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# Lost and Found: Bespoke Memory Testing for Alzheimer's Disease and Semantic Dementia

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**Abstract**. The neural network activated during Topographical Memory (TM) tasks in controls overlaps with the earliest affected regions in Alzheimer's disease (AD) but not with those of Semantic Dementia (SD). This suggests that clinical TM tests could be more bespoke to neural dysfunction in early AD and therefore more sensitive and specific. We hypothesized that TM impairment would be characteristic of AD but not of SD making it useful both for early diagnosis and differential diagnosis. TM was assessed in 69 patients (22 mild AD, 15 SD, 32 with mild cognitive impairment (MCI)) and 35 controls, using three tasks: the four mountains test and two novel tests in a virtual town (the Virtual Route Learning Test (VRLT) and the Heading Orientation Test). AD patients were impaired on all TM tasks. The VRLT was the most discriminatory; had the highest correlation with caregiver reports of navigation problems; and correlated strongly with memory, attention/executive function, and to a lesser degree, visuospatial ability. In contrast, SD patients performed well on the TM battery only becoming abnormal with very advanced dementia and performance correlated exclusively with attention/executive function. The VRLT achieved 95% sensitivity and 94% specificity in discriminating AD patients from controls; at the same cut-off, 70% of MCI patients were impaired. When combined with either naming performance or global dementia severity, there was complete separation of AD from SD. The VRLT is ecologically valid, highly sensitive to early AD, and useful in discriminating AD from the non-Alzheimer dementia, SD.

Keywords: Mild cognitive impairment, topographical memory, virtual environment

Supplementary data available online: http://www.j-alz.com/issues/21/vol21-4.html#supplementarydata03

## INTRODUCTION

Patients with Alzheimer's disease (AD) get lost; this reflects a deficit in topographical memory (TM), defined as the ability to navigate to new locations and to remember the way to known places [1]. Functional imaging studies of navigation by healthy volunteers show activation in a reproducible network, including the medial temporal lobe (MTL), which may include the hippocampus and parahippocampal gyrus (PHG), the retrosplenial cortex (RSC)/posterior cingulate (PC), the prefrontal cortex, and caudate nucleus [2–7].

There is considerable lesion evidence implicating the MTL in TM [8]. The PHG is considered important in scene perception [9,10], while the hippocampus is thought to be necessary for spatial memory [11]; for maintaining representations of a cognitive map [12, 13]; in route-learning [14] and in navigation [15,16]. Similarly, although cases are sparse, RSC/PC lesions have been linked to TM impairments in humans [17–20] (for a review, see [21]).

The navigational network revealed in fMRI studies, and the distribution of focal lesions causing TM im-

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pairment, are homologous with the landscape of early degeneration in AD. The earliest hypometabolic region in AD is the RSC/PC [22,23], MTL atrophy is an established feature of AD [24], and, at the prodromal stage of AD (i.e., in patients with mild cognitive impairment (MCI) who later progressed to AD), there is significant and comparable atrophy of the hippocampus and RSC/PC [25,26]. Given the degree of overlap between the navigational network and the earliest affected areas in AD, it has been hypothesized that TM impairment would be a highly sensitive marker of early AD [27]. This possibility has already been indicated in a single case of very early AD who presented with progressive TM and word-finding difficulties [28].

Ecologically, 25% of AD patients experience TM impairment at presentation, and 50% of patients will develop TM impairment within three years, according to caregiver reports [29]. Caregiver reports may underestimate the magnitude of TM impairment, however, as patients may compensate by restricting themselves to over-learned routes. For instance, anecdotal clinical observation suggests that caregivers often first become aware of a memory problem when patients fail to learn new routes in unfamiliar environments, such as on holiday. TM is not routinely tested in the clinic, and conventional tests of visuospatial ability, memory, or even pen-and-paper tests purported to assess TM, such as the Porteus maze, Money Road Map, and "stepping-stone" tests, lack validity for real-world TM ability [30]. Indeed, some patients with real-world TM impairment can apparently perform normally on such tests [1,31].

Real-world TM tasks, on the other hand, do have ecological validity for this domain [30]. With quantitative assessment of TM ability, beyond symptom reporting, studies of real-world ability such as route-learning in a hospital lobby [31], have reported objective TM impairment in patients with AD [32,33] and MCI [27,34, 35]. While these methods are useful for research, they are impractical in a clinical neuropsychology setting and performance cannot be compared directly between centers because each testing environment is unique. More recently, navigational paradigms in virtual environments, whose advantage is that they can be applied in different places, have been shown to reflect real-world TM abilities [36], and have been used successfully in the elderly [4]. Virtual navigation studies to date have shown anterograde TM impairment in AD but not MCI patients [36], and navigational impairments associated with MTL damage, particularly on the right [15, 16].

Another important potential application of clinical TM testing is in differential diagnosis. Patients with Semantic Dementia (SD), the temporal variant of frontotemporal dementia (FTD) [37], are often misdiagnosed with AD. Similar to AD, patients and caregivers frequently report the primary symptom as being a "memory problem" (albeit memory for names and word meanings if asked to elaborate) and they perform poorly on standard verbal memory tests such as word-list learning [38,39] or story recall [40]. Furthermore, patients with AD develop semantic memory impairment as the disease evolves [40]. As such, the two disorders can appear to merge together if the assessment is not focused on the relative impairments and strengths of each cognitive profile. TM assessment could be particularly useful in this setting because clinical observation suggests that patients with SD often have preserved navigational abilities even at advanced stages. There are two case reports assessing TM in SD: the first showed intact TM in spite of impaired anterograde non-verbal memory (delayed recall of the Rey Complex Figure (RCF)) [41] while the other showed normal TM despite impaired verbal and non-verbal memory impairment [42] – both patients had asymmetrical, left-predominant temporal lobe atrophy. In addition, patients with FTD have been shown to have normal performance in the Four Mountains test, a test of short-term TM, whereas AD and MCI patients were impaired [43]. These findings suggest that a double dissociation between semantic knowledge and TM may have potential to reliably discriminate between AD and SD.

In summary, recent findings from functional imaging studies of healthy subjects performing TM tasks, and of the neural landscape of early AD, suggest a convergence of both onto a common neural network involving MTL and retrosplenial regions. Therefore, like DeIpolyi et al. [27] and Bird et al. [43], we hypothesized that these observations might translate to TM being particularly useful and sensitive in the clinical assessment of early AD. Secondly, we hypothesized that when contrasted to semantic memory, TM performance may have a specific role in the differential diagnosis of AD and SD. TM was assessed with a variety of recently developed tests as well as with two novel virtual navigation tasks (the virtual route learning test (VRLT) and the heading orientation test (HOT)), using a virtual environment previously employed in cognitive neuroscience experiments [15,16]. These tests were chosen to assess the various functions of TM, namely memory for large-scale allocentric space memory (Four Mountains test), route learning (VRLT) and heading orientation (HOT), also known as "dead reckoning". The VRLT, in particular, was designed to be an ecologically valid, graded clinical test of TM.

Table 1
Demographicss

| | MCI | AD | SD | Controls | F (df) | *p* |
|---|---|---|---|---|---|---|
| Gender, M:F | 18:14 | 12:10 | 10:5 | 17:18 | $\chi^2(3) = 1.43$ | 0.70 |
| Age, years | 71.0 (5.1) | 67.7 (6.9) | 64.9 (7.7) | 68.7 (5.6) | 3.65 (3,100) | 0.02* |
| Education, years | 13.6 (3.1) | 12.0 (2.7) | 12.4 (2.6) | 13.5 (2.5) | 2.05 (3,100) | 0.11 |
| Disease duration, years | 4.4 (2.6) | 5.8 (2.4) | 4.8 (2.4) | N/A | 2.02 (2,66) | 0.14 |

KEY: M = Male, F = Female, F = ANOVA statistic, df = degrees of freedom, N/A = Not Applicable. All values are presented as mean (standard deviation). * *Post hoc* pairwise comparison shows that MCI are significantly older than SD only.

## MATERIALS AND METHODS

### *Subjects*

Sixty-nine patients were recruited from the Cambridge Memory Clinic: 32 with MCI [44], 22 with probable mild-to-moderate AD according to NINCDS-ADRDA criteria [45], and 15 diagnosed with SD according to consensus criteria [37,46].

Thirty-five controls were also recruited. All controls were screened to exclude neurological or major psychiatric illness; all performed normally on the Addenbrooke's Cognitive Examination-Revised (ACE-R) [47] and none reported any memory symptoms.

All subjects had visual acuity better than 6/12 on the Snellen chart, plus absence of alcohol, illicit drug, or sedative (e.g., benzodiazepine) use. None of the subjects reported prior experience with first-person computer games or virtual environments. Written informed consent was obtained from all participants. The study was approved by the Local Regional Ethics Committee and conducted in accord with the Helsinki Declaration of 1975.

Table 1 shows that all groups were matched for gender, education, and disease duration, but the MCI patients were older than the SD patients.

