Clinical referral patterns and cognitive profile in mild cognitive impairment

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Background
There is current interest in exploring the different subtypes of mild cognitive impairment (MCI), in terms of both their epidemiology and their cognitive profile.

Aims
To examine the frequency of MCI subtypes presenting to a memory clinic and to document detailed neuropsychological profiles of patients with the amnestic subtype.

Method
Consecutive tertiary referrals (n=187) were psychiatrically evaluated; 45 patients met criteria for amnestic mild cognitive impairment (aMCI). A subgroup of 33 patients with aMCI as well as 21 healthy controls took part in a thorough neuropsychological examination.

The diagnosis of mild cognitive impairment (MCI) represents an attempt to define features of the dementias in their preclinical phases. Petersen and colleagues developed research criteria with a cut-off for verbal recall performance as objective evidence of episodic memory impairment. This approach has been challenged because it excludes patients who display exclusively visual episodic memory impairment. Moreover, the pure amnestic subtype of mild cognitive impairment is rare, and mild cognitive impairment case definition varies as a function of the neuropsychological tests used. It is not clear how the Petersen criteria might best be translated into clinical practice. There is little information detailing the frequency with which each of the subtypes presents to memory clinics. Our aim was to examine the diagnostic profile of patients with amnestic mild cognitive impairment (aMCI) referred to our tertiary assessment service. We also sought to evaluate a comprehensive battery of neuropsychological measures for their usefulness in this patient group.

Sample
We retrospectively analysed 187 consecutive referrals to the Edinburgh Neuropsychological Assessment Service for Older People between the months of September 2004 and April 2006. Referrals were received at a tertiary level, stemming from consultation or, in a small proportion of cases, by a score greater than 10 on the Geriatric Depression Scale within the context of a clinical interview with the patient and the patient's primary carer (when available). A total of 112 patients fulfilled one or more of the following exclusion criteria and were therefore excluded from the analyses:

(a) dementia (MMSE score < 24/30 or ACE score < 80/100, plus fulfilling DSM–IV criteria);
(b) depression, assessed either by way of formal psychiatric consultation or, in a small proportion of cases, by a score greater than 10 on the Geriatric Depression Scale or clinical assessment by one of the authors (J.A.L.);
(c) one or more medical or psychiatric conditions that could conceivably account for the patient's cognitive impairment (head injury, schizophrenia, evidence of stroke or tumour on neuroimaging, alcoholism, epilepsy, cranial radiotherapy).

Of the remaining 75 patients, 15 showed cognitive impairments outside the domain of episodic memory, 15 returned a 'normal' cognitive profile and 45 showed memory function emission computed tomography) prior to being referred to our service. All but three patients were over the age of 50 years.

Results
Of the patients who were examined in greater neuropsychological detail, ten had pure aMCI (none with visual memory impairment only). Fifteen met criteria for non-amnestic MCI. Fifteen had normal neuropsychological profiles. Using more than one test increased sensitivity to detect episodic memory impairment.

Conclusions
Amnestic MCI is an important diagnosis in secondary and tertiary memory clinics. There is scope to improve the efficacy and sensitivity of the clinical assessment of this impairment.

Declaration of interest
None.
impaired for age (with or without additional areas of cognitive impairment). We present detailed neuropsychological baseline findings for 33 of these 45 patients as well as for 21 healthy individuals from the community who agreed to participate as a control group in a continuing longitudinal study examining neuropsychological markers of preclinical dementia. Control group participants were recruited through a local dementia support group or were spouses or carers of patients who had attended the neuropsychological assessment service.

**Neuropsychological assessment measures**

All the participants were given a comprehensive battery of neuropsychological tests. These tests were selected on the basis of their demonstrated validity for use within a population with MCI, and assessed the primary domains of verbal and visual episodic memory, semantic memory and language, processing speed, attention/executive function and visuospatial ability.

**Premorbid intellectual ability**

The National Adult Reading Test (NART) was administered in order to assess probable premorbid level of intellectual function.

