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# Topographical Short-Term Memory Differentiates Alzheimer's Disease From Frontotemporal Lobar Degeneration

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**ABSTRACT: We used a recently developed test of spatial memory—the Four Mountains Test—to investigate the core cognitive processes underpinning topographical disorientation in patients with amnestic mild cognitive impairment (a-MCI) and mild Alzheimer's disease (AD). Performance of these clinical groups was compared with age-matched controls, patients with frontotemporal lobar degeneration (FTLD), and patients with subjective memory impairments. We investigated the perception (concurrent match-to-sample) and short-term retention (2-s delayed match-to-sample) of the configuration of topographical features in computer-generated landscapes shown from different viewpoints. Thirty-one patients were tested (7 AD, 6 a-MCI, 7 temporal variant FTLD, 5 frontal variant FTLD, 6 subjective memory impairment) and 25 age- and gender-matched controls. Brain MRI was available for 27 patients; medial temporal lobe atrophy was assessed using a visual rating scale. Patients with a-MCI or mild AD were impaired on topographical short-term memory, but not perception. No other group differences were found on the topographical subtests. Notably, patients with temporal variants of FTLD performed normally, regardless of the laterality of damage. Subtests for the perception and retention of nonspatial aspects of the landscapes (weather conditions, seasonal and daily variations in lighting and color) were poor at differentiating the patient groups. These results indicate a core deficit in representing topographical layout, even for very short durations, within the context of more general long-term memory impairments found in AD, and suggest that this function is particularly sensitive to the earliest stages of the disease.** © **2009 Wiley-Liss, Inc.**

**KEY WORDS: dementia; navigation; hippocampus; spatial; neuropsychology**

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## INTRODUCTION

Topographical disorientation—getting lost whilst navigating in familiar or unfamiliar environments—is one of the earliest symptoms of Alzheimer's disease (AD: Reisberg, 1983) and has a significant impact on the lives of the patient and their carer. However, navigation is a multifaceted skill, and it is unclear which cognitive processes are first impaired in AD. Identification of these processes would facilitate the development of compensatory aids and the ability to identify those most at risk of progressing to AD during the prodromal stages of the disease (often characterized as amnestic mild cognitive impairment, a-MCI). Indeed, the differentiation of AD from other neurodegenerative disorders, such as frontotemporal lobar degeneration (FTLD), is becoming increasingly important as drug treatments with the capacity to modify the course of the disease become available (Nestor et al., 2004).

Here we investigate the nature of the topographical processing deficit in patients with a-MCI and very early AD, using the recently developed "Four Mountains Test" (Hartley et al., 2007). The performance of these patients was compared with a large sample of age-matched healthy controls, patients with FTLD, predominantly affecting either the frontal or temporal cortices, and a group with subjective memory complaints. We aimed to test the hypothesis that topographical processing forms one of the core deficits in a-MCI and early AD. As such we had three main aims: (i) to assess whether topographical processing is differentially impaired in AD vs. FTLD and individuals with subjective memory complaints; (ii) to investigate whether patients with a-MCI, believed to be in the prodromal stage of AD, perform similarly to those fulfilling criteria for AD; (iii) to ascertain whether topographical processing deficits in these patients are related to difficulties in perceiving topographical features or to the retention of topographical information over very short intervals.

## Amnestic MCI as a Prodromal Stage of AD

A diagnosis of probable AD requires an impairment of memory and additional cognitive functions, resulting in a state of dementia (McKhann et al., 1984). This definition necessarily excludes earlier stages of AD in which the level of cognitive impairment does not interfere with activities of daily living, leading to development of the concept of mild cognitive impairment (MCI: Smith et al., 1996) as a transitional state between normal ageing and established dementia. More recently, MCI has been recognized to be heterogeneous in terms of clinical presentation and underlying pathology, resulting in subclassifications of MCI to reflect the nature of the principal cognitive deficits (Petersen, 2004). Amnestic MCI (a-MCI) represent those MCI subtypes in which a disorder of memory is pre-eminent, in isolation (single domain a-MCI) or as part of more widespread cognitive impairment (multi-domain a-MCI). Patients with a-MCI are at a high risk of developing AD, with estimates of conversion rates varying from around 7–16% per annum (Ganguli et al., 2004; Petersen et al., 2005). Furthermore, conversion rates in a-MCI patients with a recent history of memory problems, and referred for investigation by primary care physicians, were much higher (41% in the first year: Geslani et al., 2005). By contrast, nonamnestic MCI subtypes are characterized by impairment in domains other than memory, and these patients are considered more likely to progress to a non-AD dementia. Unsurprisingly, given that topographical disorientation is one of the first symptoms of AD, patients with MCI and in particular a-MCI also show topographical deficits in tasks that assess real-world navigation (e.g., deIpolyi et al., 2007; Cushman et al., 2008).

The initial stages of AD are associated with pathology in the medial temporal lobe. For example, neuropathological studies of the histological markers of AD (neurofibrillary tangles and amyloid plaques) over disease progression implicate the entorhinal cortex (EC) (Braak and Braak, 1991), and regions such as EC and hippocampus show atrophy predating the onset of symptoms in patients with familial AD (Fox et al., 1996; Schott et al., 2003). The view that a-MCI represents a prodromal stage of AD is supported by studies showing raised densities of neurofibrillary tangles in the temporal cortices of a-MCI subjects (Guillozet et al., 2003). In addition, gray matter loss and hypometabolism in the temporal lobes is seen in patients with a-MCI, particularly those who rapidly converted to AD (Chetelat et al., 2002, 2005 Anchisi et al., 2005). While early pathology in the medial temporal lobes has received most attention, other regions associated with Papez's circuit, including the posterior cingulate/retrosplenial cortex have also been implicated in a-MCI and early in the course of AD (Nestor et al., 2003, 2006).

## Topographical Processing

The locus of early pathology in AD is consistent with the observation of topographical deficits. The mammalian hippocampus has been associated with topographical processing ever since the discovery of "place cells" in the hippocampus of rodents in the1970s (O'Keefe, 1976). The firing of these cells encode the location of the animal relative to the layout of environmental boundaries (O'Keefe and Burgess, 1996; Cressant et al., 1997), irrespective of the animal's heading direction (Muller, 1996). The human hippocampus has likewise been associated with spatial memory for locations irrespective of point of view (Abrahams et al., 1999; Holdstock et al., 2000; King et al., 2002) and specifically relative to environmental boundaries (Doeller et al., 2008). However, it is also well-established that aspects of topographical processing, such as navigation in large-scale environments, recruits a widespread network of brain regions, including the precuneus, retrosplenial, posterior parietal, and parahippocampal cortices (Aguirre and D'Esposito, 1997; Maguire et al., 1998; Aggleton and Brown, 1999; Burgess et al., 2001; Ino et al., 2002). Several studies have found topographical processing to be impaired in AD and a-MCI using tasks that required learning routes, remembering places that have been visited and detecting differences between scenes (Monacelli et al., 2003; deIpolyi et al., 2007; Lee et al., 2006, 2007; Cushman et al., 2008).

The Four Mountains test was developed to investigate topographical processing in humans, as an extension of Piaget and Inhelder's "three mountains" test (Piaget and Inhelder, 1956). It comprises four subtests to independently assess the perception and short-term retention of different types of information contained within pictures of landscapes. The computer-generated stimuli were constructed by independently varying the topographical (i.e., surface geometry) and nonspatial (e.g., lighting, cloud cover) features of the landscape, as well as the viewpoint from which landscapes were observed. Importantly, none of the subtests are associated with ceiling or floor effects, and are difficulty-matched in young adults (difficulty-matching between the perceptual and short-term memory subtests is achieved by manipulating the viewpoint shift and the similarity of the foil scenes to the target). Hartley et al.'s (2007) study demonstrated that focal hippocampal damage impaired topographical short-term memory but not short-term memory for the nonspatial aspects of the scenes. Topographical perception was mildly impaired in two of the four hippocampal patients, but intact in the others.

