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Parkinson's Disease-Cognitive Rating Scale: A New Cognitive Scale Specific for Parkinson's Disease

Javier Pagonabarraga, MD, Jaime Kulisevsky, MD, PhD,* Gisela Llebaria, MD, Carmen García-Sánchez, MD, PhD, Berta Pascual-Sedano, MD, PhD, and Alexandre Gironell, MD, PhD

Movement Disorders Unit, Neurology Department, Sant Pau Hospital, Autonomous University of Barcelona, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

Abstract: Cognitive defects associated with cortical pathology may be a marker of dementia in Parkinson's disease (PD). There is a need to improve the diagnostic criteria of PD dementia (PDD) and to clarify the cognitive impairment patterns associated with PD. Current neuropsychological batteries designed for PD are focused on fronto-subcortical deficits but are not sensitive for cortical dysfunction. We developed a new scale, the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), that was designed to cover the full spectrum of cognitive defects associated with PD. We prospectively studied 92 PD patients [30 cognitively intact (CogInt), 30 mild cognitive impairment (MCI), 32 PDD] and 61 matched controls who completed the PD-CRS and neuropsychological tests assessing the cognitive domains included in the PD-CRS. Acceptability, construct validity, reliability, and the discriminative properties of the PD-CRS were examined. The PD-CRS included items assessing fronto-subcortical defects and items assessing cortical dysfunction. Construct validity, test-retest and inter-rater reliability of PD-CRS total scores showed an intraclass correlation coefficient >0.70. The PD-CRS showed an excellent test accuracy to diagnose PDD (sensitivity 94%, specificity 94%). The PD-CRS total scores and confrontation naming item scores-assessing "cortical" dysfunction—independently differentiated PDD from non-demented PD. Alternating verbal fluency and delayed verbal memory independently differentiated the MCI group from both controls and CogInt. The PD-CRS appeared to be a reliable and valid PD-specific battery that accurately diagnosed PDD and detected subtle fronto-subcortical deficits. Performance on the PD-CRS showed that PDD is characterized by the addition of cortical dysfunction upon a predominant and progressive fronto-subcortical impairment. © 2008 Movement Disorder Society

Key words: Parkinson's disease; cognition; dementia; rating scale; neuropsychological

Some degree of cognitive impairment is common in nondemented Parkinson's disease patients (PD-ND) and eventually progress to dementia in 24 to 31% of patients.[1] In population-based and cohort studies, from 23.5 to 55% of PD-ND patients show mild cognitive defects since the early stages of the disease.[2–4] The cognitive changes in PD are characterized by a frontal-subcortical impairment with decreased attention and executive function leading to progressive impairment in prefrontal tasks, visuospatial skills, and memory.[2,5,6] Still, 20 to 25% of PD-ND patients may exhibit a pattern of cortical impairment with memory tasks and confrontation naming defects,[2] and cognitive findings associated with cortical pathology, such as language errors, develop in many patients with PD with dementia (PDD).[7]

Accordingly, neuroimaging and pathological studies have variably correlated the development of PDD with both frontal-subcortical and cortical alterations. Decreased fronto-striatal dopaminergic activity,[8,9] widespread decrease of cortical cholinergic activity,[10,11] and higher cortical degeneration in the limbic/paralimbic system have all been reported.[12–14] Thus, to capture the whole spectrum of cognitive defects associated with PD, neuropsychological evaluation should include items sensitive to cortical and frontal-subcortical dysfunction.

Only two published neuropsychological batteries have been specifically designed to target the most specific cognitive deficits in PD.[15,16] The Mini-Mental

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*Correspondence to: Jaime Kulisevsky, Movement Disorders Unit, Neurology Department, Sant Pau Hospital, Sant Antoni M, Claret 167, 08025 Barcelona, Spain. E-mail: jkulisevsky@santpau.es

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Parkinson[15] is a brief screening test aimed at identifying PD patients who require a more comprehensive cognitive assessment. Only the pilot study was published, and the scale was not subjected to extensive clinimetric evaluations.[15] The SCOPA-COG is a short, reliable and valid instrument sensitive to measure cognition in PD.[16] However, the scale was constructed with items assessing frontal-subcortical functions, but did not include items sensitive to cortical dysfunction.

To address the need for a more comprehensive but still practical tool for cognitive assessment we developed the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), a new PD-specific cognitive scale aiming to capture the whole spectrum of cognitive functions impaired over the course of PD. The information provided by the assessment of fronto-subcortical and cortical cognitive functions may help to increase the sensitivity and specificity to diagnose PDD, to separate subgroups of patients according to their pattern of cognitive impairment since the early stages of the disease, and to detect those subjects with a higher risk to eventually develop dementia.

PATIENTS AND METHODS

Subjects

Ninety-two patients with idiopathic PD fulfilling diagnostic criteria for PD[17] were prospectively recruited from a sample of outpatients regularly attending the Movement Disorders Clinic at Sant Pau Hospital, Barcelona. Each patient was interviewed regarding disease onset, education level, medication history and current medications and dosage.[18] PD patients were at stable doses of medication the 4 weeks before inclusion and during the study.

Motor status and disease severity were assessed by the Unified Parkinson's Disease rating scale (UPDRS) and Hoehn and Yahr scale (H&Y).[19] In accordance with published research criteria, we used the 1-year rule to distinguish between PDD and DLB.[20,21] All experimental participants scored <4 on the Ischemia Score of Hachinski et al.[22] to rule out vascular dementia. To screen for mood disorders, individuals with a cut-off score ≥ 11 in the Hospital Anxiety and Depression Scale (HADS)[23] were excluded, as were those with abnormalities on brain CT or MRI in the past 12 months, abnormal blood tests or non-compensated systemic diseases, or inability to read or understand Spanish.