### *MCI definition and sub-classification*

MCI is a concept designed to identify patients at the earliest stage of AD; however, although many patients thus classified do have prodromal AD, some have non-AD pathology or no neurodegenerative pathology at all. MCI was defined by the presence of informant-corroborated memory complaints in patients who had preserved activities of daily living; absence of dementia and an Mini Mental State Exam (MMSE) score $>$ 23/30; but with objective evidence of cognitive impairment (worse than 1.5 SD below control mean) on any neuropsychological test from a detailed battery used in a previous longitudinal MCI study [48]. Based on scores from this battery, 14 patients had pure amnestic MCI – impairment in the memory domain only (aMCI); 15 patients had so-called multi-domain MCI (mdMCI, also known as "amnestic-plus" MCI, [49]) – memory test impairment plus impairment in a non-memory domain; 3 patients had non-amnestic MCI (naMCI) – impairment only in a non-memory domain.

### *Left versus right temporal lobe predominant SD*

It has been recently suggested that right temporal lobe predominant SD may be a separate FTD subtype, with predominant way-finding symptoms compared to left temporal lobe SD [50]. In our study, visual inspection of coronal T1-weighted MRI scans at the level of the temporal lobes indicated that of the 15 SD patients, 11 had predominantly left temporal lobe atrophy, three had predominantly right atrophy and one had symmetrical temporal lobe atrophy.

### *Neuropsychological assessment*

*Novel tests of navigation.* Novel tests of navigation were developed in-house using first-person three-dimensional virtual town software (which has been adapted from a computer game) [15,16]. These tests were administered using a Dell Latitude D820 laptop with an Intel Core Duo processor (2.6 GHz), 1 GB RAM and 15.4" screen, and navigation was performed using an Attack$^{\mathrm{TM}}$ 3 Logitech joystick.

*Virtual Route-learning test* (*VRLT*). At first, the subjects were introduced to the town environment by asking them to navigate, using the joystick, along a predefined practice route by following a set of arrows on the ground that pointed the way. At the outset, the main landmark, an obvious black and yellow cinema billboard was pointed out, as well as the fact that the central junction, where the cinema is located, would be the starting point for all learning trials (see Supplemental Fig. 1; available online: http://www.j-alz.com/issues/21/vol21-4.html#supplementarydata03). It

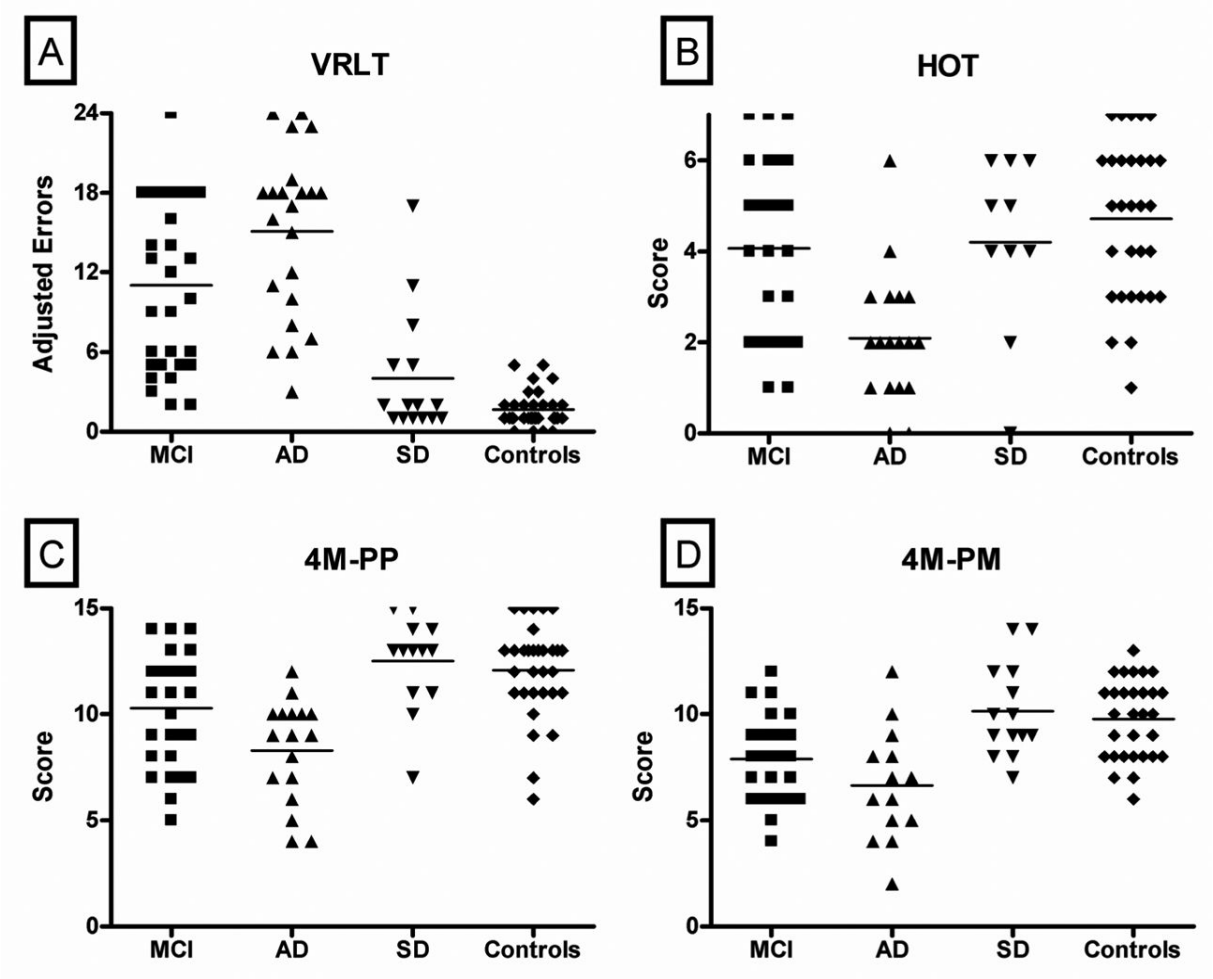


Fig. 1. TM task performance by group. The VRLT is scored in errors, so a high score indicates a poor performance, while the others score correct answers.

should be noted that this familiarization phase took place in the test environment (the same virtual town) but that all participants (patients and controls) received exactly the same amount of exposure by following the arrow-marked practice route.

After familiarization with joystick use, four routes of increasing complexity were sequentially shown to the subject: the subject navigated by following the administrator's verbal directions ("go forward", "turn left", etc.) as well as visual pointers. The administrator gave as much help as necessary to the subjects in order for them to complete the routes under his instruction, except that, apart from pointing out the cinema, names of potential landmarks that might provide a verbal advantage to the subject (e.g., bar, arcade, underground station, karaoke, etc.) were avoided. When names had to be used, they were of non-unique items, e.g., door. At the end of the route, the examiner took control of the joystick and navigated back to the starting point, along pre-defined routes. The subject was then asked to perform the same route from memory. If a subject made a mistake during recollection of the route, the trial was terminated. The administrator navigated back to the beginning of the route, and, with the subject navigating, showed the route again, before asking the subject to re-attempt it. The first route was very simple, requiring a single left turn; subsequent routes were of increasing complexity: routes two, three and four involved six, seven and nine turns respectively. The latter routes were designed to exceed the spatial span of elderly subjects [51], thus requiring supraspan learning that would be more sensitive to impairments in AD patients. See Appendix A for the route plans.

The number of trials (maximum of six) that were re-

quired before successful completion of a route (errors to criterion) was recorded. If a subject failed to learn a given route (six erroneous trials), the test was terminated and no further routes were attempted. The subject's score was equal to the total number of errors incurred over all four routes. As the test may have been terminated before all routes were attempted, an adjusted score was calculated, by assuming that if the subject failed a given route, he or she would fail all subsequent routes as well (as they are more complex), and therefore incur six errors for each unattempted route. For example, a subject who performed the first route flawlessly (no errors), but then failed the second route (six errors), would end the test and the total adjusted score would be 18 (0+6+6+6).

*Heading-orientation test* (*HOT*). After the VRLT, the subject was introduced to the HOT. The cinema was again emphasized as the important landmark. Using the same starting point as before, where the cinema is in view (Supplemental Fig. 1), the subject was instructed to navigate (as before, with the subject using the joystick and the administrator giving instructions) to seven predetermined locations in the town and face a specific direction. At each of these locations, the subject was then asked to indicate the direction of the landmark (the cinema), with a forced choice of four cardinal egocentric points (ahead, behind, to the left, or to the right). Note that the subject was unable to see the cinema from the new location. Before beginning the task, the subject was asked to demonstrate understanding by indicating the egocentric direction of the cinema billboard after a single 90° right turn from the starting point. After each exemplar, the subject was returned to the starting point by the examiner and the subject navigated to the next location under the administrator's guidance. There were seven exemplars in this task, and the subjects scored one point per correct answer.

*The Four Mountains Test* [52]. This is a paper-based test has been described in detail before [43,53] and will only be summarized here. The spatial perception and short-term memory subtests were administered, which both comprise 15 four-alternative forced-choice test items, and performance is measured as the total number of correct items. Both subtests were preceded by three practice examples where feedback was given.