**Episodic memory**

To assess verbal episodic memory, participants were given the Hopkins Verbal Learning Test – Revised (HVLT–R). In this test participants are asked to recall as many words as possible immediately after presentation of a 12-item word list on three consecutive learning trials. Measures included total number of words recalled across three registration trials (maximum 36), total number of words recalled following a 30 min delay (maximum 12) and a discrimination index score representing a participant’s ability to discriminate between old and new list items. Visual episodic memory was assessed by means of two different tasks. The CANTAB Paired Associate Learning (PAL) test is a computerised measure of visuospatial learning ability requiring participants to learn the locations of an increasing number of patterns – one, two, three, six and then eight; the score of interest was the number of pattern-position errors at the six-pattern level. Participants were also administered the Rey Complex Figure Test. For this test, participants are asked to make a copy of a complex figure, with no time restriction. Immediately after presenting the figure, and again following a 30 min delay, participants are required to make another copy from memory.

**Semantic memory**

Participants completed the Graded Naming Test, the Boston Naming Test and the Edinburgh Exemplar Naming Test (EENT; further details available from the authors). The Graded Naming Test and Boston Naming Test require participants to name line drawings of increasing difficulty, whereas the Graded Faces Test requires participants to name a series of 30 famous faces. The EENT was developed by one of the authors (J.A.L.) in an effort to improve the sensitivity of existing confrontation naming measures to early semantic memory failure. In this test the participant is required to name 50 line drawings of low-frequency animate objects with sizeable feature overlap. Participants were also asked to complete a category fluency task, requiring them to name as many animals as they could in 1 min.

**Attention/executive functioning**

As a means of examining attention/executive function and visuomotor processing speed, participants were asked to produce as many words as possible beginning with the letter P in 1 min (letter fluency task). In addition, participants were administered parts A and B of the Trail Making Test; in this test participants are required to join up as quickly as possible numbered circles in ascending order (part A) and numbers and letters in ascending alternating sequence (part B), while the time to completion is recorded.

**Visuospatial skills**

Visuospatial skills were assessed by means of the Rey Complex Figure Test copy task described above.

**Comparison with other memory clinics**

We searched the literature for studies employing neuropsychological test batteries similar to ours to examine the comparability of our sample with other published data.

**Statistical analysis**

We calculated z-scores to determine where scores fell below the tenth percentile of control performances. Visual inspection together with a one-sample Kolmogorov–Smirnov goodness-of-fit test indicated that the data were normally distributed. Group means were compared using independent sample t-tests. To determine whether there is an association between general level of cognitive function and the consistency of episodic memory impairment, we divided the participants with cognitive impairment into two groups: those who displayed episodic memory impairment on a single measure only and those who showed impairment on two or more episodic memory tests. Their Addenbrooke’s Cognitive Examination and MMSE scores were compared using an independent samples t-test. Diagnostic categories between memory clinics were compared using chi-squared tests for diagnostic categories.

**Results**

**Literature search**

We identified one other study reporting consecutive referrals to a memory clinic using similar diagnostic criteria and assessment measures.

**Comparability of referral patterns and cognitive profiles**

A striking similarity in referral patterns was observed between our Neuropsychological Assessment Service for Older Adults and data reported recently from the Cambridge Memory Clinic. When the 150 pre-excluded referrals from the Cambridge Memory Clinic were accounted for, over half (60%) of referrals from both centres were excluded on the grounds of an established dementia or depressive disorder, or one or more medical conditions that could account for the patient’s cognitive impairment ($\chi^2=0.015, P=0.90$). Close to 40% of referrals from both centres fell within the non-demented and non-depressed category ($\chi^2<0.001, P=0.995$). Just over half of these patients in both centres met Petersen’s expanded criteria for aMCI ($\chi^2=0.46, P=0.50$), representing close to a fifth of overall referrals from both centres. Of the remaining 40% of patients in the non-demented, non-depressed category, half demonstrated cognitive deficits of a non- amnestic variety (in one or more domains) and half returned ‘normal’ cognitive profiles. Although referral patterns for aMCI were similar
across the two centres, there was a greater proportion of patients with non-amnestic MCI and fewer with visual-only impairment in our sample ($\chi^2=13.23$, d.f.=3, $P=0.004$; Fisher–Freeman–Halton exact test, $P=0.003$). Mean scores for both the aMCI and control groups across all neuropsychological measures were similar to those previously reported.

