CME

Population norms for the MMSE in the very old

Estimates based on longitudinal data

C. Dufouil, PhD; D. Clayton, MSc; C. Brayne, MD; L.Y. Chi, PhD; T.R. Dening, MD; E.S. Paykel, MD; D.W. O'Connor, MD; A. Ahmed, MA; M.A. McGee, MSc; and F.A. Huppert, PhD

Article abstract—*Objective:* To report the percentile distribution of Mini-Mental State Examination (MMSE) scores in older people by age, sex, and education level, estimated from longitudinal data, after correcting for loss due to dropout. *Methods:* The Cambridge City over 75 Cohort is a population-based study of a cohort of 2106 subjects age 75 years and older at study entry followed up over 9 years. At each of the four waves, cognitive function was assessed using MMSE. Based on these data, the relationship between age and MMSE score was modeled. Percentile distributions by age, sex, and education level were provided using inverse probability weighting to correct for dropouts. *Results:* Performance on MMSE was related to age in men and women. In women, at age 75, MMSE score ranged from 21 (10th percentile) to 29 (90th percentile). At age 95, the range was 10 (10th percentile) to 27 (90th percentile). The upper end of MMSE distribution was slightly modified with age, whereas the lower end of the distribution was very sensitive to age effect. A similar pattern was observed in both sexes. *Conclusion:* These findings provide norms for MMSE scores in subjects age 75 years and older from longitudinal population-based data. Such norms can be used as reference values to determine where an individual's score lies in relation to his or her age, sex, and education level.

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The Mini-Mental State Examination (MMSE) is a brief neuropsychological test for evaluating cognitive status.[1] In drug trials for dementia, MMSE score has been suggested for use in entry criteria for dementia drug administration (MMSE score between 10 and 24[2]) and is used as an outcome to monitor progress.[3]

MMSE scores are affected by age and education level, with lower scores being associated with increasing age and lower educational level.[4-5] The widespread use of MMSE tends to be based on simple cut-points and little attempt has been made to provide population-based norms. Some norms have been published from a few cross-sectional studies.[6-8] Cross-sectional data for population norms are limited because the effects of age and cohort are confounded and longitudinal data should be used. Longitudinal observation of MMSE scores over time is rare and usually based on short follow-up studies. In addition, MMSE is usually studied as a continuous variable although its distribution is not normal. Rather than using means, a knowledge of percentile distributions by age and sex allows placement of an individual in the context of the distribution for that age, much as in growth charts in childhood. The objective of this article is to provide a set of clinically useful normative distributions for MMSE that have been corrected for loss due to dropout.

Materials and methods. *Sample description.* We performed a longitudinal study of cognitive decline and dementia in Cambridge, UK. Ethical approval for the study was obtained from the ethical committee in accordance with standard practice. A complete sample of subjects age 75 years and over was selected from four general practices in the city, with systematic selection of one in three from a further practice. These individuals were approached for interview by a trained lay interviewer who elicited information on sociodemographic variables, social and service contacts, activities of daily living, physical health, and cognitive status using the MMSE. Participation rate is de-

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From MRC Biostatistics Unit (Dr. Dufouil, D. Clayton, and M.A. McGee); Department of Community Medicine (Drs. Brayne and Chi, and A. Ahmed), Institute of Public Health; Psychiatric Services for the Elderly, Addenbrooke's NHS Trust (Dr. Dening); Department of Psychiatry (Drs. Paykel and Huppert), University of Cambridge, UK; and Department of Psychological Medicine (Dr. O'Connor), Monash University, Australia. Dr. Dufouil was a visiting scientist from INSERM Unit 360 (Paris, France).

