective cognitive complaints are also frequent in PD patients [9], but their clinical meaning is unclear. An essential question is whether SCD in PD (PD-SCD) is related to objective cognitive status, and if the subjective complaints

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can be considered as a risk factor for PD-MCI and PDD development. To date, there are few available investigations that have focused on the study of PD-SCD and its relationship with cognitive impairment and their results are not conclusive. Some studies reported an association between SCD and poor cognitive performance [9–13], whereas other investigations failed to find clear relationships [14, 15]. These discrepancies can be explained by differences in the experimental design and methodological approach. Most of the studies are only focused on memory symptoms, using a brief questionnaire [9, 16], or a simple yes/no question [10–12]. This approach is probably based on the studies of SCD with AD patients, in which the memory complaints are considered the gold standard. Despite the fact that the cognitive impairment in PD differs to that of AD, and other cognitive domains should be explored to assess the clinical importance of SCD in PD, only a few authors have explored SCD beyond memory complaints [13–15]. Moreover, none of the studies compared different procedures of SCD assessment, and a subsample of healthy controls was not available in many of the studies with the consequent limitation about the interpretation of the results [11, 13–16]. To date, only two investigations conducted a follow-up study focused on PD-SCD and its relationship with cognitive impairment. The preliminary results suggest that cognitive complaints at the baseline can predict cognitive impairment. However, these studies were limited to a 2-year follow-up period and neither of the them reported on PDD development [10, 11].

There are no previous studies, to the best of our knowledge, which have focused on studying SCD in PD patients by a long-term follow-up study. Therefore, the aims of this study were (1) to investigate the neuropsychological profile of PD-SCD, (2) to compare different methodologies to assess subjective cognitive complaints (assessing different cognitive domains or only focusing on memory complaints), (3) to study the proportion of PD-SCD patients who progress to dementia after a mean follow-up of 7.5 years and, (4) to explore which components of the neuropsychological profile at the baseline better predict the development of PDD.

Methods

Subjects

The study included 43 PD patients and 20 healthy controls (HC). Patients were recruited consecutively by a neurologist specialising in movement disorders and were evaluated in the "on" state. The Hoehn and Yahr Scale [17] and the Unified Parkinson's Disease Rating Scale (UPDRS) [18] were applied. All the patients met the clinical criteria for the diagnosis of PD [19]. Exclusion criteria were as follows: (a) global cognitive deterioration defined by the Mini-Mental State Examination (MMSE) score < 24 [20] or dementia associated with PD [21], (b) major psychiatric disorder, (c) drug or alcohol abuse, (d) visual and/or auditory perception disorders limiting the ability to take the test, and (e) history of stroke and/or head injury with loss of consciousness. All patients were taking antiparkinsonian drugs: three patients received a monotherapy with dopamine agonist, 19 patients were treated with dopamine agonist and levodopa, and 21 patients received different combinations of levodopa, dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, and amantadine. Vivid dreaming was reported by only two PD patients and "benign" hallucinations with insight retained were reported by three patients. Patients and HC were matched in terms of age, education, gender, manual preference and estimated IQ (Information subtest) [22]. The Beck Depression Inventory was administered for the assessment of mood state [23] (Table 1).

Neuropsychological assessment

Patients and controls were evaluated with the following protocol of cognitive tests, grouped by domains. Attention was examined using the Digit span backward [24] and the Stroop color–word Test [25]. This version of the Stroop Test includes an index to assess the interference related to the word–color conflict by comparing the subject's performance in the third sheet (word–color) with the same subject's performance in the other two neutral conditions (word and color sheets). Executive functions were assessed by verbal fluency tasks [26] and the Wisconsin Card Sorting Test (WCST) [27]. Verbal fluency tasks consist of asking the participants to quickly generate words beginning with a given letter (phonemic fluency–FAS) and to generate only animals (semantic fluency). Memory was assessed by the California Verbal Learning Test (CVLT) [28] and the 8/30 Spatial Recall Test (8/30 SRT), a 7/24 SRT adaptation [29]. The CVLT includes learning over a five-trial presentation of a 16-word list, free and cued delayed recall and recognition. In the 8/30 SRT the subjects must learn the spatial location of eight black circles displayed in a matrix of 6×5 boxes. When the sheet is removed the subject must place the eight circles in the corresponding locations on an empty matrix. The test includes five trials of learning and two trials of delayed recall (short and long term). Visuospatial functions were examined using the Judgment of Line Orientation Test (JLOT, 15 items simplified version) [30] and a simplified version of the Block design subtest (WAIS-III, 6 designs simplified version) [22]. Finally, language was assessed by the Naming Test, a task of 20 pictorial visual stimuli representing actions [31].