## Distinguishing AD and FTLD

Frontotemporal lobar degeneration (FTLD) is the second most common cause of dementia in under 65 yr olds (Neary et al., 1998). Unlike AD, this neurodegenerative condition is associated with several distinct pathological substrates, including: tau-positive inclusion bodies (Pick bodies); ubiquitin-positive, τ-negative inclusion bodies; and, rarely, neuronal intermediate filament inclusion body disease. Three syndromic variants of FTLD have been identified; frontal variant FTLD and semantic dementia (SD) as well as progressive nonfluent aphasia. SD is characterized by progressive loss of word meaning, fluent but empty spontaneous speech and associative

visual agnosia, and predominantly left-sided atrophy of the anteromedial temporal lobe (Chan et al., 2001; Galton et al., 2001; Seeley et al., 2005). By comparison with SD, patients with predominantly right-sided temporal variant FTLD typically present with behavioral disorders such as disinhibition and disorders of emotional processing, often in association with prosopagnosia (Edwards-Lee et al., 1997; Thompson et al., 2003; Chan et al., 2009). Patients with frontal variant FTLD typically present with a dysexecutive syndrome and loss of insight, often in association with behavioral disorders.

Despite the well described clinical features that characterize the different variants of FTLD and AD, there is considerable overlap in both their pathology and behavioral symptoms, making classification difficult in the early stages of disease (Mendez et al., 1993; Varma et al., 1999; Rosen et al., 2002). For example, both conditions result in pathological changes in the temporal and frontal cortices and medial temporal lobe damage can be at least as pronounced in temporal variant FTLD as it is in AD (Chan et al., 2001; Galton et al., 2001). Equally, episodic memory can be as severely impaired in FTLD as it is in AD (Scahill et al., 2005), and both behavioral symptoms (Robert et al., 2005) and semantic memory problems (Grossman et al., 1996) occur in AD. Nonetheless, subtle pathological differences between AD and FTLD do exist. For example, the pattern of medial temporal lobe damage in temporal variant FTLD is more asymmetric than in AD (Chan et al., 2001; Galton et al., 2001) while increased anterior vs. posterior medial temporal lobe damage has been reported in temporal variant FTLD but not in AD (Chan et al., 2001; Laakso et al., 2000; Davies et al., 2004). In addition, some authors have proposed that FTLD involves primarily the temporal and frontal lobes while AD may involve the wider set of structures comprising Papez's Circuit, including the thalamus, mammillary bodies, and posterior cingulate gyrus (Minoshima et al., 1997; Diehl et al., 2004; Nestor et al., 2003, 2006). Here we investigate a potential behavioral difference in topographical processing, which is very often impaired in AD, but is frequently well preserved in FTLD (Maguire and Cipolotti, 1998).

## METHODS

Patients were recruited from three centers: (1) the Dementia Research Centre, Institute of Neurology, London, UK, (2) the Cognitive Disorders Clinic at Hurstwood Park Neurological Centre, Sussex, Brighton, UK, (3) the Alzheimer Center, VU Medical Center, Amsterdam, The Netherlands. A comparison group of age-matched, cognitively intact control subjects were also recruited. Participants gave written consent and the study was approved by the hospitals' local research ethics committees.

### Participants

Fifty-six participants took part in this study. These included 31 patients and 25 healthy controls.

#### *Patients (N = 31)*

All the patients had undergone extensive neurological examination including, in the majority of cases, administration of the Mini-mental state test (Folstein et al., 1975), the taking of a family history, a full neuropsychological assessment, analysis of cerebrospinal fluid (CSF), volumetric MRI, and EEG. The patients with a-MCI met consensus diagnostic criteria for a-MCI ($N = 6$: Petersen et al., 1999). In these patients, objective memory impairment was greater than 1.5 standard deviations below control mean, but performance on other cognitive tests was normal. Although almost all individuals with AD initially pass through a stage of a-MCI, not all individuals with a-MCI will progress to AD. In this study, patients were only selected if, based on the results of extensive neurological and neuropsychological investigations, it was felt that they were highly likely to progress to AD (to date, four of the six have converted). Accordingly, these patients were included as a prodromal AD group.

The diagnosis of probable AD ($N = 7$) was made according to NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke, Alzheimer's Disease and Related Disorders Association) criteria (McKhann et al., 1984). All patients with AD presented with cognitive impairment primarily affecting episodic memory.

There were 12 patients with FTLD (Neary et al., 2005). These patients were split into three groups; left temporal variant FTLD ($N = 3$: Edwards-Lee et al., 1997; Thompson et al., 2003), right temporal variant FTLD ($N = 4$: Thompson et al., 2003; Chan et al., 2009), frontal variant FTLD ($N = 5$: Neary et al., 1998). The first group presented clinically with features of semantic dementia, with a profound impairment of naming and a loss of word meaning as the central symptoms. The latter two groups both presented with marked and progressive behavioral changes, but the right temporal variant group also had clear asymmetric anterior temporal lobe atrophy on neuroimaging (greater on the right side). All five patients with right temporal FTLD were included in a recent report describing this syndromic variant of FTLD (Chan et al., 2009).

We also included a group of individuals with subjective memory impairment ($N = 6$). These patients had reported a decline in memory in adult life sufficient to prompt referral to medical services, did not have a major depressive disorder and formal neuropsychological testing revealed satisfactory performance across all cognitive domains. Investigations to exclude identifiable causes of cognitive dysfunction—including MRI brain scans—were normal. The rationale for their inclusion was that individuals presenting at a neurology clinic on the basis of subjective memory complaints may be more anxious than our population of healthy volunteers and this may impact

negatively on performance on the Four Mountains Test. We wished to establish whether this was the case.

Exclusion criteria were a history of learning disability or psychiatric illness including substance abuse, evidence of significant vascular lesions on neuroimaging, and/or inability to tolerate up to 2 h of attentionally demanding cognitive tasks.

### *Controls (N = 25)*

The control group consisted of spouses/partners of the participating patients as well as other age-matched adults recruited through a volunteer database. The same exclusion criteria were applied as for the patients with the added conditions that no individual had a history of neurological injury and that they had never contacted their General Practitioner because they were worried about memory loss/dementia. They were not formally screened for a-MCI but none performed in the impaired range on the topographical recognition memory test (see later).

## Quantification of Medial Temporal Lobe Atrophy

All but two patients (1 AD group, 1 subjective memory impairment group) underwent MRI brain scanning on 1.5T scanners as part of their clinical diagnostic workup. A total of 26 patients underwent scanning using a volumetric scan protocol to provide 1.5 mm thickness contiguous slices in the coronal plane. Three patients were scanned using a nonvolumetric protocol with 3 mm coronal slice thickness and an interslice gap of 5 mm. Scans were unavailable for two individuals (both from the a-MCI group). In view of the heterogeneity of the scan protocols, and the multiple scan sites used in the study, medial temporal lobe atrophy (MTA) was determined using a visual rating scale as introduced by Scheltens and colleagues (Wahlund et al., 1999, 2000; van de Pol et al., 2006). This qualitative technique is applicable to nonvolumetric as well as volumetric MRI scans. It has been found to correlate well with stereological assessments of atrophy in nondemented and demented subjects (Wahlund et al., 1999) and has also been demonstrated to be of similar diagnostic value as medial temporal lobe volumetry when applied to patients with AD (Wahlund et al., 2000). The rating scale is based on hippocampal appearance and the size of the adjacent CSF spaces and therefore does not assess atrophy in adjacent cortical regions.

MTA is rated according to a five-point scale using the following guidelines:

0 normal;
1 widening of the choroidal fissure;
2 additional widening of the temporal horn of the lateral ventricle; widening of temporal lobe sulci (e.g. collateral sulcus, fusiform sulcus);
3 pronounced volume loss within the hippocampus;
4 end stage atrophy.

Representative scans from an individual in the AD, right temporal variant FTLD and subjective memory impairment groups, together with the corresponding MTA ratings are shown in Figure 1.

## Cognitive Tasks

At the time of testing, patients were administered the Four Mountains Test (see below for details) and the following neuropsychological tests.

