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Addenbrooke's Cognitive Examination validation in Parkinson's disease

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Background: There is a clear need for brief, sensitive and specific cognitive screening instruments in Parkinson's disease (PD). *Objectives:* To study Addenbrooke's Cognitive Examination (ACE) validity for cognitive assessment of PD patient's using the Mattis Dementia Rating Scale (MDRS) as reference method. A specific scale for cognitive evaluation in PD, in this instance the Scales for Outcomes of Parkinson's disease – Cognition (SCOPA-COG), as well as a general use scale the Mini-mental state examination (MMSE) were also studied for further correlation. *Methods:* Forty-four PD patients were studied, of these 27 were males (61%), with a mean (SD) age of 69.5 (11.8) years, mean (SD) disease duration of 7.6 (6.4) years (range 1–25), mean (SD) total Unified Parkinson's Disease Rating Scale (UPDRS) score 37 (24) points, UPDRS III 16.5 (11.3) points. MDRS, ACE and SCOPA-COG scales were administered in random order. All patients remained in on-state during the study. *Results:* Addenbrooke's Cognitive Examination correlated with SCOPA-COG ($r = 0.93$, $P < 0.0001$), and MDRS ($r = 0.91$ $P < 0.0001$) and also with MMSE ($r = 0.84$, $P < 0.001$). Area under the receiver-operating curve, taking MDRS as the reference test, was 0.97 [95% confidence interval (CI): 0.92–1.00] for ACE, 0.92 (95% CI: 0.83–1.00) for SCOPA-COG and 0.91 (95% CI: 0.83–1.00) for MMSE. Best cut-off value for ACE was 83 points [Sensitivity (Se) = 92%; Specificity (Sp) = 91%; Kappa concordance (K) = 0.79], 20 points for the SCOPA-COG (Se = 92%; Sp = 87%; K = 0.74) and 26 points for MMSE (Se = 61%; Sp = 100%; K = 0.69). *Conclusion:* Addenbrooke's Cognitive Examination appears to be a valid tool for dementia evaluation in PD, with a cut-off point which should probably be set at 83 points, displaying good correlation with both the scale specifically designed for cognitive deficits in PD namely SCOPA-COG, as well as with less specific tests such as MMSE.

Introduction

According to a consensus recently published by the Movement Disorders Dementia Task Force [1], the diagnosis of dementia in Parkinson's disease (PD) should rely first on presence of PD fulfilling United Kingdom Parkinson's Disease Brain Bank criteria. PD should have developed prior to the onset of dementia, and decreased global cognitive efficiency, measured by the MMSE with a proposed cut off score < 25 points, should be present. Finally, cognitive deficiency should be severe enough to impair daily life, and more than one cognitive domain (memory, attention, visuoconstructive ability and executive function) should be affected. The prevalence of dementia in PD has been estimated to range from 20% to 40% [2–5]. This wide variability may depend on several factors, including the assessment method, with higher prevalence reported in studies using comprehensive neuropsychological instruments compared with those screening global cognitive function [6]; the number of patients with early versus late onset of Parkinson's symptoms, with prevalence of dementia higher in patients with late onset illness [7]; the definition of dementia applied, whether dementia was diagnosed based on standardized versus *ad hoc* criteria [8] and motor impairment severity, with prevalence of dementia reported to increase as disease progresses [0% in Hoehn & Yahr (H&Y) stage I, 6% in stage II, 16% in stage III, 35% in stage IV and 57% in stage V; 9].

Cognitive skill evaluation in PD is not simple, and the need for brief, sensitive and specific cognitive screening instruments clearly exists. The best test for assessment of global cognitive efficiency appears to be the Mattis Dementia Rating Scale (MDRS), which evaluates several aspects of mental functioning, such as attention, perseveration, conceptualization and memory [10,11]. The scale has been validated for use in

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idiopathic as well as secondary PD [10]. Nonetheless, MDRS is not simple to administer because of its length and the need for special materials [10,12].