Table 1 Demographic data and clinical characteristics

Variable	HC ($n=20$) M (SD)	All PD ($n=43$) M (SD)	PD-nSCD ($n=8$) M (SD)	PD-SCD ($n=13$) M (SD)	PD-MCI ($n=22$) M (SD)
Gender (men/women)	9/11	24/19[a]	6/2	8/5	10/12
Age (years)	60.85 (12.26)	59.19 (9.64)	50.38 (10.94)	62.31 (8.73)	60.55 (8.06)
Education (years)	8.55 (2.72)	7.88 (2.75)	8.50 (1.51)	9.23 (3.47)	6.86 (2.25)
MMSE	28.20 (1.58)	27.42 (1.76)	28.75 (0.71)	28.15 (1.91)	26.50 (1.44)[c,d,e]
Information (WAIS-III)	14.30 (5.32)	12.50 (5.78)	17.75 (6.96)	15.25 (5.17)	9.09 (2.84)[c,d,e]
BDI score	7.88 (4.94)	13.33 (9.37)[b]	11.63 (5.97)	12.15 (7.17)	14.64 (11.42)
HY stage		2.26 (0.73)	2.00 (0.76)	2.08 (0.76)	2.45 (0.67)
HY stage (range)		1–3	1–3	1–3	1–3
UPDRS Motor Score		28.46 (13.96)	27.57 (11.39)	27.83 (17.15)	29.15 (13.32)
England scale		86.31 (10.54)	90.00 (7.56)	86.92 (11.09)	84.52 (11.17)
Age at onset		50.88 (9.26)	41.88 (7.37)	54.15 (9.33)	52.23 (8.02)
Years since diagnosis		8.30 (6.33)	8.50 (8.60)	8.15 (6.41)	8.32 (5.64)
Cognitive complaint interview					
Attention (%)		1/43 (2.3)		1/13 (7.7)	0/22 (0.0)
Memory (%)		22/43 (51.2)		10/13 (76.9)	12/22 (54.5)
Spoken language (%)		4/43 (9.3)		2/13 (15.4)	2/22 (9.1)
Naming (%)		26/43 (60.5)		10/13 (76.9)	16/22 (72.7)
Written language (%)		3/43 (7.0)		1/13 (7.7)	2/22 (9.1)
Visuoperceptual skills (%)		5/43 (11.6)		2/13 (15.4)	3/22 (13.6)
Executive functions (%)		6/43 (14.0)		3/13 (23.1)	3/22 (13.6)

N number of the sample in each group, *HC* healthy controls, *PD* Parkinson's disease, *PD-nSCD* PD patients without subjective cognitive decline, *PD-SCD* PD patients with subjective cognitive decline, *PD-MCI* PD patients with mild cognitive impairment, *M* mean, *SD* standard deviation, *MMSE* Mini-Mental State Examination, *WAIS-III* Wechsler Adult Intelligence Scale third edition, *BDI* Beck Depression Inventory, *HY* Hoehn and Yahr scale, *UPDRS* Unified Parkinson's Disease Rating Scale

[a]Pearson's chi-squared test was not significant

[b]Comparisons between healthy controls and PD group was significant

[c]Comparisons between HC and PD-MCI was significant

[d]Comparisons between PD-nSCD and PD-MCI was significant

[e]Comparisons between PD-SCD and PD-MCI was significant

Diagnosis of PD-SCD and PD-MCI

The PD-SCD was established on the basis of a semi-structured interview (see supplementary material). The patient and care partner provided their subjective opinions regarding whether the patient had experienced changes in each of the following cognitive functions: attention, memory, spoken language (expression and/or comprehension), naming, written language (reading and/or writing), visuoperceptual skills and executive functions. These responses were recorded as "yes, frequently", "yes, occasionally" and "no". PD-SCD was considered if the patient refers to complaints in at least one cognitive domain ("yes, frequently" or "yes, occasionally"). For each domain, the interviewer provided specific examples of what might indicate impairment in each domain. Additionally, PD-SCD was also only established on the basis of the interview question concerning memory complaint.

