DOI: 10.1093/brain/awg236 Advanced Access publication July 22, 2003 *Brain* (2003), **126,** 2350–2362

Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55 cases

Matthew A. Lambon Ralph,[1] Karalyn Patterson,[1] Naida Graham,[1] Kate Dawson[2] and John R. Hodges[1,2]

[1]*MRC Cognition and Brain Sciences Unit and* [2]*University Neurology Unit, Addenbrooke's Hospital, Cambridge, UK*

Correspondence to: Professor M. A. Lambon Ralph, Department of Psychology, University of Manchester, Oxford Road, Manchester M13 9PL, UK
E-mail: matt.lambon-ralph@man.ac.uk or Professor J. R. Hodges, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK
E-mail: john.hodges@mrc-cbu.cam.ac.uk

Summary

This study investigated cross-sectional and longitudinal neuropsychological data from 55 patients: 38 with Alzheimer's disease and 18 with mild cognitive impairment (MCI). The analyses were designed to investigate two issues: the relationship of MCI to Alzheimer's disease, and that of atypical to typical Alzheimer's disease. When longitudinal data were averaged across individual patients, a consistent staging of neuropsychological deficits emerged: the selective amnesia characteristic of the MCI phase was joined next by semantic and other linguistic impairments plus emerging difficulties with demanding visuospatial tasks. A two-stage statistical procedure was used to extract underlying factors that corresponded to the severity-governed decline in neuropsychological test scores and then to the consistent deviations away from this typical longitudinal profile; i.e. identifying patterns of atypical Alzheimer's disease. The severity-based factor accounted for nearly 60% of the variance in this MCI–Alzheimer's disease longitudinal and cross-sectional database. This suggests that there is a fairly high degree of homogeneity within this group of patients, and that most of their longitudinal progression can be predicted by dementia severity alone. There were also two main patterns of atypical variation corresponding to patients with exaggerated semantic or visuospatial deficits. Although such cases may mimic more focal lobar degenerative conditions, patients with atypical Alzheimer's disease have pronounced episodic memory impairments, suggesting amnesia as a critical diagnostic feature.

Keywords: Alzheimer's disease; mild cognitive impairment; episodic memory; semantic memory

Abbreviations: MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PCA = principal components analysis; TROG = Test for the Reception of Grammar

Introduction

Accurate and early identification of Alzheimer's disease has become increasingly important since the advent of disease-modifying drugs. Critical to early diagnosis is a fuller understanding of the possible range of presenting cognitive features and progression of disease. Once full-blown dementia with prominent amnesia is present, diagnosis presents relatively little difficulty and current diagnostic criteria are accurate, as measured against the standard of confirmed Alzheimer neuropathology (for review see Salmon and Hodges, 2001). Such criteria may not, however, be optimal for both early and accurate differential diagnosis for two reasons: (i) there is almost certainly a 'prodromal' or preclinical phase in many, if not all, cases (Hodges, 1998; Petersen *et al*., 1999, 2001; Collie and Maruff, 2000), and (ii) there are patients with confirmed Alzheimer's disease who have a highly atypical presentation and clinical course (Galton *et al*., 2000). The current evidence for each of these is reviewed below.

The stereotypical presentation of patients with Alzheimer's disease is dominated by an anterograde episodic memory impairment plus usually less severe deficits in attention and executive processes, semantic memory and/or visuospatial

abilities (Grady *et al*., 1988; Hodges and Patterson, 1995; Perry and Hodges, 2000*b*; Perry *et al*., 2000). Many patients present with this combination of impairments and fulfil the formal criteria for Alzheimer's disease (McKhann *et al*., 1984). Another substantial group present with mild cognitive deficits but later go on to develop full-blown Alzheimer's disease [described variously as 'amnestic prodrome', 'preclinical Alzheimer's disease', 'questionable Alzheimer's disease', 'minimal Alzheimer's disease' or 'mild cognitive impairment' (MCI)] (Hodges, 1998; Collie and Maruff, 2000; Petersen *et al*., 2001; Swainson *et al*., 2001).

Patients in this early stage (hereinafter MCI) can be difficult to differentiate from individuals with normal age-related cognitive decline or mild memory loss associated with depression (e.g. Ritchie *et al*., 2001). In general, though, the contemporary literature on MCI is beginning to reveal a consistent pattern that makes up the early phase of Alzheimer's disease, in terms of both neuropsychology and neuroimaging. The first neuropsychological symptom is anterograde amnesia that is typically severe enough to differentiate patients with MCI from age-matched controls (Fox *et al*., 1998; Arnaiz *et al*., 2000; Perry and Hodges, 2000*b*). Longitudinal studies employing neuropsychological assessment in small groups of subjects have suggested that, following the amnesia-only phase, deficits in attention and/or semantic memory arise before all domains of cognitive processing become affected (Perry and Hodges, 1999; Perry and Hodges, 2000*b*).

These hypothesized stages in the natural history of Alzheimer's disease (amnestic only → amnesia + semantic/attentional impairment → generalized cognitive decline) are supported by findings from various forms of neuroimaging. MRI studies have shown that there is early atrophy of the medial temporal area and that the rate of loss matches the dementia severity of the subjects (Fox *et al*., 1996; Jack *et al*., 2000). Kogure and colleagues (Kogure *et al*., 2000) used SPECT to detect the initial and longitudinal changes in regional cerebral blood flow (rCBF) in 32 patients who progressed from MCI to Alzheimer's disease during a 2-year period. At first, the patients showed significantly reduced rCBF in the posterior cingulate gyrus and precuneus bilaterally when compared with controls. After two years, the patients showed further rCBF reduction in the left hippocampus and parahippocampal gyrus in addition to decline in the cerebral association cortex more generally. Likewise, Arnaiz *et al*. (2001) were able to demonstrate reduced glucose metabolism in temporoparietal regions in individuals who had progressed from MCI to Alzheimer's disease. The progression of neuropsychological and neuroimaging changes provides a close match to the known spread of pathology in typical Alzheimer's disease (Braak and Braak, 1991, 1995). Following initial transentorhinal involvement, neurofibrillary tangles encroach on the hippocampus proper before involving the posterior association cortex.

The early and accurate diagnosis of Alzheimer's disease is challenged by increasing numbers of Alzheimer's disease patients who present with atypical non-amnestic neuropsychological profiles. Factor analyses of large patient databases and retrospective studies of patients with autopsy-proven Alzheimer's disease have identified at least three broad classes of atypical Alzheimer's disease presentation (Neary *et al*., 1986; Becker *et al*., 1988, 1992; Fisher *et al*., 1999; Galton *et al*., 2000). The first is progressive atrophy of the posterior occipitoparietal cortex, leading to either visual agnosia or symptoms of Balint's syndrome, i.e. visual disorientation, simultanagnosia and optic ataxia (Hof *et al*., 1989; Ball *et al*., 1993; Levine *et al*., 1993; Mackenzie-Ross *et al*., 1996). The second is one of the progressive aphasic syndromes, which can be either fluent and reflect a semantic deficit, or non-fluent with slow and halting speech output alternatively with disrupted phonology (Croot, 1997; Neary *et al*., 1986; Galton *et al*., 2000). A third, less well documented subtype, a progressive apraxia syndrome, can include patients with limb apraxia, apraxia of speech, buccofacial apraxia and extrapyramidal symptoms such as rigidity and myoclonus (Neary *et al*., 1986; Green *et al*., 1995; Giannakopoulos *et al*., 1998; Kawamura and Mochizuki, 1999). Precise premorbid diagnosis is difficult in these different types of atypical Alzheimer's disease because the neuropsychological and neurological symptoms overlap with those of other non-Alzheimer diseases (Neary *et al*., 1986). For example, the fluent aphasic presentation of Alzheimer's disease can be confused with semantic dementia (Snowden *et al*., 1989; Hodges *et al*., 1992; Hodges, 2001), although the Alzheimer's disease patients typically have amnesia and concomitant disorientation for time/place. Likewise, the apraxia variant can be similar to corticobasal degeneration (Dick *et al*., 1989).

