A score based on screening tests to differentiate mild cognitive impairment from subjective memory complaints

Fábio Henrique de Gobbi Porto,1 Lívia Spindola,1 Maira Okada de Oliveira,1 Patricia Helena Figuerêdo do Vale,1 Marco Orsini,2 Ricardo Nitrini,1 Sonia Maria Dozzi Brucki3
1Behavioral and Cognitive Neurology Unit, Department of Neurology, Cognitive Disorders Reference Center, das Clinicas Hospital, University of São Paulo; 2Neurology Department, Antonio Pedro University Hospital, Federal Fluminense University, Rio de Janeiro, Brazil

Abstract

It is not easy to differentiate patients with mild cognitive impairment (MCI) from subjective memory complainers (SMC). Assessments with screening cognitive tools are essential, particularly in primary care where most patients are seen. The objective of this study was to evaluate the diagnostic accuracy of screening cognitive tests and to propose a score derived from screening tests. Elderly subjects with memory complaints were evaluated using the Mini Mental State Examination (MMSE) and the Brief Cognitive Battery (BCB). We added two delayed recalls in the MMSE (a delayed recall and a late-delayed recall, LDR), and also a phonemic fluency test of letter P fluency (LPP). A score was created based on these tests. The diagnoses were made on the basis of clinical consensus and neuropsychological testing. Receiver operating characteristic curve analyses were used to determine area under the curve (AUC), the sensitivity and specificity for each test separately and for the final proposed score. MMSE, LDR, LPP and delayed recall of BCB scores reach statistically significant differences between groups (P=0.000, 0.03, 0.001 and 0.01, respectively). Sensitivity, specificity and AUC were MMSE: 64%, 79% and 0.75 (cut off <29); LDR: 56%, 62% and 0.62 (cut off <3); LPP: 71%, 71% and 0.71 (cut off <14); delayed recall of BCB: 56%, 82% and 0.68 (cut off <9). The proposed score reached a sensitivity of 88% and 76% and specificity of 62% and 75% for cut off over 1 and over 2, respectively. AUC were 0.81. In conclusion, a score created from screening tests is capable of discriminating MCI from SMC with moderate to good accuracy.

Introduction

Mild cognitive impairment (MCI) is a heterogeneous condition characterized by subjective complaints of cognitive decline, supported by objective decline in neuropsychological evaluation and relative preservation of functionality, which does not meet criteria for the diagnosis of dementia.14 It may be due to degenerative diseases,2 vascular lesions,4 be associated with psychiatric disorders,2 or have other causes and may represent a transitional state between the cognition of normal aging and mild dementia.4 Patients with subjective complaints of cognitive decline but without abnormalities in objective testing have been defined as pre-mild cognitive impairment (pre-MCI).15 As there are not enough data to indicate that all of these patients will become MCI, we prefer to refer to them as subjective memory complainers (SMC). Despite the fact that some patients after neurophysiological testing (NT) have been diagnosed as non-amnestic MCI, almost all patients complained of memory problems. Because of this, we called them subjective memory complainers. They represent an understudied population with unknown etiological diagnosis and long-term outcomes.16 Further studies are needed to better characterize this population until a definitive labeling of pre-MCI is possible.

Although there are no approved drugs for MCI,1 some non-pharmacological interventions such as physical exercise and cognitive training have been shown to be effective.12-15 Physical exercise and cognitive rehabilitation are examples of interventions that may delay the progression of MCI to dementia. New drugs are being studied in MCI, such as intranasal insulin and a nicotine patch.16-17 Furthermore, with the possibility of disease-modifying treatments,18 such as anti-amyloid beta monoclonal antibody, the identification of MCI is becoming more important.

In practice, health-care providers frequently have to deal with complaints of memory problems.19 The prevalence of memory complaints varied widely across several studies, ranging from 11% to 70%.20 In a busy daily practice where time is an important and limiting factor, coupled with the unavailability of formal NT for all patients, cognitive evaluation screening could provide important clues to the correct differential diagnosis between SMC and MCI.

The objective of this study was to evaluate the diagnostic accuracy of simple cognitive screening tests to differentiate SMC from MCI and to propose a score derived from these tests to try to improve differentiation between the two conditions.