The Four Mountains-Place Perception (4M-PP) subtest employs a concurrent match-to-sample test format (Supplementary Fig. 2). The sample image shows a computer-generated landscape containing four mountains. Below the sample image are 4 landscapes (the target and 3 foils). The target shows the same topographical layout of the 4 mountains as in the sample image but seen from a different viewpoint (viewpoint shift was variable and in the range 15–90 degrees). The foils show a different topographical layout of the same mountains or different mountains altogether. Both the target and the foils are rendered under different lighting conditions and with different colored vegetation so that the task can be solved only on the basis of the topography of the landscapes (supplementary Fig. 2). For each test item, if no response was made within 30 s, the participant was asked to guess.

The Four Mountains-Place Memory (4M-PM) subtest, was always administered after the 4M-PP subtest. The procedure for the 4M-PM subtest, including how the materials were generated, was essentially the same as for the 4M-PP task except that it employed a 3-s delayed match-to-sample format. Thus, for each test item, the sample image was shown in isolation for 12 s. After a 3-s delay, the subject was shown the target and 3 foil images. Again, for each test item, if no response was made within 30 s, the participant was required to guess.

*Standard neuropsychological assessment*. A standard neuropsychological assessment was performed for each subject, as per a previously published protocol [48]. This included: the MMSE [53]; ACE-R [47]; the National Adult Reading Test (NART) [54]; the Rey Auditory Verbal Learning Test (RAVLT) [55]; the Paired-Associates Learning test (PAL) [56]; the RCF copy and recall [55,57]; three elements of the Visual Object and Space Perception battery [58] (Position Discrimination, Number Location and Cube Counting) (VOSP-PD, -NL and -CC); the Position of Gap test from the Birmingham Object Recognition Battery [59] (BORB-PG); the Trail Making tests A and B [60]; and the Graded Naming Test (GNT) [61]. The Hospital Anxiety and Depression Scale (HADS) [62] and the Geriatric Depression Scale (GDS) [63] were used to assess affective symptoms. Note that wherever mention of the RAVLT is made, this refers to the 30 minute delayed recall score of list A (i.e., RAVLT A30).

A caregiver-based questionnaire was administered to probe topographical disorientation symptoms in the patient groups. This was modified from existing scales and questionnaires [29,64], see Appendix B. Caregivers of patients who were not independently mobile were not asked to fill this in, as these patients would not be able to demonstrate their TM abilities. The questionnaire included 19 questions probing for TM symptoms, graded 1 to 5 for frequency or severity and a final question asking the caregiver to assess the duration of way-finding difficulties.

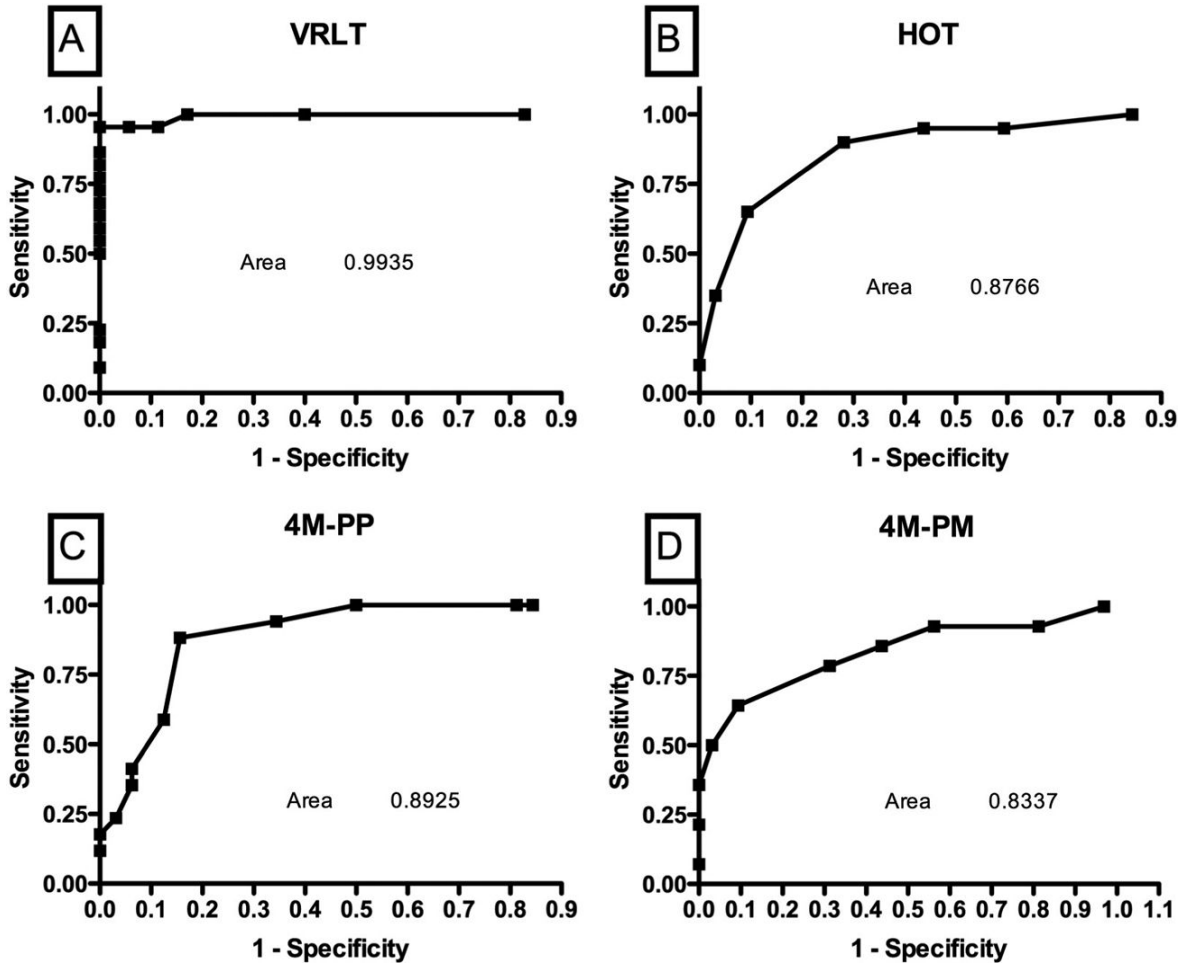


Fig. 2. TM ROC curves in AD versus controls.

*Statistical analyses*

Statistical analyses were performed using the statistical software package GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA) and SPSS, version 15.0.

*Univariate analyses.* Univariate analyses by group (MCI, AD, SD, and controls) were performed using parametric methods (one-way ANOVA, with *post hoc* Bonferroni-corrected pairwise comparisons) where all data were normally distributed. If any group violated normality assumptions, by failing to pass a normality test ($\alpha = 0.05$), then a Kruskal-Wallis test was performed, and *post hoc* pair wise comparisons were performed using Dunn's multiple comparisons correction. If a significant group effect was not found, then no *post hoc* tests were performed.

*ROC analyses.* The diagnostic accuracy of TM and conventional tests was assessed using ROC curves, performed between AD patients and controls and between SD and AD patients.

*Correlations.* In order to explore the possible cognitive underpinning of TM performance in AD and SD, correlations were undertaken between TM scores and cognitive measures of verbal and non-verbal memory, visuospatial ability and attention/executive function, using Pearson product-moment correlation coefficients (or Spearman's $\rho$, if the data were not normally distributed). For these analyses, the mdMCI group ($n = 15$) and AD group ($n = 22$) were combined to form a single group of likely AD patients ($n = 37$) so as to increase the spread of scores thereby minimizing floor effects and rendering the data more distributed for correlation analyses. The rationale for including mdMCI, but not the other MCI groups, was based on prior work showing that (i) mdMCI patients are highly likely to have prodromal AD; (ii) pure aMCI are a more het-