Patients were classified as cognitively intact (CgInt), PD with mild cognitive impairment (MCI) or PD with dementia (PDD). Intact cognition was diagnosed when patients had a score of 0 on the Clinical Dementia Rating Scale (CDR),[24] MCI when the score was 0.5, and PDD wshen the score was ≥one and when they met 294.1 criteria for PDD on the Diagnostic and Statistical Manual of Mental Disorders, revised Fourth Edition (DSM IV-TR).[25] Patients with motor fluctuations were examined during the "on" state.

Sixty-one age-, sex- and education-matched healthy subjects, most of whom were spouses or caregivers of the patients, served as the control group. None of the controls had cognitive complaints or prior history of cardiovascular risk factors or neurological or psychiatric illness.

Informed consent to participate in the study was obtained from all patients or caregivers, as appropriate, and from controls. The study was approved by the Local Ethics Committee.

Procedure and Assessment of the Psychometric Properties of the Scale

The PD-CRS items were selected to cover the full spectrum of cognitive changes seen in PD. We divided the items as either "subcortical-type" or "cortical-type", depending on the neural correlates reported in previous neuropsychological and neuroimaging studies. Description and rationale for the selection of the PD-CRS items included in the initial version of the scale (content validity) is provided in E-Appendix 1.

The initial PD-CRS included 10 "subcortical-type" items (attention, working memory, Stroop test, phonemic, semantic, alternating, and action verbal fluencies, immediate and delayed verbal memory, clock drawing), and two "cortical-type" items (naming, copy of a clock).

Each patient was scheduled for four visits. At the first visit, a neurologist (JP) administered the Mattis Dementia Rating Scale (MDRS)[26] and classified patients into cognitive groups according to the CDR. A neuropsychologist (GL) blinded to the MDRS and CDR scores administered a comprehensive neuropsychological battery with validated cognitive tasks that assessed the same cognitive domains as those evaluated by the PD-CRS. To assess concurrent validity and test-retest reliability, the same neuropsychologist (GL) administered the PD-CRS at the second and third visits. Inter-rater reliability was assessed by another neuropsychologist (CG) at the fourth visit. The interval between first and second visits was 2 weeks and the interval between second, third and fourth visits was 6 ± 2 weeks.

Concurrent validity was assessed with the following comparisons: total PD-CRS scores with total MDRS scores; attention and working memory with the digit span forward and backward subtests of the WAIS-III[27]; verbal fluencies with the verbal fluencies in the WAIS-

III[27]; immediate and delayed verbal memory with the Rey Auditory Verbal Learning Test[28]; naming with the Boston Naming Test[29]; and drawing and copy of a clock with the Judgement of Line Orientation Test (JLOT).[30]

Test-retest and inter-rater reliability were measured for both total and individual item scores. Internal consistency was assessed with Cronbach's α. Intraclass correlation coefficients[31] were used to calculate concurrent validity and reliability analysis.

Acceptability was considered appropriate for each PD-CRS item if there was <5% of missing values and <15% of the respondents with the lowest and highest possible scores (floor and ceiling effect).[32]

An initial discriminative validity analysis was carried out to determine the ability of the PD-CRS items to differentiate between PD cognitive groups. One-way ANOVA, the Kruskal-Wallis test, ANCOVA with age, education, and the motor part of the UPDRS as covariates, and logistic regression analysis were used.

To design the final version of the PD-CRS we selected those items with an appropriate concurrent validity, reliability, and acceptability that showed the best discriminative ability between cognitive groups. Once the final version of the PD-CRS was constructed, we calculated the discriminative properties of the total, subcortical and cortical PD-CRS scores, and the validity and reliability of PD-CRS and individual item scores. Finally, ROC curves were constructed to assess PD-CRS screening test accuracy for dementia in PD. Significance was set at $P < 0.05$ for all the analyses, performed with the SPSS 13.0 statistical software.

RESULTS

Demographics

Ninety-two PD patients and 61 control subjects participated in the study. There were no significant differences in age, education or gender between PD patients and controls (Table 1). The study population consisted of three cognitive groups: 30 CgInt patients (age 64.1 ± 9 years, education 11.1 ± 5 years); 30 patients with MCI (age 70 ± 7 years, education 9.6 ± 5 years); and 32 patients with PDD (age 77.7 ± 5 years, education 6.6 ± 4 years). One-way ANOVA showed significant differences between PD groups for both age [$F(2, 89) = 17.4$; $P < 0.001$] and education [$F(2, 89) = 6.4$; $P < 0.001$].

TABLE 1. *Demographic and clinical characteristics of matched PD and CG*

	PD patients ($n = 92$)	CG ($n = 61$)	P
Age (yr)	71.2 ± 9.1	69 ± 8.0	0.13[a]
Education (yr)	8.9 ± 5.3	10.3 ± 4	0.10[a]
Men (%)	59.3%	53.1%	0.49[b]
MDRS	123 ± 17	138.3 ± 2.9	<0.0001[a]
PD duration (yr)	8.2 ± 5	–	–
Hoehn & Yahr (%)		–	–
1	8.8%	–	–
2	38.5%	–	–
3	39.6%	–	–
4	13.1%	–	–
5	0%	–	–
UPDRS-III	25.6 ± 12	–	–
Levodopa (mg/day)	609.7 ± 408	–	–
DA-LED (mg/day)	163.1 ± 168	–	–
Total LED (mg/day)	774.7 ± 460	–	–

Values are expressed as mean ± SD, or percentage of subjects (%).
PD: Parkinson's disease; CG: Control Group; MDRS: Mattis dementia rating scale; UPDRS: Unified Parkinson's disease rating scale; DA: Dopamine agonists; LED: levodopa equivalent dose.
[a]*T*-tests for independent samples.
[b]χ^2 test.

Clinimetric Characteristics of the PD-CRS

Concurrent Validity

The intraclass correlation coefficient (ICC) of total scores on the initial version of the PD-CRS showed a strong concurrent validity with the total score on the MDRS (ICC = 0.86). Strong concurrent validity was also obtained for immediate (0.86) and delayed memory (0.85), alternating verbal fluency (VF) (0.80), action VF (0.86), phonemic VF (0.87), semantic VF (0.85), attention (0.80), naming (0.71), and both drawing (0.71) and copy (0.73) of a clock. Scores on working memory showed a moderate concurrent validity with digit span backward scores (0.64).