### Sample characteristics

Our final sample for analysis consisted of 33 patients with aMCI (13 men and 20 women, with a mean age of 74.0 years, s.d.=6.4; social class I n=9, II n=12, IIIIN n=9, social class not known n=3) and 21 healthy community-dwelling older adults without cognitive complaints (7 men and 14 women, with a mean age of 69.5 years, s.d.=7.4). These groups did not differ in terms of estimated premorbid level of intellectual function. The mean age of our control group was, however, significantly lower than that of our aMCI patient group, a finding similar to previous reports.2,4

### Comparison of aMCI and control groups

Despite a mean ACE score that exceeded suggested cut-off points for dementia,12 the aMCI group had significantly lower mean scores than the control group on all neuropsychological measures, with the exception of the Rey Complex Figure Test copy task, the Trail Making Test part A and the letter (phonemic) fluency task. These findings were confirmed when the analysis was re-run with age as a covariate, with the exception of performance on the CANTAB PAL and the Trail Making Test part B, which just failed to reach significance. Demographic data and mean scores for the two groups on the individual neuropsychological measures are provided in Table 1. All aMCI group means are based on data from 33 participants, with the exception of the final three semantic memory measures, for which the participant numbers ranged between 13 and 31.

### Amnestic MCI group performance

#### Episodic memory

The neuropsychological performances of 33 of 45 patients who fulfilled Petersen’s expanded criteria9 for aMCI were examined in greater detail. As in the Cambridge Memory Clinic study,7 not all of these participants demonstrated impairment across all episodic memory measures: 11 (33%) showed impairment on a single test, 9 (27%) showed impairment on two memory measures and the remaining 13 (39%) were impaired on three or more tests. Mean MMSE and Addenbrooke’s Cognitive Examination scores for participants who were impaired on more than one episodic memory measure were significantly lower than for those showing impairment on a single test ($P<0.05$). Just over half of our aMCI subgroup showed both verbal and visual episodic memory impairment. Although a significant proportion (45%) demonstrated memory impairment of a verbal nature only, none of our patients in this group exhibited a pure visual memory deficit.

#### Non-memory measures

Only ten (30%) patients in our aMCI subgroup exhibited an isolated impairment of episodic memory function. All the other patients (70%) exhibited deficits in one or more additional domains of cognition, most commonly that of semantic memory function, followed by attention and executive function (Table 2).