Regarding the mild cognitive impairment (MCI) diagnosis, the PD-MCI criteria proposed by the Movement Disorder Society (MDS) were applied (level 1) [32]. Impairment should be present in at least two tests, either within a single cognitive domain or across different cognitive domains. Impairment in neuropsychological tests may be demonstrated by the performance of 1.5 standard deviations or more below the mean of the control group. The absence of significant functional decline was confirmed based on a structured interview and clinical impression of the subject's general cognitive function.

Follow-up assessment and diagnosis of dementia

The patients' follow-up assessments were to a mean of 7.5 (6.3–8.4) years after the baseline. A diagnosis of PDD was made on the basis of the MDS criteria [21]. Decreased global cognitive functioning and deficits severe enough to

impair daily life should be present, according to level 1 of the MDS criteria [33].

Statistical analysis

A nonparametric statistic was used to evaluate differences between groups because the Shapiro–Wilk *W* test showed that data deviated from the standard normal distribution. The Mann–Whitney and Kruskal–Wallis tests were used to compare the means in pairs of groups and multiple groups, respectively. If the Kruskal–Wallis test result was significant, the 2-tailed Mann–Whitney *U* test was used to assess the paired difference between groups (with the Bonferroni correction for multiple comparisons applied). Multinomial logistic regression analyses were performed to investigate the sociodemographic and clinical variables as predictors of PD groups (PD-nSCD vs PD-SCD vs PD-MCI). Discriminant function analyses and stepwise logistic regression analyses were conducted to examine the contribution of cognitive performance at the baseline to PDD diagnosis in the follow-up assessment. Finally, receiver operating characteristic (ROC) curves were graphed and the area under the curves was compared. Optimal cut-offs were defined as the greatest combined sensitivity and specificity, with sensitivity greater than 80%. $p < 0.05$ was set as the level of statistical significance. All the analyses were performed with SPSS-PC software version 24.0 for Windows.

Results

Diagnosis of PD-SCD and PD-MCI

PD patients and controls did not differ in age, years of education, and estimated IQ. PD patients were classified as PD-SCD or PD-MCI according to results of the interview and the MDS Task Force criteria, respectively. Thirteen patients (30.2%) met the criteria for PD-SCD diagnosis and twenty-two patients (51.2%) were classified as PD-MCI. The remaining eight patients (18.6%) were classified as PD-nSCD. Only three patients who met the objective criteria for PD-MCI diagnosis did not report cognitive complaints. These three patients were classified as PD-MCI for future analyses. Difficulties in naming and memory were the most frequent cognitive complaints. Alternatively, patients were classified as PD-SCD based only on the memory question. The results showed that 10 PD patients met the criteria for PD-SCD. Moreover, 10 of the 22 PD patients diagnosed as PD-MCI (45.5%) reported no memory complaints. Table 1 summarizes the demographic features and clinical scores for HC and PD groups.

The results of neuropsychological testing for HC and PD patients (PD-nSCD, PD-SCD, PD-MCI) are shown Table 2. PD-MCI performed poorly compared to the HC, PD-nSCD and PD-SCD groups, in categories of WCST, letter fluency, JLOT and block design. PD-MCI also performed poorly compared to HC and PD-nSCD (but not when compared to PD-SCD), in the Stroop test, visuospatial memory and naming. No significant differences were found between HC, PD-nSCD and PD-SCD, in any of the neuropsychological measures. The visuospatial functions were the cognitive domain with the highest percentage of impairment in PD-MCI patients (95.5%), followed by memory (54.5%), executive functions (50%) and language (40.9%). The percentage of PD-MCI patients with an altered performance in attention/working memory domain was 22.7%. Multiple domain impairment was more frequent than single domain impairment, and occurred in 91% of the PD-MCI patients. Concerning the PD-SCD group, the percentage of patients with an altered performance in the language domain (naming) was 30.8%, followed by visuospatial domain with 23.1% and domains of memory and executive functions, both with 15.4%.