Raven's advanced progressive matrices Set 1; a test of abstract problem solving and a proxy measure of current intellectual functioning (Raven, 1976).

The Flags test—a test of mental rotation that requires the test to match a simple design that has been rotated in one dimension (Thurstone and Jefferys, 1956). The foils are reflected versions of the design that have also been rotated.

The Topographical Recognition Memory Test (the TRMT) from the Camden Memory Tests (Warrington, 1996). The stimuli are pictures of outdoor scenes containing distinctive objects and in some items, people. The TRMT has 30 items and uses a three-alternative forced-choice test format where the target is the same photo as the study item and foils are different views of the same location.

The Doors and People Test—a battery of recall and recognition memory tests for verbal and nonverbal materials (Baddeley et al., 1994). The subtests are (1) verbal recall—the names and professions of four people have to be learned (e.g., *Jim Green* is the Minister); (2) verbal recognition—24 names are presented singly during the study period and then at test the targets must be recognized from three similar foils (e.g., John Wilby, John Wilkie, *John Wilkins*, John Willis); (3) visual recall—four simple shapes have to be learnt; (4) visual recognition—24 photographs of doors are presented singly during the study period and then at test the targets must be recognized from three visually similar foils.

The Object Decision subtest of the Visual Object and Space Perception battery (Warrington and James, 1991). The Object Decision subtest involves choosing the silhouette of a real object where the three foils are black nonsense shapes.

In some cases, it was not possible to administer all of these additional tests due to time constraints or when English was not the first language (for example, the five patients recruited from the VU Medical Centre in Amsterdam were not administered the verbal subtests of the Doors and People Test). Controls were administered the Four Mountains Test as well as Raven's advanced progressive matrices Set 1, the Flags test and the TRMT. All testing was carried out in a quiet room.

## The Four Mountains Test

This task has been described in detail by Hartley et al. (2007). Therefore, it will only be summarized here.

## Materials

Landscape stimuli contained four hills in the central foreground of the scene, with a semicircular mountain range in the background. Hills varied in shape, size, and relative location to create a unique set of topographical features for each test item. The nontopographical characteristics of the scenes were also varied to create unique prevailing conditions corresponding to different times of day and times of year. These nontopographi-

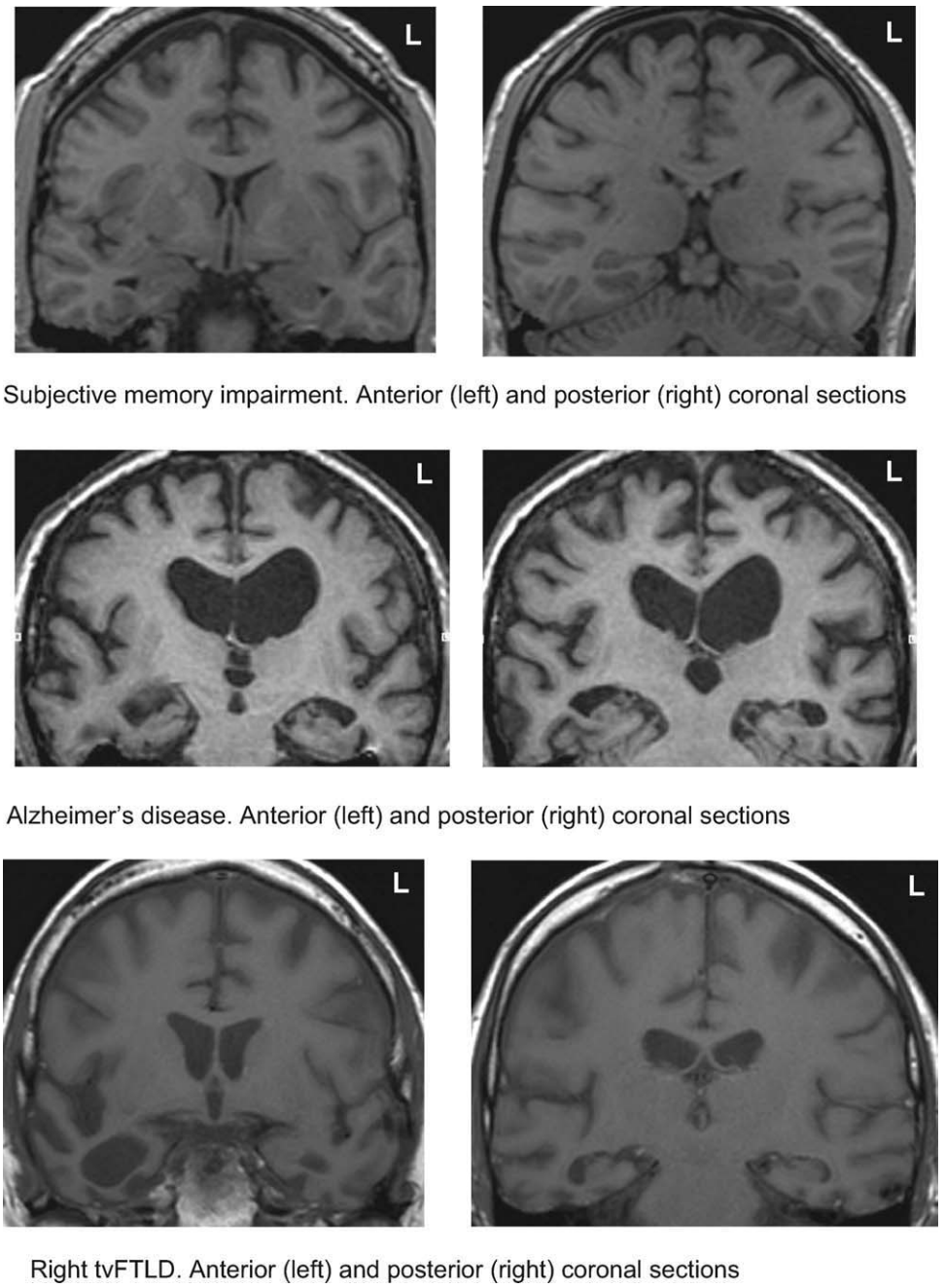


**FIGURE 1. Anterior (left column) and posterior (right column) coronal sections showing representative scans of a patient with (top) subjective memory impairment with a MTA rating of 0 bilaterally, (middle) AD with a MTA rating of 3 bilaterally, (bottom) Right temporal variant FTLD with a MTA of 1 in the left hemisphere and 4 in the right hemisphere.**

cal features were sunlight direction (elevation), cloud cover, atmospheric conditions, and the color and texture of the surfaces. Each scene was rendered from a virtual camera facing the center and placed at one of seven predefined viewpoints. See Figure 2 for examples of the images.

Stimuli were systematically generated to fit the constraints described below, while ensuring that the peaks of all four hills were visible in each rendered scene. There were 15 items in each task, each item being composed from five images. No image was repeated.

## Experimental Tasks

The four experimental tasks are summarized in Figure 2: a topographical perception task and a topographical short-term memory task (match the "place"), a nonspatial perception task and a nonspatial memory task (match the "time of day and time of year"). All participants completed the tasks in this order. Each task was presented in a separate A4 booklet, with the experimenter turning the pages to control the timing of the stimulus presentation and responses. Instructions were given orally and