### Table 1 Demographic data and performance of the sample on our neuropsychological test battery

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Control group (n=21)</th>
<th>aMCI group (n=33)</th>
<th>V. aMCI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean (s.d.)</td>
<td>Mean (s.d.)</td>
<td>Mean (s.d.)</td>
<td></td>
</tr>
<tr>
<td>NART score</td>
<td>118.3 (2.8)</td>
<td>116.4 (8.5)</td>
<td>0.331</td>
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<tr>
<td>MMSE score</td>
<td>29.1 (0.8)</td>
<td>28.0 (1.8)</td>
<td>&lt;0.01**</td>
<td></td>
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<tr>
<td>ACE score</td>
<td>Total (100)</td>
<td>94.6 (3.3)</td>
<td>88.2 (5.9)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>Delay (7)</td>
<td>6.4 (0.9)</td>
<td>3.9 (2.3)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Rey Complex Figure Test scores</td>
<td>Copy (36)</td>
<td>34.0 (2.4)</td>
<td>34.2 (2.5)</td>
<td>0.729</td>
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<tr>
<td></td>
<td>Immediate recall (36)</td>
<td>19.1 (6.3)</td>
<td>12.3 (6.0)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td>Delayed recall (36)</td>
<td>17.4 (7.4)</td>
<td>10.8 (6.9)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>HVL1–T score</td>
<td>Total recall (12)</td>
<td>24.3 (3.0)</td>
<td>18.2 (4.6)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>Delayed recall (12)</td>
<td>8.19 (2.8)</td>
<td>4.8 (3.2)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td></td>
<td>Discrimination (12)</td>
<td>10.3 (1.9)</td>
<td>8.5 (2.2)</td>
<td>&lt;0.01**</td>
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<tr>
<td></td>
<td>PAL 6 errors</td>
<td>7.8 (6.9)</td>
<td>16.6 (14.8)</td>
<td>&lt;0.01**</td>
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<tr>
<td>Trail Making Test score</td>
<td>Part A, s</td>
<td>40.3 (11.2)</td>
<td>48.6 (20.0)</td>
<td>0.095</td>
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<td></td>
<td>Part B, s</td>
<td>87.5 (31.6)</td>
<td>131.7 (78.4)</td>
<td>&lt;0.01**</td>
</tr>
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<td>Animal fluency score</td>
<td>21.1 (5.7)</td>
<td>15.1 (4.5)</td>
<td>&lt;0.001***</td>
<td></td>
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<tr>
<td>P words score</td>
<td>15.7 (5.8)</td>
<td>16.0 (4.8)</td>
<td>0.860</td>
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<tr>
<td>Boston Naming Test score</td>
<td>57.4 (3.1)</td>
<td>53.6 (5.5)</td>
<td>&lt;0.01**</td>
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<td>EENT score</td>
<td>46.8 (3.0)</td>
<td>43.6 (4.5)</td>
<td>&lt;0.01**</td>
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<tr>
<td>Graded Faces Naming Test score</td>
<td>20.8 (3.1)</td>
<td>16.3 (4.9)</td>
<td>&lt;0.001***</td>
<td></td>
</tr>
<tr>
<td>Graded Naming Test score</td>
<td>23.4 (3.2)</td>
<td>19.5 (4.2)</td>
<td>0.015*</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05; P<0.01; P<0.001.

#### Discussion

##### Referral patterns

In this study we have shown that people who are neither depressed nor demented but who fulfil Petersen’s expanded criteria for aMCI make up a significant proportion of referrals to our Old Age Clinical Neuropsychology service. Roughly a quarter of all patients referred during an 18-month period met Petersen’s criteria9 for aMCI were examined in the study by the Cambridge Memory Clinic (23%),2 and is a very similar figure to the 20% of patients seeking help in Lehrner et al’s clinic who met criteria for aMCI.25 Furthermore, the observation that the highest numbers of people with MCI were those with aMCI make up a significant proportion of referrals to our Old Age Clinical Neuropsychology service. Roughly a quarter of all patients referred during an 18-month period met Petersen’s criteria9 for aMCI were examined in the study by the Cambridge Memory Clinic (23%),2 and is a very similar figure to the 20% of patients seeking help in Lehrner et al’s clinic who met criteria for aMCI.25 Furthermore, the observation that the highest numbers of people with MCI were those with

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Neuropsychological profile of aMCI

The applicability of Petersen’s research criteria to clinical practice has recently been challenged on the grounds of exclusion of a significant number of patients who display episodic memory impairment of a visual nature only. In contrast to the results from the Cambridge Memory Clinic reported by Alladi et al., around half of the participants with aMCI in our study showed impairment of both verbal and visual memory, whereas all of the remaining participants with aMCI exhibited memory impairment of a verbal nature only. That is to say, we failed to uncover any case of isolated visual memory impairment.

A recent study supports the notion that the type of episodic memory measure used may affect whether or not impairments are detected – a point we will return to later in the discussion. However, the absence of participants showing episodic memory impairment of a solely visual nature in our sample cannot be readily explained in terms of differential test sensitivities, because near-identical neuropsychological measures were used in previous studies (e.g. that of Alladi et al.) to assess visual memory function. Only a small proportion of our patients with aMCI demonstrated impairment on the visual episodic memory tasks per se. Administrative procedures might go some way to explain this observation. Specifically, our inclusion of an immediate Rey Complex Figure Test recall trial might have resulted in higher delay scores, thus serving to reduce the sensitivity of this measure in our aMCI group.