Reliability

The ICC of individual items, and total, cortical and subcortical scores on the initial version of the PD-CRS showed both a high test-retest and a high inter-rater reliability.[33] When evaluating test-retest reliability, the ICC of individual items ranged from 0.84 to 0.91, and the ICC of total, subcortical, and cortical scores were ≫0.90. Evaluation of the inter-rater reliability showed the ICC of individual items to range from 0.77 to 0.88, and that of the total, subcortical and cortical scores were ≥0.93. The PD-CRS showed a high internal consistency (Cronbach's α = 0.85). The corrected item-total correlations for the PD-CRS ranged from 0.73 (naming) to 0.87 (working memory). No item improved Cronbach's α if removed.

Acceptability

The percentage of missing values was <5% for all items. No floor effect or outliers were observed for any

TABLE 2. *Analysis of covariance (ANCOVA) between controls and PD cognitive groups (CgInt, MCI, and PDD), with age, education, and UPDRS-III as covariates*

Dependent Variable	*F*	*P*	Post-hoc analysis (significant relationships)
Attention	53.1	0.0004	MCI vs. controls
Working memory	41.8	0.0002	-Immediate memory ($P = 0.016$) -Delayed memory ($P < 0.001$)
Phonemic fluency	16.8	0.0001	-Phonemic VF ($P < 0.001$) -Semantic VF ($P = 0.001$)
Semantic fluency	25.6	0.0002	-Alternating VF ($P < 0.001$) - Action VF ($P < 0.001$)
Alternating fluency	25.5	0.0002	-Attention ($P = 0.001$) -Working memory ($P < 0.001$)
Action fluency	27.0	0.0006	Clock drawing ($P = 0.03$)
Immediate verbal memory	31.5	0.0001	MCI vs. CgInt
Delayed verbal memory	17.5	0.0009	-Alternating VF ($P = 0.006$)
Naming	23.0	0.0003	-Working memory ($P = 0.04$)
Clock drawing	39.3	0.0001	
Copy of a clock	27.7	0.0003	PDD vs. MCI All "subcortical-type" items ($P < 0.003$) -Naming ($P = 0.0007$) -Copy of a clock ($P < 0.001$)

PD: Parkinson's disease; CgInt: Cognitively intact; MCI: mild cognitive impairment; PDD: Parkinson's disease with dementia; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; CDT: Clock Drawing Task.

cognitive item. When evaluating the PD group as a whole, a ceiling effect (>15% of the respondents with the highest possible score) was observed in naming and the copy of a clock. However, this effect was eliminated when we analyzed separately the PDD group, in which no floor or ceiling effect was shown. Therefore, none of the items was initially deleted.

Discriminative Validity

Univariate Analysis. Both the one-way ANOVA and Kruskal-Wallis test analysis showed significant differences between controls, CgInt, MCI, and PDD groups for all the PD-CRS items (all *P*-values < 0.001). Since age, education, and the motor part of the UPDRS [$F(2, 89) = 28.7$; $P < 0.001$] were significantly different between cognitive groups in the univariate analysis, we conducted an ANCOVA analysis with age, education, and motor function as covariates. Tests of between-subjects effects showed all the PD-CRS items ($P < 0.001$) to be significantly different between cognitive groups (Table 2). In the post hoc comparisons, working memory was the only item to differentiate controls from CgInt, all the "subcortical-type" items -but neither naming nor the copy of the clock- differed MCI from controls, MCI differed from the CgInt group by the alternating VF and working memory, and both the "cortical-type" and "subcortical-type" items differentiated PDD from MCI, CgInt and controls (see Fig. 1). Thus, "cortical-type" item scores were not significantly different between the control, CgInt and MCI groups, but selectively helped to differentiate PDD from each cognitive group. A post hoc analysis considering only PD patients with mild dementia (CDR = 1; $n = 10$) also showed this group to score significantly lower than the MCI group in the two "cortical-type" items [naming ($P < 0.001$), copy of the clock ($P = 0.004$)], and in action VF ($P = 0.01$).

No evidence of heteroscedasticity was found when examining the residuals for each cognitive item in the scale.

Multivariate Analysis. Stepwise logistic regression analysis (forward: conditional) showed that naming ($P = 0.046$; OR = 0.18, CI95% 0.32–0.96), action VF ($P = 0.034$; OR = 0.21, CI95% 0.05–0.89), and immediate memory ($P = 0.02$; OR = 0.06, CI 95% 0.01–0.36) independently differentiated PDD from the PD-ND group. The MCI group was independently differentiated from CgInt patients by the alternating VF ($P = 0.008$; OR = 0.79, CI 95% 0.66–0.94) and delayed memory ($P = 0.04$; OR = 0.75, CI 95% 0.56–0.99).

Selection and Clinimetric Assessment of the Final Version of the PD-CRS. For their greater ability to discriminate between cognitive groups, alternating and action verbal fluencies were finally selected. The computerized version of the Stroop test did not displayed appropriate discriminative properties, so that this item was excluded from the final version of the scale.

Total scores of the final version of the PD-CRS showed a strong concurrent validity with the total MDRS scores (ICC = 0.87, CI 95% 0.82–0.90). The individual items, total, cortical and subcortical scores of the final version of the PD-CRS showed also a high test-retest and a inter-rater reliability, with ICC ranging from 0.75 to 0.94, as well as a high internal consistency (Cronbach's $\alpha = 0.82$).