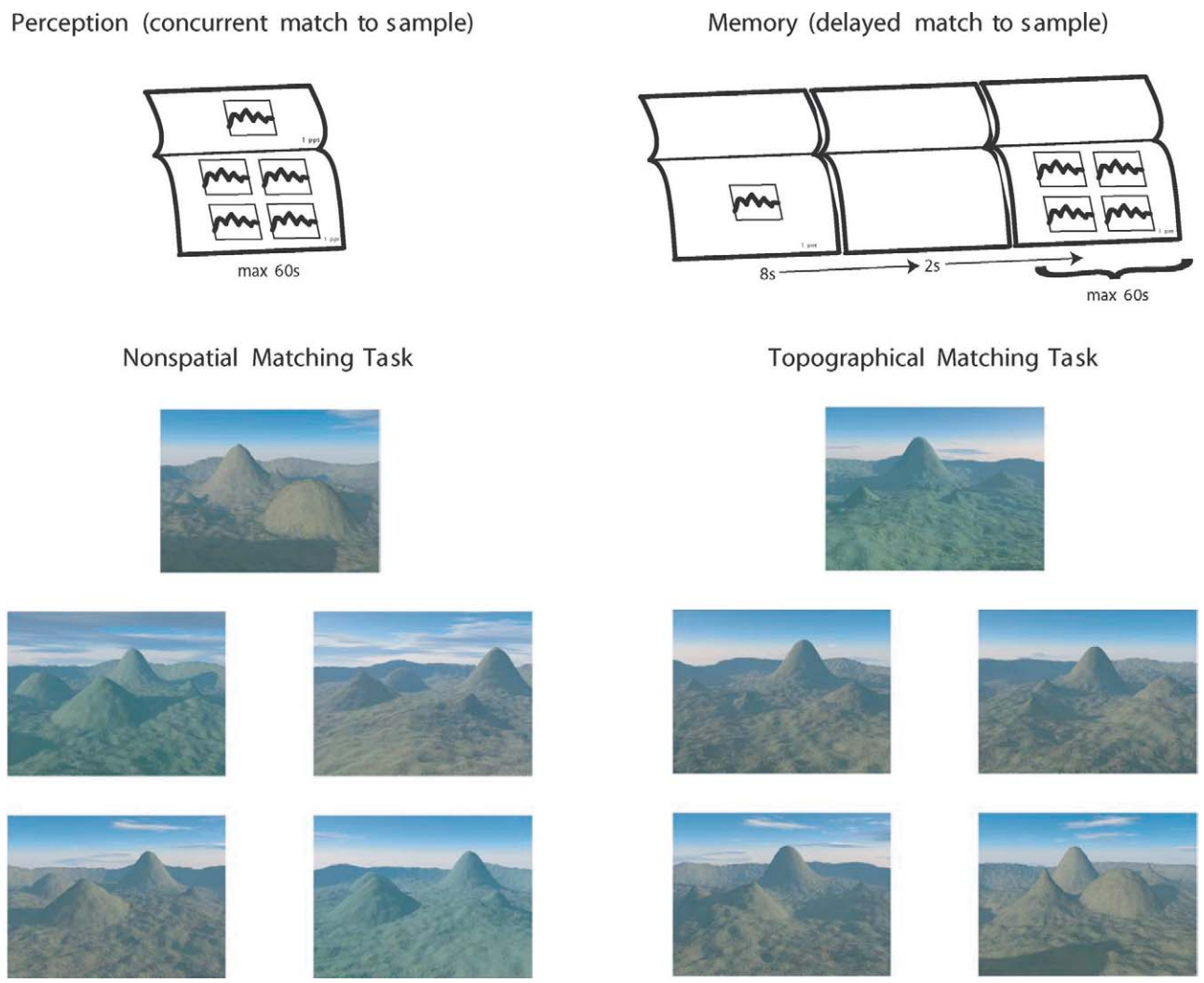


**FIGURE 2. Top: Timing and layout of test items. Perceptual tests used a concurrent match to sample task. Participants had to choose one picture from four alternatives (on the lower page of the test booklet) that matched the sample image (upper page). Memory tests used a delayed match to sample task, interposing a 2 s delay (during which a blank page was shown) between sample and test images. In both cases participants had a maximum of 60 s to make a response. Bottom: Examples of nonspatial and topographical items. In nonspatial tests participants had to match images based solely on the nonspatial features in the scene; cloud cover, lighting, texture, and color of vegetation. The target is shown at the bottom left of the four choices. Topographical features were varied between sample and test images. In topographical tasks subjects had to match images based solely on the topographical features; viewpoint and nonspatial features were varied between sample and test images. The target is shown at the top left of the four choices. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

each task began with three practice items, with feedback from the experimenter that drew their attention to relevant features of the stimuli. Typed instructions were present throughout testing.

## Topographical Perception and Short-Term Memory

The participant was presented with a sample image, and a four-alternative choice of test scenes arranged in a 2 × 2 grid. In the perception task, the test scenes were on the facing page of the test booklet (Fig. 2). In the short-term memory task, the sample image was presented in isolation for approximately 8 s. The page of the booklet was turned and participants then saw a blank page for approximately 2 s before being presented with the four way choice on the next page (Fig. 2). In both tasks, if the participant had made no response within 30 s they were given a neutral prompt for an answer. If they had made no response within a minute they were asked to guess.

The sample image showed one viewpoint of a landscape at a particular time of day and year. The four test scenes showed the target and three foil items. All four test scenes were landscapes rendered under the same prevailing conditions as each other (they showed the same time of day and year), but with different prevailing conditions and viewpoint from the sample image. However, the test scenes showed different topographical

*TABLE 1.*

*Demographic Variable*

| Group | Sex | Age | MMSE (/30) | Estimated premorbid IQ | Right MTA | Left MTA |
|---|---|---|---|---|---|---|
| Controls | ♀9:16♂ | 65.3 (7.6)<br>51–79 | n.t. | 112.7 (12.2)<br>85–130[a] | n.t. | n.t. |
| a-MCI | ♀5:1♂ | 65.3 (11.0)<br>51–77 | 27.0 (1.5)<br>25–29 | 114.3 (8.7)<br>100–127[b] | 0.5 (0.6)<br>0–1[c] | 0.5 (0.6)<br>0–1[c] |
| AD | ♀2:5♂ | 66.6 (7.5)<br>57–79 | 26.1 (2.8)<br>22–29 | 114.9 (12.5)<br>90–128[b] | 2.0 (1.4)<br>0–4[d] | 2.0 (1.4)<br>0–4[d] |
| RTvFTLD | ♀1:3♂ | 65.0 (11.5)<br>50–77 | 25.5 (0.8)<br>23–24[c] | 108.3 (12.2)<br>90–116[b] | 3.0 (0.8)<br>2–4 | 2.25 (1.3)<br>1–4 |
| LTvFTLD | ♀0:3♂ | 70.7 (3.2)<br>67–73 | 27.3 (0.6)<br>27–28 | 106.7 (2.5)<br>104–109[b] | 2.7 (1.2)<br>2–4 | 3.3 (0.6)<br>3–4 |
| FvFTLD | ♀0:5♂ | 65.4 (5.1)<br>58–72 | 28.2 (2.1)<br>26–30[d] | 106.1 (11.6)<br>90–128[b] | 1.2 (1.3)<br>0–3 | 1.4 (1.1)<br>0–3 |
| Subj | ♀2:4♂ | 65.6 (7.5)<br>56–74 | 29.3 (1.1)<br>28–30[d] | 108.0 (15.6)<br>90–117[b] | 0.4 (0.5)<br>0–1[d] | 0.2 (0.5)<br>0–1[d] |

Mean scores with standard deviations in parentheses and the range. MTA, ratings of medial temporal lobe atrophy; n.t., not tested.
[a]Based on Matrices score (age corrected).
[b]Based on National Adult Reading Test (2nd Ed; Nelson, 1991) or estimated from demographic variables (Crawford and Allen, 1997).
[c]Two participants' scores missing.
[d]One participant's score missing.

features from each other (they showed different places). The task was to identify the target image that matched the topography of the sample image. Each of the three foil scenes was constructed so as to resemble the target in different ways (see Hartley et al., 2007; for more details).

### Nonspatial Perception and Short-Term Memory

In these tasks, the sample and test images were presented in the same way as in the topographical tasks. The timings for making a response were also the same.

The sample image showed one viewpoint of a landscape at a particular time of day and year. The four test scenes showed the target and three foil items. All four test scenes were landscapes showing the same topography as each other (they showed the same place), but with different topography and viewpoint from the sample image. However, the test scenes were rendered under different prevailing conditions from each other (they showed different times of day and year). The task was to identify the target image that matched the time of day and time of year as the sample image. Only the combination of texture/color, lighting, and cloud cover was unique to target and sample images-individual elements might also match in foil scenes.