Materials and Methods

This study involved volunteers living within a community environment aged over 60 years who complained of memory problems, recruited mostly from community centers for the elderly. The complaints needed to be expressed spontaneously by the subjects and were also evaluated by the Memory Complaint Questionnaire.24 Study subjects were submitted to a clinical evaluation and screening cognitive battery which included the Mini Mental State Examination (MMSE)25 and Brief Cognitive Battery (BCB).26,27 The BCB is a visual learning test in which subjects have 3 attempts to learn 10 simple line drawings: shoe, house, comb, key, airplane, turtle, book, spoon, tree, and bucket. Initially, the 10 figures are shown and the subjects are instructed to name them. After that, the pictures are withdrawn and they are asked to remember the name of the pictures spontaneously. The pictures remembered are scored as incidental memory. The pictures are then shown again for 30 seconds (s) and subjects are asked to try...
to memorize the figures on them. The pictures are removed and subjects have one minute to remember the name of the objects. This is repeated once (2 attempts of 30 s to learn the 10 pictures). The number of pictures learned after the second attempt is scored as learned memory. After, functioning also as a distractor activity, subjects perform a categorical fluency test (number of animals in 1 min) and the clock drawing test (CDT). The next step is a delayed recall of drawings where subjects have one minute to try to remember the pictures (called delayed recall) and a recognition of the previous learned drawings combined with 10 other drawings. This battery has shown good accuracy in diagnosing early dementia, with little influence of level of education. In an attempt to evaluate an easy and fast way to improve the accuracy of both tests for this population, we added two delayed recalls of the three words of the MMSE, one after the MMSE itself, which we called delayed recall (DR), and another after the BCB (carried out in sequence after the MMSE), called late-delayed recall (LDR). We also included a phonemic verbal fluency test (number of words in 1 min) with the letter P (LPF) in the BCB after the animal fluency test (also increasing the distraction interval of the test). We used the Geriatric Depression Scale (GDS) and the Geriatric Anxiety Inventory (GAI) to evaluate the intensity of depressive and anxiety symptoms, respectively. The Functional Activities Questionnaire (FAQ) was used to evaluate functional status. We excluded individuals with FAQ over 4 and/or GDS over 5 or those considered to have dementia, or other active neuropsychiatric conditions through consensus discussion. Subjects with a past history of or neurological evidence of stroke, neurodegenerative disorders, head injury, serious non-compensated medical illness, drug abuse, hearing, visual or motor impairment that could have affected their cognitive performance were not included. For this analysis, we included only patients with over eight years of formal education. After the initial evaluation, all eligible patients were admitted to NT with a neuropsychologist with experience in cognitive testing. NT were composed of visual and verbal psychologist with experience in cognitive skills and interpretation of the results obtained in all tests were performed according to each reference guide.

The final diagnosis was established by a consensus of neurologists with expertise in cognitive and behavioral neurology. Patients were classified as MCI or SMC according to the presence or absence of cognitive deficits in NT (considered the gold standard in this study). We considered a cognitive function to be impaired if the score on that function were lower than −1.5 standard deviation (SD) in one test or if in more than one test of the same function, the scores were between −1 and −1.5 SD.

Statistical analysis was carried out using SPSS software, version 17.0 (SPSS, Inc, Chicago, IL, USA). We used the Kolmogorov-Smirnov test to verify the normality of the data, Student’s t-test scores for comparative differences between MCI and SMC, and ROC curve analysis to determine accuracy, sensitivity and specificity of different tests. After that, we created a proposal score with the tests with greater area under the curve (AUC). For all analyses 0.05 was considered significant. The study was approved by our institutional ethics committee. All patients taking part in the study gave written informed consent before evaluation.

Results

A total of 106 patients (32 SMC and 74 MCI) were included in our study sample. Demographic data, scores of GAI, GDS, and screening cognitive tests are shown in Table 1.

### Table 1. Comparison between demographic data, screening tests and proposed score.

|           | N=106 | SMC=32 | MCI=74 | Sig (P)* |
|-----------|-------|--------|--------|----------|
| Age (y)   | 68.5 (5.3) | 69.8 (6.6) | 0.136 |
| School (y) | 15.3 (4)   | 13.7 (4.5) | 0.066 |
| GDS       | 1.5 (1.4)  | 1.5 (1.3)  | 0.926 |
| GAI       | 5.8 (4.2)  | 6 (4.7)    | 0.976 |
| FAQ       | 0.5 (1.2)  | 0.9 (1.7)  | 0.380 |
| MMSE      | 28.1 (9.9) | 27.9 (14.4) | 0.000 |
| DR        | 2.4 (0.7)  | 2.3 (0.7)  | 0.816 |
| LDR       | 2.4 (0.7)  | 2 (1.0)    | 0.034 |
| IM-BCB    | 5.8 (1.7)  | 5.4 (1.5)  | 0.224 |
| LM-BCB    | 9.1 (1.9)  | 8.7 (1.1)  | 0.153 |
| DR-BCB    | 8.7 (1.8)  | 7.9 (1.5)  | 0.014 |
| CFA       | 17.5 (4.4) | 16.5 (3.6) | 0.250 |
| LPF       | 14.8 (4.6) | 11.4 (4.4) | 0.001 |
| CDT       | 8.5 (1.9)  | 8.3 (1.6)  | 0.501 |
| FSC       | 1.7 (1.6)  | 3.8 (1.3)  | 0.000 |