While there is now clear evidence for these three types of neuropathologically confirmed but atypical forms of Alzheimer's disease, the literature is mainly limited to a series of small retrospective studies (e.g. Neary *et al*., 1986; Galton *et al*., 2000). One study has attempted to relate the distribution of Alzheimer's disease pathology to the patterns of premorbid neuropsychology in a much larger patient sample. Kanne *et al*. (1998) used factor analysis to reveal three psychometric factors (mental control, verbal memory and visuospatial function) underpinning the neuropsychological profile of 407 patients. The distributions of neurofibrillary tangles and senile plaques were quantified on average 5 years later. Premorbid scores on mental control, verbal memory and visuospatial function were systematically related to the burden of senile plaques in the frontal, temporal and parietal regions, respectively. Similarly, Galton *et al*. (2000) found that typical cases with amnesia as a primary feature, plus other cognitive deficits, were associated with the standard pathological distribution (Braak and Braak, 1991): most pronounced in the transentorhinal region and the hippocampal complex, spreading to the temporal neocortex and the frontal and parietal association areas. By contrast, the aphasic presentation was mirrored by an atypical distribution of Alzheimer's disease pathology with involvement of

language areas but relative sparing of the hippocampus and entorhinal cortex, whereas patients with progressive visuospatial difficulties had a severe burden of tangles and plaques involving the parietal cortices bilaterally. Their one patient with primary visual failure had unusually severe Alzheimer's disease neuropathology in the primary visual cortex. The link between neuropsychology and underlying neuropathology mirrors the findings from the few studies that have investigated patterns of hypometabolism in typical and atypical Alzheimer's disease. Martin *et al*. (1986) found global cortical hypometabolism in all Alzheimer's disease patients that was most pronounced in bilateral temporoparietal regions for the typical Alzheimer's disease subgroup. This pattern varied significantly for two atypical groups. Patients with pronounced word-finding difficulties had much greater hypometabolism in the left temporal region, whereas those with prominent visuospatial deficits had much lower metabolic rates in the right temporal and parietal areas.

The lack of direct comparison between typical and atypical cases in the current literature leaves certain clinical questions unanswered. In particular, it is unclear whether the various forms of atypical Alzheimer's disease represent categorically distinct variants or whether, in fact, there are neuropsychological–neuropathological continua linking typical and atypical variants. There are hints in the existing literature that the latter may be nearer the truth. Previous studies that have used factor analysis to identify subtypes of Alzheimer's disease presentation have always found continua between typical and atypical cases rather than discrete subgroups (Becker *et al*., 1988, 1992; Kanne *et al*., 1998; Fisher *et al*., 1999). In a recent study, Caine and Hodges (2001) assessed two unselected groups of patients with presumed Alzheimer's disease and found that 10% of the patients presented with early and pronounced visual perceptual deficits indicative of the visual variant subtype of Alzheimer's disease. Importantly, there was not an absolute differentiation between the visual variant subset and the remainder; all patients had unequivocal deterioration in memory and general cognitive abilities, consistent with a diagnosis of dementia of the Alzheimer type.

The present study used a rich longitudinal and cross-sectional neuropsychological database to address the two themes outlined above: the relationship of MCI to Alzheimer's disease and the relationship of atypical to typical cases. Specifically we addressed the following four questions. (i) What is the staging of neuropsychological deficits when moving from normal controls through MCI to Alzheimer's disease proper? (ii) Are there any qualitative or merely quantitative differences in the longitudinal decline of patients who present either at the MCI or the Alzheimer's disease stage? (iii) Within a relatively unselected set of Alzheimer's disease patients, is it possible to identify statistically meaningful variations in neuropsychological performance? (iv) What is the relationship between these atypical cases and standard Alzheimer's disease?

Patients and methods

Patients

A total of 55 patients took part in this study which was approved by The Cambridge and Huntingdon Local Research Ethics Committee. All patients (and their carers) gave signed, informed consent. These patients presented to the Memory Clinic at Addenbrooke's Hospital, Cambridge, between 1991 and 1993 and were willing to be enrolled in a longitudinal study of cognitive deficits in Alzheimer's disease. It is important to note at the outset that the MCI group was biased towards patients with amnesia as the predominant cognitive deficit and did not include patients with other focal cognitive deficits, such as isolated frontal–executive, linguistic or visuospatial deficits. Patients fulfilling the criteria for one of the variants of frontotemporal dementia (progressive non-fluent aphasia, semantic dementia, frontal variant frontotemporal dementia) were also excluded from this study and thus could not appear as atypical subtypes in the statistical analyses described below. Likewise, any patient with a history of depression, apparent age-related cognitive decline, vascular risk factors, heavy alcohol intake, head injury or other neurological diseases was excluded. These strict screening criteria were adopted to maximize the likelihood of selecting only patients in the Alzheimer's disease prodrome (MCI) or with Alzheimer's disease proper. Patients were divided into four groups: mild cognitive impairment (MCI, n = 17); mild Alzheimer's disease (n = 22); moderate Alzheimer's disease (n = 8); and severe Alzheimer's disease (n = 8). Patients with MCI presented with complaints of poor memory, substantiated by a spouse/family member, with preservation of activities of daily life plus evidence, on neuropsychology assessment, of impairment (<1.5 SDs) on at least one test of memory but normal performance on a range of other routine tests of language, visuospatial and executive function administered in the memory clinic (Hodges *et al*., 2000), and a Mini-Mental State Examination (MMSE; Folstein *et al*., 1975) score of >24. This subgroup corresponds to that described as minimal Alzheimer's disease in our earlier publications (Greene *et al*., 1995; Hodges and Patterson, 1995; Garrard *et al*., 1998; Perry *et al*., 2000). Patients with Alzheimer's disease fulfilled NINCDS–ADRDA (National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria (McKhann *et al*., 1984) and were subdivided according to MMSE score in line with prior publications: mild Alzheimer's disease = MMSE 17–24; moderate = 11–16; severe ⩽10. None of the patients received anticholinergic therapies which were not widely available at the inception of this study.

Longitudinal neuropsychological data were collected from each patient at approximately 6-month intervals until the patient was no longer able or willing to continue. On average, the patients completed 3.7 rounds of testing (minimum = 1 round; maximum = 9 rounds). All but two cases (both from the moderate group) have been followed clinically even

Table 1 *Averaged, cross-sectional neuropsychological data for four levels of dementia severity.*

