RESEARCH ARTICLE

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Staging of the cognitive decline in Alzheimer's disease: insights from a detailed neuropsychological investigation of mild cognitive impairment and mild Alzheimer's disease

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Objective: The decline of episodic memory in Alzheimer's disease (AD) is well established, but the exact appearance and staging of deficits in other cognitive domains is sometimes contentious. The current investigation attempted to elucidate the appearance of additional cognitive deficits in the non-episodic domains and to understand these deficits with respect to the known pathological staging of AD.

Methods: A cross-sectional investigation compared cognitively normal age-matched controls with patients with mild AD and mild cognitive impairment (MCI) using a detailed neuropsychological assessment.

Results: The systematic investigation of cognitive performance across the major cognitive domains demonstrates that the appearance of additional cognitive deficits in MCI and AD can be predicted, with impaired semantic cognition performance pre-empting the appearance of attention/executive dysfunction and visuospatial deficits in the majority of patients with MCI.

Conclusions: This progressive pattern of cognitive deficits fits with the known pathological staging of AD, and the data further highlight the relative rarity of pure amnestic MCI. These results indicate that any neuropsychological test battery used to assess patients with MCI should include language and semantic memory tests in addition to typical episodic memory tests, as changes within this domain might be a sensitive indication of incipient AD. Copyright © 2011 John Wiley & Sons, Ltd.

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Introduction

Mild cognitive impairment (MCI) is now commonly accepted to reflect an Alzheimer's disease (AD) prodrome, specifically amnestic MCI (Dubois *et al.*, 2007). The criteria for presence and staging of the cognitive deficits associated with both mild AD and MCI, however, are contentious. Understanding the link between neuropathology and neuropsychology is key to understanding the cognitive deficits of AD in its earliest stages. Accordingly, a brief review of the three key neuropathological changes (amyloid deposition, neurofibrillary tangle formation and loss of cholinergic innervation) is first provided. We then consider what these might predict about the staging of cognitive decline in AD.

Abnormal aggregation and deposition of amyloid-β (Aβ) is neurotoxic leading to neurodegeneration (Braak and Braak, 1991). Amyloid-β deposition follows a distinct pattern in which regions of the medial temporal lobe (MTL) become hierarchically involved (Thal *et al.*, 2000; Thal *et al.*, 2002). Amyloid deposits are first found in the temporal neocortex and sequentially spread to the entorhinal cortex (ErC), followed

by the subiculum/CA1 and finally the CA4 hippocampal subfield. Intraneuronal neurofibrillary tangles (NFTs) are neurotoxic to their host neuron (Bancher *et al.*, 1989; Braak and Braak, 1991, 1998; Santacruz *et al.*, 2005). The distribution of NFTs, like amyloid deposition, can be hierarchically characterised, and NFT formation correlates with both the degree of Aβ pathology and the gradual decline in cognitive functions (Braak and Braak, 1991; Sassin *et al.*, 2000; Shoghi-Jadid *et al.*, 2002; Thal *et al.*, 2002). Early NFT-related changes occur in the basal forebrain and spread to the hippocampal formation, amygdala and neocortical regions (Bancher *et al.*, 1996; Sassin *et al.*, 2000; Shoghi-Jadid *et al.*, 2002). Both patients with MCI and AD can have NFT and amyloid pathology in the hippocampus and ErC (Troncoso *et al.*, 1996; Price and Morris, 1999; Petersen *et al.*, 2006).

Cholinergic dysfunction is also strongly associated with AD. The basal nucleus of Meynert is a predilection site affected very early in AD by NFTs (Whitehouse *et al.*, 1982; Coyle *et al.*, 1983). The cholinergic projections from the basal forebrain to the neocortex and thalamus are fundamental in controlling attention, modulating cortical information processing and conscious awareness (Baxter and Chiba, 1999; Perry *et al.*, 1999).