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Address correspondence and reprint requests to Dr. C. Dufouil, INSERM Unit 360, Hôpital La Salpétrière, 75651 Paris Cédex 13, France; e-mail: dufouil@chups.jussieu.fr

scribed elsewhere.[9] Based on MMSE scores, a sample was selected for further interview with a psychiatrist or trained nurse using a standardized psychiatric interview (the Cambridge Examination for Mental Disorders in the Elderly).[10] At 2.4 years after first interview, all surviving individuals who had not received a diagnosis of dementia at this interview were reapproached for interview. The same procedure was carried out with trained lay interviewers administering a slightly modified interview at 6 and 9 years. Prevalence and incidence of dementia and subtypes and cognitive decline from first to second interview have been reported previously.[11] Follow-up was achieved by checking with the general practitioners on each occasion, and by flagging individuals at the Office of National Statistics for date and cause of death. MMSE was coded according to previous conventions, in that refused items were coded to zero, as were items where the respondent was unable to perform the item because of physical or sensory difficulty.[12] Interviewers were encouraged to ask the questions wherever possible, not assuming that items could not be attempted.

Statistical method. The evolution of MMSE scores in this cohort will undoubtedly be influenced by mortality, as subjects with low MMSE scores have higher mortality rates.[13] Thus, trends in the distribution of MMSE in the cohort may differ substantially from individual trajectories. Here our interest is in the former, but even this aim is affected by the relatively large number of subjects who dropped out for other reasons. Two simple analyses suggest themselves: 1) comparing the distributions of subjects seen at each visit, or 2) analyzing only the subjects with complete records. Both of these analyses are flawed.[14] The latter analysis concentrates on an atypical "survivor" population of subjects who are both healthy and compliant. The former analysis would be satisfactory if dropout were unrelated to MMSE and its determinants, but this cannot be assumed. This difficulty is addressed by a two-stage analysis. In the first analysis, we related the probability of dropping out at each stage to age, sex, and MMSE at the previous visit using logistic regression. Conventional life table calculations can then be used to calculate, for each subject–visit observed, the fitted probability that the subject would have remained in the study thus far. If this probability turns out to be 0.5, for instance, then this implies that it is to be expected that one other similar subject was in the original cohort but dropped out of the study. Thus, this subject should be counted as two subjects rather than one in subsequent analyses. In general, we assign weights that are the inverses of the fitted probabilities of remaining in the study. So, an MMSE measured at visit i is weighted by one over the fitted probability that this subject was still in the study at visit i, given his or her age and past MMSE scores. This was obtained by a life table calculation. For example, if p_1 is the probability of dropout between visits 1 and 2, p_2 the probability of dropout between visits 2 and 3, and so on, the probability of remaining in the study until visit i is:

$$(1 - p_1) * (1 - p_2) * \ldots * (1 - p_{i-1}).$$

Each dropout probability, p_{i-1}, may depend on variables measured at visits up to and including visit i, and was estimated by logistic regression. This approach to the analysis of incomplete longitudinal data is described in detail by Robins.[15]

Note that the estimated probabilities p_1, p_2, p_3 refer to the probability of dropout conditional upon remaining alive. Thus, the weighted analysis seeks to reproduce patterns that would be observed in a longitudinally observed population with no dropout but in which mortality operates. Because the cognitively impaired have increased mortality, these profiles may be rather different from the trajectories of specific individuals.[16]

We divided the cohort by age at entry into the study into three groups: 75 to 79, 80 to 84, and 85+. Using the weights described above, we then calculated 10th, 25th, 50th, 75th, and 90th quantiles for each of these groups at each visit.[17-18] Finally, we constructed age–quantile charts by weighted quantile regression, regressing quantiles of MMSE against age, fitted as cubic splines with internal knots at ages 80, 85, and 90. That is, different cubic splines were fitted in each 5-year age band, constrained so that the aggregate curve varies smoothly across boundaries.[19] The fitted values were rounded to the nearest integer.

Table 1 *Compliance and mortality in the longitudinal study*

Visit	Time since first visit, y	Subjects with valid MMSE, n	Dropouts/ no valid MMSE, n	Dead, n
1	—	2106	—	—
2	2.4	1116	598	392
3	6	569	219	328
4	9	301	123	145

MMSE = Mini-Mental State Examination.

Results. Table 1 shows the number of individuals with a valid MMSE score at each stage. Of the 2106 subjects interviewed at onset, 301 completed MMSE at each stage.