Assessment	Maximum score	Control mean	MCI	Mild DAT	Moderate DAT	Severe DAT	Control minimum	Control SD
MMSE	30	28.7	26.9	**21.4**	**14.0**	**6.9**	25	1.32
No. of patients	–	–	26	33	15	13	–	–
No. of observations	–	–	63	105	24	14	–	–
Episodic memory								
Logical memory (immediate)	20	11.87	**5.42**	**2.93**	**1.35**	**0.84**	6.5	3.82
DRS: memory	25	24.22	**17.95**	**12.33**	**8.63**	**7.86**	22	1.00
Digit span forwards	N/A	6.78	6.74	6.09	4.88	**3.71**	4	1.00
Digit span backwards	N/A	4.78	4.85	3.92	**2.71**	**1.93**	3	1.24
Semantic memory								
Semantic features	192	181.82	175.21	**164.45**	**144.87**	**127.54**	153	7.71
Category fluency	N/A	111.54	82.92	**53.15**	**26.58**	**9.29**	65	25.12
Sorting by feature	72	68.91	68.34	**65.02**	**59.08**	**53.21**	66	1.74
Word-picture matching	48	47.58	47.08	**45.55**	**41.21**	**38.5**	44	0.92
Picture naming	48	43.58	42.19	**38.56**	**31.04**	**21.43**	38	2.32
Naming to description	24	22.44	20.89	**17.37**	**10.33**	**4.15**	18	1.64
Language								
Token Test	36	35.65	**33.76**	**31.23**	**24.35**	**12.08**	34	0.55
Letter fluency (FAS)	N/A	44.26	36.97	**26.23**	**14.29**	**4.14**	34	10.25
TROG	80	78.89	77.69	**72.93**	**57.5**	**42.36**	73	1.79
Spelling to dictation	36	35.22	34.94	**32.27**	**22.38**	**12.62**	34	0.90
Reading exception words	42	40.22	39.29	38.03	**35.83**	**30.64**	35	1.93
Reading regular words	42	41.35	41.61	40.79	40.42	**38.00**	35	1.53
NART	50	36.72	34.62	28.05	22.73	**16.75**	16	9.62
Perception and attention								
Rey copy (immediate)	36	34.00	31.36	**22.5**	**12.7**	**8.61**	23	3.01
Object matching	40	37.83	37.52	35.28	**31.26**	**28.86**	33	1.77
DRS: attention	40	36.04	35.85	34.66	**32.08**	**24.43**	34	0.82

Bold figures denote the patient scores that either fall below the lowest score of the control subjects or are >2 SDs below the control mean. DAT = dementia of Alzheimer type; DRS = Disease Rating Scale.

beyond the stage of being able to complete formal neuropsychological assessment. Of the 17 MCI cases, 14 have converted to Alzheimer's disease (82.3%) and three have improved and presumably had non-organic causes for initial memory underfunctioning or have remained stable. Of the 14 who progressed, six have died with advanced dementia and five are in full-time residential care, with only three remaining in their own homes (death 35%, death or residential care 65%). Of the 22 in the mild Alzheimer's disease group, all have progressed inexorably, 14 have died and seven are in full-time care (death 64%, death or care 95%). Of 16 in the moderate and severe groups, for whom follow-up data are available, 13 have died and one is in care (death 92%, death or care 100%). Of the 33 patients who have died, 11 have come to autopsy: all 11 had neuropathologically confirmed Alzheimer's disease (data courtesy of Dr John Xuereb).

Neuropsychological tests

In addition to the MMSE (Folstein *et al*., 1975), a large battery of neuropsychological assessments were administered at each testing round. The results from 18 tasks were selected on the basis that there was minimal missing data both longitudinally and cross-sectionally. These neuropsychological assessments can be grouped under four broad headings.

Episodic memory

(i) Logical memory (Wechsler, 1987)—immediate recall only; (ii) memory subtest from the Dementia Rating Scale (Mattis, 1977).

Semantic memory

Six subtests were taken from the Hodges–Patterson semantic battery on the basis of a common corpus of 48 pictures or words, half of which represented living items and half man-made items (Hodges and Patterson, 1995). The subtests were (iii) category fluency (eight categories); (iv) picture naming; (v) word–picture matching; (vi) picture sorting (according to a specific feature); (vii) naming to verbal description; and (viii) semantic feature questions.

Language

(ix) Token test: shortened 36-item version (De Renzi and Vignolo, 1962); (x) letter fluency (FAS); (xi) Test for the Reception of Grammar (TROG; Bishop, 1989); (xii) spelling to dictation (Graham *et al*., 2000); (xiii) reading of words with exceptional spelling–sound correspondences (Patterson and Hodges, 1992); (xiv) reading of words with regular

spelling–sound correspondences (Patterson and Hodges, 1992); (xv) National Adult Reading Test (Nelson, 1982).

Perception and attention

(xvi) Rey complex figure (immediate copy); (xvii) object matching (Riddoch and Humphreys, 1992); (xviii) attention subtest from the Dementia Rating Scale (Mattis, 1977).

Results

Staging of neuropsychological deficits in typical Alzheimer's disease: normal → MCI → Alzheimer's disease

For these analyses, longitudinal data were combined into a cross-sectional format by moving a patient to the next severity band as his or her MMSE crossed a boundary. Table 1 shows the averaged neuropsychology results for the four levels of patient severity (MMSE bands) as well as for a group of 48 control subjects (matched to the patients for age and education). Abnormal scores, i.e. those >2 SDs below the control mean or below the worst individual control score, are highlighted. While there was a gradual decline in all test scores, Table 1 reveals a clear staging of neuropsychological deficits. The MCI group were characterized by one specific deficit: amnesia. The group, as a whole, fell below the control range for the Logical Memory and memory subtest from the Dementia Rating Scale. Interestingly, the MCI group were also impaired on the Token Test, traditionally regarded as a test of language comprehension. Further analysis of the groups' performance showed that all errors occurred in the final section, consisting of syntactically complex sentences, which also place heavy demands on working memory and attentional–executive skills. In contrast, the MCI group performed as well as control subjects in all other domains, including digit span, semantic memory, language, perception and attention.

Once patients have moved from MCI to Alzheimer's disease proper (denoted here as 'mild Alzheimer's disease'), a range of other deficits emerges. This group demonstrated impaired performance on all tasks requiring semantic memory, including tests of comprehension (e.g. word–picture matching, semantic feature questions, etc.) and production (e.g. category fluency and picture naming). Whereas concurrent amnesia and subtle executive impairments might influence performance on tests that require active mental manipulation of the semantic knowledge base (e.g. semantic feature questions and category fluency), impaired performance on automatic tasks such as picture naming and simple tests like word–picture matching supports previous claims for an early deficit of semantic memory in Alzheimer's disease (Hodges and Patterson, 1995).

The mild Alzheimer's disease patients also began to demonstrate subtle but definite impairments of language and perception. Letter fluency became compromised along with comprehension of syntactically complex sentences (as measured by the TROG). The patients also showed subtle problems with spelling to dictation, most commonly characterized by phonologically plausible misspellings (e.g. 'wade' → WAID; Hughes *et al*., 1997). In addition, there was a sizeable drop in performance on the immediate copy of the Rey complex figure, which may reflect impairments of the patients' perceptual, spatial or constructional abilities. In summary, the mild Alzheimer's disease (MMSE 17–24) patients as a group demonstrated at least some degree of cognitive deficit across virtually all cognitive domains.

At the moderate Alzheimer's disease stage, patients exhibited a significant decline in test scores across the board except for forward digit span and reading. Finally, in the group with severest dementia all neuropsychological tasks were compromised.

Longitudinal decline of patients presenting with MCI versus Alzheimer's disease

The longitudinal data collected as a part of this study allowed us to compare MCI and early Alzheimer's disease directly and thus led us to the hypothesis that MCI represents the earliest stage of Alzheimer's disease. Figure 1 shows the averaged longitudinal data for those patients first presenting at the MCI versus mild Alzheimer's disease stage. Four representative neuropsychological assessments are shown for each cognitive domain investigated (episodic and semantic memory, language and visuospatial ability). These show quite clearly that the longitudinal neuropsychological profiles for the two groups are effectively identical, albeit starting at different points. The MCI cases are amnestic-only in the first stage with relative preservation of all other areas of cognitive function. Once patients fall into the Alzheimer's disease category, all areas of function become increasingly compromised. The two groups were not significantly different from each other in terms of age at presentation (MCI, 68.2 years; mild Alzheimer's disease, 66.2 years; $t = 0.83$, not significant) or years of education (MCI, 11.8 years; mild Alzheimer's disease, 11.4 years; $t = 0.41$, not significant). These findings confirm that MCI and Alzheimer's disease represent points on a continuum.