It is well established that lesions to the MTL can induce amnesia (Fleischman and Gabrieli, 1999; Scoville and Milner, 2000). The primary MTL structures of interest for AD include the hippocampus, the ErC, the perirhinal cortex and the parahippocampal gyrus. The functional roles of the hippocampus include intermediate term memory storage, memory consolidation, spatial processing, cross-modal associations and recollection (Squire and Zola-Morgan, 1991; Eichenbaum *et al.*, 1994; McClelland *et al.*, 1995). The MTL regions outlined are also integrated within a larger MTL-memory network. Connected regions include the amygdala, the thalamus, the mamillary bodies, the posterior cingulate cortex, the temporal cortex and the medial frontal cortex (Aggleton and Brown, 1999, 2006).

The pathological hallmarks of AD clearly affect the MTL-memory network in the disease's earliest stages (Figure 1 displays the key regions involved in the MTL-memory network that are affected by AD pathology). The idea that pathology and neurodegeneration affect cognition is supported by both structural magnetic resonance and positron emission tomography (PET) imaging findings. A study by Wilson *et al.* (1996) demonstrated that hippocampal volume in patients with AD was positively correlated with delayed story recall performance. Hypometabolism of the temporoparietal and posterior cingulate cortices measured by FDG-PET is a routinely found phenomenon in patients with MCI and AD (Herholz, 2003). The neocortical hypometabolism matches the observed

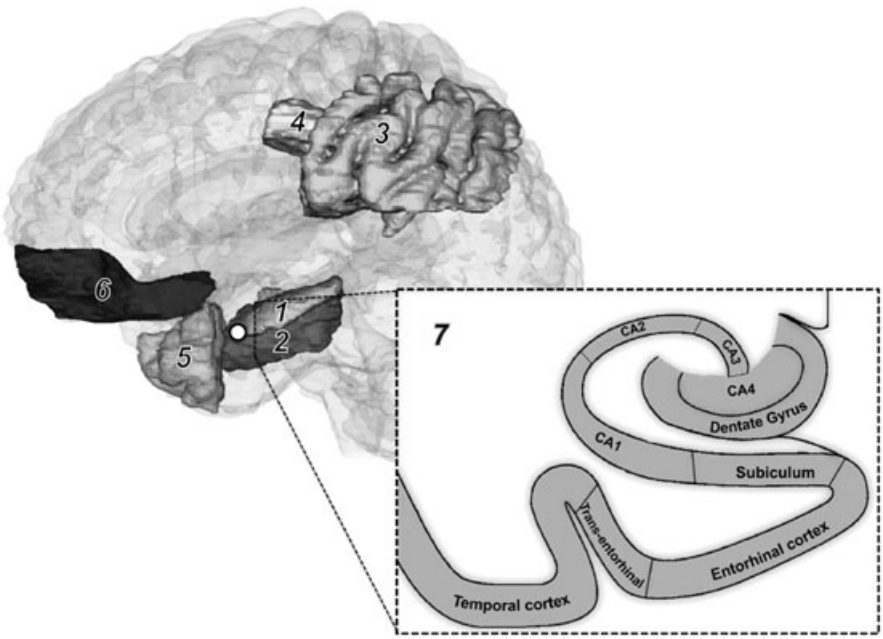

Figure 1 Regions involved in the pathological progression and neuropsychological dysfunction of Alzheimer's disease (1) Hippocampus: (2) parahippocampal gyrus; (3) temporoparietal cortex; (4) posterior cingulate cortex; (5) anterior temporal lobe; (6) medial prefrontal cortex; and (7) cross section of the MTL displaying the regions were the earliest NFT and Aβ pathology begins. White circle positioned at the anterior hippocampus represents the basal nucleus of Meynert from which most of the neocortex receives its cholinergic innervation.

clinical symptoms of AD, which include impairments of memory and associative thinking (Herholz *et al.*, 2007). Numerous pathological, volumetric and PET based studies demonstrate a clear link between the episodic memory impairment of AD and changes throughout the brain (Deweer *et al.*, 1995; Fox *et al.*, 1996; Stout *et al.*, 1999; Edison *et al.*, 2007; Jack *et al.*, 2008).