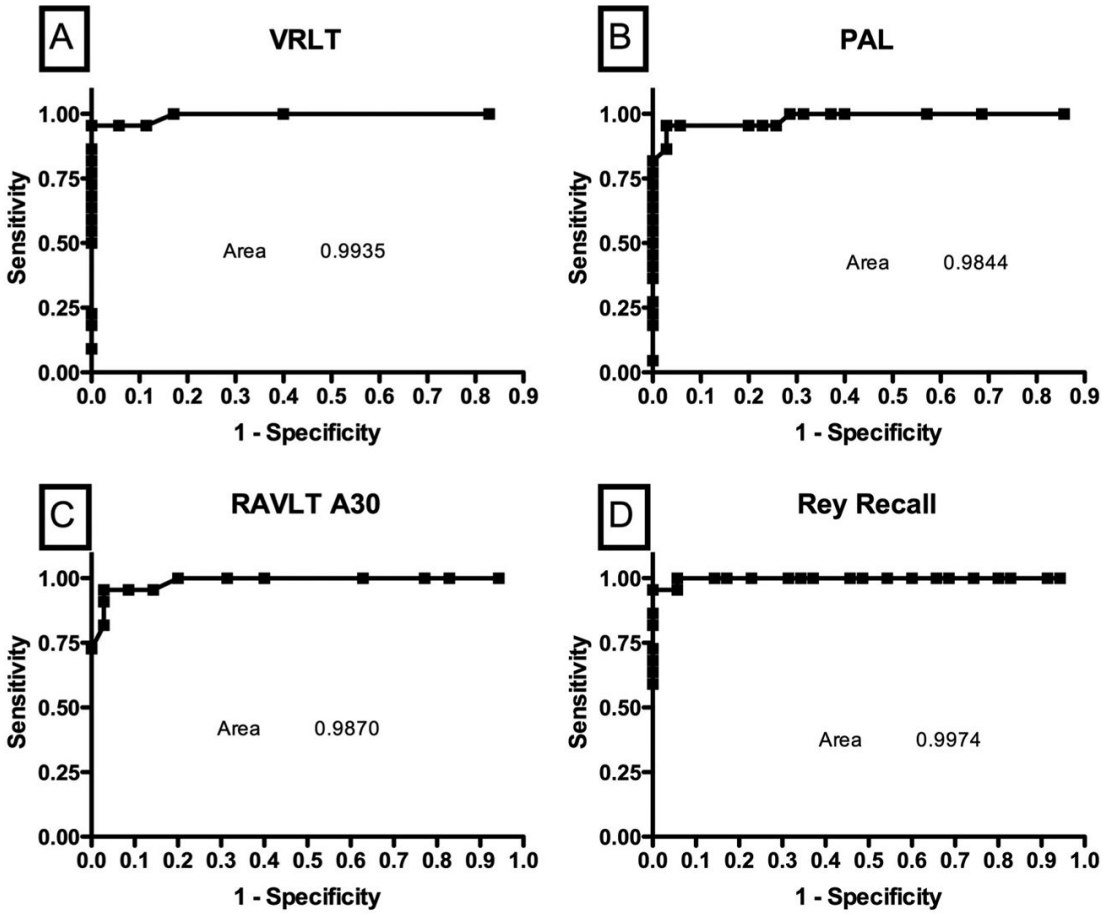


Fig. 3. ROC curves of the best conventional tests compared to the VRLT in AD versus controls.

Table 2
Topographical memory: Subject numbers by test

| | MCI | AD | SD | Controls | Total |
|---|---|---|---|---|---|
| **Total n** | 32 | 22 | 15 | 35 | 104 |
| **VRLT** | 30 | 22 | 15 | 33 | 100 |
| **HOT** | 28 | 20 | 10 | 32 | 89 |
| **4M-PP** | 28 | 17 | 14 | 32 | 91 |
| **4M-PM** | 28 | 14 | 14 | 32 | 88 |

erogeneous group (only a minority decline to AD with medium term follow-up whereas many improve); while (iii) naMCI are unlikely to have prodromal AD [49,65, 66].

## RESULTS

### *Tolerability of TM tasks*

The number of subjects who were able to complete the novel tasks is shown in Table 2. In the computer-generated navigational tasks, two MCI and two control subjects (3.8%) could not complete the VRLT due to nausea from perceived motion (optic flow); an additional two MCI and three SD patients experienced nausea in the HOT, causing termination of the test. All subjects (including the SD patients) understood the VRLT and no dexterity or joystick manipulation problems were found. The HOT was more difficult to explain, and two SD patients could not complete it for this reason; the most impaired SD patient was also unable to understand the Four Mountains task.

### *Univariate analyses*

The univariate results for each test are presented in Table 3. Figure 1 illustrates the TM results. Only the VOSP-PD test failed to detect any differences between groups. In all other tests, the AD group performed poorly. The SD group, on the other hand, showed no difference from controls in Trails A and B and all

Table 3
Univariate analyses

| | MCI | AD | SD | C | F (df) | p | Pairwise comparisons† | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | MCI vs. C | AD vs. C | SD vs. C | AD vs. SD |
| **Global cognition** | | | | | | | | | | |
| **MMSE** | 26.5 (1.5) | 22.7 (3.0) | 22.3 (5.6) | 29 (28–30)# | H = 69.2 (4) | **** | *** | *** | *** | NS |
| **ACE–R** | 81.4 (6.2) | 68.2 (10.4) | 53.9 (16.4) | 94.0 (3.5) | 87.5 (3,100) | **** | *** | *** | *** | *** |
| **NART IQ** | 114.7 (10.5) | 102.9 (11.8) | 78.8 (12.3) | 113.1 (10.8) | 35.4 (3,97) | **** | NS | ** | *** | *** |
| **Naming** | | | | | | | | | | |
| **GNT** | 21.0 (5.0) | 16.6 (6.3) | 1.1 (1.8) | 24.7 (2.6) | 110.2 (3,100) | **** | ** | *** | *** | *** |
| **Executive function** | | | | | | | | | | |
| **Trails A** | 47.6 (16.9) | 79.5 (54.2) | 50.7 (16.0) | 37.6 (11.0) | 10.4 (3,100) | **** | NS | *** | NS | * |
| **Trails B** | 156.6 (81.1) | 300 (129–300)# | 131.2 (69.2) | 93.9 (45.6) | H = 41.2 (4) | **** | *** | *** | NS | ** |
| **Visuospatial function** | | | | | | | | | | |
| **VOSP-PD** | 20 (19–20)# | 20 (18.5–20)# | 20 (20–20)# | 20 (20–20)# | H = 6.8 (4) | NS | N/A | N/A | N/A | N/A |
| **VOSP-NL** | 10 (9–10)# | 6.5 (3.3) | 10 (9–10)# | 10 (9–10)# | H = 25.9 (4) | **** | NS | *** | NS | *** |
| **VOSP-CA** | 10 (9–10)# | 8.1 (2.4) | 10 (9–10)# | 10 (10–10)# | H = 11.7 (4) | ** | NS | ** | NS | NS |
| **BORB-PG** | 35.9 (2.4) | 33.5 (3.1) | 37.7 (1.5) | 36.2 (2.1) | 10.1 (3,100) | **** | NS | *** | NS | *** |
| **RCF Copy** | 31.7 (5.0) | 23.7 (10.4) | 33.6 (3.0) | 35 (33–36)# | H = 27.2 (4) | **** | NS | *** | NS | *** |
| **Memory** | | | | | | | | | | |
| **RCF Recall** | 5.4 (4.4) | 0 (0–3.5)# | 13.2 (6.6) | 17.3 (5.8) | H = 69.4 (4) | **** | *** | *** | NS | *** |
| **PAL** | 28.3 (21.2) | 44.5 (21.0) | 14.9 (15.7) | 4 (2–11)# | H = 50.5 (4) | **** | *** | *** | NS | ** |
| **RAVLT** | 0 (0–2)# | 0 (0–1)# | 1.9 (2.7) | 8.6 (2.8) | H = 65.8 (4) | **** | *** | *** | *** | NS |
| **Topographical Memory** | | | | | | | | | | |
| **VRLT** | 11.0 (6.3) | 15.1 (6.3) | 4 (4.7) | 1 (1–2)# | H = 64.4 (4) | **** | *** | *** | NS | *** |
| **HOT** | 4.1 (1.9) | 2.1 (1.4) | 4.2 (1.9) | 4.7 (1.7) | 9.7 (3,86) | **** | NS | *** | NS | ** |
| **4M-PP** | 10.3 (2.7) | 8.3 (2.4) | 12.5 (2.1) | 12.1 (2.2) | 12.0 (3,87) | **** | ** | *** | NS | *** |
| **4M-PM** | 7.9 (1.9) | 6.6 (2.6) | 10.1 (2.2) | 9.8 (1.8) | 11.4 (3,84) | **** | ** | *** | NS | *** |
| **Mood** | | | | | | | | | | |
| **GDS** | 1 (1–3.5)# | 4.0 (2.8) | 5.7 (2.8) | 0 (0–2)# | H = 35.9 (4) | **** | NS | *** | *** | NS |
| **HADS-D** | 2.4 (2.0) | 2.9 (1.5) | 4.4 (2.8) | 1 (1–2)# | H = 14.4 (4) | ** | NS | * | ** | NS |
| **HADS-A** | 4.6 (3.1) | 5.6 (2.6) | 5.7 (3.6) | 4.4 (2.9) | 1.2 (3,98) | NS | N/A | N/A | N/A | N/A |

Key: C = Controls, F = ANOVA statistic, df = degrees of freedom, H = Kruskal-Wallis statistic, N/A = not applicable. MMSE = Mini Mental State. Examination, ACE-R = Addenbrooke's Cognitive Examination – Revised, NART = National Adult Reading Test, GNT = Graded Naming Test, VOSP-PD = Visual Object and Space Perception – Position Discrimination, -NL = Number Location, -CA = Cube Analysis, BORB-PG = Birmingham Object Recognition Battery – Position of Gap, RCF = Rey Complex Figure, PAL = Paired Associates Learning, RAVLT = Rey Auditory Verbal Learning Test, VRT = Virtual Route Learning Test, HOT = Heading Orientation Test, 4M-PP = Four Mountains – Place. Perception, -PM = Place Memory, GDS = Geriatric Depression Scale, HADS-A = Hospital Anxiety and Depression Scale – Anxiety, -D = Depression. Values are means (standard deviation), except where # = non-Gaussian distribution, and therefore they are medians (25th–75th centile).
p values: **** $< 0.0001$, *** $< 0.001$, ** $< 0.01$, * $< 0.05$, NS = Non-significant, † = multiple comparisons correction.

visuospatial tasks (VOSP-NL, -CC, BORB-PG, PAL, RCF Copy and Recall). Most importantly, there was no difference between SD and controls in any of the TM tasks. The SD patients performed poorly, as expected, in the GNT, NART (because of surface dyslexia), and RAVLT.