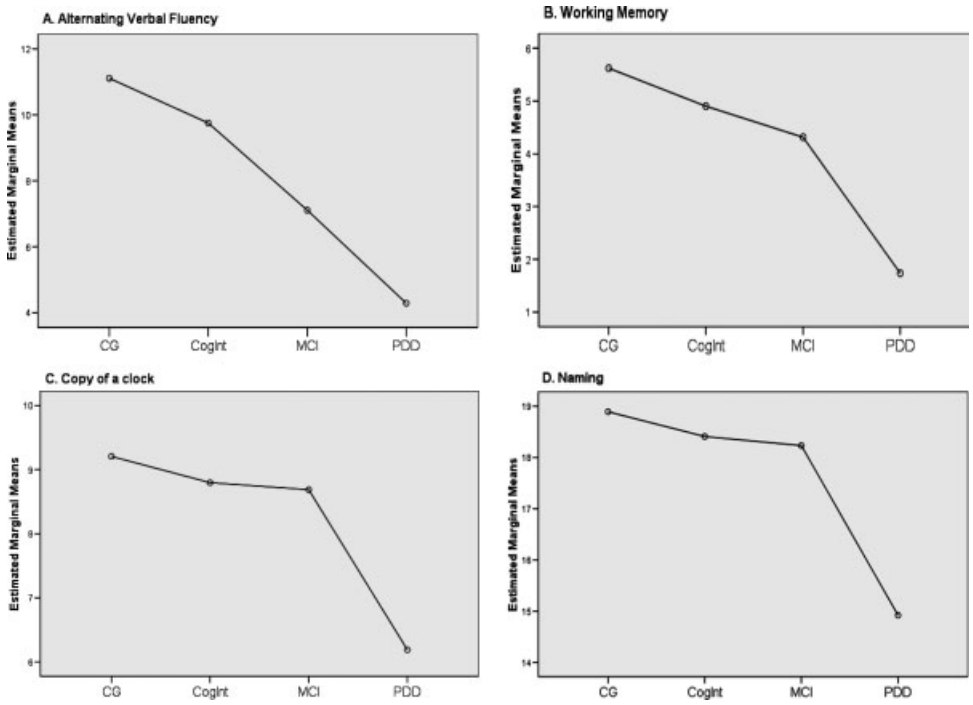

FIG. 1. Comparative progression of impairment of "subcortical-type" (**A**, **B**) and "cortical-type" (**C**,**D**) items in controls and PD cognitive groups, showing an abrupt decrease in "cortical-type" items scores in PDD. CG: control group; MCI: mild cognitive impairment; PDD: Parkinson's disease with dementia.

One-way ANOVA and Kruskal-Wallis test analysis showed significant differences between controls, CgInt, MCI, and PDD groups for total ($P = 0.0002$;), cortical ($P = 0.0001$), and subcortical ($P = 0.0009$) PD-CRS scores (see Fig. 2). In the ANCOVA analysis, both total and subcortical PD-CRS scores did not separate controls from CgInt patients, but separated controls and CgInt from MCI, and MCI from PDD patients. PD-CRS cortical scores differentiated PDD from MCI and CgInt, but did not differentiate MCI from controls or CgInt patients. All these relationships had a significance level of $P < 0.01$.

In the multivariate analysis, PDD were independently differentiated from the PD-ND group by the PD-CRS total score ($P = 0.0002$; OR = 0.79, CI95% 0.70–0.89). Then, we used Receiver Operating Characteristic (ROC) curve analysis to determine the optimal cutoff score for the screening of dementia in our sample. ROC curve showed that a cut-off score of $\leq$64 on the PD-CRS total score yielded high sensitivity (94%) and specificity (94%), and positive and negative predictive values (PPV 91%, NPV 96%). The area under the ROC curve was 0.98 (CI 95% = 0.96–0.99). ROC curve analysis to discriminate MCI from CgInt patients yielded moderate sensitivity and specificity for total PD-CRS scores (sensitivity 73%, specificity 84%) or subcortical PD-CRS scores (sensitivity 77%, specificity 71%).

The overall duration of the final version of the PD-CRS was 16 $\pm$ 3.6 min in the PD-ND group and 24 $\pm$ 7.8 min in the PDD group. The content, instructions

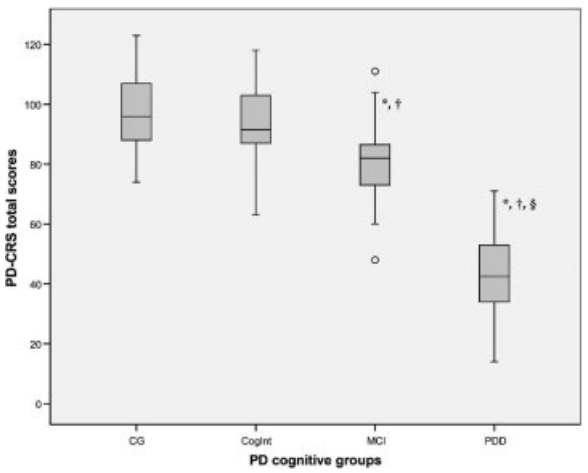

FIG. 2. Comparison of PD-CRS total scores between cognitive groups and controls (ANOVA, $F[3, 149] = 128.2$; $P = 0.0002$). *Post hoc significant differences from controls ($P < 0.01$). † Post hoc significant differences from CgInt ($P < 0.01$). § Post hoc significant differences from MCI ($P < 0.01$). The box plots show the median values (center line of box), the 25th (lower line of box), 75th (upper line of box), 10th (lower T bar), and 90th centiles (upper T bar) in each group. Open circles (○) indicate mild outliers (1.5–3 interquartile range). CG: Control Group; CogInt: Cognitively intact; MCI: mild cognitive impairment; PDD: Parkinson's disease with dementia.

and scoring of the final version of the PD-CRS are provided in the E-Appendix 2.

DISCUSSION

The main results of our study show that the PD-CRS: (1) is a valid, reliable and useful neuropsychological battery that accurately diagnoses PDD; (2) detects mild fronto-subcortical deficits in PD-ND patients; and (3) shows that the transition from MCI to PDD is characterized by the addition of "cortical-type" cognitive defects upon a progressive and predominant fronto-subcortical impairment.