Multinomial logistic regression analysis was conducted to determine which clinical variables had the greatest ability to differentiate between PD groups. Education, BDI, Hoehn and Yahr stage, age at onset of the disease and PD duration were included in the regression analysis as independent variables, and the diagnosis (PD-MCI vs PD-SCD vs PD-nSCD) was the dependent variable. An overall test of the model indicated that the variables that were introduced into the equation significantly impacted the dependent variable ($X^2 = 30.51$; $p = 0.002$). The deviance statistic was not significant ($X^2 = 56.98$, $p = 0.902$), suggesting a goodness-of-fit for the model. Education contributed significantly to the model ($X^2 = 10.82$, $p = 0.004$), with significant differences in PD-MCI compared to PD-SCD ($WALD = 4.37$, $p = 0.037$) and PD-nSCD ($WALD = 5.14$, $p = 0.023$). The age at onset of the disease also contributed significantly to the model ($X^2 = 16.60$, $p = 0.000$), with significant differences in PD-MCI compared to PD-nSCD ($WALD = 6.09$, $p = 0.014$). Hoehn and Yahr stage ($X^2 = 8.56$, $p = 0.073$), PD duration ($X^2 = 1.83$, $p = 0.400$) and mood state ($X^2 = 3.45$, $p = 0.178$) did not reach statistical significance.

Follow-up assessment and diagnosis of dementia

Conversion to dementia during the follow-up study was more frequent in patients with PD-MCI (50%) compared to patients with PD-SCD (33.3%) and more frequent in the PD-SCD group compared to patients with PD-nSCD (14.3%). Four PD patients did not participate in the follow-up study (Fig. 1). The baseline clinical characteristics (Table 3) and cognitive performance (Table 4) of patients who converted to dementia and those who did not (PDND) were analyzed. PDD differed significantly at the baseline, compared to

Table 2 Neuropsychological test scores for PD patients and healthy controls

Variable	HC ($n=20$)	PD-nSCD ($n=8$)	PD-SCD ($n=13$)	PD-MCI ($n=22$)	χ^2	p value	HC vs PD-MCI		PD-nSCD vs PD-MCI		PD-SCD vs PD-MCI	
	M (SD)	M (SD)	M (SD)	M (SD)			p value	r	p value	r	p value	r
Attention–working memory												
Digit Span backward	4.32 (1.34)	4.88 (1.13)	3.77 (1.09)	3.32 (0.89)	12.459	0.006 [b]			0.009	0.57		
Stroop test—Word	93.70 (15.23)	109.00 (22.17)	82.17 (11.83)	66.91 (21.70)	24.357	0.000 [a,b]	0.001	0.59	0.000	0.64		
Stroop test—Color	60.50 (12.07)	70.38 (19.85)	52.83 (9.10)	48.05 (11.63)	14.167	0.003 [a,b]	0.015	0.48	0.013	0.50		
Stroop test—Word–color	31.85 (11.73)	40.75 (10.55)	28.92 (10.34)	25.00 (8.75)	11.163	0.001[b]			0.008	0.59		
Stroop test—Interference	− 4.68 (8.21)	− 2.10 (5.17)	− 3.14 (7.40)	− 2.49 (7.11)	1.199	0.753						
Executive functions												
WCST (categories)	3.88 (1.97)	4.50 (2.14)	2.69 (1.44)	1.00 (1.02)	26.751	0.000 [a,b,c]	0.000	0.66	0.000	0.65	0.032	0.57
Letter fluency	25.47 (9.55)	31.75 (7.67)	26.62 (0.16)	16.86 (6.17)	20.759	0.000 [a,b,c]	0.011	0.50	0.000	0.67	0.017	0.53
Animals	17.00 (5.24)	17.75 (5.18)	16.38 (3.38)	14.59 (2.72)	5.320	0.150						
Learning and memory												
CVLT—Trial 1	6.60 (2.68)	6.13 (1.36)	6.42 (2.71)	5.36 (2.56)	3.009	0.390						
CVLT—Trial 5	12.95 (2.61)	12.00 (1.60)	11.50 (1.45)	10.36 (2.92)	9.520	0.023 [a]	0.014	0.44				
CVLT—Total learning	52.95 (12.76)	51.00 (4.63)	49.25 (9.86)	42.50 (11.94)	8.156	0.043 [d]						
CVLT—Delay	11.80 (3.94)	11.25 (2.49)	10.33 (2.67)	9.23 (3.64)	5.522	0.137						
CVLT—Delay (semantic cued)	12.80 (3.05)	11.38 (2.00)	10.92 (2.91)	9.86 (3.20)	8.652	0.034 [a]	0.024	0.43				
8/30 SRT—Trial 1	5.00 (1.60)	4.63 (1.51)	3.92 (1.90)	3.71 (1.45)	6.267	0.099						
8/30 SRT—Trial 5	6.90 (1.37)	7.39 (0.92)	5.54 (2.33)	4.91 (1.97)	15.127	0.002 [a,b]	0.009	0.51	0.011	0.54		
8/30 SRT—Total learning	30.32 (7.62)	30.75 (5.75)	25.39 (6.91)	21.29 (6.40)	16.841	0.001 [a, b]	0.001	0.53	0.019	0.56		
8/30—Delay	5.74 (1.97)	6.00 (2.33)	5.08 (1.85)	4.10 (1.87)	8.388	0.039 [d]						
Visuospatial functions												
JLOT	13.26 (1.37)	13.38 (1.51)	13.25 (1.36)	8.82 (3.49)	24.194	0.000 [a,b,c]	0.000	0.66	0.006	0.57	0.002	0.61
Block design	15.58 (3.98)	17.00 (6.33)	15.33 (5.61)	7.24 (4.12)	27.128	0.000 [a, b, c]	0.000	0.73	0.001	0.61	0.002	0.62
Language												
Naming test	18.74 (1.45)	19.00 (0.54)	17.92 (1.89)	16.18 (2.91)	14.386	0.002 [a, b]	0.001	0.53	0.003	0.55		