Beyond the MTL-memory network, two candidate cognitive domains have been suggested to be impaired early in AD. These impairments potentially reflect the pathological progression reviewed earlier. The first candidate domain is impairment of semantic cognition. Semantic dysfunction has been related to temporal neocortical volume but not to hippocampal volume (Wilson *et al.*, 1996). Although the anatomical locus of language deficit in AD is often debated, it is consistent with pathological progression to anterior and lateral aspects of the temporal lobes. These regions are associated with semantic memory (Hodges and Patterson, 1995; Garrard *et al.*, 1998; Mummery *et al.*, 1999). When semantic memory has been comprehensively tested in patients with MCI, it is impaired relative to controls. Mild AD patients have an even more pronounced semantic impairment, suggesting a link with disease severity and pathological locus (Hodges and Patterson, 1995; Hodges *et al.*, 2006; Ahmed *et al.*, 2008; Lonie *et al.*, 2008).

Other investigations have suggested that attention/executive functions become impaired early in AD. In a review of the AD literature on attention and executive deficits (Perry and Hodges, 1999), it was suggested that, after the amnestic stage, attention might be the first non-memory domain affected, before semantic cognition and visuospatial deficits. Both neurodegeneration of the MTL and of the basal forebrain and/or a disconnection of the attentional cortical regions, along with loss of cholinergic innervation have been provided as neuroanatomical explanations for attention deficits (Parasuraman and Nestor, 1993; Baxter and Chiba, 1999; Perry *et al.*, 1999; Bohnen *et al.*, 2003). Neurofibrillary and Aβ pathology affect regions that support attention (fronto-parietal regions, including the dorsolateral prefrontal cortex, parietal lobes, anterior cingulate cortex, thalamus and basal ganglia). Perry *et al.* (2000) demonstrated heterogeneity in performance between different classifications of AD. Moderate patients with AD were impaired on all attentional tasks, and minimally impaired patients demonstrated selected deficits. A meta-analysis incorporating 47 studies (Backman *et al.*, 2005) investigating the cognitive impairment in preclinical AD also suggested that deficits in executive functioning and perceptual speed closely follow episodic impairment.

Typically, visuospatial functions are only affected once AD has fully progressed; however, some patients demonstrate visuospatial deficits early and before other domains (Caine and Hodges, 2001).

The link between MTL lesions and episodic memory deficits in many MCI and mild AD patients is not disputed. What is less clear is the sequence in which other cognitive domains become dysfunctional. It is possible that as the disease spreads to the neocortical regions in the anterior temporal lobes (ATL), semantic cognition should be impaired next. Alternatively, cholinergic impairment of the neocortex occurs early during disease progression, so it is not unreasonable to expect attention and information-processing speed to be affected first, before semantic cognition. The aim of the present cross-sectional investigation was to provide evidence about which cognitive domains become affected after episodic memory and to test a comprehensive neuropsychological battery that can detect these cognitive changes in an old-age memory clinic.

Materials and methods

Participants

Thirteen cognitively normal (CN) controls, 17 patients with MCI and 15 patients with mild AD, participated in this investigation that was approved by the Central Manchester Research Ethics Committee (UK). All patients (and their carers/next of kin) gave signed, informed consent. All patients were recruited consecutively without selection bias from those presenting at the memory clinic within Wythenshawe Hospital, Manchester, UK. Patients with mild AD and MCI were classified as such following clinical evaluation at a consensus committee involving old age psychiatrists, clinical neuropsychologists and specialist research nurses. Patients with mild AD had a Mini mental state examination (MMSE) score of ≤ 25 and fulfilled the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). Patients with MCI had MMSE scores of ≥ 26; the classification of MCI was determined on the basis of the criteria established by Petersen (2004), and they did not meet the NINCDS-ADRDA criteria. Individuals with alcoholism, previous head injury, stroke, epilepsy, other neurological disease or major medical illness (e.g. cancer, thyroid dysfunction, anaemia, etc.) were excluded, as were those with an unstable psychiatric illness; patients

with stable treated depression were included. Patients underwent brain imaging (CT scan and EEG) as well as the usual blood screening tests to exclude treatable causes of dementia. All patients from both groups were living without institutional support. All the patients with AD were being treated with cholinesterase inhibitors in this investigation.