Table 2 *Logistic regression results for the probability of dropout*

Variable	Coefficient	Standard error	OR (95% CI)	p Value
Visit 3 vs visit 2	−0.358	0.099	0.70 (0.58–0.85)	<0.001
Visit 4 vs visit 2	−0.551	0.132	0.58 (0.44–0.75)	<0.001
Female vs male	0.032	0.091	1.03 (0.86–1.23)	NS
Age at previous visit	0.032	0.011	1.03 (1.01–1.06)	<0.05
MMSE at previous visit	−0.161	0.011	1.17 (1.16–1.19)	<0.001

MMSE = Mini-Mental State Examination.

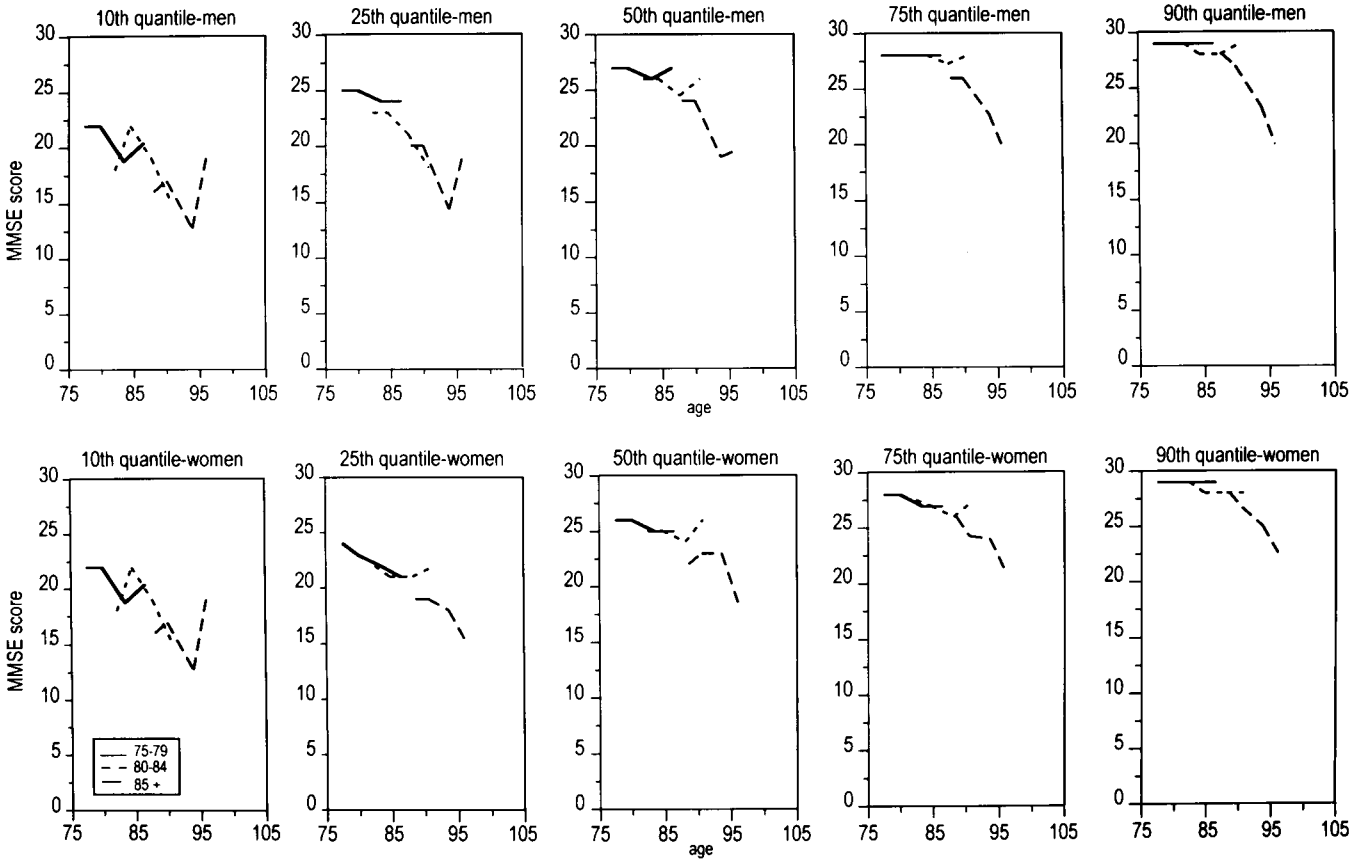

Figure 1. Mini-Mental State Examination selected quantiles longitudinal trajectories by age at entry and gender.