The MCI group was impaired in verbal (RAVLT) and non-verbal memory (RCF Recall, PAL), including TM tests (VRLT, 4M-PP, and 4M-PM), but not in any basic visuospatial tests. As a group, they were also impaired on the GNT and Trails B. Examining the MCI subgroup performance on the TM tasks, VRLT performance was impaired in the mdMCI and aMCI ($p < 0.0001$ for both compared to controls) but not in the naMCI; HOT performance was not impaired in any MCI subset; 4M-PP and 4M-PM was impaired only in the mdMCI subgroup ($p < 0.01$ and $p < 0.001$ respectively) (see Table 4).

The mood questionnaires showed that the AD and SD patients were mildly depressed compared to controls, but there were no differences between AD and SD. There were no differences between groups in terms of anxiety endorsements.

### *The diagnostic accuracy of TM*

The diagnostic value of the TM tests on an individual patient basis was assessed using ROC curves. The TM tasks were highly accurate in AD versus controls (area under the curve $> 0.8$ for all tests). However, the VRLT task had the best potential as a diagnostic test (area under the curve $= 0.99$) (Fig. 2). The ROC curves of the conventional memory tests are illustrated for comparison in Fig. 3.

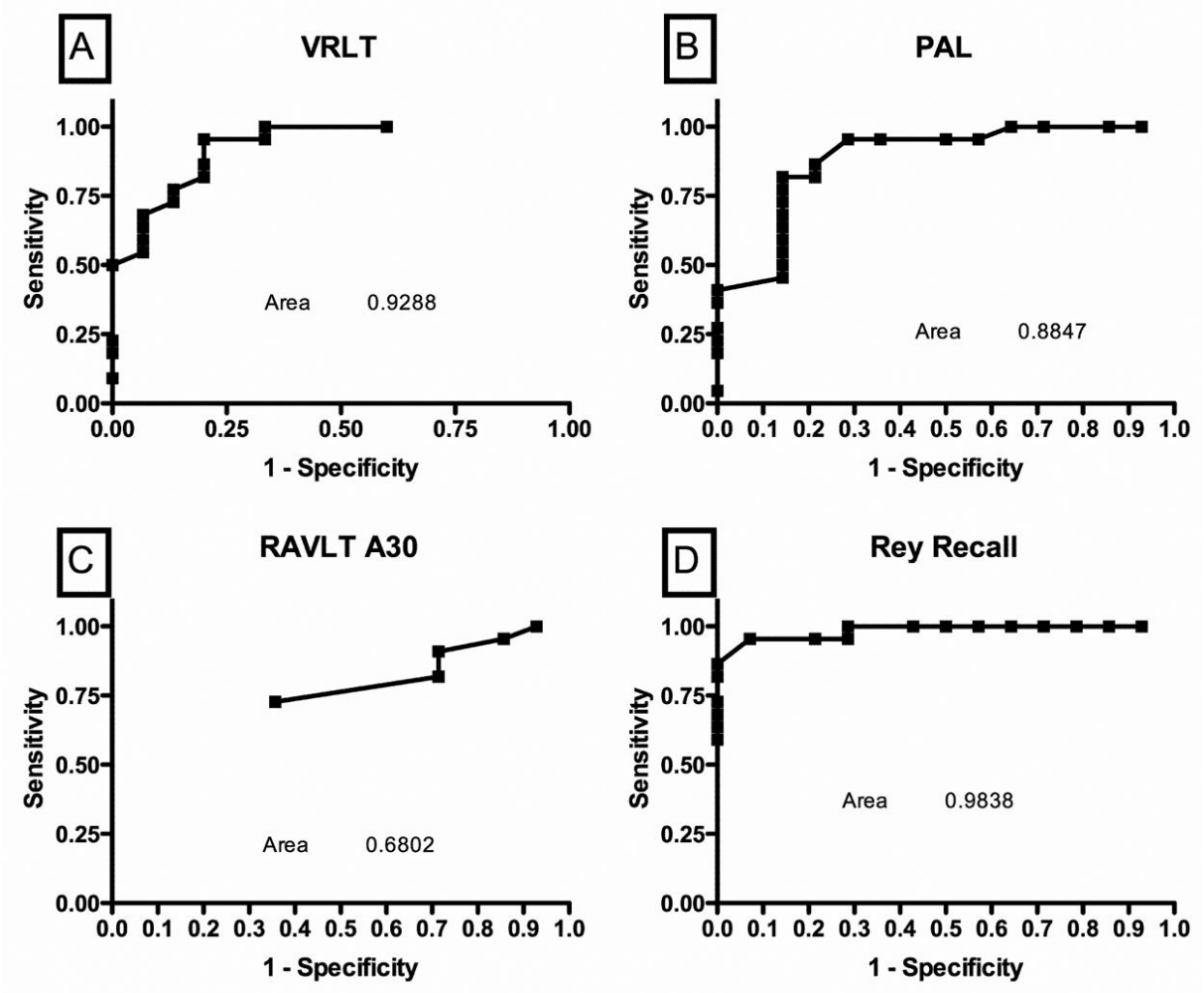


Fig. 4. ROC curves in AD versus SD.

Tests of verbal memory (e.g., RAVLT) are expected to be sensitive for AD, but not specific, as patients with SD are also impaired in this ability, while TM was predicted to discriminate between AD and SD; therefore, ROC curves of AD versus SD were performed to determine which test impairments were specific to AD. As predicted, and illustrated in Fig. 4(c), verbal memory did not discriminate AD from SD, while non-verbal memory measures were much more successful. At a cut-off $\geqslant 6$ errors, the VRLT has a sensitivity of 95% and a specificity of 80% (area under the curve = 93%) for discriminating AD from SD (Fig. 4). The HOT, 4M-PP and 4M-PM areas under the curve were 82%, 92%, and 85% respectively, further demonstrating that the domain of TM (and not only the VRLT) is a good discriminator between AD and SD.

The double dissociation between semantic and topographical memory in AD and SD could be captured by summing the GNT correct score and VRLT error score for each AD and SD patient. This composite score completely separated the two groups (SD mean = 5.1, Range = 1–17; AD mean = 31.6, range = 19–42; unpaired t-test $p < 0.0001$).

*VRLT as a function of global cognitive performance and details of two outliers*

Examination of individual subjects' TM scores (Fig. 1) indicated that the VRLT was the most discriminatory task. As the cognitive profile of degenerative dementias is also a function of stage and not just pathological type, and the SD patients in this study spanned a far wider range of dementia severity, the results of

Table 4
Univariate analyses of TM tasks by MCI subgroup

| | aMCI | mdMCI | naMCI | C | F (df) | p | Pairwise comparisons† | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | aMCI vs. Controls | mdMCI vs. Controls | naMCI vs. Controls | aMCI vs. mdMCI |
| **VRLT** | 14.5 (5.8–18)# | 10.4 (6.3) | 3.5 (2–5)# | 1 (1–2)# | H(4) = 42.6 | **** | **** | **** | NS | NS |
| **HOT** | 4.5 (2.3–6)# | 3.5 (2–5.5)# | 4.5 (4–5)# | 5 (3–6)# | H(4) = 2.1 | NS | NS | NS | NS | NS |
| **4M-PP** | 11.2 (2.9) | 9.3 (2.2) | 10 (7–13)# | 12.5 (11–13)# | H(4) = 10.8 | * | NS | ** | NS | NS |
| **4M-PM** | 8.8 (1.8) | 6.8 (1.8) | 9 (7–9)# | 10 (8–11)# | H(4) = 17.0 | *** | NS | *** | NS | NS |

**Key**: C = Controls, F = ANOVA statistic, df = degrees of freedom, H = Kruskal-Wallis statistic, N/A = not applicable.
Values are means (standard deviation), except where # = non-Gaussian distribution, and therefore they are medians ($25^{th}$–$75^{th}$ centile).
p values: **** < 0.0001, *** < 0.001, ** < 0.01, * < 0.05, NS = Non-significant, † = with multiple comparisons correction.