The Mini-mental state examination (MMSE) has been proposed as a first line assessment tool for global cognitive efficiency in PD because of its simplicity and wide use in dementia [1,13]. Early cognitive alterations in PD such as executive dysfunction however, are frequently missed by MMSE, limiting its usefulness [14]. Recently, the Scales for Outcomes of Parkinson's disease – Cognition (SCOPA-COG) have been developed, they represent a short and practical instrument, sensitive only to specific cognitive deficits in PD [15,16]. This tool has received only partial validation, thus also reducing its applicability [15,16]. Finally, Addenbrooke's Cognitive Examination (ACE) was developed to provide a brief test sensitive in early stage dementia, and capable of differentiating between dementia subtypes including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy and other parkinsonian syndromes [17–22]. ACE includes the MMSE, but extending it to encompass important areas not covered by it, such as frontal-executive function and visuospatial skills. The ACE has comparable sensitivity to the Dementia Rating Scale [19], a well-established dementia screening tool, widely used in research, but, not in clinical practice because of its length and difficult administration. ACE use in PD has not been evaluated, reason for which we set up this protocol to study ACE validity in initial assessment of global cognitive efficiency taking MDRS as reference method. For further correlations SCOPA-COG and MMSE were also studied as part of the protocol.

Methods

Study sample

Forty-four consecutive PD outpatients from our tertiary movement disorders clinic were included in this study. Only idiopathic PD patients according to United Kingdom PD Brain Bank Society criteria [23] were included. Following the recommendations of the movement disorders task force for diagnosis of dementia, major depression, delirium and other abnormalities that could obscure the diagnosis of dementia were also ruled out [1]. To exclude severe depression diagnostic and statistical manual of mental disorders-IV (DSM-IV), as well as the Montgomery-Asberg Depression Rating Scales [24] were used. Dopamine dysregulation syndrome [25], cognitive decline secondary to systemic or degenerative disease as well as history of drug abuse were also explored. The protocol was approved by the Institutional Review Board. All patients signed informed consent prior to entry. Sample size calculations were conducted to considered statistical power levels. A minimum of 40 subjects were deemed necessary to detect a moderate relationship ($r \geq 0.5$), with powe $r = 0.8$ and allowing for multiple correlation.

Patient evaluation

Patients were evaluated initially using Unified Parkinson's Disease Rating Scale (UPDRS) [26] and H&Y [27]. Medical and drug history were obtained from the clinical chart. Mood state was evaluated using the Montgomery-Asberg Depression Rating Scale [24]. Cognitive function was then studied in patients meeting study criteria. Other causes of PD or dementia were ruled out after careful analysis of brain MRI images.

Cognitive evaluation

Cognitive function was evaluated through application of the following battery of tests: ACE, MDRS, SCOPA-COG and MMSE, conducted in random order with patients in on-state. When exhaustion or off-periods were detected, patients were allowed to take a break and/or medication.

Tests

Mattis Dementia Rating Scale validated for dementia evaluation in PD was applied to study cognitive function in five sub-domains: attention, initiation/perseveration, construction, conceptualization and short-term visual and verbal memory [10,16]. Although results may vary across cultures it has been suggested that normal cut-off values adjusted for education level could range from: >119 points if patient education level corresponded to <8 years, >126 points if education had lasted 8–13 years and >132 points if longer [10] Maximum possible score is 144.

Addenbrooke's Cognitive Examination evaluated six cognitive domains totalling 100 points: orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points) and visuospatial abilities (5 points) [28,29]. Scores ≤86 points were considered indicative of cognitive impairment [28,29]. Average time needed to complete the ACE test is approximately 16–20 min in different studies, no special material nor expertise are required. Maximum possible score is 100.

Mini-mental state examination considered an extremely short evaluation totaling 30 points. Scores ≤25 were interpreted as indicative of cognitive impairment and dementia in agreement with Movement Disorders Dementia Task Force clinical criteria [1].

Scales for Outcomes of Parkinson's disease – Cognition is specifically designed for cognitive evaluation in PD [16]. Scores ≤20 points were considered indicative of cognitive impairment [30]. Maximum possible score is 43.

Statistical analysis

Scale scores were correlated by nonparametric Spearman's Rho coefficient. Scale-by-scale correlation coefficient comparison was carried out using the Fisher's exact test. Receiver-operating curve (ROC) were then employed for ACE, SCOPA-COG and MMSE diagnostic performance evaluation, with MDRS used as the reference test [31]. Finally, sensitivity (Se), specificity (Sp) and kappa concordance values (K) were calculated for several cut-off values aside from those described above. The cut-off points with the highest Se, Sp and K values were selected as best cut-off point value for dementia diagnosis in each of the scales evaluated. Alfa was set at 0.05.