For this investigation, participants underwent extensive neuropsychological investigation that was separate from their normal clinical evaluation. Wherever possible, neuropsychological testing was done in a single session. However, as this was not always feasible, particularly with the patients with mild AD, the test battery would be completed over two sessions. Testing sessions were never more than 4 weeks apart.

Materials

Global cognition. The Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi *et al.*, 2006), is a detailed measure of global cognition that tests various cognitive domains, including some (e.g. delayed recall) not included in the MMSE. It consists of five sub-components: (1) attention and orientation (/18); (2) memory (immediate and delayed recall of a name and address, measures of retrograde memory: /26); (3) verbal fluency (letter and category: /14); (4) language (repetition, comprehension and naming: /26); and (5) visuospatial function (/16). The ACE-R has a maximum score of 100 and incorporates the MMSE (Folstein *et al.*, 1983) so that it is possible to simultaneously obtain an MMSE score.

Episodic memory tests. The Face Place Test (FPT) (Dudas *et al.*, 2005) involves participants looking at pictures of faces, some of which are famous (politicians, actors/TV personalities and singers) and others are non-famous. The FPT assesses several different aspects of declarative memory; familiarity, recognition, spatial memory and semantic memory. The maximum score for the FPT is 100.

Other standard episodic memory tests included: the story recall task taken from the Wechsler memory scale-III (Wechsler, 1997), the California Verbal Learning Test (Delis *et al.*, 1987) and recall of the Rey Complex Figure Test (RCFT) (Meyers and Meyers, 1995).

Language/semantic memory tests. Letter fluency, category fluency (Garrard *et al.*, 2001) and the Graded Naming Test (McKenna and Warrington, 1983) were administered. Components of the ACE-R and the FPT also give measures within the domains of language and semantic function (Table 2).

Executive/attention tests. Two tasks were adopted from the Test of Everyday Attention (Robertson *et al.*, 1994): elevator counting with distraction and map search. The first is an auditory task with a maximum score of 10, and the second is a timed visual search task with a maximum score of 80. Both parts of the digit span task (forward and reverse) were taken from the Wechsler memory scale-III (Wechsler, 1997). A simplified version of the Stroop (Trenerry *et al.*, 1989) paradigm was adopted. Participants' reading speed was measured first (by reading aloud the names of colours printed on a sheet), then in the same amount of time (45 s), they were asked to name as many incongruent colours as possible (e.g. the word 'red' printed in blue ink). The Stroop score was determined by simply calculating, as a percentage, the number of items read aloud in the incongruent condition as a proportion of the individuals' baseline reading speed. The Wisconsin Card Sorting Test (Nelson, 1976) was administered to the participants, and the number of successful category shifts was recorded. The attention and orientation component from the ACE-R was also incorporated into this domain.

Visuospatial tests. The RCFT-copy and the ACE-R visuospatial components were used as visuospatial measures. The RCFT-copy test involves participants drawing the Rey complex figure (maximum score = 36); there is minimal demand placed on memory during the copy condition. The visuospatial subcomponent of the ACE-R involves participants copying pictures (e.g. interlocking pentagons) or drawing from memory (e.g. a clock face with a specific time). The visuospatial subcomponent of the ACE-R has a total score of 16.

Results

All data analyses were performed with PASW 18.0 for Mac (IBM Corporation, Somers, NY, USA). Basic demographic data for the three groups can be seen in Table 1. There was no significant difference between the groups for age and education. For the neuropsychological battery, equal variances were not assumed and Tamhane's T2 *post hoc* testing was used for investigating inter-group differences. Tamhane's T2 is a conservative pairwise comparison test used when equal variances are not assumed.

The mean scores, standard deviations, F and p values (ANOVA) for the main group effect are summarised in Table 2. Figure 2 illustrates each group's performance on the ACE-R (error bars represent +/− 1 SD). The

Table 1 Descriptive statistics for basic demographic information

	CN		MCI		AD	
	Mean	SD	Mean	SD	Mean	SD
Age	73.5	4.7	73.3	9.7	77.3	5.6
Gender (M/F)	5/8		10/7		5/10	
Years of education	13.2	3.5	11.8	3.7	10.7	2.5
MMSE	29.5[b,c]	0.52	28.0[a,c]	1.5	22.3[a,b]	3.5

There was a significant group difference for MMSE score $F(2, 42) = 45.3$ $p = < 0.001$. MMSE, Mini mental state examination; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease.
[a]Significantly different to CN.
[b]Significantly different to MCI.
[c]Significantly different to AD.