The PD-CRS showed a strong concurrent validity with the MDRS, a test of global cognitive function that is specially useful in PD,[34] and with cognitive tasks widely accepted to assess each cognitive domain included in our scale. This reflects the ability of the PD-CRS to measure the cognitive functions impaired in PD. No floor effect was observed in any item of the scale, which indicates that patients do not obtain minimum scores before severe cognitive impairment is reached. When analyzing the PD group as a whole, a ceiling effect was observed only in the "cortical-type" items. This effect disappeared when the PDD group was analyzed separately. This indicates the heterogeneous distribution of "cortical-type" item scores in our sample, almost normal in the PD-ND group and abruptly decreasing in the PDD group.

The discriminative analysis showed the ability of the PD-CRS to detect the progressive decline in cognitive function that is characteristic of PD.[35] Total, cortical, and subcortical PD-CRS scores, and items assessing executive function presented a progressive impairment within PD cognitive groups (see Fig. 2).

Particularly, MCI subjects differed from controls only in the "subcortical-type" items, whereas the two "cortical-type" items selectively appeared impaired in the transition from MCI to PDD. Logistic regression analysis showed the total PD-CRS score and naming to independently differentiate PDD from PD-ND, although cortical PD-CRS score did not differentiate PDD from PD-ND. We acknowledge that PDD is a predominantly attentional-executive dementia. Nevertheless, a cortical item such as naming independently predicted the presence of dementia in our sample. This reinforces the hypothesis that cognitive decline leading to PDD is associated with the development of cognitive defects associated with cortical pathology,[7] and replicates results showing that PDD subjects have a higher frequency of aphasic features than PD-ND individuals.[36] On the other hand, in a recent community-based longitudinal study of newly diagnosed PD patients, picture copying and semantic rather than phonemic verbal fluency appeared as the most significant neuropsychological predictors of cognitive decline in early PD-ND.[37] The higher value of semantic verbal fluency in predicting cognitive decline suggests that a breakdown in the semantic system, whose neural substrate is thought to lie within the temporal neocortex, accounts for a higher risk of developing PDD.[38] Naming is very sensitive to the integrity of the semantic system and imposes fewer demands on effortful self-initiated retrieval than semantic fluency.[38] Thus, if confirmed that PD-ND with cortical abnormalities represents a group at risk for PDD,[37] using a scale with cortical items could provide us with a useful predictive instrument for dementia in PD.

Further, detection of cortical cognitive alterations might help elucidate whether the coexistence of Alzheimer-type pathology in PD has a relevant impact on the pattern and evolution of cognitive impairment in PD.[39]

The finding that alternating VF independently differentiated MCI from CgInt patients replicates previous results pointing towards this verbal fluency as the most sensitive task to detect mild cognitive defects in PD-ND.[40] Consistent also with previous studies, action VF appeared as an early indicator of the conversion from PD-ND to PDD.[41] Although clock-drawing tasks might be confounded by PD motor symptoms, ANCOVA analysis with motor function as a covariate still showed clock-drawing to differentiate MCI from controls and the copy of a clock to differentiate PDD from PD-ND patients.

We acknowledge some limitations of our study. First, as we have not compared the PD-CRS with existing rating scales for cognitive dysfunction in PD, we cannot demonstrate that a scale with subcortical and cortical items performs better than a scale with subcortical items only. Second, the absence of a consensus on the definition of "mild cognitive impairment" in PD[42] led us to adopt MCI criteria used to classify subjects at risk for Alzheimer's disease to categorize our subjects as CgInt or MCI subjects. A more appropriate definition of MCI specific for PD could improve the discriminant ability of PD-CRS to screen for MCI in PD.

Overall, our results show that the PD-CRS appears to be a valid neuropsychological battery specific for PD. It may prove useful in clinical research since it is sensitive to mild fronto-subcortical deficits, follows the progressive impairment of executive function throughout the course of the disease, and includes "cortical-

type" cognitive tasks that may improve detection of the transition from MCI to dementia. The discriminant ability to diagnose dementia in PD shown by the PD-CRS total score in the ROC analysis suggests that this scale may also be a good instrument for screening purposes.

Future prospective studies could assess the ability of the PD-CRS to detect patterns of cognitive impairment with a distinct risk to develop dementia from the early stages of the disease. Further investigation on the transcultural validation of the PD-CRS, is also warranted.

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Content, instructions, and scoring of the final version of the Parkinson's Disease Cognitive Rating Scale (PD-CRS)

Items are administered to the subjects in the same order as presented below.

1. Immediate free recall verbal memory.

Instruction: The subject is asked to read aloud the written words shown on 12 consecutive cards. Three trials are performed, and the subject is asked to recall as many words as possible after each trial.

Content:

Words
LIGHT
SILK
SAND
EYELASH
RICE
TIE
BLACKBOARD
BICYCLE
STAR
LION
RING
FRAGRANCE

Score: 1 point for each word recalled. The highest number of words recalled in any one trial is the score. (0-12)

2. Confrontation naming.

The subject is asked to name the line drawings shown on 20 consecutive cards. There is no time limit for response, and only one trial is given. No semantic or phonemic cues are provided. When objects are included in their context (bib, buckle, mane, hook, jingle bell, and hoof), the examiner is allowed to indicate the part of the line drawing to be named.

Content:

Images (see line drawings at the end of the appendix)
BIB
CANDLE
CHERRY
STOOL
ANCHOR
TURTLE
KITE
FISHBOWL
BULB
GUITAR
BUCKLE
MANE
HOOK
SCREWDRIVER

PANEL SCREEN
SAFETY PIN
JINGLE BELL
HOOF
EXTINGUISHER
DOOR BOLT

Score: 1 point for each line drawing correctly named. (0-20)

3. Sustained attention.

Instruction: An ascending series of letters and numbers are read to the subjects. The subject is asked to report the number of letters in the sequence. Ten series of letters and numbers are presented, divided into five levels of ascending complexity. Two training series are provided at the beginning of the test.