Results

Demographics

Forty-four patients, 27 of whom were males (61%), were evaluated. Mean (SD) age was 69.5 (11.8) years, and mean (SD) disease duration 7.6 (6.4) years. Mean (SD) total UPDRS score was 37 (24) points, and UPDRS III 16.5 (11.3) points. Mean H&Y was 2.6, range 1–5, with the following distribution, H&Y: I 11.3% (5), H&Y II: 36.3% (16), H&Y III: 40.9% (18), H&Y IV: 9% (4) and H&Y V: 4.5% (2). Mean (SD) MDRS was 12.5 (6.6). Four extra subjects were approached but either did not consent or presented exclusion criteria precluding participation.

Forty patients (91%) were treated with L-Dopa and/or dopamine agonists (DA), three of whom received only DA, 19 only levodopa and 18 a combination of both (7%, 48% and 45% of treated patients respectively). Seven levodopa treated patients were on amantadine, and two on monoamine oxidase-B (MAO-B) inhibitors. All L-Dopa naïve patients were on MAO-B inhibitors. None of the patients were receiving anticholinergic drugs.

Cognitive evaluation

Mean scores on ACE, SCOPA-COG, MMSE and MDRS scales were 84.45 ± 10.87, 24.2 ± 6.1, 27.8 ± 2.4 and 131.4 ± 12.1, respectively. Thirteen patients (29.9%), scored below the MDRS cut off point and were classified as demented. All patients fulfilling movement disorders dementia task force criteria showed MDRS values below the cutoff point. Demographic data from patients classified as demented and non-demented are compared on Table 1.

Positive and significant correlations between scales were observed. ACE correlated with SCOPA-COG ($r = 0.93$, $P < 0.0001$), MDRS ($r = 0.91$ $P < 0.0001$) and MMSE ($r = 0.84$, $P < 0.001$). Correlation coefficient between MMSE and MDRS was significantly lower than the correlation between ACE and MDRS ($t = 2.2$ $P < 0.03$) but not different to the correlation between SCOPA and MDRS ($t = 0.8$ $P = 0.4$).

Area under ROC curve, taking MDRS as reference test, was 0.97 [95% confidence interval (CI): 0.92–1.00, Fig. 1) for ACE, 0.92 (95% CI: 0.83–1.00) for SCOPA-COG and 0.91 (95% CI: 0.83–1.00) for MMSE. Table 2 shows sensitivity, specificity and kappa values for the different scale cut-off points. Best cut-off value for ACE was 83 points (Se = 92%; Sp = 91%; K = 0.79), 20 points for the SCOPA-COG (Se = 92%; Sp = 87%; K = 0.74) and 26 points for MMSE (Se = 61%; Sp = 100%; K = 0.69). Cognitive dysfunction according to PD severity was further explored. In Table 3, ACE subdomain scores in H&Y groups are shown. All cognitive functions were more severely affected in H&Y III–V PD patients.

Table 1 Demographic data from demented and non-demented subjects

	Non-demented ($n = 31$)	Demented ($n = 13$)	*P*-value
Males (%)	18 (58)	9 (69)	0.48
Age (years)	68.6 ± 11.5	71.9 ± 10.5	0.35
Education (years)	14.3 ± 3.4	11.9 ± 5	<0.08
MMSE	29 ± 1	25.2 ± 2.7	<0.001
ACE	89.8 ± 6.1	71.7 ± 8.9	<0.001
SCOPA	27 ± 4.7	17.8 ± 3.9	<0.001
UPDRS I	3.8 ± 2.1	6.6 ± 2.4	<0.001
UPDRS II	8.8 ± 5.5	20.1 ± 11.3	<0.001
UPDRS III	12.1 ± 5.6	27.2 ± 14.5	<0.001
UPDRS IV	3.2 ± 3.3	6.9 ± 5.8	<0.01
Hoehn & Yahr	2.2 ± 0.7	3.5 ± 0.9	<0.001
Disease duration	7.5 ± 7	8.2 ± 5.3	0.68
MADRS	11.1 ± 7.2	15.7 ± 3.4	<0.006
L-Dopa dose (mg/day)	460.1 ± 353.4	855.8 ± 269.3	<0.001
Dopamine agonist (%)	18 (58)	3 (23)	<0.03
Atypic neuroleptics (%)	5 (16)	2 (15)	0.85
Colinesterase inhibitors(%)	1 (3)	5 (38)	<0.002
Antidepressants (%)	5 (16)	3 (23)	0.56

MMSE, Mini-mental state examination; ACE, Addenbrooke's Cognitive Examination; SCOPA, Scales for Outcomes of Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale – part I: mentation; part II: daily activities; part III: motor evaluations and part IV: levodopa complications.