Discussion

In everyday clinical practice, it is sometimes difficult to distinguish between pathological cognitive decline and aging-related cognitive decline. Complaints such as subtle forgetfulness, problems in remembering names, misplacing objects, and a lack of attention are very common among elderly people and may not necessarily be a sign of cognitive disorders. Furthermore, the relationship between memo-
ry complaints and cognitive performance may not be straightforward. Most studies have found that subjective memory complaints have a better relationship with psychiatric symptoms rather than cognitive performance on NT.\textsuperscript{20,21,23-25} Although worse cognitive performance has been demonstrated,\textsuperscript{24,26} some authors have even suggested that memory complaints should be removed from the diagnostic criteria of MCI because of its poor relationship with cognitive performance.\textsuperscript{4,6} Even though NT is not essential to the diagnostic criteria for MCI,\textsuperscript{14} it is very useful in assessing people with memory complaints, especially in borderline cases (the so-called early MCI).\textsuperscript{6} Furthermore, NT may be helpful in differentiating amnesic from non-amnesic patients and in grading the cognitive decline. Although it is not to be taken as a rule, on average the suggested intensity of cognitive decline in MCI is between −1 and −2 SD. However, NT is not available for every patient, mainly in the primary care setting where most patients are initially seen. A rapid, sensitive and easy to apply screening test is useful for referring suspect patients to a specialized center.\textsuperscript{47}

In this study, we used two quick screening tests (MMSE and BCB), and added two delayed recalls of the words of the MMSE and one phonemic fluency test (letter P). From these tests, a score was created in an attempt to improve diagnostic accuracy. The approximate duration of the tests was less than 15 min. Our results showed that when compared with NT, screening cognitive tests had only a moderate accuracy in differentiating between MCI and SMC. AUC in ROC ranged from 0.62 to 0.75, sensitivity ranged from 56% to 71% and specificity from 62% to 82%. A score derived from these tests could improve the accuracy (AUC−0.81). Sensitivity ranged from 76% to 88% and specificity from 62% to 75%, depending on the cut-off value. These results are comparable to the accuracy of other brief neuropsychological batteries while having the advantage of being quicker and saving time. The CAMCOG battery has been shown to have a sensitivity of 64%, specificity of 88% and AUC of 0.83 when used to compare controls and MCI patients.\textsuperscript{48} In a study of screening tests for MCI, a combination of the MMSE, a categorical fluency test (animals) and the CDT, the authors have concluded that the combination of tests does not have a good diagnostic accuracy for identifying cases of MCI, in spite of their usefulness in the diagnostic screening for dementia.\textsuperscript{49} Others attempted to combine MMSE and CDT, showing a sensitivity of approximately only 50%.\textsuperscript{50} Combination of MMSE with an informant-based functionality scale, the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE), also showed only moderate accuracy when attempting to discriminate MCI from controls (AUC 0.7, sensitivity 73.7%, specificity 62.7%).\textsuperscript{51}

Despite being the most known, most used, and most cited tool for cognitive screening, the MMSE has been shown to have little sensitivity for anterograde amnesia and executive function, especially in borderline cases.\textsuperscript{24,26} Other authors have already proposed delayed recalls of the words of the MMSE to improve its accuracy for detecting memory impairment. Loewenstein et al.,\textsuperscript{52} added three delayed recalls of the words, have shown a sensitivity of 83.3% and specificity of 9.0.4% in differentiating MCI from control.\textsuperscript{29} In our sample, a delayed recall of the words of the MMSE could improve the detection of early memory impairment. In the MMSE itself, there was no statistically significant difference between groups in the recall of the three words (P=0.457). The strategy of prolonging the time available and including more tasks of distraction between exposure and recall probably makes more demands on the anterograde memory systems, making this a more sensitive task.