Table 2 Means and standard deviations for neuropsychological test scores

	CN		MCI		AD			
	Mean	SD	Mean	SD	Mean	SD	$F(2, 42)$	p
Total ACE-R	95.4[b,c]	3.2	80.1[a,c]	10.4	63.5[a,b]	11.6	39.8	< 0.001
Episodic memory								
ACE-memory	23.7[b,c]	1.8	16.4[a,c]	4.7	7.9[a,b]	2.9	72.1	< 0.001
FPT	91.6[b,c]	4.9	76.7[a,c]	14.5	58.3[a,b]	12.0	28.9	< 0.001
FPT-familiarity	19.2	1.1	17.9	2.6	17.7	2.2	1.8	ns
FPT-recognition	39.3[b,c]	0.6	36.7[a,c]	3.6	30.3[a,b]	7.0	14.5	< 0.001
FPT-placing	17.5[b,c]	1.7	12.8[a,c]	6.0	7.0[a,b]	3.9	19.4	< 0.001
STOREC-immediate	48.4[b,c]	7.9	29.2[a,c]	13.1	11.9[a,b]	6.8	46.9	< 0.001
STOREC-delayed	30.3[b,c]	7.6	12.4[a,c]	11.9	0.1[a,b]	0.5	44.8	< 0.001
RCFT-delayed	19.6[b,c]	7.9	11.2[a,c]	7.4	3.4[a,b]	4.6	19.9	< 0.001
CVLT	9.8[b,c]	2.4	6.8[a,c]	2.6	3.6[a,b]	1.3	27.1	< 0.001
CVLT-delayed	10.5[b,c]	3.5	4.9[a,c]	3.8	0.2[a,b]	0.6	31.6	< 0.001
Digit span-forwards	6.3	1.1	5.5	1.5	5.4	1.1	2.3	ns
Language/semantic memory								
ACE-fluency	12.5[b,c]	1.1	9.6[a,c]	2.7	6.7[a,b]	3.5	16.3	< 0.001
ACE-language	25.5[c]	0.9	23.9	2.9	22.7[a]	3.5	5.5	< 0.01
FPT-naming	15.6[b,c]	3.7	9.2[a,c]	6.2	4.7[a,b]	4.6	16.2	< 0.001
FAS-total	50.2[b,c]	10.4	38.6[a,c]	13.7	25.6[a,b]	9.9	15.6	< 0.001
Category fluency-total	98.4[b,c]	14.5	69.1[a,c]	18.2	45.2[a,b]	15.7	36.7	< 0.001
Graded naming	26.1[b,c]	1.9	19.4[a]	7.2	16.5[a]	10.2	5.9	< 0.01
Attention/executive								
ACE-attention and orientation	17.9[c]	0.3	17.7[c]	0.7	14.1[a,b]	2.6	28.4	< 0.001
Digit span-backwards	4.1[c]	1.1	3.8[c]	1.1	2.7[a,b]	0.7	7.0	< 0.01
TEA-map search	46.7[c]	16.6	41.1	22.2	28.5[a]	16.9	4.4	< 0.05
TEA-elevator counting	8.2[c]	2.6	6.3	2.9	4.3[a]	2.8	6.8	< 0.01
STROOP-words	87.5[c]	16.8	63.1	28.8	56.3[a]	22.3	7.8	0.01
STROOP-colours	33.5[b,c]	10.8	27.8[a,c]	23.6	9.9[a,b]	11.6	15.2	< 0.001
STROOP-percentage	37.6[c]	8.0	31.1[c]	19.0	11.6[a,b]	8.2	15.2	< 0.001
WCST-category shifts	3.3	1.3	2.3	1.4	2.5	5.5	0.4	ns
Visuospatial								
RCFT-copy	34.5[c]	2.5	30.4	8.4	24.2[a]	10.2	5.9	< 0.01
ACE-visuospatial	15.5	0.9	14.1	3.1	13.3	2.8	2.8	ns