n number of the sample in each group, *HC* healthy controls, *PD* Parkinson's disease, *PD-nSCD* PD patients without subjective cognitive decline, *PD-SCD* PD patients with subjective cognitive decline, *PD-MCI* PD patients with mild cognitive impairment, *M* mean, *SD* standard deviation, *WCST* Wisconsin Card Sorting Test, *CVLT* California Verbal Learning Test, *8/30 SRT* 8/30 Spatial Recall Test, *JLOT* Judgment of Line Orientation Test

[a]Comparisons between HC and PD-MCI was significant

[b]Comparisons between PD-nSCD and PD-MCI was significant

[c]Comparisons between PD-SCD and PD-MCI was significant

[d]No significant after Bonferroni correction

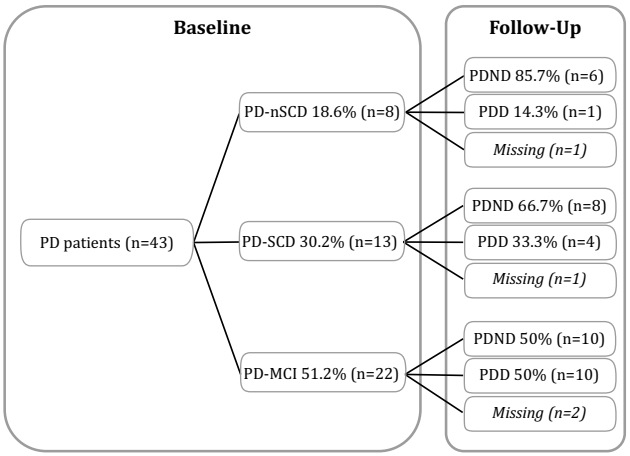

Fig. 1 Percentage of patients that developed dementia

PDND in age and age at onset of the disease. Moreover, PDD performed poorly compared to PDND in the MMSE. No significant differences were found between the groups in the remaining demographic and clinical variables. The results concerning neuropsychological assessment at the baseline showed that PDD performed poorly compared to PDND in the Stroop test (word score and color score), CVLT (learning and long delay), 8/30 SRT (learning), and naming.

The utility of cognitive performance at the baseline for classifying patients into PDD and PDND was evaluated using discriminant function analyses. A general index for each cognitive domain was obtained by calculating the mean of the z-score of the test used to assess each domain. Each cognitive domain (memory, attention, executive, visuospatial, language) was entered into the discriminant function. The overall classification rate was 71.8% for the language domain and 70.3% for the memory domain. The overall classification rates for the attention, executive and visuospatial domains were below 70%. The discriminant function analyses can be seen in Table 5. A stepwise logistic regression analysis was performed to determine which cognitive functions, evaluated at baseline, had the greatest ability to differentiate PD patients with and without dementia. The general index for each cognitive domain was entered into the regression analysis as an independent variable, while the diagnosis of dementia (PDD vs PDND) was the dependent variable. The Hosmer and Lemeshow Test was not significant ($X^2 = 6.72$, $p = 0.458$), suggesting a goodness-of-fit for the model. The analysis showed that only the memory domain significantly contributed to the prediction ($WALD = 6.77$, $p = 0.009$). An overall test of the model was significant ($X^2 = 9.61$; $p = 0.002$).