## RESULTS

### Demographic Variables

The characteristics of the participant groups are shown in Table 1. For each of the demographic variables, the mean of each group was compared using an oneway analysis of variance (ANOVA) and subsequent Tukey's post hoc tests to control for multiple comparisons. To have groups large enough for meaningful statistical comparisons, the three FTLD groups were combined, although to allow qualitative comparison, these groups are shown separately in Table 1. There were no group differences in terms of age or estimated premorbid IQ (both cases, $F(4,51) < 1$; Tukey's test, $P > 0.5$). The patients with AD had significantly lower MMSE scores than the subjective memory impairment group ($F(3,23) = 3.6$, $P = 0.073$; Tukey's test, $P < 0.05$), but there were no significant differences in MMSE scores between the a-MCI, AD, and FTLD groups (Tukey's test, $P > 0.3$). The FTLD group had significantly higher ratings of MTA in both hemispheres than the subjective memory impairment group ($F(3,23) > 4.0$, $P < 0.02$; Tukey's test, $P < 0.05$), and a trend towards higher ratings than the a-MCI group in the right and left hemispheres (Tukey's test, $P = 0.095$ and $P = 0.078$, respectively). There was also a trend towards higher ratings of MTA in the AD group when compared with the subjective memory impairment group in the left hemisphere (Tukey's test, $P = 0.067$; all other group comparisons $P > 0.14$).

### Four Mountains Test

The scores for the four subtests of the Four Mountains Test for all of the controls and the patients are shown in Figure 3 and Table 2. For each task, the mean performance of each group was compared using an oneway ANOVA and subsequent Tukey's post hoc tests to control for multiple comparisons. In order to have groups large enough for meaningful statistical comparisons, the three FTLD groups were combined, although

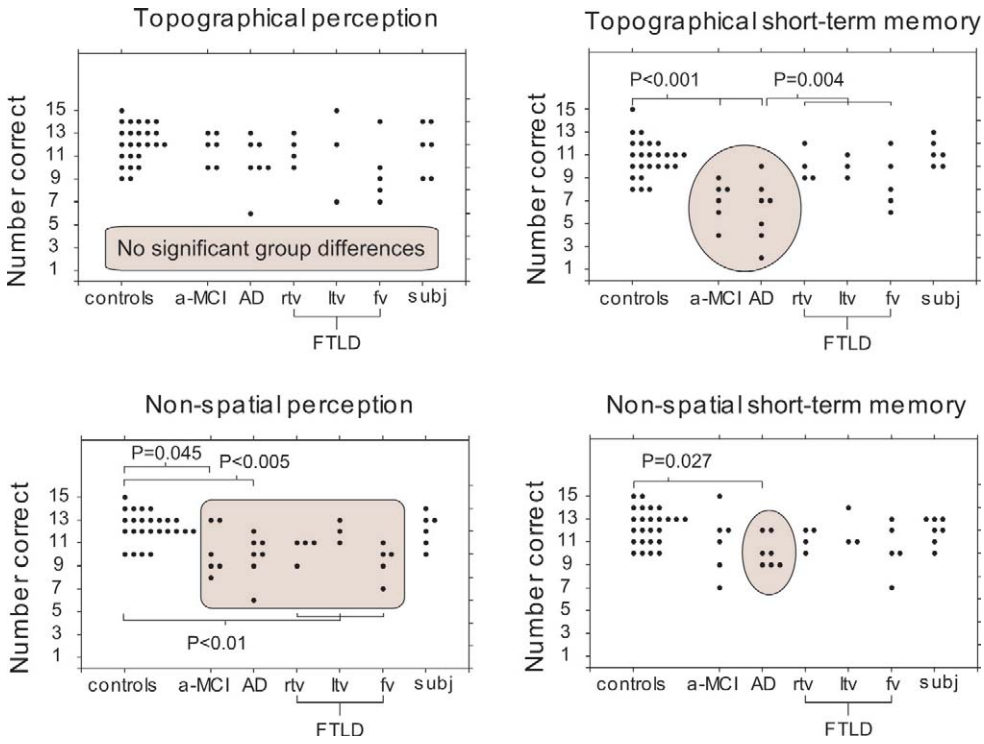


**FIGURE 3. Performance on all subtests of the Four Mountains Test in the patient groups. Individual scores are shown as dots. Significant group differences are indicated and groups that were impaired relative to the controls are highlighted. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

to allow qualitative comparison, these groups are shown separately in Figure 3 and Table 2.

## Topographical Perception

As shown in Figure 3 and Table 2, performance of all the patient groups was relatively high. There were no significant group differences ($F(4,51) = 1.6$; Tukey's test, $P > 0.25$).

## Topographical Short-Term Memory

In contrast to the place perception subtest, the performance of both the a-MCI group and the AD group was significantly below that of the controls and the group with subjective memory complaints ($F(4,51) = 12.8$, $P < 0.001$; Tukey's test, $P < 0.005$ in all comparisons). However, patients with FTLD performed no differently from the controls (Tukey's test, $P = 0.26$). Interestingly, patients with FTLD performed significantly better than the patients with AD (Tukey's test, $P = 0.004$) and also better than the a-MCI group although this comparison was only marginally significant (Tukey's test, $P = 0.063$ all other group comparisons $P > 0.3$). Inspection of Figure 3 demonstrates that all of the temporal variant patients with FTLD were performing at approximately the same level as the controls.

*TABLE 2.*

*Performance on the Four Mountains Task*

| Group | Topographical perception (/15) | Topographical short-term memory (/15) | Nonspatial perception (/15) | Nonspatial short-term memory (/15) |
|---|---|---|---|---|
| Controls | 12.1 (1.67) | 10.7 (1.67) | 12.4 (1.35) | 12.4 (1.55) |
| a-MCI | 11.7 (1.37) | 7.0 (1.79) | 10.3 (2.16) | 11.0 (2.76) |
| AD | 10.4 (2.30) | 6.1 (2.67) | 9.86 (1.95) | 10.1 (1.35) |
| Combined FTLD | 10.7 (2.64) | 9.4 (1.83) | 10.4 (1.56) | 11.1 (1.78) |
| RTvFTLD | 11.5 (1.29) | 10.0 (1.41) | 10.5 (1.00) | 11.3 (0.96) |
| LTvFTLD | 11.3 (4.04) | 10.0 (1.00) | 12.0 (1.00) | 12.0 (1.73) |
| FvFTLD | 9.60 (2.70) | 8.6 (2.40) | 9.4 (1.52) | 10.4 (2.30) |
| Subj | 11.7 (2.25) | 11.2 (1.17) | 12.2 (1.47) | 12.3 (0.82) |

Mean scores with standard deviations in parentheses.

## Nonspatial Perception

Several of the patients performed poorly on this task, with the a-MCI, AD, and FTLD groups all performing significantly below the controls ($F(4,51) = 6.3$, $P < 0.001$; Tukey's test, $P < 0.05$, $P < 0.005$, and $P < 0.005$, respectively) and there was a trend for the AD group to perform below the group with subjective memory complaints (Tukey's test, $P = 0.08$, other comparisons $P > 0.19$). However, there were no differences between the patient groups (Tukey's test, $P > 0.9$). As discussed later, this may be due to some patients being unable to cope flexibly with the task demands, failing to focus on the nonspatial aspects of the scenes and perseverating in focusing on the spatial features.

## Nonspatial Memory

Performance was relatively high although the patients with AD performed significantly below the controls ($F(4,51) = 3.3$, $P < 0.02$; Tukey's test, $P = 0.027$). There were no differences between the patient groups (Tukey's test, $P < 0.15$).

## Further Analyses

We considered the group of patients with a-MCI, selected for their likelihood to progress to AD, as a prodromal AD group. In support of this assumption, four of the six patients have progressed to a full diagnosis of AD at the time of writing. We compared the performance of these four patients with controls on the Four Mountains Test. Their pattern of performance was identical to the full a-MCI group: a significant impairment on the topographical short-term memory subtest ($t(27) = 3.7$, $P = 0.001$) but not on the topographical perception subtest ($t(27) > 0.5$), and impaired nonspatial perception ($t(27) = 4.8$, $P < 0.001$) but not nonspatial memory ($t(3.2) = 1.1$, $P = 0.36$, equal variance not assumed). Thus, the impairment seen in the a-MCI group is likely to be caused by pathological changes associated with prodromal AD, as indicated by the performance of those patients with a-MCI who have now converted to AD.