Superscript letters indicate significant pairwise comparisons revealed by *post hoc* testing (Tamhane's T2, $p < 0.05$). ns = not significant. ACE-R, Addenbrooke's Cognitive Examination-Revised; ACE, Addenbrooke's Cognitive Examination; FPT, Face Place Test; RCFT, Rey Complex Figure Test; CVLT, the California Verbal Learning Test; TEA, Test of Everyday Attention; WCST, the Wisconsin Card Sorting Test.
[a]Significantly different to CN.
[b]Significantly different to MCI.
[c]Significantly different to AD.

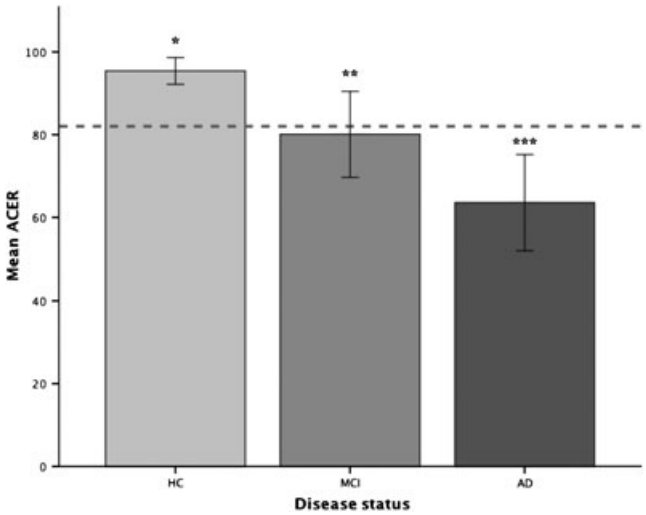

Figure 2 Bar chart displaying mean scores for the ACE-R. The difference between groups is significant $F(2, 42) = 39.8$, $p = < 0.001$, *post hoc* testing reveals a three-way group difference (CN > MCI > AD). * indicates significantly different to MCI and AD; ** significantly different to CN and AD; *** significantly different to CN and MCI. Error bars represent +/–1 SD. The dotted reference line (ACE-R score of 82) is a cut-off point for incipient dementia that gives 84% sensitivity and 100% specificity (based on 63 controls aged 52–75 years and 146 patients with dementia aged 46–86 years Mioshi *et al.*, 2006).

group difference was significant for both the ACE-R and the MMSE. *Post hoc* testing revealed that, for both measures, each group was significantly different from each other.

Episodic memory

Most tests revealed a hierarchical performance, which followed CN > MCI > AD. The two exceptions to this pattern were the FPT familiarity component and the forward digit span, which revealed no significant group effect.

Language/semantic memory

All the semantic cognition tests revealed an overall group effect. The total category fluency, letter fluency, the fluency component of the ACE-R and the FPT naming subcomponent significantly separated the three groups such as CN > MCI > AD. The graded naming test, revealed a significant inter-group difference as follows: CN > MCI = AD. The less demanding language component of the ACE-R only revealed a group difference between CN and patients with AD.

Attention/executive

Both the attention and orientation component of the ACE-R and the backwards digit span revealed significant inter-group differences (CN = MCI > AD). The elevator counting with distraction and the map search only significantly separated the CN and patients with AD. For the Stroop tests, each component revealed a significant group effect, although only the incongruent condition significantly separated the three groups (CN > MCI > AD). There was no group effect for the Wisconsin Card Sorting Test.

Visuospatial

The RCFT-copy and the ACE-R visuospatial measures revealed that only the RCFT-copy revealed a group effect. It significantly separated the CN and the patients with AD.

Mild cognitive impairment heterogeneity

Using the current comprehensive neuropsychological test battery, it is possible to determine a more specific individual MCI profile. When using the tests from each domain that had the largest group effect and significantly separated the three groups (ACE-R memory, category fluency, stroop-colours and the RCFT-copy; Figure 3), 15 were impaired (>1.5 *SD* below control mean) on the ACE-R memory. From this small MCI sample, only two patients met Petersen *et al.*'s (Petersen *et al.*, 2001) criteria for pure amnestic MCI; the majority of patients ($N = 13$) were characterised as amnestic multiple domain MCI.