Identifying and comparing atypical versus typical Alzheimer's disease

One of the main aims of the present study was to identify atypical patients from a relatively unselected group of MCI and Alzheimer's disease cases, and to do so without specifying atypical profiles *a priori*. Having identified atypical profiles in this way, we would then be able to compare them directly with the typical longitudinal neuropsychological profile. A two-stage statistical procedure was adopted, using principal components analysis (PCA) in both

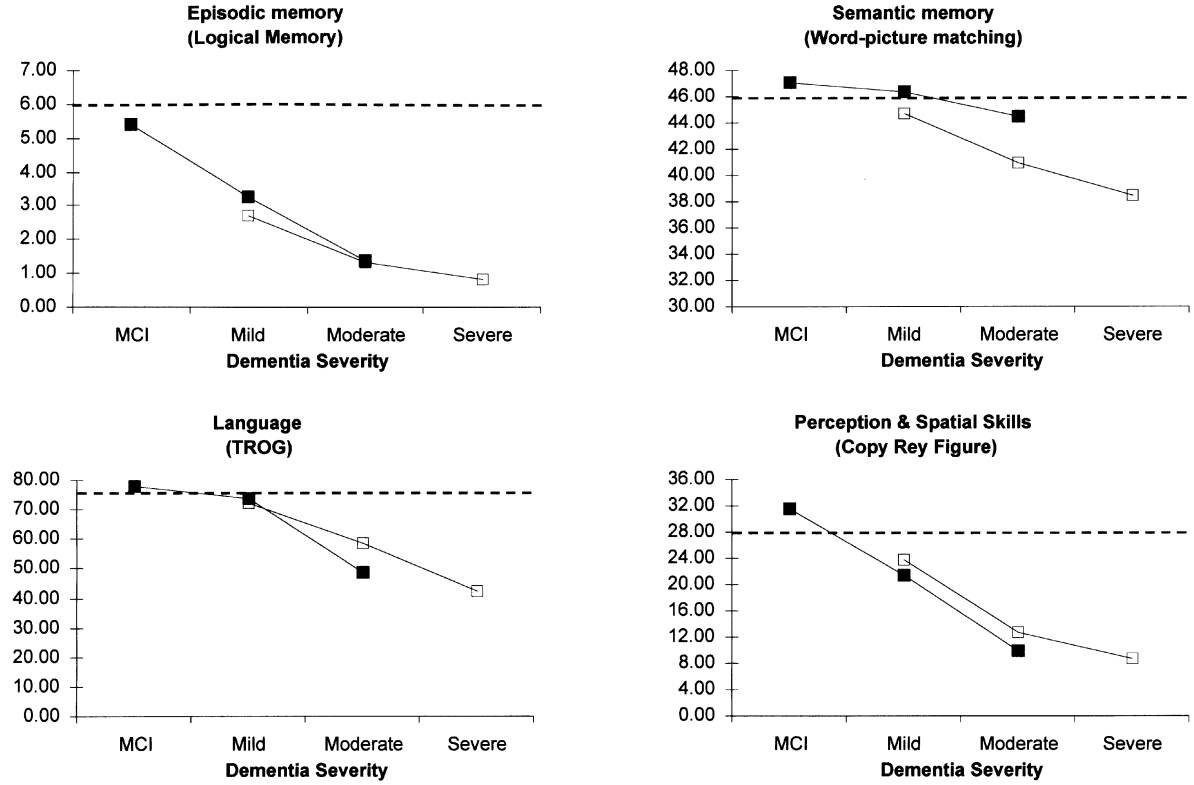

Fig. 1 Comparison of longitudinal neuropsychology in patients presenting with MCI versus Alzheimer's disease. Filled boxes represent patients presenting at the MCI stage; unfilled boxes represent patients presenting at the stage of 'mild' dementia of the Alzheimer type. Dashed lines show the normal the cut-off scores for the specific tests.

stages. This is a statistical device that uncovers a series of factors that best explain variation in a set of data—in the present study, the variation in neuropsychological scores for the patient cohort.

The first PCA analysis of the longitudinal data was used to extract the prototypical Alzheimer's disease pattern. When applied to the present data, an unrotated PCA produced a single factor that accounted for a large proportion in the variation of scores (0.59). Each individual neuropsychological test loaded highly on this single factor, confirming that the factor related to patient severity. The loading for test scores varied from 0.52 (for regular word reading) to 0.90 (for MMSE). This analysis suggests that there is substantial homogeneity in the pattern of decline in Alzheimer's disease. Nearly 60% of the patients' variation in test scores could be predicted by a single underlying severity factor. This finding mirrors previous longitudinal studies, all noting that global severity was a strong predictor of decline (Heyman *et al*., 1987; Katzman *et al*., 1988; Drachman *et al*., 1990; Haxby *et al*., 1992).

The second stage of the analysis investigated whether there were any statistically meaningful deviations away from a purely severity-governed decline in behavioural scores. The single factor extracted by the PCA reduces each patient's scores at each testing round to a single number, based on the overall severity of the patient at that stage (in comparison with all the other rounds of data for all the patients). It is then possible to use this estimate of overall severity to predict individual test scores for each patient at each testing round (the loadings or weightings of each test score on the severity factor are incorporated into a linear regression model to produce the expected scores). One can then search for cases that deviate significantly from the predicted scores. In order to look for co-occurring patterns of atypical presentations, we took the difference between observed and expected scores (standardized residuals) for all patients at all testing rounds and subjected them to a second, rotated PCA. This is very similar to an unrotated solution except that, having extracted orthogonal underlying factors that explain the maximal amount of the residual variation, the factors are statistically manipulated such that some test results load heavily on one factor and minimally on all the others. Such rotation of the underlying factors makes interpretation of them easier.

The second PCA revealed four underlying factors (four factors corresponds to the first scallop in the eigenvalue, scree plot). The four-factor solution accounted for 52% of the variance in residual scores and significant individual differences between patients were confirmed [between-subjects variance was significantly greater than within-subject variance on all four measures: all $F(52,172) > 11.4$, $P < 0.001$]. For all four factors, the majority of patients fell at or close to zero, denoting that their longitudinal neuropsychological