The aforementioned analyses indicate a failure of the AD and a-MCI groups in retaining topographical information over a few seconds. In contrast, there were no differences on the topographical subtests between the controls and the FTLD group. These two findings are complemented by the fact that there was a significant difference on the topographical short-term memory subtest between the AD and FTLD groups and a marginally significant difference between the a-MCI and FTLD groups. Further analyses were conducted specifically to test whether the AD and a-MCI groups performed significantly worse on the topographical memory subtest in comparison to their performance on the other subtests.

Separate $2 \times 2 \times 2$ repeated measures ANOVAs were carried out to compare the AD group and the a-MCI group with the controls. The first repeated factor was material (topographical vs. nonspatial) and the second repeated factor was delay (immediate vs. 2-s), with the between subjects factor being health (AD or a-MCI vs. controls). For both the AD group and the a-MCI group, there were significant main effects of health (AD: $F(1,30) = 46.6$, $P < 0.001$; a-MCI: $F(1,29) = 19.7$, $P < 0.001$), material (AD: $F(1,30) = 10.0$, $P = 0.004$; a-MCI: $F(1,29) = 6.5$, $P = 0.016$), and delay (AD: $F(1,30) = 17.7$, $P < 0.001$; a-MCI: $F(1,29) = 23.0$, $P < 0.001$) reflecting the fact that performance was poorer in the patient groups, in the spatial tasks and in the tasks with a delay. Critically however, in both cases there was a significant health by material by delay interaction (AD: $F(1,30) = 8.4$, $P = 0.007$; a-MCI: $F(1,29) = 9.1$, $P = 0.005$), confirming that the difference between these groups' performance on the topographical memory subtest compared with other subtests was greater than this difference in the control group. In other words, the AD and MCI groups both exhibited a disproportionate impairment on the topographical memory subtest.

The same analyses were also carried out on the data from the FTLD group. The main factors of health ($F(1,35) = 13.9$, $P = 0.001$), material ($F(1,35) = 8.1$, $P < 0.01$), and delay ($F(1,35) = 5.2$, $P < 0.05$) were all significant, again reflecting the fact that overall performance was poorer in the patient groups, in the spatial tasks and in the tasks with a delay. However, the critical health by material by delay interaction was not significant ($F(1,35) = 0.3$, $P = 0.59$), demonstrating the lack of any disproportionate deficit on the topographical memory subtest.

In a final analysis of this type, to investigate how effectively the Four Mountains Test differentiated the a-MCI and AD groups from the FTLD group, we performed the same $2 \times 2 \times 2$ repeated measures ANOVA with patient group as the between subjects factor (a-MCI or AD vs. the FTLD group). Given the small groups involved, we combined the a-MCI and AD groups into one. There were again significant main effects of material ($F(1,23) = 6.4$, $P = 0.02$) and delay ($F(1,23) = 13.6$, $P = 0.001$), reflecting the poorer performance on the spatial tasks and tasks with a delay. There was no main effect of group ($F(1,23) = 2.8$) indicating similar overall levels of performance on the test, and there was also no significant material by group interaction ($F(1,23) = 0.9$) indicating similar overall levels of performance on the topographical vs. the nonspatial tasks. However, there was a significant delay by group interaction ($F(1,23) = 7.6$, $P = 0.01$) due to poorer overall performance on the tasks with a delay in the a-MCI/AD group. Importantly, there was a significant material by delay by group interaction ($F(1,23) = 5.1$, $P = 0.03$), driven by the poorer performance of the a-MCI/AD group specifically on the topographical short-term memory subtest. This underlines the usefulness of the topographical short-term memory subtest in differentiating these two clinical populations.

Although the subtasks of the Four Mountains Test were all difficulty matched in young controls (Hartley et al., 2007), the topographical short-term memory subtest was somewhat more difficult for the older adult controls (see Supp. Info.). To ensure that the impairment of the a-MCI and AD groups on the topographical short-term memory subtest was not simply due to its slightly greater difficulty, we performed an additional

*TABLE 3.*

*Performance on Other Cognitive Tasks*

| Group | Matrices (/12) | Flags (/10) | TRMT (/30) | Obj Dec (/20) | DPT | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Visual recall (/36) | Verbal recall (/36) | Visual recognition (/24) | Verbal recognition (/24) |
| Controls | 8.7 (1.8) | 9.7 (0.5) | 27.4 (2.6) | n.t. | n.t. | n.t. | n.t. | n.t. |
| | 5–12[a] | 9–10 | 21–30 | | | | | |
| a-MCI | 8.3 (2.9) | 9.0 (0.9) | 20.8 (4.6) | 17.3 (2.0) | 17.3 (10.1) | 16.8 (8.4) | 12.5 (2.9) | 11.8 (3.2) |
| | 4–12 | 8–10 | 15–26 | 15–20 | 8–36 | 5–29 | 9–16 | 9–17 |
| AD | 5.0 (1.41) | 9.3 (0.8) | 16.2 (1.8) | 16.7 (2.0) | 13.2 (8.5) | 10.5 (6.8) | 12.3 (1.9) | 11.8 (1.9) |
| | 3–6[b] | 8–10 | 15–19[b] | 14–19 | 5–29[a] | 3–22[a] | 10–15[a] | 9–14[b] |
| RTvFTLD | 5.7 (2.1) | 9.2 (1.0) | 19.3 (4.6) | 16.0 (3.6) | 24.5 (16.3) | 20.0 (9.9) | 15.0 (2.8) | 18.5 (0.7) |
| | 4–8[a] | 8–10 | 14–22[a] | 12–19 | 13–36[b] | 13–27[b] | 13–17[b] | 18–19[b] |
| LTvFTLD | 7.5 (2.1) | 9.0 (1.0) | 20.0 (2.8) | 16.7 (0.6) | 16.3 (2.3) | 9.5 (7.8) | 10.0 (1.7) | 9.5 (6.4) |
| | 6–9[a] | 8–10 | 18–22[a] | 16–17 | 15–19 | 4–15[a] | 8–11 | 5–14[a] |
| FvFTLD | 5.5 (4.1) | 9.4 (0.5) | 23.4 (6.0) | 16.2 (4.3) | 21.6 (12.0) | 22.0 (11.1) | 15.2 (7.0) | 18.0 (6.9) |
| | 1–9[a] | 9–10 | 13–28 | 9–20 | 10–36 | 10–32[b] | 7–23 | 10–22[b] |
| Subj | 8.3 (0.6) | 9.5 (0.5) | 24.7 (3.5) | 17.8 (1.7) | 28.3 (4.8) | 25.0 (5.7) | 18.8 (3.4) | 17.5 (5.0) |
| | 8–9 | 9–10 | 21–27 | 16–20 | 22–36 | 18–32 | 13–22 | 10–23 |

Mean scores with standard deviations in parentheses and the range. TRMT, topographical recognition memory test; Obj Dec, object decision test; DPT, Doors & People Test.
[a]One participant's score missing.
[b]Two participants' scores missing.