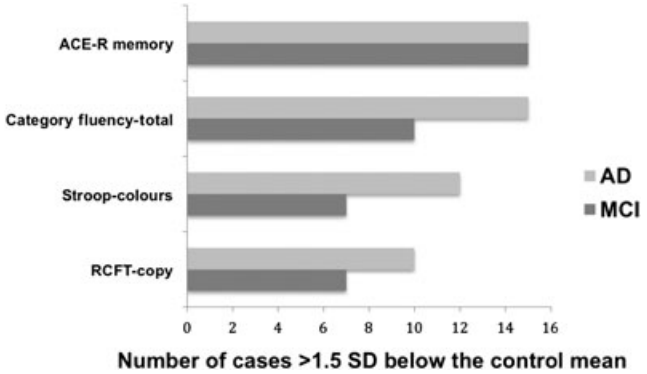

Figure 3 Bar chart displaying the heterogeneity of MCI. Bar chart displays the number of cases, more than 1.5 SD below the control mean, for the tests within each cognitive domain that had the largest group effect and were the most sensitive at significantly separating the three groups (see Table 2).

Discussion

This systematic, cross-sectional investigation of the performance of controls, MCI and patients with mild AD demonstrates that following episodic memory deficits, deficits in semantic cognition performance pre-empt the appearance of attention/executive dysfunction and visuospatial impairment in the majority of patients. Only two patients with MCI could be characterised as having pure amnestic MCI. The remainder were characterised as multi-domain MCI (Figure 3). This finding is supported by other studies (Ahmed *et al.*, 2008; Lonie *et al.*, 2008; Libon *et al.*, 2010) and highlights the relative rarity of pure amnestic MCI.

The idea that pathology affecting the MTL leads to dysfunctional episodic memory in MCI and patients with AD is supported by the current investigation as the vast majority of tests revealed a significant group effect. The FPT, in particular, demonstrated that the patients had deficits in all subcomponents, except familiarity. This finding fits with the pathological staging of AD as pathology spreads from the ErC to the hippocampus and beyond (Braak and Braak, 1991; Thal *et al.*, 2000; Thal *et al.*, 2002; Petersen *et al.*, 2006). In addition to the FPT, the AD group was also impaired on both verbal and visuospatial episodic memory tasks; this might reflect the further spread of pathology to regions outside the MTL including the parietal and anterolateral aspects of the temporal lobe.

Regions outside the MTL have also been implicated in the episodic memory network. Metabolic reductions have been found in the medial thalamus and mamillary bodies in patients with mild AD and MCI (Nestor *et al.*, 2003b). The retrosplenial and posterior cingulate cortices are also functionally important to declarative memory function (Gron *et al.*, 2000; Deckersbach *et al.*, 2006; Ries *et al.*, 2006; Vann *et al.*, 2009) and are hypometabolic in patients with MCI and AD (Kennedy *et al.*, 1995; Minoshima *et al.*, 1997; Drzezga *et al.*, 2003; Ouchi *et al.*, 2004). Nestor *et al.* (2006) showed that the episodic memory impairments in AD are related to a dysfunction (atrophy and hypometabolism) of the MTL-memory network. It is likely that the posterior cingulate is lesioned in both the current patients with MCI and mild AD.

All semantic cognition tests revealed group differences; only the ACE-language and graded naming test did not significantly separate the three groups. The semantic cognition deficits could be explained by pathological progression to the ATL (Braak and Braak, 1991; Hodges and Patterson, 1995). There is neuropsychological and neuroimaging evidence to suggest that the failures of semantic cognition in the patients with MCI and AD are associated with loss of two cognitive processes, which are dependent on ATL, frontal and temporoparietal integrity (Devlin *et al.*, 2000; Jefferies and Lambon Ralph, 2006; Stopford *et al.*, 2008; Corbett *et al.*, 2009; Visser *et al.*, 2010). These two processes include loss of amodal semantic representations from the ATL and loss of semantic control, regulated by the temporoparietal regions. Support for this suggestion comes from the fact that hypometabolism of the temporoparietal and posterior cingulate cortex is regularly found very early in AD (Minoshima *et al.*, 1997; Herholz, 2003; Nestor *et al.*, 2003b; Nestor *et al.*, 2006; Herholz *et al.*, 2007). In addition to its role in episodic memory, the posterior cingulate has also recently been implicated in semantic cognition (Binder *et al.*, 2009). The finding of a breakdown in semantic cognition is consistent with the AD staging hypothesis (Braak and Braak, 1991; Thal *et al.*, 2000; Thal *et al.*, 2002) as the initial NFT pathology spreads to the ATL, which is probably