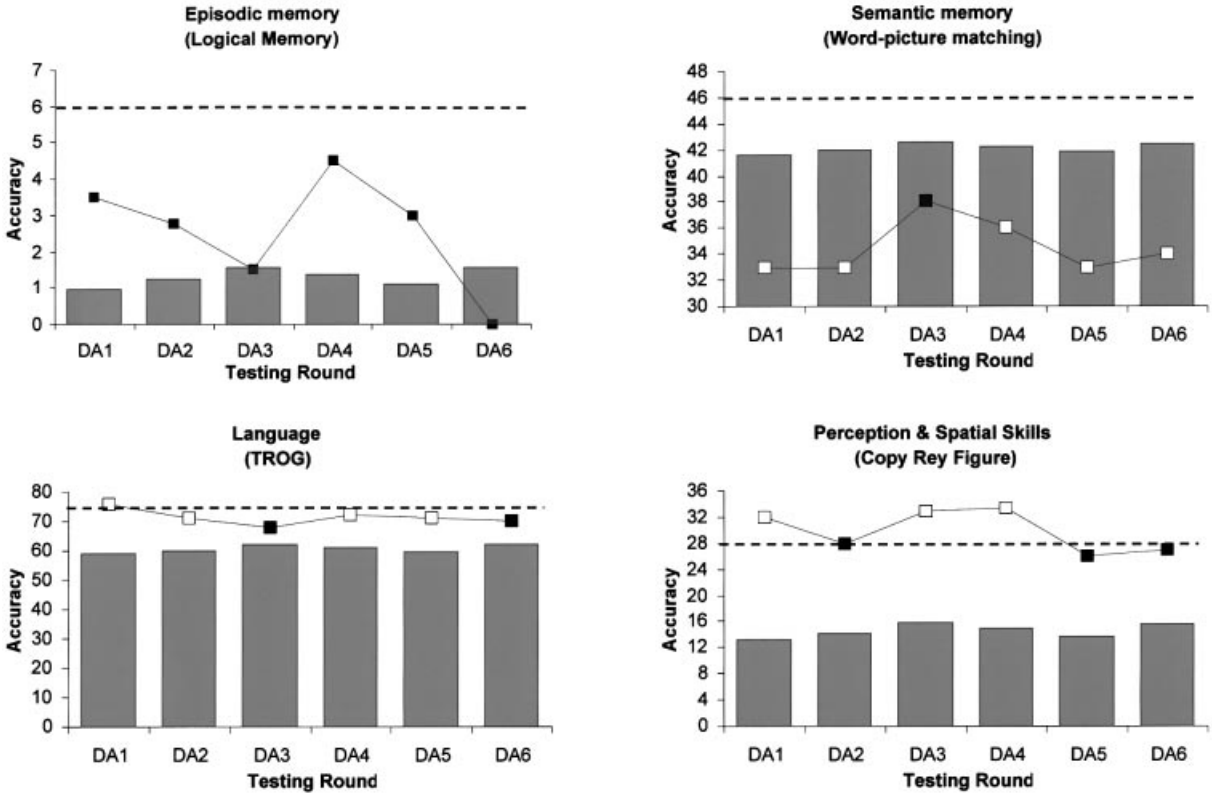

Fig. 2 Atypical semantic subtype of Alzheimer's disease (patient DA). Filled bars indicate predicted scores at each longitudinal point; black lines indicate scores observed at each longitudinal point; white boxes indicate observed scores deviating by at least 2 standard errors from the predicted score; dashed lines indicate the normal cut-off scores for the specific tests.

performance was near to that predicted by overall severity. Of more interest were the cases that fell away from zero on each factor. We selected patients whose profile placed them $\geqslant 2$ SDs from that expected. The predicted and observed scores for each of these outlying patients were inspected individually in order to ascertain the patterns of atypical Alzheimer's disease presentation extracted by the PCA.

Two of the four extracted factors corresponded to patients with semantic or visuospatial deficits greater than those predicted by severity alone. An example of the atypical semantic Alzheimer's disease longitudinal profile is shown in Fig. 2 for a patient with autopsy-confirmed Alzheimer's pathology. Like patients with semantic dementia (Snowden *et al*., 1989; Hodges *et al*., 1992), patient D.A. performed worse than expected on a series of semantic memory tasks (word–picture matching – as shown in Fig. 2, picture naming, picture sorting and semantic feature questions). In contrast, D.A. performed significantly better than predicted on a test of grammatical comprehension (TROG) and on visuospatial assessments, on which she scored at the lower end of the normal range. Unlike patients with semantic dementia, however, in addition to her semantic impairment D.A. also had a significant episodic memory deficit. This is shown in Fig. 2 as poor performance on the logical memory test in all six testing rounds. Critically, D.A. also performed very poorly on tests of episodic recall and recognition involving non-verbal materials (e.g. recall of the complex Rey figure, 0/36; recognition of novel faces in Warrington's recognition memory test, 24/50 = chance) and showed deficits of attention. As noted in the Introduction, other studies have reported the occurrence of Alzheimer's disease patients with severe semantic memory impairment (Galton *et al*., 2000; Caine and Hodges, 2001). The ability to compare individual patients against both normal control performance and a severity-based estimate of the patients' expected score, however, highlights the difficulty in diagnosing this subtype. Patients with Alzheimer's disease normally have impaired semantic memory (Hodges and Patterson, 1995), and patient D.A. was therefore expected to have a mild impairment in this cognitive domain (the grey bars denote severity-based predicted scores that consistently fall below the cut-off for normal subjects). In cases like D.A., therefore, the semantic impairment has been accelerated presumably by greater than normal pathology in the inferolateral aspects of the temporal lobes (cf. patient O.M.; Galton *et al*., 2000). Without severity-based predicted scores, it is very difficult to detect this form of augmented semantic deficit.

Figure 3A shows three testing rounds of data for patient M.P., an atypical, visuospatial case. While patient M.P. performed as predicted for semantic memory and other language assessments, his ability to copy the complex Rey figure was extremely impaired. Clinically, M.P. developed

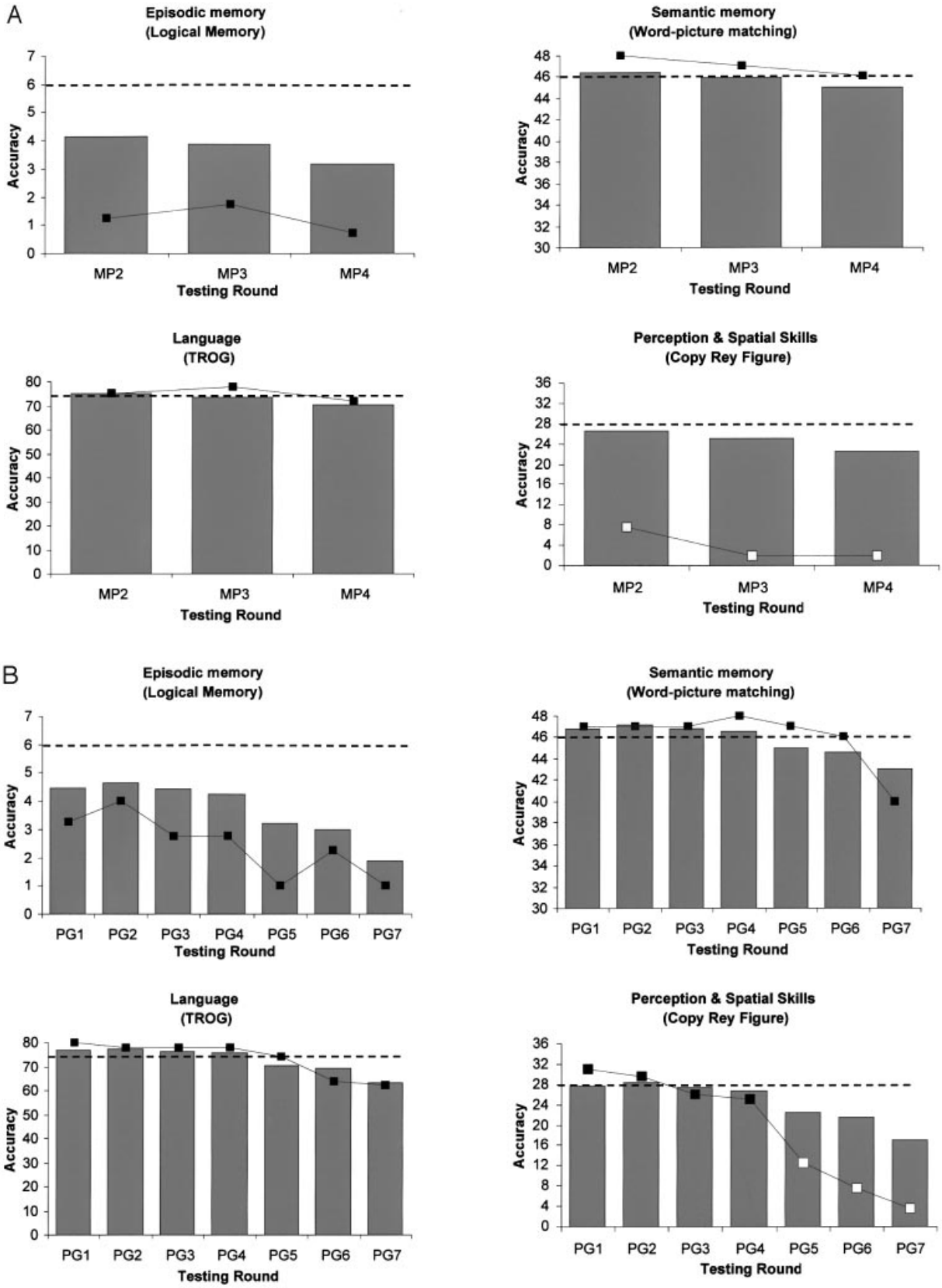

Fig. 3 (**A**) Atypical visuospatial subtype of Alzheimer's disease (Patient M.P.) and (**B**) progression into an atypical visuospatial subtype (Patient P.G.). Filled bars indicate predicted scores at each longitudinal point; black lines indicate observed scores at each longitudinal point; white boxes indicate observed scores that deviated by at least 2 SDs from the predicted score; dashed lines indicate the normal cut-off scores for specific tests.