Findings of studies examining patients who are at risk of developing Alzheimer’s disease suggest that measures of verbal episodic memory are most sensitive to changes early in the disease course, followed by measures of visual memory. It is therefore conceivable, taking into account our aMCI group’s higher mean score on the Addenbrooke’s Cognitive Examination, that our sample contained a greater number of patients who were at an earlier stage of their disease course. Longitudinal follow-up, in particular observation of annual performances on these visual episodic memory measures, will determine whether this is indeed the case.

Several studies have drawn attention to the substantial variability in MCI case definition as a function of the specific neuropsychological tests used. Consistent with this, in our study there was variability among the aMCI group as to which and how many episodic memory measures were impaired. This finding was previously demonstrated, and highlights the inherent difficulty in specifying the use of any single measure as a means of establishing impaired episodic memory function in aMCI. Our aMCI sample could be roughly divided into thirds in terms of numbers of participants exhibiting impairment on one, two and three or more episodic memory measures. A similar breakdown in numbers has been previously reported. It would appear entirely reasonable and indeed a matter of good clinical practice to seek to establish consistency in performance across a range of episodic memory measures in defining aMCI and it will be of interest to see whether this is a significant determinant of outcome.

The variability in case definition of aMCI as a function of the cognitive measures employed, coupled with the inherent difficulties in specifying the use of a single common measure in the evaluation of this condition, poses a major challenge for clinicians. Our findings suggest that employing Petersen’s expanded criteria for MCI could conceivably lead to a patient’s condition being classified as single-domain aMCI, multiple-domain aMCI or ‘worried well’, depending on the cognitive measures that were employed. If the MCI subdivisions prove useful in a prognostic sense, the means by which the cognitive aspects of the criteria are put into operation by clinicians will require further clarification.

Mean scores on cognitive screening measures were significantly lower for participants showing impairment on more than one episodic memory measure. This may reflect a more advanced disease course in this group. It is also possible that the single-measure impairment group will prove to be a less stable one over time, with a number of patients returning normal neuropsychological profiles when tested again at a later date. Alternatively, in cases in which participants show impairment on a single verbal memory measure only, this might have arisen secondarily to impairment in another cognitive domain, for example expressive language or attention/executive function (in which case the person’s condition might be more accurately conceptualised as non-amnestic MCI). These possibilities and the prognostic implications of consistency and pervasiveness of impaired episodic memory performances remain to be examined by way of longitudinal follow-up.

Our study adds to the growing body of evidence supporting the rarity of a pure amnestic MCI syndrome and demonstrates that additional impairment often goes unnoticed unless participants undergo thorough neuropsychological assessment. Among 33 patients with aMCI, only 10 (30%) presented with isolated memory impairment. This figure is well within the range of previously reported rates. For example, Tabert and colleagues...
found that, following comprehensive neuropsychological assessment, only 19% of their aMCI cases were categorised as pure aMCI, whereas this figure reached 35% in the study by Alladi et al. It should be borne in mind, however, that the rate of cases with purely amnestic MCI will vary in accordance with how impairment is defined. For example, Kramer and colleagues showed that the number of cases classified as pure aMCI was considerably higher (27%) when a cut-off of 1.5 s.d. below the mean, as opposed to 1 s.d. (resulting in a 5% rate), was used. If therefore remains a possibility that our less stringent definition of impairment (i.e. 1 s.d. below the mean performance of the healthy control group) might have resulted in an overestimation of the frequency of cases with non-pure aMCI. Identifying accompanying non-memory cognitive impairment none the less appears important in light of recent evidence indicating a higher risk of conversion to Alzheimer’s disease in patients with aMCI who show additional areas of cognitive impairment compared with patients with pure aMCI.

The results of our study are also consistent with evidence indicating accompanying semantic memory impairment in aMCI, with just 10 patients of 33 exhibiting episodic memory impairment in isolation, and 22 of the remaining 23 displaying evidence of semantic memory compromise. This finding may reflect an increased risk of conversion to Alzheimer’s disease from aMCI, although early semantic memory failure is by no means specific to the former disease, and although some studies report prognostic significance of performance on semantic memory measures; others have failed to do so. The stage at which impairments in this domain become apparent does appear to vary in accordance with the sensitivity of the measure employed. The intact performance of participants with aMCI on measures of lexical (letter) fluency, also previously reported, suggests that the ‘initiation’ aspects of semantic fluency tasks do not pose any difficulty to patients with this impairment subtype.