As discussed above, the MMSE has low sensitivity to detect mild executive function impairment, so letter P fluency was added to the BCB (that already includes a categorical fluency test) to try to improve detection of executive dysfunction. Even though both categorical and phonemic fluency tests involve word production (language), the former is dependent on semantic memory systems and the latter on executive control, to implement mental planning and searching strategies.\textsuperscript{6,53} It has been shown to represent a surrogate of dorsolateral pre-frontal cortex function, bilaterally.\textsuperscript{6} Letter P fluency had the biggest isolated AUC in our sample. Interestingly, our results showed that categorical fluency did not differentiate between SMC and MCI: M (SD); 17.4 (4.4) and 16.5 (3.8); P=0.338. This is the opposite to that found in some reports in which categorical verbal fluency (a marker of semantic knowledge) was found to be more impaired in MCI in relation to control than phonological fluency,\textsuperscript{7} which maintains the same pattern as patients with Alzheimer’s disease when compared with healthy control.\textsuperscript{8} On the other hand, some authors found no such dissociation, reporting impairment in both fluency tests.\textsuperscript{24,50} In our sample, phonemic fluency (letter P) was shown to be superior than a categorical fluency (animals) test in differentiating early cognitive impairment from subjective memory complainers. This could be due to an early executive dysfunction in patients with MCI. Taking into account that we excluded patients with GDS over 5 or with other active psychiatric disorders, in our sample no differences were seen between scores of depression and anxiety scales assessed by GDS and GAL, respectively. Although the majority of authors have correlated the presence of memory complaints to psychological symptoms,\textsuperscript{20,21,23-25} our results cannot confirm this because in our sample all subjects studied had memory complaints. However, poorer cognitive performance in the MCI group could not be explained by more intense depressive or anxiety symptoms.

### Conclusions

In conclusion, our results demonstrated that a score derived from screening tests can discriminate between MCI and SMC with moderate to good accuracy. Simple modifications may improve accuracy and make such tests better able to identify those who will be diagnosed to have MCI in the NT. Phonological fluency test (letter P) and a delayed recall of the words of the MMSE were shown to improve the accuracy of screening tests. Although screening tests may be appropriate in primary care or at first visit, these findings underline the importance of NT for better evaluation of those patients in whom there is a suspicion of early cognitive impairment.

Our study has some limitations. Firstly, we included only patients with more than eight years of formal education and excluded patients with GDS over 5. This could reduce the relevance of our results in developing countries with low levels of education and also for patients with depressive symptoms. It is possible that when

| N=106 | Cut off SENS* | SMC=32 SPEC* | MCI=74 | AUC |
|-------|--------------|--------------|--------|-----|
| MMSE  | <29          | 64           | 79     | 0.75|
| LDR   | <3           | 56           | 62     | 0.62|
| DR-BCB| <9           | 56           | 82     | 0.68|
| LPF   | <14          | 71           | 71     | 0.71|
| FSC   | >1           | 88           | 62     | 0.81|
| FPF   | >2           | 76           | 75     | -   |

AUC, area under the curve; DR-BCB, delayed recall in brief cognitive battery; FSC, final score; LDR, late-delayed recall of mini mental state examination’s words; LPF, letter P fluency; MCI, mild cognitive impairment; MMSE, mini mental state examination; SENS, sensitivity; SMC, subjective memory complaint; SPEC, specificity. *Percentage.
used in subjects with less than eight years of formal education, these screening tests and the proposed score might have lower sensitivity and specificity. We chose to set this education level as part of inclusion criteria to avoid differences between groups in this variable. Also, schooling showed a trend for non-statistically significant difference between SMC and MCI. In our study, both groups were highly educated so level of education cannot be responsible for the differences observed between groups. Besides this, all NT scores were adjusted according to schooling. Second, we used NT as gold standard of the diagnosis. Even though there is no consensus about the use of formal assessment as gold standard to diagnose MCI, it is a well-accepted practice. In our opinion, NT is important for early diagnosis of MCI. Also, we did not differentiate between the subtypes of MCI. Since the main objective of the study was to evaluate the usefulness of screening tests before NT, such a subdivision would be unfair. Most of the patients were amnestic MCI. Lastly, our results need to be prospectively tested in a different population.