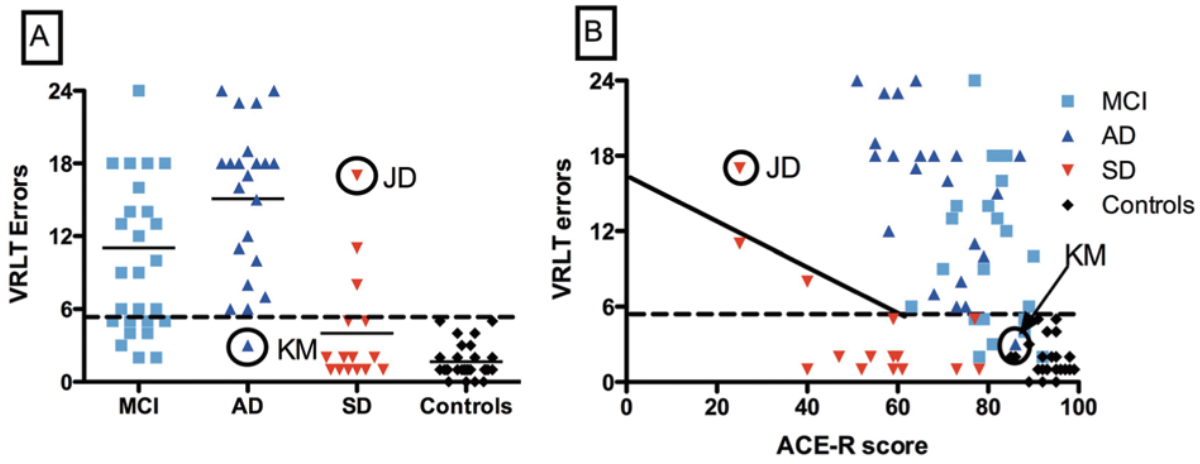


Fig. 5. In both graphs, the control range lies below the horizontal dashed line. JD is the SD outlier, while KM is the AD outlier. A) VRLT errors by group. Notice that KM lies in the normal range and JD is as impaired as AD subjects. B) VRLT errors by ACE-R score. The oblique solid line intersecting the dashed line delineates the SD patients: AD patients performing at the same level as SD patients have much higher ACE-R scores.

the VRLT were plotted against global cognitive function as measured by the ACE-R (Fig. 5b). Using a VRLT cut-off score of $>$ 5 errors (5 errors was the worst control performance) to define abnormality, one patient diagnosed with AD scored in the control range with only three errors (KM) (Fig. 5). Three SD cases scored outside this control range (Fig. 5a), though these patients were at a more advanced stage of global impairment as defined by the ACE-R than any of the AD group (Fig. 5b). Nevertheless, one of these patients (JD) scored 17 errors which makes him an outlier, according to Chauvenet's criterion, from the remainder of the SD group ($z = -2.8$ compared to whole SD group); this score was also worse than the mean for the AD group.

These two outliers were therefore investigated further to assess whether they represented a failure of the VRLT to discriminate groups or whether they had been clinically misdiagnosed – this included review of their structural imaging; $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) in JD; and amyloid PET imaging with $^{11}$C-Pittsburg compound-B (PIB). Patient JD, a 71 year-old, right-handed male, had presented with a semantic syndrome seven years prior to testing and was diagnosed with SD. His MRI scan at the time of diagnosis showed bilateral, asymmetric, left-predominant temporal lobe atrophy, but this was qualitatively different from SD cases due to FTD pathology [67], in that there was relative preservation of the inferior temporal cortex (Fig. 6a). The FDG-PET showed severe hypometabolism of the left temporal lobe (consistent with his semantic syndrome) (Fig. 6b), but also showed hypometabolism of posterior parietal association cortex more consistent with AD pathology (Fig. 6c). Finally, PIB-PET imaging revealed cortical amyloid plaque tracer binding indicative of AD pathology (Fig. 6d). In summary, imaging data offered strong evidence that this patient was either a false-positive diagnosis of SD (semantic syndrome due to AD pathology) or has dual pathology.

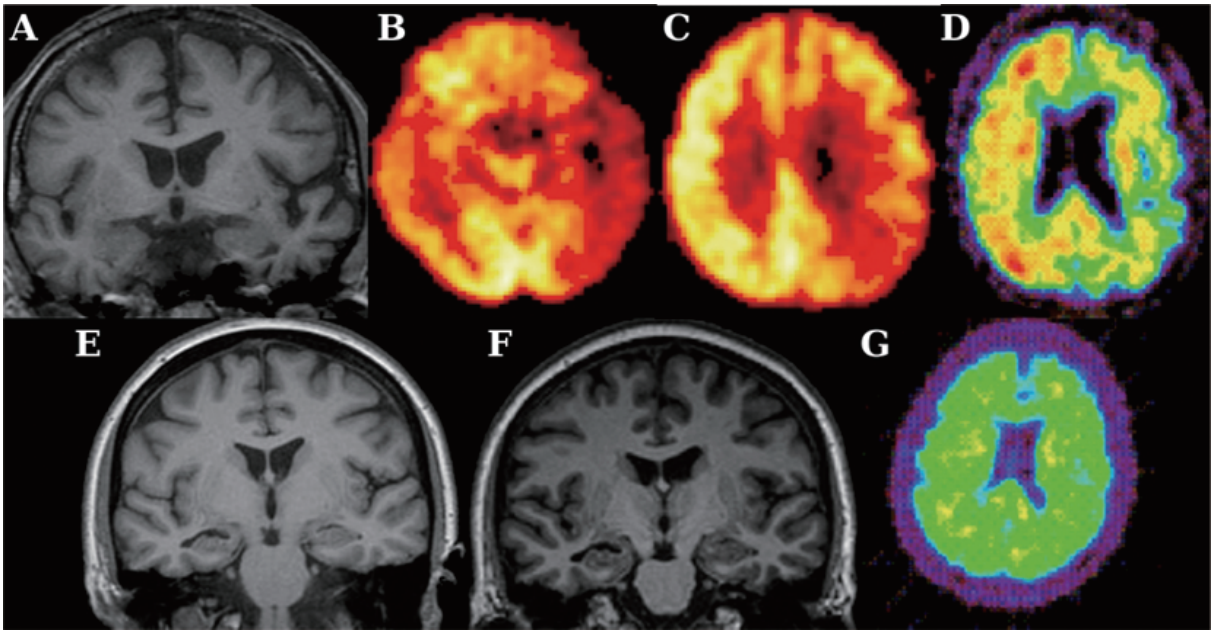


Fig. 6. A-D) Patient JD. A) Coronal T1 MRI showing diffuse left temporal lobe atrophy 5 years ago; B) FDG-PET showing left temporal and C) parietal hypometabolism; D) PIB-PET showing cortical amyloid deposition. E-G) Patient KM. E) Coronal T1 MRI showing possible right hippocampal atrophy 4 years before testing. F) MRI at time of current testing, showing lack of change over 4 years. G) PIB-PET (at the same intensity thresholds as panel D) showing absence of cortical amyloid deposition.

The other anomalous patient, KM, was a 58 year-old, right-handed female, who presented four years previously with memory complaints. She scored 28/30 and 78/100 on the MMSE and ACE-R respectively, and showed poor verbal and non-verbal memory recall and recognition, including famous faces; her RCF copy was also poor. Her initial MRI suggested possible mild right hippocampal atrophy (Fig. 6e). She met criteria for MCI. Within 18 months, her husband reported further deterioration in her memory. Her MMSE dropped to 21/30 and her ACE-R to 70/100. She was diagnosed with probable AD and started on donepezil. Within three months of starting donepezil, a marked improvement was seen: MMSE and ACE-R improved to 26/30 and 86/100 respectively and then to 29/30 and 87/100 six months later. Over the last 18 months, bi-annual neuropsychological and MRI assessment revealed no change (Fig. 6f). She did not undergo FDG-PET scanning due to diabetes mellitus. A PIB study was negative for cortical amyloid binding (Fig. 6g); in other words, not consistent with AD pathology. In light of the normal imaging and subsequent improvement and then stabilization of cognitive performance, the early apparent decline was likely to have represented a pseudodementia.

*Relationship of TM to general neuropsychological performance and demographic factors*

The two outliers described above were excluded from the correlation analyses. As described above, the AD group included AD and mdMCI patients. In this expanded AD group, VRLT and HOT tests correlated with non-verbal memory (PAL, RCF Recall), visuospatial ability (RCF Copy, BORB-PG, and VOSP-NL) and executive function (Trails B). As expected, the 4M-PP (non-memory condition) did not correlate with verbal or non-verbal memory tests, but was correlated with visuospatial and executive tests; the 4M-PM test did not correlate with any conventional task in AD (see Table 5 for details).

In SD, there was a strong correlation of the VRLT and 4M-PP test with Trails B, most notably the VRLT ($R = 0.87$). This remained significant even when the most impaired subject was removed from the analysis ($p < 0.05$, $R = 0.68$). Trails B did not correlate with any other tests in SD. Although the VRLT correlated with Trails B in the AD group as well, the correlation was weaker than in SD, and not exclusive, as the VRLT correlated with non-verbal skills and memory as well.

The effects of gender, age, education, and mood on TM performance were assessed using normal controls (see the e-supplement for details).