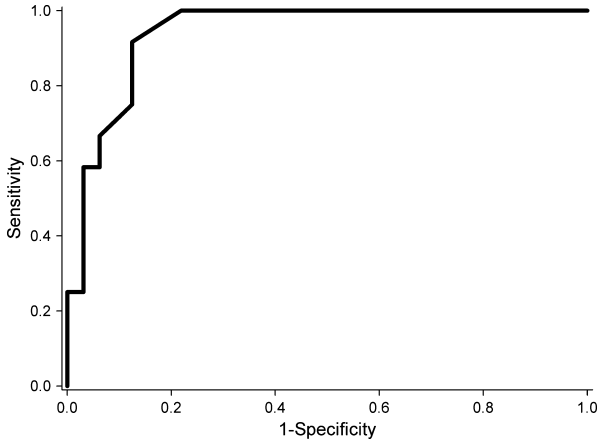

Figure 1 Receiver-operating curve of diagnostic performance of Addenbrooke's cognitive examination (ACE) for dementia. Mattis Dementia Rating Scale was used as reference. Area under the curve was 0.97 (95% CI: 0.92–1.00).

Table 2 Sensitivity, specificity and Kappa concordance values for different Addenbrooke's Cognitive Examination cut-off points

Cut-off value	Sensitivity (%)	Specificity (%)	Kappa concordance
86	100	77	0.67
85	100	81	0.71
84	100	81	0.71
83	**92**	**90**	**0.79**
82	85	90	0.73

Bold data represents the cut-off value with the highest sensitivity, specificity and Kappa values.

Table 3 ACE subscores according to PD severity

	H&Y I–II (n = 20)	H&Y III–V (n = 24)	P-value
Orientation score	9.6 ± 0.1	7.3 ± 0.7	< 0.01
Memory score	27.5 ± 0.8	21.2 ± 1.0	< 0.01
Attention	7.76 ± 0.9	7.33 ± 0.50	0.52
Verbal fluency score	10.6 ± 0.4	7.2 ± 1.3	< 0.01
Language skills score	27.4 ± 0.2	23.8 ± 1.1	< 0.01
Visuospatial skill score	3.7 ± 0.2	1.7 ± 0.6	< 0.01
Total score	86.9 ± 1.4	68.8 ± 4	< 0.01

ACE, Addenbrooke's Cognitive Examination; PD, Parkinson's disease; H&Y, Hoehn & Yahr.

Discussion

The need for brief, sensitive and specific, cognitive screening instruments clearly exists as potential therapeutic approaches for PD dementia become available [12]. The Movement Disorder Society Task Force on Dementia in PD [1] have proposed that for those cases where dementia diagnosis remains uncertain or equivocal after the first level of evaluation, a second level should be executed using more specific cognitive tests, in order to specify the pattern and severity of the dementia. Second level evaluations consist in a series of qualitative tests, which allow for a more comprehensive assessment of cognitive functions including MDRS. ACE evaluation however was not included at any of the assessment levels.

The present study showed that ACE demonstrated excellent correlation with both comprehensive and validated tools like MDRS, as well as with the PD-specific scale SCOPA-COG, which finally proved to be superior to MMSE regarding its clinometric properties in PD patients. When ACE cut-off scores were set at 83 points, dementia diagnosis sensitivity and specificity in PD patients was 92% and 90% respectively. We found that not all patients classified as non-demented by MDRS in our study fulfilled the corresponding clinical criteria for dementia diagnosis recommended by the movement disorders society. Thirty-nine per cent of patients classified as demented by MDRS did not meet the clinical criteria for dementia diagnosis recommended by the movement disorders society because MMSE was above their proposed cut-off score. We think that this may be as a result of the fact that MMSE does not measure visuospatial functions well in PD dementia.