severe visual disorientation with some features of Balint's syndrome (e.g. problems with spatial judgements and misreaching) and limb apraxia. M.P.'s profile is a striking example of this form of atypical presentation, especially as the severity-based predicted scores for him were only just outside the cut-off for normal subjects. As noted above for patient D.A. (and for the cases reported by Caine and Hodges, 2001), M.P.'s specific impairment was accompanied by pronounced amnesia with very low observed and expected scores for the logical memory test. Pathological confirmation of diagnosis was not available in case M.P.

Patients D.A. and M.P. demonstrated atypical semantic and visuospatial impairments throughout the longitudinal period over which they were assessed. Identification is easier when the atypical pattern occurs at presentation because it is less likely to be masked by generalized deficits across all domains. It should be possible, at least theoretically, to identify certain patients who start out matching a typical profile and gradually become atypical. In practice, typical $\rightarrow$ atypical longitudinal profiles are hard to establish because all neuropsychological data are confounded with decline due to disease severity. The statistical procedure adopted in this study makes it somewhat easier to identify such patients because the use of predicted scores provides a different baseline against which individual profiles can be compared. Figure 3B shows the longitudinal data of patient P.G. This patient is of added interest because at presentation she fell into the MCI/amnestic prodrome category. At that early stage her scores were in the normal range with the exception of episodic memory tests (her MMSE was 26/30 until the fifth testing round). In subsequent testing sessions, P.G.'s scores declined. The gradual drop in performance for assessments of semantic memory and language processing was in line with the severity-based predicted scores. The deterioration on visuospatial tasks, however, was much steeper than that predicted. On the Rey figure copy her scores at sessions 5–7 fell to more than 1.5 standard errors below those predicted on the basis of severity alone. Likewise, performance on the test of object matching deviated to the same degree from that predicted for testing rounds 4–7 (and was over 2 standard errors away from that predicted for rounds 5 and 7).

The other two factors extracted by the second PCA revealed two types of deviation different from severity-governed decline. As noted in the Introduction, MCI can be difficult to differentiate from normal age-related cognitive decline or from mild memory loss associated with depression (e.g. Ritchie *et al*., 2001; Swainson *et al*., 2001). One of the PCA factors highlighted three specific cases as unexpected. The neuropsychology of each was characterized by relatively good performance. Scores matched those predicted by the severity-based model because at the early stages very few Alzheimer's disease patients have abnormal ability (see MCI in Table 1). The three were atypical, however, in that they scored significantly better than expected and within the normal range on the logical memory test. In the time since these data were collected, we have been able to establish that there is no evidence of pathological decline in these patients even though their memory and cognitive skills were questioned when patients were enrolled into this longitudinal study. Of course, it would have been tempting to remove these patients from the analysis on the basis of hindsight, but their identification by the statistical procedure adopted in this study is testament to its ability to pick out unusual longitudinal profiles whether they are good or bad.

Discussion

This study investigated cross-sectional and longitudinal data of 55 patients: 17 with MCI and 38 with Alzheimer's disease. The analyses were designed to investigate two issues: the relationship of MCI to Alzheimer's disease and of atypical to typical Alzheimer's disease. We have demonstrated that MCI and Alzheimer's disease represent two points on a continuum. The neuropsychological profile of MCI is dominated by anterograde amnesia and patients score above 24/30 on the MMSE, which is traditionally considered to be the cut-off score for dementia. This result fits with the known distribution of neuropathology in which the entorhinal cortex and hippocampus are the first to be affected (Braak and Braak, 1991, 1995). It is also consistent with the finding that there is early atrophy in this medial temporal region (Jack *et al*., 1999; Galton *et al*., 2000; Killiany *et al*., 2000; Xu *et al*., 2000). Although MCI has become the most commonly used term to refer to such patients, the previously-used alternative of 'amnestic prodrome' would seem to describe the neuropsychological profile at this early stage. The finding of subtle, but definite, impairment on the Token test requires further study. We doubt whether this reflects a deficit in syntactic comprehension since patients performed almost perfectly in the TROG, which contains grammatically complex constructions. It is likely to reflect impaired working memory and/or attentional–executive processing.

When longitudinal data were averaged across individual patients, a consistent staging of neuropsychological deficits emerged. This pattern was unaffected by whether the patients initially presented with MCI or met the formal criteria for probable Alzheimer's disease. The selective amnesia characteristic of the MCI phase was joined next by semantic and other language impairments, plus emerging difficulties with demanding visuospatial tasks, such as copying the Rey complex figure. Again, this is consistent with the known spread of pathology to posterior association cortical regions and the basal forebrain. Furthermore, metabolic studies that have compared individuals at the MCI and Alzheimer's disease stages have found that the change in dementia severity is characterized by a reduction in glucose metabolism in the temporoparietal regions (Arnaiz *et al*., 2001). Patients in the moderate (MMSE between 11 and 16) and severe (MMSE <11) Alzheimer's disease groups exhibited increasing deficits in these domains, leading ultimately to impairments across all tests administered.

In this study we have applied the term MCI in a specific context to describe patients presenting with significant, yet relatively isolated, impairment of episodic memory. Such patients are clearly at very high risk of conversion to Alzheimer's disease. There are, however, other types of patients with isolated cognitive deficits involving different domains (language, executive, visuospatial abilities) who could also be classified as having MCI but many of whom are unlikely to have early-stage Alzheimer's disease. There is also the problem of classification of patients with more pervasive impairment who do not yet meet the criteria for dementia. We have deliberately chosen to restrict the inclusion criteria to examine the fate of those with the amnestic form of MCI. Future studies should perhaps include subgroups with different variants of MCI as defined more broadly. Our study also raises issues concerning the boundary between MCI and dementia as we have shown that there is, in fact, a continuum with a gradual accumulation of increasing and broadening cognitive deficits.

A two-stage statistical procedure was used to extract underlying factors that corresponded to the severity-governed decline in neuropsychological test scores and then to the consistent deviations from this typical longitudinal profile; i.e. identifying patterns of atypical Alzheimer's disease. The severity-based factor accounted for nearly 60% of the variance in this longitudinal and cross-sectional database. Like previous studies, this suggests that there is a fairly high degree of homogeneity within this group of patients and that most of their longitudinal results can be predicted by dementia severity alone (Heyman *et al*., 1987; Katzman *et al*., 1988; Drachman *et al*., 1990; Haxby *et al*., 1992). Over and above the typical profile governed by global severity, two main patterns of atypical variation were also identified: those with marked semantic impairment and those with a visuospatial variant (Neary *et al*., 1986; Becker *et al*., 1988, 1992; Fisher *et al*., 1999; Galton *et al*., 2000).