Table 5
TM test correlations in disease

| | RAVLT | PAL | RCF Copy | RCF Recall | Trails B | VOSP-NL | BORB-PG |
|---|---|---|---|---|---|---|---|
| mdMCI/AD | | | | | | | |
| VRLT | −0.18# | 0.58** | −0.45** | −0.54#** | 0.62#** | −0.48#** | −0.44#** |
| HOT | 0.12# | −0.58#** | 0.15# | 0.56#** | −0.53#** | 0.43#** | 0.37#* |
| 4M-PP | 0.14# | −0.31 | 0.51** | 0.08# | −0.39#* | 0.40#* | 0.51#** |
| 4M-PM | 0.22# | −0.27 | 0.18 | −.04# | −0.14# | 0.26# | 0.09# |
| SD | | | | | | | |
| VRLT | −0.31 | 0.13 | −0.46* | −0.44 | 0.87** | 0.11# | −0.40 |
| HOT | −0.72* | 0.52 | 0.75* | 0.22 | −0.30 | −0.14# | 0.14 |
| 4M-PP | 0.43 | −0.16 | 0.50* | 0.35 | −0.61* | 0.24# | 0.58* |
| 4M-PM | 0.39 | 0.31 | −0.24 | −0.33 | −0.47 | 0.62#* | 0.57* |

KEY: All values are Pearson R coefficients, except where # indicates non-Gaussian distribution and Spearman $\rho$ is reported instead. * p (1-tailed) $< 0.05$, ** p (1-tailed) $< 0.001$.

Table 6
TM tests correlate with carers' reports

| | R | $R^2$ | p |
|---|---|---|---|
| Symptoms vs. VRLT | 0.53 | 0.28 | $< 0.0001$ |
| Symptoms vs. HOT | −0.34# | | $< 0.05$ |
| Symptoms vs. 4M-PM | −0.32 | 0.10 | $< 0.05$ |

KEY: # = non-Gaussian distribution, Spearman $\rho$ performed.

### *Ecological validity*

The total sum of way-finding symptoms scored by severity and frequency, as reported in the caregiver-based questionnaire, was correlated with the TM tasks in all three patient groups (MCI, AD, and SD). All TM tests significantly correlated with caregivers' reports of symptoms, with the VRLT having the highest correlation (Table 6).

## DISCUSSION

The present study confirmed the main two hypotheses: AD patients were impaired on TM tasks, while the SD patients were relatively unimpaired. All TM tasks (VRLT, HOT, and Four Mountains) achieved diagnostic accuracies of over 80% in distinguishing AD from controls, with the VRLT providing the best separation (area under the curve = 99%). The conventional verbal and non-verbal memory tests employed (PAL, delayed recall of RAVLT, and RCF) also achieved very high accuracy levels in discriminating AD versus controls (area under the curve: 98.4, 98.7, and 99.7% respectively). The specificity of TM impairment was demonstrated in distinguishing AD from SD: the VRLT achieved high accuracy again (area under curve = 93%), together with other topographical tests (HOT, 4M-PP, and 4M-PM, area under curve 82, 92, and 85% respectively), and non-verbal memory assessments (PAL and delayed RCF recall, area under curve 89 and 98% respectively), but verbal memory offered poor specificity (RAVLT, area under curve = 68.0%) consistent with previous findings [40]. Although delayed RCF recall was also very good at discriminating AD from SD, the VRLT had certain advantages: absence of a delayed recall condition made it faster to administer and obviated the need for 'filler' tests between copy and delayed recall phases. Furthermore, administration of delayed RCF recall can be problematic in patients with severe semantic impairment because, after 30 min, some cannot understand that they need to draw the figure again. In this cohort, the most impaired SD patient (ACE-R = 25) could not perform the delayed task for this reason, yet was able to complete all four VRLT routes (albeit with 11 errors). Finally, while the VRLT identified KM as performing normally, this subject was impaired on delayed RCF recall.

The VRLT was designed to be a graded clinical test that simulated real-world navigation. After exclusion of the two outliers, the VRLT achieved 100% accuracy in detecting AD from controls and 86% sensitivity and 100% specificity in distinguishing AD from SD. It was the most ecologically valid of the TM tests studied, as measured by correlations with the caregiver-based questionnaire of TM symptoms. The virtual environment tests (VRLT and HOT) correlated with non-verbal memory and executive function and to a lesser extent with visuospatial ability (Table 4). Features of the VRLT such as its graded design, emphasis on supra-span learning and ecological validity with real-world navigational ability may be the reasons for its diagnostic accuracy. The task was easy to understand and execute using the joystick, despite an absence of prior computer game experience in any subject; however, a small percentage of subjects experienced motion sickness, a side effect noted previously in virtual environments [16], presumably caused by the mismatch of

expected (virtual motion caused by optic flow) versus actual motion (subjects are static).

The only other study of virtual navigation in MCI ($n = 12$) failed to show differences between MCI and age-matched controls; the authors suggested the heterogeneity of MCI as a potential explanation [36]. In contrast, using a larger MCI sample, we found group impairment on the VRLT and Four Mountains tests, though some individual patients were within the normal range. Longitudinal evidence of decline is necessary to confirm that MCI status is due to AD, however, at the time of writing, there has been insufficient follow-up time and therefore predictive diagnostic accuracies in this MCI group were not assessed. Given the high degree of separation of AD from controls by the VRLT, it is plausible that the MCI patients who are impaired on this test will progress to clinical AD. Consistent with this interpretation, it was notable that impairment in the mdMCI sub-group – who from prior knowledge are highly likely to have incipient AD – was most significant and involved both VRLT and 4M-PM, whereas in pure aMCI, impairment only involved the VRLT and in naMCI (albeit only 3 cases) neither test was significantly impaired. Longitudinal assessment is underway to establish the positive and negative predictive values of the VRLT in MCI.

The SD group performance on the VRLT was similar to controls, although three individuals showed impairment using the cut-off of $\geqslant 5$ errors. One of these was an outlier from the SD group and, in fact, incurred a slightly higher error score than the AD mean. Further investigations were, however, consistent with Alzheimer pathology, most notably a positive PIB-PET scan indicating amyloid deposition. This illustrates the potential use of this test in difficult cases though this, of course, can only be definitively verified in a prospective study in which a large group have pathology confirmation. The remaining two SD patients with $> 5$ errors were at a far more advanced stage of global decline – in a plot of the VRLT error score against global function as measured by the ACE-R (Fig. 5B), these SD cases did not overlap with the AD cluster. As predicted, summing GNT score and VRLT error score also achieved 100% separation of SD from AD emphasizing the clinical utility of contrasting naming with navigation in differential diagnosis of these two disorders; this finding highlights a broader principle that neuropsychological *differential* diagnosis in dementia depends on the pattern of strengths and weaknesses rather than just documenting impairments. After exclusion of the misdiagnosed patient (JD), there was high correlation of the VRLT with Trails B time in SD ($R^2 = 0.75$), while Trails B in turn did not correlate with any other cognitive test, suggesting that this impairment was not due to global dementia or, more specifically, to memory dysfunction but, rather, related to attention/executive dysfunction, as captured by the Trails B test. An executive contribution to navigation has been noted in healthy elderly [4,68] and a case report of AD [69], but has never been examined in an SD cohort before. The correlation indicates that when errors in virtual navigation start to emerge in SD, they have a qualitatively different neural explanation from the true learning impairment seen in AD. This correlation in SD (part of the FTD spectrum) was not surprising given that, with advancing disease, additional frontal lobe degeneration would not be unexpected.

The preservation of topographical memory in SD raises the issue of laterality of temporal lobe involvement in TM. Many studies have shown greater right MTL dependence for spatial (object location) memory [11,70,71] and TM [8,16]. Furthermore, 65% of patients with right temporal lobe atrophy studied by Chan et al. [50] were reported to have way-finding symptoms, although it should be noted that TM was not objectively assessed and the clinical phenotype or disease pathology was not taken into account; in fact, one of the two patients who came to necropsy had dementia with Lewy bodies in that series. Therefore, one potential explanation might be that TM is a non-verbal memory ability, subserved by the right hemisphere, and that SD patients with predominantly left-sided pathology would be expected to do well while those with right-sided damage would not; therefore, the fact that the left-side atrophy predominant SD patients were the majority (10 left: 3 right) may have masked impairments in the right-sided cases. Comparison of the ten left-predominant SD (excluding JD) versus three right-predominant patients in our study yielded no significant difference in VRLT errors (unpaired t test, $p = 0.69$). Furthermore, examination of the scores revealed that while the left-sided SD patients ranged from 1–8 errors, the right-sided patients scored 2, 2, and 5 errors; in other words, all three were within the control range ($< 6$ errors). These findings are consistent with another study using the Four Mountains test that showed that right predominant SD ($n = 4$) did not differ from left predominant SD ($n = 3$) patients [43]. An alternative explanation for the preservation of TM in SD is the proposal of differences along the antero-posterior axis of the MTL: the posterior, rather than anterior hippocampus is thought to be important in allocentric nav-

igation [72,73] and, whereas AD affects the MTL uniformly, SD has a gradient of atrophy with the anterior MTL being worse affected [74,75]. Nestor et al. [76] also found a gradient of hypometabolism in the long axis of the MTL in SD (worse rostrally), and a uniform gradient in AD, but atrophy was equivalent between AD and SD in all MTL subregions, and neither volume nor metabolic rate in the MTL could explain the poor episodic memory of AD versus SD patients [76]. This finding leads to the third possibility, that the behavioral differences between AD and SD relate to cumulative damage in a distributed network; most notably, in incipient AD, the posterior cingulate is significantly atrophic [25,26,77] and hypometabolic [22,23,78], whereas it is spared in SD [76]. The relationship of TM performance to structural and functional imaging with TM in neurodegenerative disease will be the topic of a future report.