Before further analysing the cognitive battery studied, we should clarify that a revised and improved version of ACE (ACE-R) has recently been made available [32]. In the original version, the naming component of ACE suffered from ceiling effects, and the visuospatial component was limited. In the revised version, the original 26 individual ACE components were combined to produce five sub-scores, each one representing a specific cognitive domain and contributing fairly equally to the total score. Despite these advantages, we decided to use the classic version because of our extensive clinical experience using it. Another limitation of the present study is that the number of demented patients studied, 13 subjects representing 29.5% of the sample, is too small to establish a reliable cut-off value, although it was clearly representative of the reported incidence of dementia in PD, which ranges between 20% and 40% [2–5]. This figure may nonetheless have limited to some extent the precision of the sensitivity and specificity estimations. This sample size allows us to have a sensitivity level of ±15% (92% ± 15% = 77–100%) and a specificity level of ±9.5% (80.5–99.5%) [33,34]. Further studies in larger samples will however be necessary to confirm our findings.

Attention, active memory, executive and visuospatial functions are especially impaired in PD, whereas verbal

functions, thinking and reasoning are relatively spared [1]. Both MMSE and ACE can evaluate many of these items. Moreover, all items of MMSE are included in the ACE, however differences between them are striking. For example, whilst memory evaluation is a small part of the MMSE, only 10% of total score, ACE assigns 35% of its total to memory, and allows evaluation of serial learning, verbal fluency and extended language by adding 10 objects to the naming-task, assigning greater depth to reading evaluation, as well as including a more stringent comprehension test. Visuospatial function evaluation is enriched by clock and cube drawings added to the MMSE pentagon-drawing task. Furthermore, MMSE includes items from less severely affected domains in PD, such as temporal orientation and language [27,35].

On comparing ACE with the SCOPA-COG, the latter focuses on domains frequently affected in PD (memory, attention and executive and visuospatial functioning) [16], making this test more sensitive to cognitive deficits present in PD. Nevertheless, SCOPA-COG assesses mainly, although not exclusively, the subcortical functions in PD. ACE on the other hand [17], was developed to provide a brief sensitive test for early stages of dementia, capable of distinguishing between subtypes including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy and other parkinsonian syndromes such as corticobasal degeneration, progressive supranuclear palsy and multiple system atrophy [17–22]. It has been used in Cambridge for over a decade, and has also been adopted by several international sites [18,36–39], making its validation in PD worthwhile.

Our results suggest that, compared to a well-established and comprehensive cognitive screening test such as MDRS, ACE has proven it is an appropriate instrument for first line global evaluation of cognitive deficits in PD patients. Future studies should be directed to verify whether ACE might be useful to distinguish dementia in PD, from dementias because of other causes such as Alzheimer's disease.

Conflicts of interest

None.

Funding

None.

References

1. Dubois B, Burn D, Goetz C, *et al*. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Movement Disorders* 2007; **22:** 2314–2324.
2. Brown RG, Marsden CD. How common is dementia in Parkinson's disease? *Lancet* 1984; **2:** 1262–1265.
3. Marttila RJ, Rinne UK. Dementia in Parkinson's disease. *Acta Neurologica Scandinavica* 1976; **54:** 431–441.
4. Tison F, Dartigues JF, Auriacombe S, *et al*. Dementia in Parkinson's disease: a population-based study in ambulatory and institutionalized individuals. *Neurology* 1995; **45:** 705–708.
5. Marder K, Tang MX, Cote L, Stern Y, Mayeux R. The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Archives of Neurology* 1995; **52:** 695–701.
6. Hobson P, Meara J. The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. *Age and Ageing* 1999; **28:** 39–43.
7. Mohr E, Mendis T, Grimes JD. Late cognitive changes in Parkinson's disease with an emphasis on dementia. *Advances in Neurology* 1995; **65:** 97–113.
8. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. *New England Journal of Medicine* 1997; **337:** 1667–1674.
9. Growdon JH, Corkin S, Rosen TJ. Distinctive aspects of cognitive dysfunction in Parkinson's disease. *Advances in Neurology* 1990; **53:** 365–376.
10. Brown GG, Rahill AA, Gorell JM, *et al*. Validity of the Dementia Rating Scale in assessing cognitive function in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology* 1999; **12:** 180–188.
11. Pillon B, Gouider-Khouja N, Deweer B, *et al*. Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58:** 174–179.
12. Miyasaki JM, Shannon K, Voon V, *et al*. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66:** 996–1002.
13. Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975; **12:** 189–198.
14. Feher EP, Mahurin RK, Doody RS, *et al*. Establishing the limits of the Mini-Mental State. Examination of 'subtests'. *Archives of Neurology* 1992; **49:** 87–92.
15. Verbaan D, Marinus J, Visser M, *et al*. Cognitive impairment in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 2007; **78:** 1182–1187.
16. Marinus J, Visser M, Verwey NA, *et al*. Assessment of cognition in Parkinson's disease. *Neurology* 2003; **61:** 1222–1228.
17. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000; **55:** 1613–1620.
18. Bier JC, Ventura M, Donckels V, *et al*. Is the Addenbrooke's cognitive examination effective to detect frontotemporal dementia? *Journal of Neurology* 2004; **251:** 428–431.