These atypical presentations of Alzheimer's disease are most likely to be confused with the focal dementia syndromes. In the case of the fluent aphasic variant of Alzheimer's disease, there is overlap with semantic dementia. The latter should be clearly distinguishable on the basis of the preserved episodic memory, and visuospatial and attention abilities in semantic dementia (Hodges *et al*., 1992; Perry and Hodges, 2000*a*). It should be noted, however, that although patients with semantic dementia typically remain well orientated, show good recall of recent life events and perform normally on visually based tests of anterograde memory, they perform poorly on verbal memory tests due, at least in part, to their poor comprehension of words and text (Hodges and Graham, 2001; Murre *et al*., 2001). It may be difficult, therefore, to separate Alzheimer's disease from semantic dementia on the basis of traditional verbal memory tests and reliance should be placed upon recall and recognition memory tests involving non-verbal materials. As noted above, patient D.A. performed at chance on the Warrington recognition memory test for both words and faces and had no recall of the Rey complex figure. In addition, she showed mild but significant deficits in attention and visuospatial ability. These findings were critical in our categorization as atypical Alzheimer's disease rather than semantic dementia.

The distinction between atypical Alzheimer's disease with prominent semantic impairment and semantic dementia is not purely academic. To date, all reported cases of semantic dementia reaching autopsy have had non-Alzheimer pathology, although the exact form of frontotemporal dementia pathology (with or without tau-positive or ubiquitin-positive inclusions) has varied between cases (Rossor *et al*., 2000; Hodges and Miller, 2001).

The distinction between atypical Alzheimer's disease with prominent visuospatial deficits and so called posterior cortical atrophy is more problematic. Unlike semantic dementia, the syndrome of posterior cortical atrophy is less clearly defined and encompasses patients with a range of different visual perceptual and spatial deficits frequently accompanied by apraxia (Black, 1996; McKenzie-Ross *et al*., 1996; Caine and Hodges, 2001). Moreover, the pathological basis of posterior cortical atrophy is usually, but not exclusively, Alzheimer's disease, making it difficult to draw a firm distinction. Finally, most patients with posterior cortical atrophy also have some degree of concurrent anterograde memory deficit by the time of presentation. For these reasons, the form of visual variant Alzheimer's disease identified in our study and the syndrome of posterior cortical atrophy should probably be regarded as a continuum pending further clinicopathological studies.

The statistical procedure adopted in this study allows individual patient scores to be compared with those expected on the basis of dementia severity alone. Without such a method it is more difficult to be confident that such individual profiles are atypical. The most striking example of the power of this technique is the ability to detect patients who move from the typical to the atypical profile. One such case illustrated here is interesting because she originally presented in the MCI stage. Her decline into Alzheimer's disease followed the typical pattern initially but then deviated such that her neuropsychological profile gradually evolved into the atypical visuospatial type.

The literature suggests that, in addition to fluent aphasic and visuospatial subtypes of Alzheimer's disease, there are also patients with atypical presentations in terms of non-fluent aphasia and/or progressive apraxia (Green *et al*., 1995; Croot, 1997; Giannakopoulos *et al*., 1998; Kawamura and Mochizuki, 1999; Galton *et al*., 2000). It is unsurprising that the statistical analyses used in this study did not identify such cases, as they were not included in this particular longitudinal study. There might, of course, be other atypical forms that we did not identify here. Recent studies have found evidence for poor attention and executive function in Alzheimer's disease in addition to amnesia, semantic impairment and visuospatial impairments (Perry and Hodges, 1999; Perry *et al*., 2000). One might expect, therefore, to find a subset of patients with a profile characterized by an exaggerated decline in attention and/or executive skills. The neuropsychological battery used

in this study had very limited assessment of attention/executive skills, but this atypical attentional/executive pattern was identified by Becker *et al*. (1988) in their cross-sectional factor analysis. Such a pattern is potentially confusable with dementia with Lewy bodies (DLB), in which poor attention is an early and primary symptom, though a combination of very poor attention-executive skills and visuospatial deficits would favour a diagnosis of DLB (Calderon *et al*., 2001; Lambon Ralph *et al*., 2001). There is also the problem of separating frontal variant frontotemporal dementia from Alzheimer's disease as executive deficits may be prominent in the former (Perry and Hodges, 2000*a*). The possibility of a frontal variant of Alzheimer's disease will have to be tested by future studies as, unfortunately, the detailed longitudinal neuropsychological investigation reported here was designed to focus on visuospatial, language and semantic disorder and contained limited assessment of attention and executive dysfunction.

Previous retrospective studies suggest that atypical neuropsychology is mirrored by an unusual distribution of pathology (e.g. Kanne *et al*., 1998; Galton *et al*., 2000). We suspect the same is true of the atypical patients described above with greater occipitoparietal involvement for the visuospatial subgroup and greater temporal neurocortical involvement for the semantic variant. If the statistical analyses reported here follow through into the neuropathological results, then there should be similar continua from typical distributions to each of the atypical subtypes (cf. Kanne *et al*., 1998). Insufficient neuropathological data are available to make a direct comparison between neuropsychology and neuropathology in the current cases but future investigations should be able to do so. Previous neuroimaging studies (structural and metabolic) have been able to detect neural correlates of neuropsychological change (Martin *et al*., 1986; Kantarci *et al*., 2000; Kogure *et al*., 2000; Arnaiz *et al*., 2001). It should be possible, therefore, to investigate the neural abnormalities that underpin typical and atypical Alzheimer's disease presentations. Unlike neuropathological analysis, such neuroimaging might also be able to track longitudinal changes in individuals. When combined with neuropsychological analysis of the form described here, it might even be possible to demonstrate the longitudinal neural/metabolic changes for patients who move between typical and atypical states during their cognitive decline.

Acknowledgements

We thank Angela O'Sullivan (Cambridge Brain Bank Laboratory) for help with data collection and analysis. This work was supported by the Medical Research Council.

References

Arnaiz E, Blomberg M, Fernaeus SE, Wahlund LO, Winblad B, Almkvist O. Psychometric discrimination of Alzheimer's disease and mild cognitive impairment. Alzheimer's Rep 2000; 3: 97–104.

Arnaiz E, Jelic V, Almkvist O, Wahlund LO, Winblad B, Valind S, et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport 2001; 12: 851–5.

Ball JA, Lantos PL, Jackson M, Marsden CD, Scadding JW, Rossor MN. Alien hand sign in association with Alzheimer's histopathology. J Neurol Neurosurg Psychiatry 1993; 56: 1020–3.

Becker JT, Huff FJ, Nebes RD, Holland A, Boller F. Neuropsychological function in Alzheimer's disease. Arch Neurol 1988; 45: 263–8.

Becker JT, Bajulaiye O, Smith C. Longitudinal analysis of a two-component model of the memory deficit in Alzheimer's disease. Psychol Med 1992; 22: 437–45.

Bishop DVM. Test for the Reception of Grammar. London: Medical Research Council; 1989.

Black SE. Focal cortical atrophy syndromes. Brain Cogn 1996; 31: 188–229.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991; 82: 239–59.

Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995; 16: 271–284.

Caine D, Hodges JR. Heterogeneity of semantic and visuospatial deficits in early Alzheimer's disease. Neuropsychology 2001; 15: 155–64.

Calderon J, Perry RJ, Erzinclioglu SW, Berrios GE, Dening TR, Hodges JR. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 70: 157–64.

Collie A, Maruff P. The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. Neurosci Biobehav Rev 2000; 24: 365–74.

Croot KP. Phonological disruption in progressive aphasia and Alzheimer's disease. MRC Applied Psychology Unit. Cambridge: University of Cambridge; 1997. p. 261.

De Renzi E, Vignolo LA. The Token Test: a sensitive test to detect receptive disturbances in aphasics. Brain 1962; 85: 665–78.

Dick JPR, Snowden J, Northen B, Goulding PJ, Neary D. Slowly progressive apraxia. Behav Neurol 1989; 2: 101–14.

Drachman DA, O'Donnell BF, Lew RA, Swearer JM. The prognosis in Alzheimer's disease. Arch Neurol 1990; 47: 851–6.