New discriminant function analyses were carried out with the aim of evaluating the utility of memory performance (total learning and long delay of CVLT and 8/30 SRT) at the baseline for classifying patients into PDD and PDND (Table 6). Total learning and long delay for verbal and visuospatial memory combined reached an overall classification rate of 86.5% (PDD 85.7%, PDND 87.0%). Visuospatial memory (learning/delay combined) reached an overall classification rate of 84.2% (PDD 85.7%, PDND 87.0%), whereas the classification rate for verbal memory (learning/delay combined) was 81.6% (PDD 80.0%, PDND 82.6%). Stepwise logistic regression analysis was performed to explore which memory variables (total learning and long

Table 3 Baseline demographic data and clinical characteristics of PD patients converted to dementia in the follow-up study

Variable	PDD ($n = 15$) M (SD)	PDND ($n = 24$) M (SD)	*U* value	*p* value	*r*
Gender (men/women)	9/6	14/10	0.011[a]	0.593	
Age (years)	64.67 (6.07)	55.54 (10.12)	288.000	0.001	0.50
Education (years)	7.80 (3.45)	8.08 (2.41)	157.500	0.521	
MMSE	26.73 (1.71)	27.92 (1.74)	111.500	0.047	0.32
Information (WAIS-III)	11.93 (6.45)	13.09 (5.49)	141.500	0.359	
BDI score	12.53 (7.69)	13.38 (10.56)	180.500	0.988	
HY stage	2.53 (0.64)	2.04 (0.75)	245.000	0.062	
HY stage (range)	1–3	1–3			
UPDRS-M	29.87 (11.38)	27.74 (15.85)	195.500	0.497	
England scale	85.67 (8.21)	86.96 (12.59)	136.500	0.286	
Age at onset	55.07 (7.54)	48.13 (9.64)	254.500	0.030	0.35
Years since diagnosis	9.60 (6.69)	7.42 (6.61)	226.500	0.182	
Follow-up time	7.53 (0.60)	7.48 (0.71)	186.500	0.853	

n number of the sample in each group, *PDD* PD patients with dementia in the follow-up study, *PDND PD* patients without dementia in the follow-up study, *M* mean, *SD* standard deviation, *MMSE* Mini-Mental State Examination, *WAIS-III* Wechsler Adult Intelligence Scale third edition, *BDI* Beck Depression Inventory, *HY* Hoehn and Yahr scale, *UPDRS-ME* Unified Parkinson's Disease Rating Scale—Motor score

[a]Pearson's chi-squared test was not significant

Table 4 Baseline neuropsychological assessment of PD patients converted to dementia in the follow-up study

Variable	PDD ($n=15$) M (SD)	PDND ($n=24$) M (SD)	U value	p value	r
Attention–working memory					
Digit Span backward	3.47 (0.99)	3.71 (1.08)	156.500	0.502	
Stroop test—word	65.60 (22.95)	87.15 (20.00)	84.500	0.007	0.42
Stroop test—Color	46.60 (12.33)	57.91 (13.81)	92.500	0.016	0.38
Stroop test—word–color	24.93 (9.92)	31.39 (10.79)	116.000	0.095	
Stroop test—interference	− 1.91 (7.46)	− 3.23 (6.75)	182.500	0.768	
Executive functions					
WCST (categories)	1.13 (0.92)	2.54 (2.15)	112.000	0.051	
Letter fluency	19.20 (10.37)	23.93 (8.86)	120.000	0.086	
Animals	14.73 (2.46)	16.21 (3.98)	144.000	0.309	
Learning and memory					
CVLT—Trial 1	4.87 (1.81)	6.65 (2.44)	101.000	0.033	0.34
CVLT—Trial 5	10.13 (2.30)	11.83 (2.23)	106.500	0.048	0.32
CVLT—total learning	42.13 (9.56)	50.00 (10.42)	102.000	0.035	0.34
CVLT—delay	7.06 (3.02)	11.61 (2.45)	49.500	0.000	0.59
CVLT—delay (semantic cued)	8.20 (2.18)	12.09 (2.37)	37.500	0.000	0.65
8/30 SRT—Trial 1	3.57 (1.22)	4.54 (1.53)	94.000	0.025	0.37
8/30 SRT—Trial 5	4.50 (2.07)	6.33 (1.81)	85.000	0.011	0.41
8/30 SRT—Total learning	20.50 (6.47)	27.71 (6.14)	72.000	0.003	0.47
8/30—delay	4.21 (2.36)	5.08 (1.93)	129.500	0.247	
Visuospatial functions					
JLOT	9.27 (4.33)	11.87 (2.74)	113.000	0.078	
Block design	9.43 (6.78)	12.34 (6.71)	119.500	0.196	
Language					
Naming test	15.80 (2.81)	18.04 (2.03)	78.500	0.003	0.48