19. Bak TH, Rogers TT, Crawford LM, *et al*. Cognitive bedside assessment in atypical parkinsonian syndromes. *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76:** 420–422.
20. Dudas RB, Berrios GE, Hodges JR. The Addenbrooke's cognitive examination (ACE) in the differential diagnosis of early dementias versus affective disorder. *Am J Geriatr Psychiatry* 2005; **13:** 218–226.
21. Galton CJ, Erzinclioglu S, Sahakian BJ, Antoun N, Hodges JR. A comparison of the Addenbrooke's Cognitive Examination (ACE), conventional neuropsychological assessment, and simple MRI-based medial temporal lobe evaluation in the early diagnosis of Alzheimer's disease. *Cognitive Behavioural Neurology* 2005; **18:** 144–150.
22. Larner AJ. An audit of the Addenbrooke's Cognitive Examination (ACE) in clinical practice. *International Journal of Geriatric Psychiatry* 2005; **20:** 593–594.
23. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery and Psychiatry* 1992; **55:** 181–184.
24. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979; **134:** 382–389.
25. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *Journal of Neurology, Neurosurgery and Psychiatry* 2000; **68:** 423–428.
26. Fahn S, Elton RL, Members of the UPDRS Committe. Unified Parkinson's disease rating scale. In: Mardsen CD, Golstein M, Calne DB, eds. *Recent Developments in Parkinson*'s Disease. New York: McMillan, 1987: 153–163.
27. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; **17:** 427–442.
28. Bak TH, Mioshi E. A cognitive bedside assessment beyond the MMSE: the Addenbrooke's Cognitive Examination. *Practice Neurology* 2007; **7:** 245–249.
29. Larner AJ. Addenbrooke's Cognitive Examination (ACE) for the diagnosis and differential diagnosis of dementia. *Clinical Neurology and Neurosurgery* 2007; **109:** 491–494.
30. Carod-Artal FJ, Martinez-Martin P, Kummer W, Ribeiro LS. Psychometric attributes of the SCOPA-COG Brazilian version. *Movement Disorders* 2008; **23:** 81–87.
31. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Preventive Veterinary Medicine* 2000; **45:** 23–41.
32. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry* 2006; **21:** 1078–1085.
33. Carley S, Dosman S, Jones SR, Harrison M. Simple nomograms to calculate sample size in diagnostic studies. *Emergency Medicine Journal* 2005; **22:** 180–181.
34. Jones SR, Carley S, Harrison M. An introduction to power and sample size estimation. *Emergency Medicine Journal* 2003; **20:** 453–458.
35. Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *Journal of Neurology* 1997; **244:** 2–8.
36. Bier JC, Donckels V, Van EE, *et al*. The French Addenbrooke's cognitive examination is effective in detecting dementia in a French-speaking population. *Dementia Geriatric Cognitive Disorders* 2005; **19:** 15–17.
37. Garcia-Caballero A, Garcia-Lado I, Gonzalez-Hermida J, *et al*. Validation of the Spanish version of the Addenbrooke's Cognitive Examination in a rural community in Spain. *International Journal of Geriatric Psychiatry* 2006; **21:** 239–245.
38. Mathuranath PS, Hodges JR, Mathew R, *et al*. Adaptation of the ACE for a Malayalam speaking population in southern India. *International Journal of Geriatric Psychiatry* 2004; **19:** 1188–1194.
39. Newman JP. Brief assessment of cognitive mental status in Hebrew: Addenbrooke's Cognitive Examination. *Israel Medical Association Journal* 2005; **7:** 451–457.