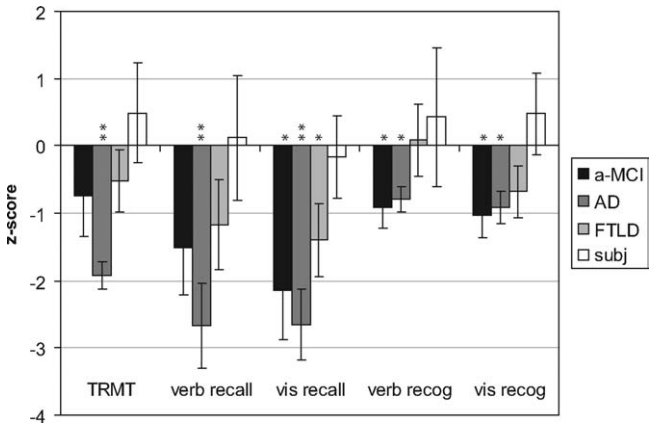


**FIGURE 4. Performance of the individuals with a-MCI, AD, FTLD and subjective memory complaints on clinical tests of episodic memory. Scores are shown as standardized (*z*) scores based on the published normative data. Impaired scores (group performance significantly less than 0) are shown for $P < 0.05$ (*) and $P < 0.001$ (**). TRMT, Topographical Recognition Memory Test; verb recall, verbal recall subtest of the Doors & People Test; vis recall, visual recall subtest of the Doors & People Test; verb recog, verbal recognition subtest of the Doors & People Test; vis recog, visual recognition subtest of the Doors & People Test.**

analysis where we equated the four tasks in terms of performance. The length of the subtests was reduced by three items; we excluded the three most difficult items from the topographical memory subtest and the three easiest items from the other three subtests, as judged from control performance. Having matched the subtests for difficulty, the a-MCI and the AD groups remained impaired on the topographical short-term memory but not perception subtests. The a-MCI, AD, and FTLD groups remained impaired on the nonspatial perception subtests. Interestingly, none of the groups, including the AD group, were impaired on the nonspatial short-term memory subtest (see Supp. Info. for further details).

## Performance on Other Cognitive Tasks

A summary of the groups' scores on various cognitive tasks are shown in Table 3 and Figure 4.

On the matrices test of abstract problem solving, the AD and FTLD groups were impaired compared to the controls ($F(4,47) = 5.8$, $P = 0.001$, Tukey's test; $P = 0.025$ and $P = 0.002$, respectively), and the FTLD group was impaired compared to the subjective memory complaint group (Tukey's test, $P < 0.05$), consistent with the fact that these disorders affect multiple cognitive domains. In comparison, the a-MCI group performed at a similar level to the controls, reflecting the isolated memory impairment in these patients (Tukey's test, $P = 0.99$; all other group comparisons $P > 0.12$). On a stringent test of visual perception (the Object Decision test) all but two patients performed within normal limits (one patient with right temporal variant FTLD and one patient with frontal variant FTLD was impaired; group comparisons $F(3,25) < 0.6$; Tukey's test, $P > 0.6$). In addition, all patients were unimpaired on the Flags test of mental rotation ($F(4,51) < 2$; Tukey's test, $P > 0.14$).

Both the a-MCI group and the AD group performed significantly below controls on the Topographical RMT, consistent with the deficit in long-term episodic memory associated with these conditions ($F(4,46) = 14.5$, $P < 0.001$; Tukey's test, $P = 0.005$ and $P < 0.001$, respectively). Interestingly however, the FTLD group also performed significantly below the controls (Tukey's test, $P < 0.005$). There was no difference between the a-MCI and FTLD groups on this test (Tukey's test, $P = 0.99$), but there was a marginally significant difference between the AD and FTLD groups (Tukey's test: $P = 0.063$). The participants with selective memory complaints performed above those with AD (Tukey's test, $P < 0.005$; all other comparisons $P > 0.2$).

There were no significant differences between the clinical groups on the subtests of the Doors and People Test ($F < 1.6$ on all subtests; Tukey's test, $P > 0.3$). This may be due to the large variability between subjects in the FTLD group, with some patients obtaining normal scores while others were markedly impaired, consistent with reported impairments of episodic memory in FTLD (Chan et al., 2009). However, the AD group was impaired relative to the subject memory complaints group on the verbal and visual recall subtests and the verbal recognition subtests ($F(3,24) > 3$, $P > 0.05$; Tukey test, $P < 0.05$). Because this test was not administered to the controls, performance was compared with the published normative data. Each individual's score was converted to a *z*-score based on the normative data for their age. *T*-tests were carried out to compare the group mean *z*-score against 0. Performance across the groups was lowest on the visual recall subtest, with the a-MCI, AD and FTLD groups all significantly impaired ($t = -2.9$, $P = 0.033$, $t = -5.1$, $P = 0.004$, and $t = 2.6$, $P = 0.029$, respectively). The a-MCI and AD groups were also impaired on the visual recognition subtest ($t = -3.3$, $P = 0.022$ and $t = -3.9$, $P = 0.011$, respectively) and the verbal recognition subtest ($t = -3.1$, $P = 0.026$ and $t = -4.2$, $P = 0.014$, respectively). The AD group was additionally impaired on the verbal recall subtest ($t = -4.2$, $P = 0.008$; all other comparisons $t > -2.2$). Because the patient groups had relatively high estimated premorbid IQ and the normative data do not take this into account, these results may underestimate the level of memory impairment.

## Correlations Between MTA and Performance on Cognitive Tasks

We investigated whether there were any correlations between ratings of medial temporal lobe atrophy (MTA) and performance on the cognitive tasks (see Supp. Info. for full results). There were no significant correlations between any subtest of the Four Mountains Test and MTA. This is unsurprising given that some of the temporal variant patients with FTLD had severe MTA and yet performed well on most of the subtests. Interestingly, there were also no significant correlations between the Four Mountains Test subtests and MTA when only analyz-

ing data from the patients with AD, a-MCI, and subjective memory impairment (i.e., excluding the FTLD patients). By contrast, MTA was correlated with more general measures of intellectual functioning such as MMSE score ($r = -0.56$ left hemisphere; $r = -0.64$ right hemisphere) and Matrices score ($r = -0.64$ left hemisphere; $r = -0.65$ right hemisphere). There were also significant correlations between the visual recognition and recall subtests and the verbal recall subtest of the Door and People test (see Supp. Info. materials).

## DISCUSSION

The main findings of this study are as follows. (i) Topographical short-term memory is impaired in AD but not in FTLD; the FTLD patients performed significantly better than the AD patients on this subtest. (ii) Patients with a-MCI, thought to be in the prodromal stage of AD (consistent with 4/6 patients with a-MCI having already converted to AD), showed the same pattern of performance as those with AD. (iii) In all patient groups, topographical perception was intact. These differences in topographical processing are not explained by differences in cognitive domains such as abstract problem solving, visual perception or general long-term memory, which was impaired to varying degrees in the AD, a-MCI, and FTLD groups. The differences are also not explained by the overall degree of medial temporal lobe atrophy.

Our results suggest a core topographical process that is impaired in the very earliest stages of AD: the maintenance of a flexible representation of the topography of a location in order to recognize it from different viewpoints and under different lighting conditions. They extend previous findings in a-MCI and AD, of a deficit in allocentric topographical processing (Hort et al., 2007; see also, Burgess et al., 2005) and navigation (Monacelli et al., 2003; deIpolyi et al., 2007; Cushman et al., 2008). We show that such deficits can be exposed using static scenes rather than actual or virtual navigation, can be isolated from other perceptual and mnemonic processes, and that these same deficits are not apparent in FTLD. Our results are consistent with a growing literature demonstrating that, for some types of stimuli, memory over short durations can be impaired by hippocampal-related aetiologies more commonly associated with long-term memory deficits (Lee et al., 2005; Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007).

### A Specific Deficit, Not a Decline in Intellect, Long-Term Memory or Perception

The patients with a-MCI or mild AD were impaired at retaining topographical information (the shape and spatial arrangement of mountains viewed from different locations), across a 2 s delay. Furthermore, they were disproportionately impaired on the topographical short-term memory subtest of the Four Mountains Test compared with the other subtests, even when the subtests were matched for difficulty. In comparison, the patients with FTLD were unimpaired on the topographical short-term memory subtest and performed significantly better than those with AD. Given that the AD and FTLD groups performed equivalently to each other, yet significantly below the level of the controls on a test of abstract reasoning, the difference in topographical memory is unlikely to represent differences in general intellectual ability. This conclusion is corroborated by the fact that the a-MCI group was unimpaired on the Matrices test of abstract reasoning.