n number of the sample in each group, *PDD* PD patients with dementia in the follow-up study, *PDND* PD patients without dementia in the follow-up study, *M* mean, *SD* standard deviation, *WCST* Wisconsin Card Sorting Test, *CVLT* California Verbal Learning Test, *8/30 SRT* 8/30 Spatial Recall Test, *JLOT* Judgment of Line Orientation Test

Table 5 Classification rates (%) for each cognitive domain from the discriminant function analyses

	PDD ($n=15$)	PDND ($n=24$)	Overall
Cognitive domain			
Attention	53.3	52.2	52.6
Executive	80.0	58.3	66.7
Memory	64.3	73.9	70.3
Language	53.3	83.3	71.8
Visuospatial	50.0	78.3	67.6

n number of the sample in each group, *PDD* PD patients with dementia in the follow-up study, *PDND* PD patients without dementia in the follow-up study

delay of CVLT and 8/30 SRT) had the greatest ability to differentiate between PDD and PDND. The Hosmer and Lemeshow Test was not significant ($X^2=4.16$, $p=0.761$), suggesting a goodness-of-fit for the model. Total learning of CVLT ($WALD=5.16$, $p=0.023$) and long delay of 8/30 SRT ($WALD=6.10$, $p=0.014$) significantly contributed to the prediction. An overall test of the model was significant ($X^2=23.76$; $p=0.000$). For a differentiation between PDD and PDND groups, the area under the ROC curve of CVLT (long delay) was 0.846 (95% CI 0.70–0.99), while the area under the ROC curve of 8/30 SRT (total learning) was 0.792 (95% CI 0.63–0.95). The optimal cut-off was 8.5 for CVLT (sensitivity 0.870, specificity 0.714) and 21.5for 8/30 SRT (sensitivity 0.870, specificity 0.643).

Discussion

The aim of the present investigation was to explore the clinical value of subjective cognitive complaints in PD patients, in terms of their relationship with objective cognitive impairment and the risk of progression to dementia. The diagnosis of SCD was based on a semi-structured interview that allowed the researchers to explore the different cognitive domains and PD-SCD was present in 30.2% of patients (13/43). However, when the identification of SCD is only

Table 6 Classification rates (%) for each memory variables from the discriminant function analyses

	PDD ($n=15$)	PDND ($n=24$)	Overall
Verbal memory			
CVLT—total learning	73.3	60.9	65.8
CVLT—long delay	73.3	78.3	76.3
Learning/delay combined	80.0	82.6	81.6
Visuospatial memory			
8/30 spatial recall test—total learning	71.4	70.8	71.1
8/30 spatial recall test—long delay	57.1	50.0	52.6
Learning/delay combined	85.7	83.3	84.2
Verbal/visuospatial memory combined			
Total learning	85.7	78.3	81.1
Long delay	85.7	78.3	81.1
Learning/delay combined	85.7	87.0	86.5

n number of the sample in each group, *PDD PD* patients with dementia in the follow-up study, *PDND PD* patients without dementia in the follow-up study, *CVLT* California Verbal Learning Test

based on memory complaints, only 23.25% of patients were classified as PD-SCD. Moreover, 45.45% (10/22) were false negative, that is, patients who met objective cognitive criteria for PD-MCI diagnosis but did not report any memory complaints. These results are highly relevant for future investigations and also for clinicians: the SCD assessment is frequently the first step of cognitive examination and can influence future decisions (e.g., to administer a screening test or a comprehensive neuropsychological assessment). Assessments that do not include procedures to adequately explore cognitive complaints may underestimate the proportion of PD-SCD and, therefore, PD-MCI and thus misclassify patients as PD with normal cognition, especially when brief cognitive examinations are chosen. Although they are limited, the results of previous studies support this interpretation. The percentage of PD patients who did not refer to cognitive complaints but did meet objective cognitive criteria for PD-MCI (false negative) was greater than 50%, when assessment was only based on memory complaints [9, 10], whereas the percentage of false negative was 22–25% when different cognitive domains were explored [14, 34].