Content:

		Correct answer
Example	2 L T 8 A 9	2 letters 1 letter
1	2 P 6 5 4 3 A 6 K L	1 letter 3 letters
2	B 9 0 4 L T 3 C P 5 7 3	3 letters 2 letters

3	3 9 5 L 4 Z A I 1 A S Q 4 1	3 letters 4 letters
4	7 5 D A 4 T B 2 9 6 8 4 3 7 L C	4 letters 2 letters
5	Z 4 9 A T D 3 8 4 9 5 M D 4 S C 3 E	4 letters 5 letters

Score: 1 point for each correct series. (0-10)

4. Working memory.

Instructions: The examiner reads aloud a randomized list of numbers and letters ranging in length from 2 to 6 letters and numbers. After each series the subject is asked to repeat the numbers first, and then the letters. This test ends when the subject is unable to give the correct answer in two consecutive series. Two training series are provided at the beginning of the test.

Content:

		Correct answer
Example	L 2 T 8 A 9	2 L T 8 9 A
1	M 3 7 P	3 M 7 P
2	G 8 M	8 G M

	9 I 6	9 6 I
3	T 0 4 A 7 V 6 J	0 4 T A 7 6 V J
4	M 6 4 N I 3 5 S G C	6 4 M N I 3 5 S C G
5	1 R 9 V B 3 M 2 7 4 Z 9	1 9 3 R V B 2 7 4 9 M Z

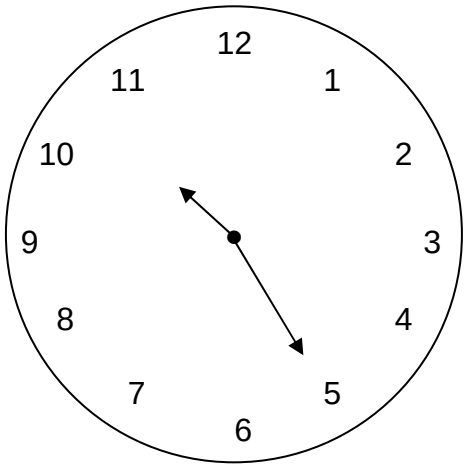
Score: 1 point for each correct series. (0-10)

Clock drawing task.

Instructions:

5. Umprompted drawing of a clock: The subject is asked to draw a clock face on a blank sheet of paper, and to set the hands at “twenty-five minutes past ten”. (0-10)

6. Copy drawing of a clock: The patient is asked to copy the presented clock. (0-10)



	Unprompted		Copy	
	Yes	**No**	**Yes**	**No**
The figure looks like a clock.				
The clock is not divided by lines or sectors.				
There is a symmetric disposition of numbers.				
Only 1 to 12 numbers are drawn.				
Hour numbers are correctly sequenced.				
Only two hands are drawn.				
Clock hands are represented as arrows.				
Hour hand is shorter than minute hand.				
No words have been written.				
The number ‘25’ has not been drawn.				

Score: 1 point for each correct item. (0-10 for each task)

7. Delayed free recall verbal memory.

Instructions: The subject is asked to recall as many words as possible from the list of words presented at the beginning of the scale.

Content:

Words
LIGHT
SILK
SAND
EYELASH
RICE

TIE
BLACKBOARD
BICYCLE
STAR
LION
RING
FRAGRANCE

Score: 1 point for each word recalled. (0-12)

8. Alternating verbal fluency.

Instructions: The subject is asked to alternately generate as many different words as possible beginning with the letter ‘S’ and words describing articles of clothing during 60 seconds. Participants are instructed not to use proper nouns or to repeat the same word with a different ending (e.g., swim, swimming, swimsuit).

Score: 1 point for each correct answer maintaining the alternation between words beginning with ‘s’ and articles of clothing. (0-20)

9. Action verbal fluency.

Instructions: We used the instructions listed in Piatt et al. (reference number 45 in the manuscript) for the action verbal fluency task. The instructions are as follows: ‘‘During 60 seconds, I’d like you to tell me as many different things as you can think of that people do. I don’t want you to use the same word with different endings, like eat, eating, eaten. Also, just give me single words such as eat, or smell, rather than a sentence”.

Score: 1 point for each correct answer. (0-30)

SCORES

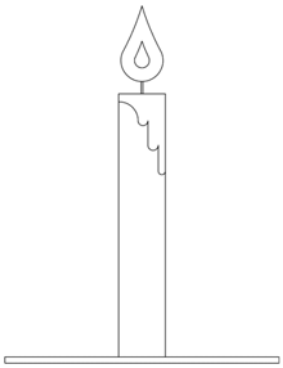
ITEM	**Points**
1. Immediate free recall verbal memory	
2. Confrontation naming	
3. Sustained attention	
4. Working memory	
5. Umprompted drawing of a clock	
6. Copy drawing of a clock	
7. Delayed free recall verbal memory	
8. Alternating verbal fluency	
9. Action verbal fluency	
SUBCORTICAL score (0-114)	
CORTICAL score (0-20)	
TOTAL score (0-134)	

Subcortical and cortical PD-CRS scores were obtained by adding the raw scores of the items within each group. Total scores on the PD-CRS were calculated by adding the subcortical and cortical PD-CRS scores.

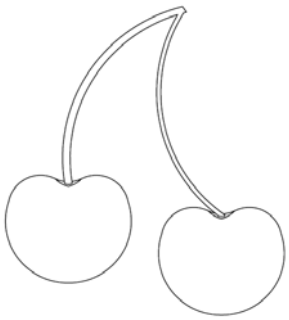
LINE DRAWINGS.