Between study entry and 9-year interview, 41% of the subjects were lost through death.

Table 2 shows the results of the logistic regression analysis of dropout from the study. The probability of dropout was lower at visit 3 than visit 2, and still lower at visit 4. Older subjects were more likely to drop out, but there was no significant difference between the sexes. There was a very strong relationship between MMSE and dropout, with subjects with low MMSE scores being much more likely to drop out. It is important to correct for this in subsequent analysis of trends in MMSE, as the subjects remaining in the study at later visits are to some extent selected. This regression analysis was used to calculate the weights for future analyses.

Figure 1 shows the trends in population quantiles calculated at each visit for groups defined in 5-year bands of age at entry. For the 50th, 75th, and 90th quantiles, the curves lie more or less on top of each other, so that longitudinal and cross-sectional analyses give similar estimates of the trend of MMSE with age. However, for the 10th and 25th quantiles, there is a suggestion that subjects who were older when they entered the study had higher MMSE scores. Although this could represent a cohort effect, it is much more likely that it represents a selection bias.

Figure 2 shows our final estimates of the trends in population quantiles, obtained by weighted quantile regression analysis, using cubic splines. Because it was suspected that selection may have affected the lower quantiles, age at entry was included as a covariate in the regressions and the curves shown are corrected back to a

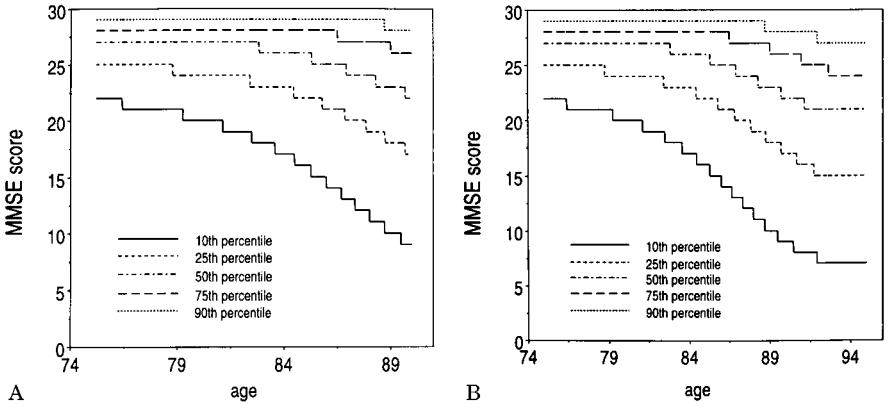

Figure 2. Mini-Mental State Examination score by age and selected quantiles by gender. A, men; B, women.