There are investigations which suggest that SCD is associated with depression or personality traits rather than objective cognitive decline [35]. The results available concerning PD patients are heterogeneous, with different authors reporting an association between mood state and SCD [9, 15], whereas other investigations failed to find equivalent results [11, 12]. Hong et al. [13] showed that cognitive complaints were associated with depression and also with neuropsychological measures. The association between cognitive complaints and objective cognitive assessment remained significant when the analyses were adjusted for the depression score. In the present study, no differences were found in depression symptoms between PD groups. Moreover, the results of the regression model showed that depression did not reach statistical significance to differentiate between the PD groups. Therefore, SCD cannot be explained by symptoms of depression. On the other hand, education and the age at onset of disease contributed significantly to the regression model differentiating between PD groups. This result was expected and is coincident with previous studies [36, 37].

An important question is whether SCD in PD patients can be used to predict future cognitive impairment. To date, different authors have reported an association between SCD in PD and cognitive impairment [9–13], but only two investigations conducted a 2-year follow-up study to explore this hypothesis. The results showed that PD-SCD exhibited a more significant annual decline in semantic fluency, visuospatial memory and naming [11], and that PD-SCD was associated with a higher rate of conversion to PD-MCI compared to PD patients without SCD [10, 11]. The present investigation is the first to study the conversion rate to dementia in PD-SCD by conducting a long-term follow-up study. The percentage of PD-SCD who develop PDD was more than double that of PD patients without SCD (33.3% vs. 14.3%), and higher in PD-MCI (50%). The neuropsychological profile at the baseline of patients with and without dementia was compared to explore which cognitive domains can be considered better predictors for the development of dementia, and if it is associated with the type of cognitive complaint. PDD was associated with a poor performance in memory (verbal and visuospatial) and linguistic functions (naming). Moreover, the results of the discriminant function analyses show that the language domain and, especially, the memory domain are good predictors for PDD development. Logistic regression and ROC curves reinforce this affirmation. This result is especially relevant and interesting, considering that difficulty in naming (60%) and memory (51%) were the more frequently described cognitive symptoms in the interview.

The clinical value of SCD as predictor of AD has been recognized. AD pathology, including low beta-amyloid levels found in cerebrospinal fluid, as well as cortical thinning (e.g., in the temporal cortex), or disintegration of the default mode network are predictors of AD dementia, and have been associated with SCD [8, 38, 39]. However, the PD-SCD construct is more recent and the underlying neuropathology remains unclear. Cognitive impairment in PD is recognized as heterogeneous in its clinical phenotype, progression rates and underlying pathophysiology [40].The present investigation is consistent with the PD dual syndrome hypothesis in which two cognitive subtypes were described: (1) the executive dysfunction profile, which is associated with frontostriatal dysfunction, dopamine depletion and COMT genotype, and (2) the posterior cortical dysfunction profile (e.g., language), which is linked to AD pathology, nondopaminergic neurotransmitters, and the MAPT genotype, with the latter having an increased risk of developing dementia [41, 42]. The studies that have focused on the association between SCD and PD-biomarkers are limited. Subjective memory complaints have been associated with cortical thinning in fronto-temporo-parietal areas [12], and disruptions in the default mode network, which have been associated with cognitive performance, have been described in PD patients with normal cognition [43, 44].

Certain limitations of the present study need to be acknowledged: (1) the sample size is relatively small, (2) neuroimaging data were not available and (3) comprehensive neuropsychological assessment during the follow-up was not included. Further studies with larger samples, neuroimaging data and which include detailed information about the cognitive performance of PDD patients would be able to confirm these findings.

In summary, the present investigation is the first to conduct a long-term follow-up study of PD-SCD and its relationship with the development of dementia, and it is also the first to compare different procedures to assess subjective cognitive complaints in PD patients. The results suggest that SCD in PD patients, measured by adequate procedures to examine subjective cognitive complaints, beyond memory symptoms, can be considered as a risk factor for developing PDD, providing relevant information for the establishment of cognitive status.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standard All participants were informed about the aims of the investigation and participated voluntarily and gave their informed consent. The data were obtained in accordance with the regulations of the local ethics Committee and in compliance with the Helsinki Declaration for Human Research.

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