Fisher NJ, Rourke BP, Bieliauskas LA. Neuropsychological subgroups of patients with Alzheimer's disease: an examination of the first 10 years of CERAD data. J Clin Exp Neuropsychol 1999; 21: 488–518.

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.

Fox NC, Freeborough PA, Rossor MN. Visualisation and

quantification of rates of atrophy in Alzheimer's disease. Lancet 1996; 348: 94–7.

Fox NC, Warrington EK, Seiffer AL, Agnew SK, Rossor MN. Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease: a longitudinal prospective study. Brain 1998; 121: 1631–9.

Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain 2000; 123: 484–98.

Garrard P, Patterson K, Watson PC, Hodges JR. Category specific semantic loss in dementia of Alzheimer's type: functional–anatomical correlations from cross-sectional analyses. Brain 1998; 121: 633–46.

Giannakopoulos P, Duc M, Gold G, Hof PR, Michel JP, Bouras C. Pathologic correlates of apraxia in Alzheimer disease. Arch Neurol 1998; 55: 689–95.

Grady CL, Haxby JV, Horwitz B, Sundaram M, Berg G, Schapiro M, et al. Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. J Clin Exp Neuropsychol 1988; 10: 576–96.

Graham NL, Patterson K, Hodges JR. The impact of semantic memory impairment on spelling: evidence from semantic dementia. Neuropsychologia 2000; 38: 143–63.

Green RC, Goldstein FC, Mirra SS, Alazraki NP, Baxt JL, Bakay RA. Slowly progressive apraxia in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1995; 59: 312–5.

Greene JDW, Hodges JR, Baddeley AD. Autobiographical memory and executive function in early dementia of Alzheimer type. Neuropsychologia 1995; 33: 1647–70.

Haxby JV, Raffaele K, Gillette J, Schapiro MB, Rapoport SI. Individual trajectories of cognitive decline in patients with dementia of the Alzheimer type. J Clin Exp Neuropsychol 1992; 14: 575–92.

Heyman A, Wilkinson WE, Hurwitz BJ, Helms MJ, Haynes CS, Utley CM, et al. Early-onset Alzheimer's disease: clinical predictors of institutionalization and death. Neurology 1987; 37: 980–4.

Hodges JR. The amnestic prodrome in Alzheimer's disease. Brain 1998; 121: 1601–2.

Hodges JR. Frontotemporal dementia (Pick's disease): clinical features and assessment. Neurology 2001; 56 (11 Suppl 4): S6–S10.

Hodges JR, Graham KS. Episodic memory: insights from semantic dementia. Philos Trans R Soc Lond B Biol Sci 2001; 356: 1423–34.

Hodges JR, Miller BL. The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: Part I. Neurocase 2001; 7: 31–5.

Hodges JR, Patterson K. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. Neuropsychologia 1995; 33: 441–59.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 1992; 115: 1783–806.

Hodges JR, Berrios GE, Breen K. The multidisciplinary memory clinic approach. In: Berrios GE, Hodges JR, editors. Memory disorders in psychiatric practice. Cambridge: Cambridge University Press; 2000. p. 101–21.

Hof PR, Bouras C, Constantinidis J, Morrison JH. Balint's syndrome in Alzheimer's disease: specific disruption of the occipito-parietal visual pathway. Brain Res 1989; 493: 368–75.

Hughes JC, Graham N, Patterson K, Hodges JR. Dysgraphia in mild dementia of Alzheimer's type. Neuropsychologia 1997; 35: 533–45.

Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999; 52: 1397–403.

Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000; 55: 484–9.

Kanne SM, Balota DA, Storandt M, McKeel DW, Morris JC. Relating anatomy to function in Alzheimer's disease: neuropsychological profiles predict regional neuropathology 5 years later. Neurology 1998; 50: 979–85.

Kantarci K, Jack CR Jr, Xu YC, Campeau NG, O'Brien PC, Smith GE, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: A 1H MRS study. Neurology 2000; 55: 210–7.

Katzman R, Brown T, Thal LJ, Fuld PA, Aronson M, Butters N, et al. Comparison of rate of annual change of mental status score in four independent studies of patients with Alzheimer's disease. Ann Neurol 1988; 24: 384–9.

Kawamura M, Mochizuki S. Primary progressive apraxia. Neuropathology 1999; 19: 249–58.

Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000; 47: 430–9.

Kogure D, Matsuda H, Ohnishi T, Asada T, Uno M, Kunihiro T, et al. Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. J Nucl Med 2000; 41: 1155–62.

Lambon Ralph MA, Powell J, Howard D, Whitworth AB, Garrard P, Hodges JR. Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review. J Neurol Neurosurg Psychiatry 2001; 70: 149–56.

Levine DN, Lee JM, Fisher CM. The visual variant of Alzheimer's disease: a clinicopathologic case study. Neurology 1993; 43: 305–13.

Martin A, Brouwers P, Lalonde F, Cox C, Teleska P, Fedio P, et al. Towards a behavioral typology of Alzheimer's patients. J Clin Exp Neuropsychol 1986; 8: 594–610.

Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellack L, Karasu TB, editors. Geriatric psychiatry: a handbook for psychiatrists and primary care physicians. New York: Grune and Stratton; 1977. p. 77–121.

McKeith IG. Dementia with Lewy bodies: clinical and pathological diagnosis. Alzheimer's Rep 1998; 1: 83–7.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW,

Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DDLB International Workshop. Neurology 1996; 47: 1113–24.

MacKenzie-Ross SJ, Graham N, Stuart-Green L, Prins M, Xuereb J, Patterson K, et al. Progressive biparietal atrophy: an atypical presentation of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1996; 61: 388–95.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–44.

Murre JMJ, Graham KS, Hodges JR. Semantic dementia: relevance to connectionist models of long-term memory. Brain 2001; 124: 647–75.

Neary D, Snowden JS, Bowen DM, Sims NR, Mann DMA, Benton JS, et al. Neuropsychological syndromes in presenile dementia due to cerebral atrophy. J Neurol Neurosurg Psychiatry 1986; 49: 163–74.

Nelson HE. National Adult Reading Test. Windsor (UK): NFER-Nelson; 1982.

Patterson K, Hodges JR. Deterioration of word meaning: implications for reading. Neuropsychologia 1992; 30: 1025–40.

Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease: a critical review. Brain 1999; 122: 383–404.

Perry RJ, Hodges JR. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. Neurology 2000a; 54: 2277–84.

Perry RJ, Hodges JR. Fate of patients with questionable (very mild) Alzheimer's disease: longitudinal profiles of individual subjects' decline. Dement Geriatr Cogn Dis 2000b; 11: 342–9.

Perry RJ, Watson P, Hodges JR. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. Neuropsychologia 2000; 38: 252–71.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303–8.

Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56: 1133–42.

Riddoch MJ, Humphreys GW. Birmingham Object Recognition Battery (BORB). Hove: Lawrence Erlbaum; 1992.

Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 2001; 56: 37–42.

Rossor MN, Revesz T, Lantos PL, Warrington EK. Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. Brain 2000; 123: 267–76.

Salmon DP, Hodges JR. Neuropsychological assessment of early onset dementia. In: Hodges JR, editor. Early onset dementia: a multidisciplinary approach: Oxford: Oxford University Press; 2001. p. 47–73.

Snowden JS, Goulding PJ, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989; 2: 167–82.

Swainson R, Hodges JR, Galton CJ, Semple J, Michael A, Dunn BD, et al. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dement Geriatr Cogn Dis 2001; 12: 265–80.

Wechsler DA. Wechsler Memory Scale—Revised. San Antonio: Psychological Corporation; 1987.

Xu Y, Jack CR Jr, O'Brien PC, Kokmen E, Smith GE, Ivnik RJ, et al. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology 2000; 54: 1760–7.

Received June 25, 2002. Revised March 17, 2003.
Accepted May 19, 2003