1. BIB

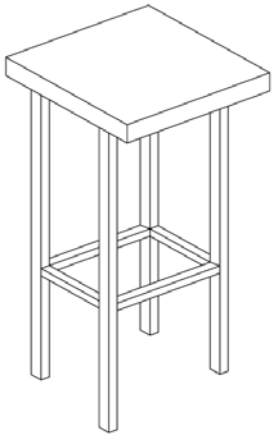
2. CANDLE



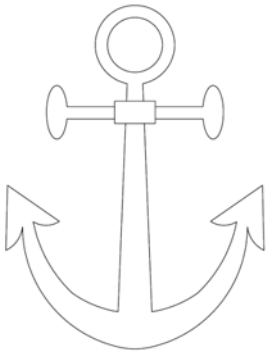
3. CHERRY



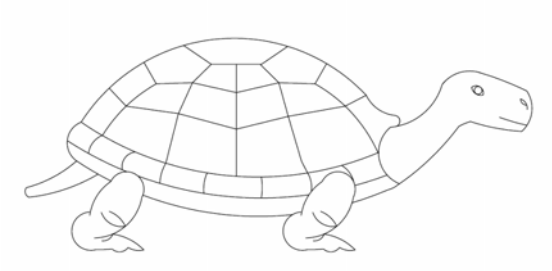
4. STOOL



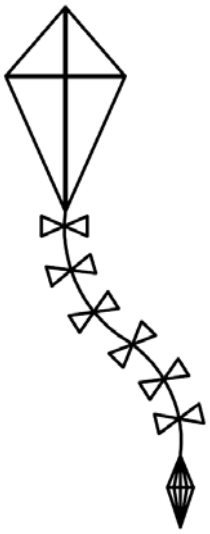
5. ANCHOR



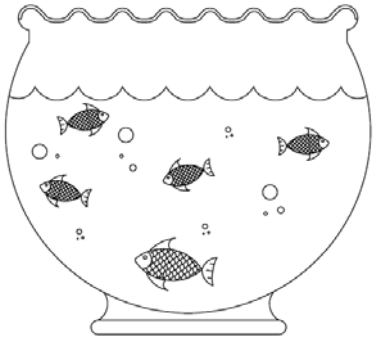
6. TURTLE



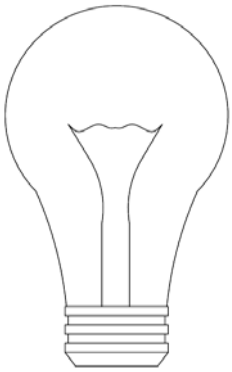
7. KITE



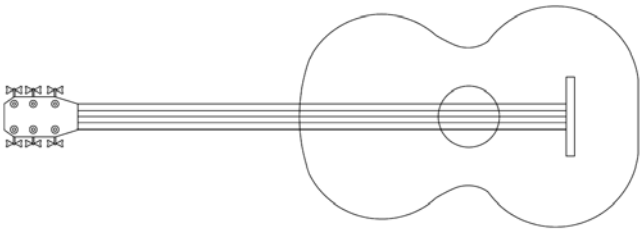
8. FISHBOWL



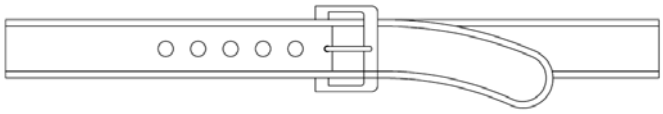
9. BULB



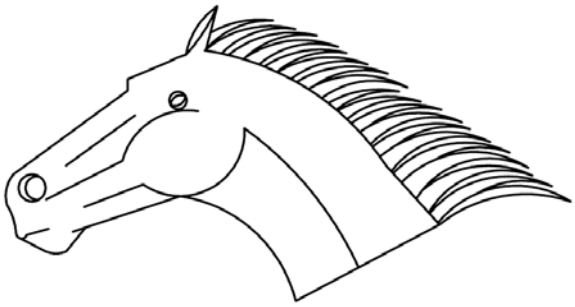
10. GUITAR



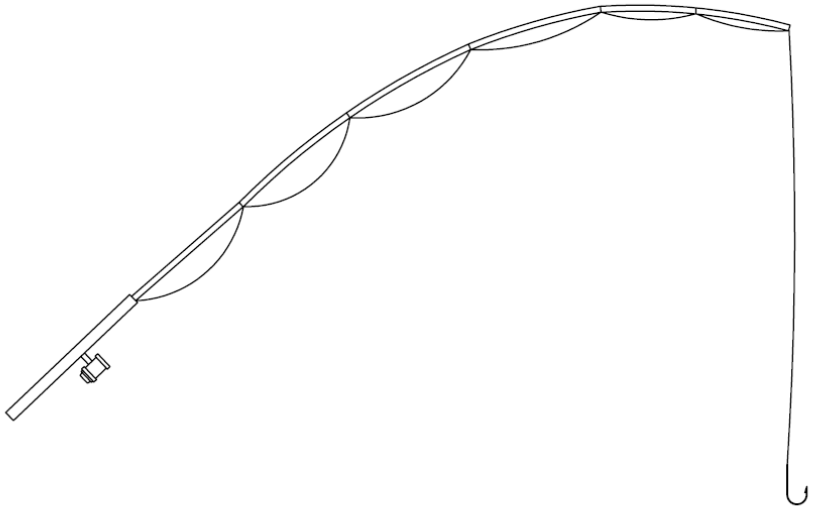
11. BUCKLE



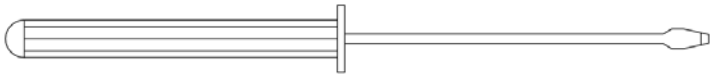
12. MANE



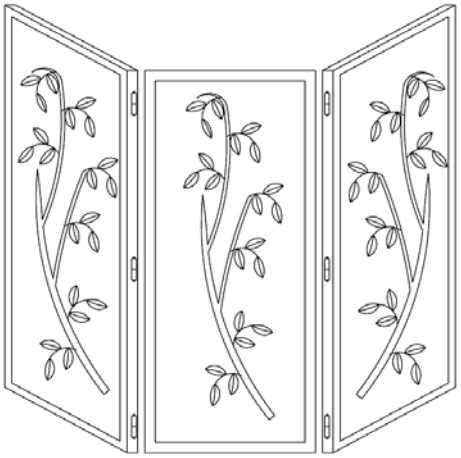
13. HOOK



14. SCREWDRIVER

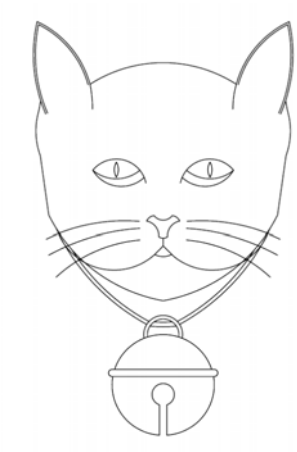


15. PANEL SCREEN

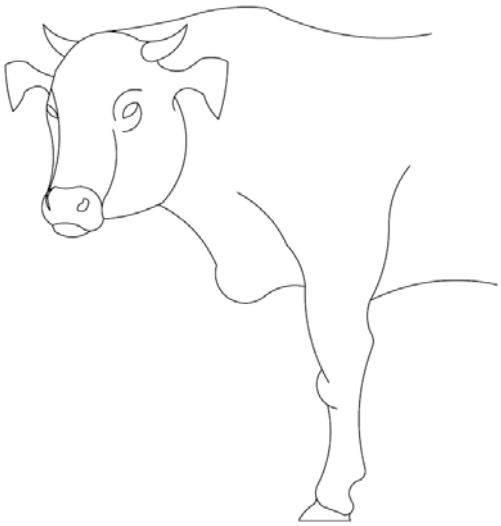


16. SAFETY PIN

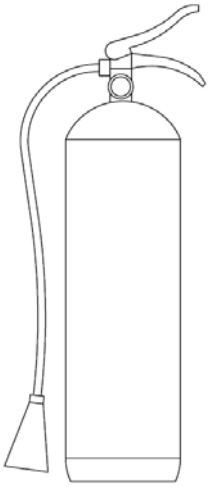
17. JINGLE BELL



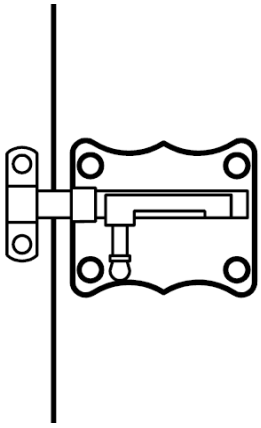
18. HOOF



19. EXTINGUISHER



20. DOOR BOLT



Description of the Parkinson's Disease-Cognitive Rating Scale (PD-CRS)

1. 'Subcortical-type' cognitive items:

- Attention/Executive functions: Disturbances in both the frontal regulation of attentional processes and working memory occur early in PD-ND patients,[1-3] and progress throughout the course of the disease.[4, 5] They both have been correlated with prefrontal atrophy, dopaminergic hypometabolism in the dorsolateral prefrontal cortex (DLPFC),[6]and underactivation of the caudate nucleus, the ventrolateral and the DLPFC.[7] Participants were asked to say how many letters were presented from among a series of letters and numbers for assessing attention, and to recall separately a randomized list of numbers and letters for assessing working memory.

- **Resistance to interference**: Susceptibility to interference is impaired in PD,[8] but discrepancies about the usefulness and early impairment of this cognitive function in PD have been reported.[2, 3] Resistance to interference relies also upon the DLPFC.[9] The test selected was a computerized version of the Stroop test.

- **Verbal fluency (VF) and cognitive flexibility**: Phonemic and semantic verbal fluencies are progressively impaired over the course of the disease[10, 11], and their deterioration is indicative of PDD development. [10] Action verbal fluency (action VF) appears to be an early indicator of the conversion from PD-ND to PDD.[12] Alternating verbal fluency (alternating VF) requires a mental shift to generate words belonging to different categories, and is impaired since the earliest stages of the disease.[13] Participants were asked to generate as many words as possible in 60 seconds for each fluency task.