Poor performance on the Four Mountains Test does not appear to simply reflect poor long-term memory. On a test of topographical long-term recognition memory (the TRMT), the AD and a-MCI groups both performed significantly below the controls, with the AD group performing significantly below the FTLD group. However, in contrast to the topographical short-term memory subtest from the Four Mountains Test, the FTLD group was also impaired when compared to the control group and they performed at a comparable level to the a-MCI group. Therefore, the TRMT is somewhat poorer at distinguishing the patient groups than the Four Mountains Test. This may be because the TRMT uses scenes that contain several distinctive features such as objects or people, so that good performance can reflect recognition of these features rather than topographical processing per se. Second, as all the study items in the TRMT are shown consecutively before memory is tested, this may cause a build up of interference between all of the test items that must be kept in memory, but this type of interference is avoided when memory is tested after each study item as in the Four Mountains Test. Thus, FTLD performance on the TRMT may suffer from nontopographical deficits, consistent with object processing deficits in SD (Hodges et al., 1992) and prefrontal involvement in dealing with interference (Incisa della Rocchetta and Milner, 1993; Simons et al., 2002; King et al., 2005). Another standardized test of episodic memory, the Doors and People Test (Baddeley et al., 1994), revealed no differences between the patient groups, although performance in the clinical groups was generally low, consistent with the observation that episodic memory is frequently impaired in FTLD (Scahill et al., 2005; Chan et al., 2009).

In contrast with the ability to retain topographical information over a few seconds, topographical perception was unimpaired in any of the patient groups. Lee et al. (2006, 2007) have documented topographical processing deficits in patients with AD but not SD, which they argued was directly related to a perceptual deficit. Here we demonstrate that there are situations when topographical perception is unimpaired in AD. It may be that the AD patients solved our perceptual task by comparing features contained in the scenes in a point-to-point manner, rather than forming a more holistic representation of the whole layout. Such a strategy might be easier in our match-to-sample test than in Lee et al.'s odd-one-out test which required a greater number of comparisons between the test items to be made. However, when holistic mental representations of the topography of the scenes are required to complete

the task, as in our short-term memory subtest, impairments become more apparent (Lee et al., 2006; Hartley et al., 2007; see Bird and Burgess, 2008; Suzuki and Baxter, 2009; for further discussion). It was unclear from Lee et al.'s studies whether unimpaired topographical processing in SD reflected a laterality effect; such patients often have greater left-sided temporal lobe atrophy, whereas the right hemisphere generally plays a greater role in visual-spatial processing (e.g., De Renzi, 1982; Burgess et al., 2002). Our data demonstrate that temporal variant FTLD is not associated with topographical processing, even when the damage is predominantly right-lateralised (Fig. 3). It has also been suggested that impaired perception of radial optic flow underlies the poor navigation of a-MCI and AD patients (Mapstone et al., 2003; Kavcic et al., 2006). Although optic flow may well be important for real-world navigation, our results, using static pictures, show that other aspects of topographical processing are impaired in AD, consistent with a deficit in topographical representation.

The two nonspatial subtests involved matching the time of day and the time of year. These subtests did not clearly differentiate the patient groups. The a-MCI, AD, and FTLD groups were impaired on the perceptual subtest, while the AD group was impaired on the memory subtest (but not significantly different from the FTLD group). The poor performance on the perceptual subtest may reflect a difficulty the patients found in switching from focusing on the topographical information to focusing on the nonspatial information (since the nonspatial subtests always followed the topographical subtests; and perceptual subtests always preceded memory subtests). Individuals from all patient groups made these perseverative errors and required frequent reminders as to which aspects of the scenes they were required to match. These procedural requirements of the task may be impaired by extra-hippocampal damage in the patient groups, given that patients with focal hippocampal damage were unimpaired on the nonspatial subtasks (Hartley et al., 2007).

## Potential Neural Substrates for the Topographical Deficit

Ratings of global MTA were unrelated to topographical short-term memory as assessed by the Four Mountains Test. Thus, within the temporal variant FTLD groups, which comprised several individuals with extensive hippocampal atrophy, none was impaired. By contrast, MTA was correlated with more general measures of intellectual functioning and memory (see Supp. Info.). The combined MTA analysis may simply reflect impairments that are common to all groups. However, the analysis restricted to a-MCI, AD, and subjective memory patients also showed no correlation with topographical memory, which is somewhat surprising given that patients with focal hippocampal damage are impaired on the task (Hartley et al., 2007).

It may be that topographical processing is influenced by the relative severity of posterior, vs. anterior, hippocampal atrophy, to which the MTA measure is insensitive. Although AD is associated with relatively uniform atrophy along the anteroposterior length of the hippocampus, there is a gradient of hippocampal atrophy in FTLD, with disproportionately severe atrophy in the anterior portion and relative preservation of the posterior hippocampus (Laakso et al., 2000; Chan et al., 2001; Davies et al., 2004). Animal studies indicate more fine-tuned spatial responses in dorsal (corresponding to posterior) than ventral (corresponding to anterior) hippocampus (Jung et al., 1994; Kjelstrup et al., 2008), while spatial navigation is more sensitive to dorsal than to ventral hippocampal lesions (Moser et al., 1995). In humans, activity in the posterior, but not anterior, hippocampus is correlated with remembering locations relative to the environmental layout (Doeller et al., 2008) while gray matter density in right posterior hippocampus (and inferior parietal cortex) correlates with navigational ability in patients with AD and a-MCI (deIpolyi et al., 2007). Furthermore, the anterior and posterior portions of the hippocampus may have partially dissociable roles in the formation and retrieval of cognitive maps, respectively, (Iaria et al., 2007) and the impairment of the a-MCI and AD groups may primarily reflect a topographical retrieval deficit. It is also possible that posterior portions of the parahippocampal gyrus, which are known to play a role in spatial processing (Bohbot et al., 1998; Aguirre and D'Esposito, 1999; Malkova and Mishkin, 2003; Epstein, 2008), may be disproportionally atrophic in AD vs. FTLD (this would not be detected by the relatively crude medial temporal lobe atrophy rating available).

An alternative possibility is that the differing test performances between the patient groups with AD and FTLD are a reflection of neocortical pathology beyond the medial temporal lobes. Several studies have documented hypometabolism in the posterior cingulate gyrus (PCG) to be one of the earliest markers of AD (Minoshima et al., 1997; Nestor et al., 2003). There is also evidence of volume reduction in the same region based on voxel-based morphometry and volumetric MRI measurements (Scahill et al., 2002; Acosta-Cabronero et al., 2008; Pengas et al., 2008). Atrophy in the PCG has also been found to be one of the anatomical features that predicted clinical progression from a-MCI to AD (Whitwell et al., 2008). By contrast, there have been no reports to date of PCG volume loss in FTLD (Nestor et al., 2006), although one study has demonstrated a similar degree of PCG hypometabolism in AD and FTLD using magnetic resonance spectroscopy (Kizu et al., 2004). Volumetric analysis of the cingulate gyrus in AD and FTLD has revealed differing patterns of atrophy within this brain region in the two patient groups, with predominantly anterior atrophy in FTLD and posterior atrophy in AD (Barnes et al., 2007). Given that there are neuropsychological and neuroimaging data linking the PCG/retrosplenial cortex to navigation in humans (Burgess et al., 2001; Maguire, 2001; Ino et al., 2002; Wolbers and Buchel, 2005) and rodents (Cooper et al., 2001; Vann and Aggleton, 2002, 2004), the additional involvement of these medial posterior regions may explain the preferential impairment of topographical short-term memory in AD.

## Conclusions

The short-term retention of topographical information was impaired in patients with AD and a-MCI but not in patients with FTLD or subjective memory impairment. By comparison, topographical perception was normal in all patient groups. These findings suggest that a core cognitive deficit associated with the earliest stages of AD is the ability to form and retain allocentric representations of large-scale environments. This is likely to contribute to the topographical disorientation associated with AD. Moreover, these topographical representations are likely to depend upon the brain regions associated with early neuropathology specific to AD, and the Four Mountains Test is more sensitive to this than other clinical memory tests. As such, the test has potential as a diagnostic tool for detection of AD in its earliest stages. Further investigation of topographical processing in these populations may also provide some insights into the anteroposterior segregation of cognitive processes in temporoparietal brain regions.

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