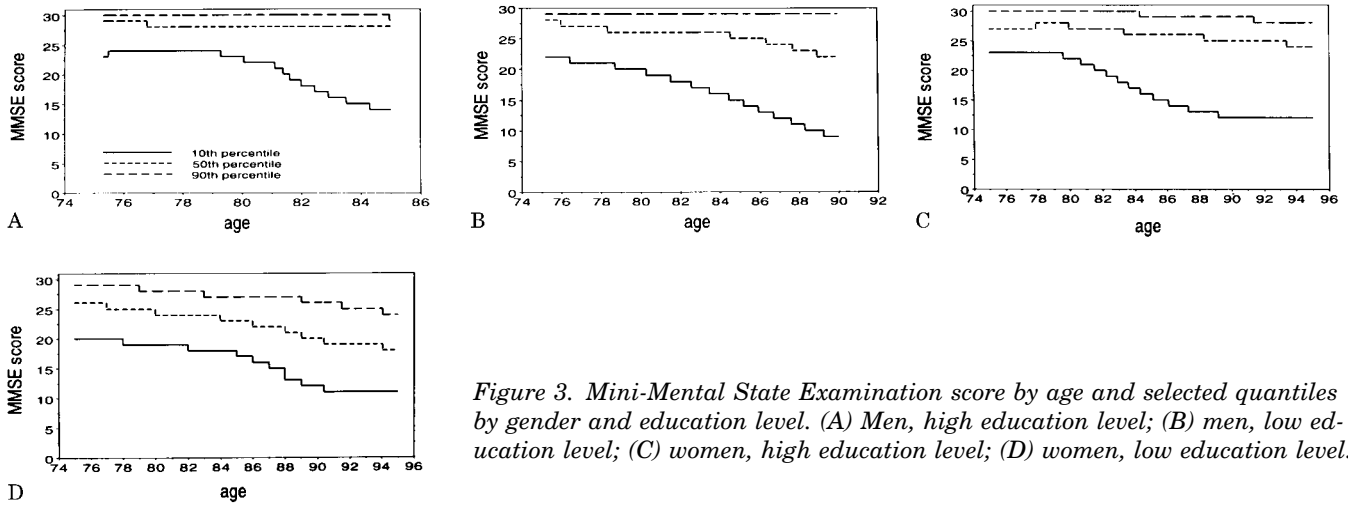

Figure 3. Mini-Mental State Examination score by age and selected quantiles by gender and education level. (A) Men, high education level; (B) men, low education level; (C) women, high education level; (D) women, low education level.

common entry age of 75. Note that this strategy ensures that trends are estimated from the longitudinal information in the study and not from the cross-sectional information. We have not plotted the trends for men beyond age 90 as the data were very sparse and estimates were unreliable. The total MMSE score was found to decrease with age in men and women. The decline was observed across all percentiles. The range of MMSE scores increased with increasing age. For example, in women, 90% of those age 75 years score 21 or higher whereas in those age 90 years, the equivalent range of scores was 10 or more. The course of cognitive decline was similar in men and women. Starting MMSE score was a bit lower in women but the patterns of cognitive decline were similar in both sexes.

Further analyses were carried out to examine the impact of education on these norms (figure 3). The results showed that the effect of education level is stronger in higher percentiles. The 90th percentile in women of high education level (leaving school at age 15 or older) was 30 at 75 years old and 28 at 95 years old; it was 29 at 75 years old and 23 at 95 years old in women who were less educated.

Discussion. This study measures the longitudinal evolution of MMSE distribution in a sample of subjects age 75 years and older. Our study is the first to provide quantile norms of MMSE based on longitudinal data. As expected, we found age to be associated with MMSE scores. Figures 2 and 3 produced by age, sex, and education level can be used in a similar manner to growth charts for children. Thus, they allow, in general or clinical practice, the evaluation of a subject of given age, sex, and education level with reference to what is observed in the population. Percentiles rather than means in clinical practice are more useful for placing individuals among their own peers. This provides clinicians with a guide to how deviant a patient's score is for a given age group, and is also helpful for pharmaceutical companies recruiting for studies to understand how generalizable their findings will be and for those who wish to monitor outcome using MMSE to understand what profile is to be expected at each age.

A limitation of these findings is that they are based on a representative sample of subjects age 75 years and older living in Cambridge. The use of these norms applied to other samples requires some caution in terms of comparability. However, these are an advance over crude recommendations of cut-points or norms based on younger age groups. A further limitation of this work is related to the nature of the longitudinal data. In correcting for dropout, we have allowed the probability to depend only on previous MMSE scores. A worst-case scenario would be that subjects who dropped out would have had lower results than those seen had the interview taken place (informative dropout). The suggestion from this work is that this may be most important at the lower end (<25th percentile) of the MMSE distribution; informative dropout is therefore a serious problem for dementia, but perhaps not so serious for normal aging.

References

1. 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;12:189–198.
2. Lovestone S, Graham N, Howard R. Guidelines on drug treatments for Alzheimer's disease. Lancet 1997;350:232–233.
3. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136–145.
4. Jacqmin Gadda H, Commenges D, Fabrigoule C, Dartigues JF. A 5-year longitudinal study of the Mini-Mental State Examination in normal aging. Am J Epidemiol 1997;145:498–506.
5. Jorm AF, Henderson AS, Kay DWK. Educational level differences on the Mini-Mental State: the role of test bias. Psychol Med 1988;18:727–731.
6. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–2391.
7. MRC CFA Study Group. Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. Psychol Med 1998;28:319–335.