In view of the sound mean performances of our participants with aMCI on cognitive screening measures (MMSE score 28/30, Addenbrooke’s Cognitive Examination score 88/100), it seems unlikely that consideration of such scores will be of any value in ruling out the presence of additional domains of cognitive impairment. Reliance on clinical judgement to determine the presence or absence of additional domains of subtly impaired cognition is similarly likely to prove difficult when dealing with patients with above-average premorbid IQ scores who are performing at sound levels on cognitive screens. Taken together, the above observations raise the question of whether global screening measures coupled with clinical judgement are a sufficient means of investigating MCI, and if not, whether additional resources or an expanded skill base will be required to handle this population clinically.

Our results reveal an absence of any significant difference in performance between the aMCI and control groups on measures of visuospatial function and processing speed. In-depth longitudinal evaluation of neuropsychological performance in MCI and questionable dementia suggests that visuospatial functions tend to fail secondarily to episodic memory and category fluency performances, although some heterogeneity is known to exist. It is therefore once again possible that our failure to demonstrate group differences on a visuospatial copying task reflects an earlier disease stage of our aMCI sample. Alternatively, it is conceivable that the varied and somewhat subjective scoring methods for the Rey Complex Figure Test copy task across different studies might be responsible for this finding. Cross-sectional findings pertaining to visuomotor processing speed in MCI vary, with some studies reporting significant differences between MCI and control groups and others, like ourselves, failing to do so. The disparity in findings may simply reflect the heterogeneity of aMCI or alternatively the disease stage. Group differences in processing speed might be more likely to exist where samples contain significant numbers of patients in the preclinical stages of a subcortical dementia of a cerebrovascular nature. For example, there is some evidence to suggest a disproportionately strong association between perceptual speed and parkinsonian signs in MCI.

Limitations
Several study limitations should be noted. The significantly higher mean age of our patient group opens up the possibility that some of their performance deficits were explicable in terms of age-related cognitive decline. Ideally, control for age should have been better. However, aMCI group participants were identified on the basis of their performance on age-standardised tests; therefore, the discrepancy would not have influenced patient group membership. Longitudinal follow-up of these patients will help to clarify the relevance of this difference. Furthermore, our aMCI sample was characterised by a high average level of estimated premorbid general intellectual function, which introduces problems of applicability. Similar issues were present in a recent comparable study, although other socio-demographic characteristics (i.e. gender, ethnicity, education and occupation) were not reported, preventing further comparison between that and our study. There may therefore be a need to replicate these findings employing greater numbers of age- and IQ-matched healthy controls and aMCI patients with average premorbid IQs, together with other socio-demographic markers more closely resembling the population mean.

Implications
Patients with MCI make up a significant number of referrals to older adult memory assessment services, with the most common referral subtype in our sample being that of aMCI, followed by equal numbers of non-amnestic MCI and worried well. Relatively few people with aMCI exhibit episodic memory compromise in isolation and fewer still show a visual but not verbal episodic memory deficit. Both the concept and criteria for MCI therefore appear to be relevant and indeed necessary adjuncts to clinical practice.

Our findings highlight the inherent difficulties of specifying a single measure in the assessment of memory and other cognitive functions in MCI, while at the same time emphasising the need for clarification of the means by which MCI criteria can be put into operation clinically. Initial attempts at better defining neuropsychological aspects of the aMCI criteria have been made, but their application in a clinical sense remains inconsistent and their poor definition has not gone unnoticed. The existence of a number of neuropsychological measures of well-documented sensitivity in aMCI and the strikingly similar mean performances of different clinic aMCI groups on such measures suggest that this need not be the case. Although the importance of exercising clinical judgement in arriving at a diagnosis of MCI cannot be ignored, it would none the less seem inevitable that further definition of the neuropsychological aspects of MCI criteria will be needed to facilitate identification of the subtypes of impairment and to further our understanding of their respective prognoses.

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