associated with the breakdown in the amodal semantic store, and Aβ is deposited throughout the neocortex including the temporoparietal and frontal regions, which become hypometabolic.

Consistent with the suggestion of impaired executive function in mild AD was this group's performance on the reverse digit span, which recruits working memory processes. The patients with AD performed worse than both the MCI and control group on this test. The performance on the incongruous condition of the Stroop followed CN > MCI > AD. The fact that the Stroop-colours test was the only assessment that patients with MCI were impaired on relative to controls, suggests that the attention system in these patients is minimaly affected. Perry *et al.*'s (2000) patients with mild AD demonstrated deficits in all their measures of attention, with the exception of the map search test; this was not the case in the current investigation. The dysfunction in the current patients with AD fits with the idea of significant cholinergic dysfunction, which are typically found in studies of acetylcholinesterase activity in AD (Herholz, 2008). Some neuropathological studies indicate preserved cholinergic function particularly in MCI (Davis *et al.*, 1999; Gilmor *et al.*, 1999; DeKosky *et al.*, 2002). It is possible that deficits in attention and in attentionally demanding executive tasks can only be detected as the cholinergic system has become sufficiently impaired in mild AD. The fact that all the patients with AD received cholinesterase inhibitors might have compensated their attention/executive function scores. In spite of this possibility, the patients withAD still had the worst performance on all tests. Because the patients with MCI were not receiving these medications and had generally preserved function within this domain, the potential effect of cholinesterase inhibition is not deleterious to the overall conclusions.

Alzheimer's disease is a heterogeneous syndrome. Heterogeneous cognitive profiles have been previously identified in AD and MCI populations (Lambon Ralph *et al.*, 2003; Snowden *et al.*, 2007; Stopford *et al.*, 2007; Stopford *et al.*, 2008; Libon *et al.*, 2010). These profiles identify sub-groups of patients that can be grouped together either based on a more pronounced language or visuospatial deficit. It is because of this heterogeneity, along with the very limited number of pure amnestic patients with MCI in the current investigation, that their prognosis is uncertain. It is possible that some patients with MCI will go on to develop a non-AD syndrome (e.g. fronto-temporal dementia), longitudinal investigation would be needed to determine this. In spite of this limitation, what should be clear from the current data is that there are pronounced episodic memory deficits in both MCI and mild AD. These deficits are undoubtedly linked to pathological lesions at the medial temporal regions of interest. The neuropsychological evidence from the current investigation clearly suggests that semantic cognition is the next domain to become affected, potentially reflecting disease progression to the ATL and temporoparietal regions.

Conclusion

Overall, the current investigation demonstrates that in an old-age memory clinic, the most likely sequence of neuropsychological change is episodic memory dysfunction, followed by semantic cognition then by attention/executive dysfunction with relative sparing of visuospatial processing. This investigation also provides evidence for an effective neuropsychological test battery to assess patients with MCI. The test battery includes semantic cognition tests in addition to the traditional memory tests, as changes within this domain might be a sensitive indication of incipient AD.

Conflict of interest

None declared.

Key points

- Amnestic MCI is relatively rare in an old-age memory clinic setting.
- Semantic cognition tends to be the next most severely affected domain following episodic memory in most patients.
- Attention, executive and visuospatial functions were relatively preserved.
- Cognitive deficits in this population fit with the pathological staging of AD.
- Neuropsychological test batteries used to assess individuals at risk of AD (e.g. MCI patients) should include semantic cognition.

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