Second, we used NT as gold standard of the diagnosis. Even though there is no consensus about the differences observed between groups. Besides this, all NT scores were adjusted according to schooling. Second, we used NT as gold standard of the diagnosis. Even though there is no consensus about the use of formal assessment as gold standard to diagnose MCI, it is a well-accepted practice. In our opinion, NT is important for early diagnosis of MCI. Also, we did not differentiate between the subtypes of MCI. Since the main objective of the study was to evaluate the usefulness of screening tests before NT, such a subdivision would be unfair. Most of the patients were amnestic MCI. Lastly, our results need to be prospectively tested in a different population with a large number of subjects and wider levels of education in order to further confirm the overall accuracy of the proposed score.

References

1. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-8.
2. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001; 58: 1985-92.
3. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447-55.
4. Mitchell AJ, Monge-Aráes JA, Sánchez-Paya J. Do CSF biomarkers help clinicians predict the progression of mild cognitive impairment to dementia? Pract Neurol 2010;10:202-7.
5. Litvan I, Aarsland D, Adler CH, et al. MDS Task Force on mild cognitive impairment in Parkinson’s disease: critical review of PD-MCI. Mov Disord 2011;26:1814-24.
6. Consoli A, Pasi M, Pantonio L. Vascular mild cognitive impairment: concept, definition, and directions for future studies. Aging Clin Exp Res 2012;24:113-6.
7. Panza F, Frisardi V, Capurso C, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry 2010;18:98-116.
8. Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med 2011;364:2227-34.
9. Duara R, Loewenstein DA, Greig MT, et al. Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates. Am J Geriatr Psychiatry 2011;19:951-60.
10. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology 2006;67:834-42.
11. Abdurrah K, Heun R. Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. Eur Psychiatry 2008;23:321-30.
12. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment. Arch Neuro 2010;69:29-38.
13. Van Uffelen JGZ, Chinapaw MJM, Van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med 2008;42:344-51.
14. Lautenschlager NT, Cox KL, Flicker L, et al. Effects of physical activity on cognitive function in older adults at risk for Alzheimer’s disease. JAMA 2008;300:1027-37.
15. Teixeira CV, Godhi LT, Corazza DI, et al. Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). Arch Gerontol Geriatr 2012;54:175-80.
16. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29-38.
17. Newhouse P, Kellar K, Aisen P, et al. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. Neurology 2012;78:91-101.
18. Ozdugru SN, Lippa CF. Disease modifying drugs targeting ß-amyloid. Am J Alzheimers Dis Other Dement 2012;27:296-300.
19. Coley N, Osset P, Andreu S, et al. Memory complaints to the general practitioner: data from the GuidAge study. J Nutr Health Aging 2008;12:665-72S.
20. Jonker C, Launer LJ, Hoosier C, Lindeboom J. Memory complaints and memory impairment in older individuals. J Am Geriatr Soc 2012:44:44-9.
21. Schofield PW, Jacobs D, Marder K, et al. The validity of new memory complaints in the elderly. Arch Neurol 1997;54:756-9.
22. Wang PN, Wang SJ, Fuh JL, et al. Subjective memory complaint in relation to cognitive performance and depression: a longitudinal study of a rural Chinese population. J Am Geriatr Soc 2000;48:295-9.
23. Stewart R, Russ C, Richards M, et al. Depression, APOE genotype and subjective memory impairment: a cross-sectional study in an African-Caribbean population. Psychol Med 2001;31:431-40.
24. Almeida OP. Memory complaints and the diagnosis of dementia. Arq Neuropsiquiatr 1998;56:412-8.
25. Brucki SM, Nitrini R. Subjective memory impairment in a rural population with low education in the Amazon rainforest: an exploratory study. Int Psychogeriatr 2009;21:164-71.
26. Crook TH, Feher EP, Larabee GJ. Assessment of memory complaint in age-associated memory impairment: the MAC-Q. Int Psychogeriatr 1992;4:165-75.
27. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
28. Brucki SMD, Nitrini R, Caramelli P, et al. Sugestões para o uso do mini-exame do estado mental no Brasil. Arq Neuropsiquiatr 2003;61:777-81.
29. Nitrini R, Caramelli P, Porto CS, et al. Uma bateria cognitiva breve com alta acurácia no diagnóstico de doença de Alzheimer em população com grande heterogeneidade educacional. Arq Neuropsiquiatr 2006;64 Suppl 1:200.
30. Nitrini R, Caramelli P, Porto CS, et al. Brief cognitive battery in the diagnosis of mild Alzheimer’s disease in subjects with medium and high levels of education. Dement Neuropsychol 2007;1:32-6.
31. Sunderland T, Hill JL, Mellow AM, et al. Clock drawing in Alzheimer’s disease: a novel measure of dementia severity. J Am Geriatr Soc 1989;37:725-9.
32. Takada LT, Caramelli P, Fichman HC, et al. Comparison between two tests of delayed recall for the diagnosis of dementia. Arq Neuropsiquiatr 2006;64:35-40.
33. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of geriatric depression screening scale: a preliminary report. J Psychiatr Res 1983;17:37-49.
34. Pachana NA, Byrne GJ, Siddle H, et al. Development and validation of the Geriatric Anxiety Inventory. Int Psychogeriatr 2007;19:103-14.
35. Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Effects of aerobic exercise on mild cognitive impairment: a pilot clinical trial. Arch Neurol 2007;64:321-30.
40. Diniz LFM, Cruz MF, Torres VM, Consenza, RM. Teste de aprendizagem auditivo verbal de Rey: normas para uma população brasileira. Ver Bras Neurol 2000;36:79-83.