8. Grigoletto F, Zappalà G, Anderson DW, Lebowitz BD. Norms for the Mini-Mental State Examination in a healthy population. Neurology 1999;53:315–320.
9. O'Connor D, Pollitt PA, Brook CP, Reiss BB, Roth M. Practice observed: do general practitioners miss dementia in elderly patients? BMJ 1988;297:1107–1110.
10. Roth M, Tym E, Mountjoy CQ, et al. The CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986;149:698–709.
11. Brayne C, Gill C, Paykel ES. Cognitive decline in an elderly population—a two wave study of change. Psychol Med 1995; 25:673–683.
12. Roth M, Huppert FA, Tym E, Mountjoy CQ. CAMDEX. The Cambridge Examination for Mental Disorders of the Elderly. Cambridge, UK: Cambridge University Press, 1988.

CME

A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia

P.S. Mathuranath, MD; P.J. Nestor, FRCAP; G.E. Berrios, MD; W. Rakowicz, MBBS; and J.R. Hodges, MD

Article abstract—*Objectives:* To validate a simple bedside test battery designed to detect mild dementia and differentiate AD from frontotemporal dementia (FTD). *Methods:* Addenbrooke's Cognitive Examination (ACE) is a 100-point test battery that assesses six cognitive domains. Of 210 new patients attending a memory clinic, 139 fulfilled inclusion criteria and comprised dementia (n = 115) and nondementia (n = 24) groups. The composite and the component scores on the ACE for the two groups were compared with those of 127 age- and education-matched controls. Norms and the probability of diagnosing dementia at different prevalence rates were calculated. To evaluate the ACE's ability to differentiate early AD from FTD, scores of the cases diagnosed with dementia with a Clinical Dementia Rating ≤ 1 (AD = 56, FTD = 24, others = 20) were compared. *Results:* Two cut-off values for the ACE composite score (88 and 83) were of optimal utility depending on the target population. The ACE had high reliability, construct validity, and sensitivity (93%, using 88 as cut-off). Using the lower cut-off of 83, the ACE had a higher sensitivity (82%) and predictive value than the Mini-Mental State Examination for a wide range of dementia prevalence. The ACE differentiated AD from FTD, and the VLOM ratio (derived using component scores: [verbal fluency + language]/[orientation + memory]) of <2.2 for FTD and >3.2 for AD was highly discriminating. *Conclusion:* The ACE is a brief and reliable bedside instrument for early detection of dementia, and offers a simple objective index to differentiate AD and FTD in mildly demented patients.

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The need for screening and diagnostic tests to provide an objective measure of cognitive function has increased over the last two decades largely as a result of three developments: 1) the realization that a substantial proportion of patients previously diagnosed with AD have other pathologies, notably dementia with Lewy bodies[1] and frontotemporal dementia (FTD)[2]; 2) the advent of disease-modifying treatments for AD, making it vital to establish an early and accurate diagnosis, preferably in the predementia stage of the disease[3]; and 3) the enormous increase in memory clinics, reflecting a growing concern in the general community about failing memory in late life.[4]

Several screening and diagnostic tests for dementia have been developed,[5,6] but no single test is the established standard.[3] More comprehensive cognitive batteries such as the cognitive section (CAMCOG) of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[7] and the Dementia Rating Scale (DRS)[8] require specialized test equipment or trained personnel to administer, and are beyond the scope of routine bedside cognitive evaluation. The Mini-Mental State Examination (MMSE)[5] is one of

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From the University of Cambridge Neurology Unit (Drs. Mathuranath, Nestor, and Hodges, and W. Rakowicz) and Department of Psychiatry (Dr. Berrios), University of Cambridge, Addenbrooke's Hospital; and MRC Cognition and Brain Sciences Unit (Dr. Hodges), Cambridge, UK.

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Address correspondence and reprint requests to Professor John R. Hodges, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK; e-mail: john.hodges@mrc-cbu.cam.ac.uk