- Verbal memory: Free recall immediate and delayed verbal memory are markedly impaired in PD-ND[2, 14] and their deterioration is indicative of PDD development. [10, 15] Impairment in free recall memory appears to be more related to the defective use of memory stores due to working memory deficits, than a reduced capacity of storing/consolidating new information in the temporal lobes.[16] The specific task selected was to recall as many words as possible from a 12-word list.

- Visuoconstructional skills/Clock drawing: PD-ND and PDD[17] are associated with marked visuospatial deficits.[17, 18] Visuoconstructional abilities depend on the functionality of both the prefrontal cortex and the posterior visual cortical areas.[19] The specific task selected for this cognitive function was the unprompted drawing of a clock set at twenty-five minutes past ten,

2. 'Cortical-type' cognitive items:

- Confrontation naming: Naming is normal in PD-ND[20, 21] but deteriorates in PDD.[20, 21] The decline in naming in PDD is even more rapid than in AD.[22] Naming has been mainly correlated with cortical activity in the anteromedial and posteromedial temporal cortex.[23, 24] In this task, participants were asked to name 20 line drawings, with no time constraint.

- Visuoperceptual skills/Copy of a clock: To assess the functionality of the posterior visual cortical areas, we assessed the copy of a clock after the unprompted drawing of such a clock, which has been shown to partially separate the frontal-subcortical from the posterior cortical component of this cognitive function.[25] The task selected was the copy of a clock set at twenty-five minutes past ten.

The initial PD-CRS included 10 'subcortical-type' items (attention, working memory, Stroop test, four verbal fluencies, immediate and delayed verbal memory, clock drawing), and two 'cortical-type' items (naming, copy of a clock). Total score ranged

from 0 to 204, subcortical score from 0 to 174, and cortical score from 0 to 30, with higher scores indicating a better functioning.

1. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988;111:299-321.
2. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239-1245.
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