41. Wechsler D. WAIS-III: Administration and scoring manual. San Antonio: The Psychological Corporation; 1997.

42. Nascimento, E. WAIS-III: escala de inteligência Wechsler para adultos: manual David Wechsler; adaptação e padronização de uma amostra brasileira. 1ª ed. São Paulo: Casa do Psicólogo; 2004

43. Raven JC, Raven J, Court JH. Manual matrizes progressivas coloridas. São Paulo: Casa do Psicólogo; 2004.

44. Minett TS, Da Silva RV, Ortiz KZ, Bertolucci PH. Subjective memory complaints in an elderly sample: a cross-sectional study. Int J Geriatr Psychiatry 2008;23:49-54.

45. Lenehan ME, Klekociuk SZ, Summers MJ. Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): is it time to abandon subjective memory complaint as an MCI diagnostic criterion? Int Psychogeriatr 2012;24:1505-14.

46. Drexler E, Voss B, Amunts K, et al. Mild cognitive impairment: advantages of a comprehensive neuropsychological assessment. Curr Alzheimer Res 2012 Jun 29. [Epub ahead of print].

47. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. Int J Geriatr Psychiatry 2010;25:111-20.

48. Nunes PV, Diniz BS, Radanovic M, et al. CAMcog as a screening tool for diagnosis of mild cognitive impairment and dementia in a Brazilian clinical sample of moderate to high education. Int J Geriatr Psychiatry 2008;23:1127-33.

49. Ladeira RB, Diniz BS, Nunes PV, Forlenza OV. Combining cognitive screening tests for the evaluation of mild cognitive impairment in the elderly. Clinics (Sao Paulo) 2009;64:967-73.

50. Ravaglia G, Forti P, Maioli F, et al. Screening for mild cognitive impairment in elderly ambulatory patients with cognitive complaints. Aging Clin Exp Res 2005;17:374-9.

51. Abreu ID, Nunes PV, Diniz BS, Forlenza OV. Combining functional scales and cognitive tests in screening for mild cognitive impairment at a university-based memory clinic in Brazil. Rev Bras Psiquiatr 2008;30:346-9.

52. Tombaugh TN, McIntyre NJ. The mini mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-35.

53. Loewenstein DA, Barker WW, Harwood DG, et al. Utility of a modified mini-mental state examination with extended delayed recall in screening for mild cognitive impairment and dementia among community dwelling elders. Int J Geriatr Psychiatry 2000;15:434-40.

54. Nutter-Upham KE, Saykin AJ, Rabin LA, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol 2008;23:229-41.

55. Kelip JG, Goryl M, Alexander GE, et al. Cerebral blood flow patterns underlying the differential impairment in category vs letter fluency in Alzheimer’s disease. Neuropsychologia 1999;37:1251-61.

56. Quinn C, Elman L, Mccluskey L, et al. Frontal lobe abnormalities on MRS correlate with poor letter fluency in ALS. Neurology 2012;79:583-8.

57. Murphy KI, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer’s type dementia. J Int Neuropsychol Soc 2006;12:570-4.

58. Chan AS, Butters N, Salmon DP, McGuire KA. Dimensionality and clustering in the semantic network of patients with Alzheimer’s disease. Psychol Aging 1993;8:411-9.

59. Brandt J, Manning KJ. Patterns of word-list generation in mild cognitive impairment and Alzheimer’s disease. Clin Neuropsychol 2009;23:870-9.