The present results with regard to the Four Mountains test are consistent with a previous, smaller, study that used this test in isolation [43]: MCI and AD patients have impaired topographical short-term memory (4M-PM) compared to controls whereas FTD patients do not. Unlike Bird et al., however, we identified impairments in topographical perception (4M-PP) in AD and (less so) in MCI compared to controls. This probably reflects the significantly greater power in the present study (Bird et al. reported on $n = 7$ AD and $n = 6$ MCI). Group demographics may have also contributed to the discrepancy in the AD groups: ours was more advanced (lower MMSE), possibly suggesting more extensive visuoperceptual deficits. It is difficult to argue this explanation for the discrepancy in MCI groups, however, as they appeared comparably impaired in the two studies, arguing that the key difference was statistical power.

In summary, after exclusion of the two outliers, the VRLT showed perfect accuracy in identifying mild AD patients from controls and, when combined with either naming or global dementia severity, 100% accuracy in separating AD from SD, while at the same time remaining independent of age, gender, anxiety, depression, and education years, giving it great potential as a diagnostic biomarker for AD. As predicted, SD patients performed well, and the poorer performances from this group were only related to worsening attention/executive function providing objective support for the anecdotal observations that these patients do not lose their way. Given its ecological validity, the VRLT has potential for assessing TM in other dementia groups. The MCI group showed a mixed picture, with some subjects being as impaired as established AD patients, while others performed within normal limits – possibly pointing to the known pathological heterogeneity of MCI. Longitudinal follow-up of this MCI cohort may establish the predictive value of the VRLT and other TM tests in MCI.

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## REFERENCES

[1] McCarthy RA, Evans JJ, Hodges JR (1996) Topographic amnesia: spatial memory disorder, perceptual dysfunction, or category specific semantic memory impairment? *J Neurol Neurosurg Psychiatry* **60**, 318-325.

[2] Ghaem O, Mellet E, Crivello F, Tzourio N, Mazoyer B, Berthoz A, Denis M (1997) Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *Neuroreport* **8**, 739-744.

[3] Mellet E, Briscogne S, Tzourio-Mazoyer N, Ghaem O, Petit L, Zago L, Etard O, Berthoz A, Mazoyer B, Denis M (2000) Neural correlates of topographic mental exploration: the impact of route versus survey perspective learning. *Neuroimage* **12**, 588-600.

[4] Moffat SD, Kennedy KM, Rodrigue KM, Raz N (2007) Extrahippocampal contributions to age differences in human spatial navigation. *Cereb Cortex* **17**, 1274-1282.

[5] Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J (1998) Knowing where and getting there: a human navigation network. *Science* **280**, 921-924.

[6] Burgess N, Maguire EA, Spiers HJ, O'Keefe J (2001) A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage* **14**, 439-453.

[7] Wolbers T, Weiller C, Buchel C (2004) Neural foundations of emerging route knowledge in complex spatial environments. *Brain Res Cogn Brain Res* **21**, 401-411.

[8] Maguire EA, Burke T, Phillips J, Staunton H (1996) Topographical disorientation following unilateral temporal lobe lesions in humans. *Neuropsychologia* **34**, 993-1001.

[9] Lee AC, Barense MD, Graham KS (2005) The contribution of the human medial temporal lobe to perception: bridging the gap between animal and human studies. *Q J Exp Psychol B* **58**, 300-325.

[10] Nakamura K, Kawashima R, Sato N, Nakamura A, Sugiura M, Kato T, Hatano K, Ito K, Fukuda H, Schormann T, Zilles K (2000) Functional delineation of the human occipito-temporal areas related to face and scene processing. A PET study. *Brain* **123**(Pt 9), 1903-1912.

[11] Smith ML, Milner B (1981) The role of the right hippocampus in the recall of spatial location. *Neuropsychologia* **19**, 781-793.

[12] Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ (2002) Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behav Brain Res* **132**, 77-84.

[13] Pearce JM, Roberts AD, Good M (1998) Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. *Nature* **396**, 75-77.

[14] Barrash J, Damasio H, Adolphs R, Tranel D (2000) The neuroanatomical correlates of route learning impairment. *Neuropsychologia* **38**, 820-836.

[15] Spiers HJ, Burgess N, Hartley T, Vargha-Khadem F, O'Keefe J (2001a) Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. *Hippocampus* **11**, 715-725.

[16] Spiers HJ, Burgess N, Maguire EA, Baxendale SA, Hartley T, Thompson PJ, O'Keefe J (2001b) Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. *Brain* **124**, 2476-2489.

[17] Ino T, Doi T, Hirose S, Kimura T, Ito J, Fukuyama H (2007) Directional disorientation following left retrosplenial hemorrhage: a case report with fMRI studies. *Cortex* **43**, 248-254.

[18] Maeshima S, Ozaki F, Masuo O, Yamaga H, Okita R, Moriwaki H (2001) Memory impairment and spatial disorientation following a left retrosplenial lesion. *J Clin Neurosci* **8**, 450-451.

[19] Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT (1987) Retrosplenial amnesia. *Brain* **110**(Pt 6), 1631-1646.

[20] Takahashi N, Kawamura M, Shiota J, Kasahata N, Hirayama K (1997) Pure topographic disorientation due to right retrosplenial lesion. *Neurology* **49**, 464-469.

[21] Maguire EA (2001) The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. *Scand J Psychol* **42**, 225-238.

[22] Nestor PJ, Fryer TD, Ikeda M, Hodges JR (2003b) Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur J Neurosci* **18**, 2663-2667.

[23] Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* **42**, 85-94.

[24] Jack CR, Jr., Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, Smith GE, Ivnik RJ, Kokmen E (1997) Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* **49**, 786-794.

[25] Pengas G, Hodges JR, Watson P, Nestor PJ (2010) Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiol Aging* **31**, 25-33.

[26] Choo IH, Lee DY, Oh JS, Lee JS, Lee DS, Song IC, Youn JC, Kim SG, Kim KW, Jhoo JH, Woo JI (2010) Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **31**, 772-779.

[27] deIpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML (2007) Spatial cognition and the human navigation network in AD and MCI. *Neurology* **69**, 986-997.

[28] Burgess N, Trinkler I, King J, Kennedy A, Cipolotti L (2006) Impaired allocentric spatial memory underlying topographical disorientation. *Rev Neurosci* **17**, 239-251.

[29] Pai MC, Jacobs WJ (2004) Topographical disorientation in community-residing patients with Alzheimer's disease. *Int J Geriatr Psychiatry* **19**, 250-255.

[30] Nadolne MJ, Stringer AY (2001) Ecologic validity in neuropsychological assessment: prediction of wayfinding. *J Int Neuropsychol Soc* **7**, 675-682.

[31] Monacelli AM, Cushman LA, Kavcic V, Duffy CJ (2003) Spatial disorientation in Alzheimer's disease: the remembrance of things passed. *Neurology* **61**, 1491-1497.

[32] Cherrier MM, Mendez M, Perryman K (2001) Route learning performance in Alzheimer disease patients. *Neuropsychiatry Neuropsychol Behav Neurol* **14**, 159-168.

[33] Tetewsky SJ, Duffy CJ (1999) Visual loss and getting lost in Alzheimer's disease. *Neurology* **52**, 958-965.

[34] Hort J, Laczo J, Vyhnalek M, Bojar M, Bures J, Vlcek K (2007) Spatial navigation deficit in amnestic mild cognitive impairment. *Proc Natl Acad Sci U S A* **104**, 4042-4047.

[35] Cushman LA, Duffy CJ (2007) The sex specificity of navigational strategies in Alzheimer disease. *Alzheimer Dis Assoc Disord* **21**, 122-129.

[36] Cushman LA, Stein K, Duffy CJ (2008) Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology* **71**, 888-895.

[37] Hodges JR, Patterson K, Oxbury S, Funnell E (1992) Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain* **115**(Pt 6), 1783-1806.

[38] Heidler-Gary J, Gottesman R, Newhart M, Chang S, Ken L, Hillis AE (2007) Utility of behavioral versus cognitive measures in differentiating between subtypes of frontotemporal lobar degeneration and Alzheimer's disease. *Dement Geriatr Cogn Disord* **23**, 184-193.

[39] Graham KS, Patterson K, Powis J, Drake J, Hodges JR (2002) Multiple inputs to episodic memory: words tell another story. *Neuropsychology* **16**, 380-389.

[40] Hodges JR, Patterson K, Ward R, Garrard P, Bak T, Perry R, Gregory C (1999) The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology* **13**, 31-40.

[41] Maguire EA, Cipolotti L (1998) Selective sparing of topographical memory. *J Neurol Neurosurg Psychiatry* **65**, 903-909.

[42] Cipolotti L, Maguire EA (2003) A combined neuropsychological and neuroimaging study of topographical and non-verbal memory in semantic dementia. *Neuropsychologia* **41**, 1148-1159.

[43] Bird CM, Chan D, Hartley T, Pijnenburg YA, Rossor MN, Burgess N (2009) Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus*, in press.

[44] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST (2001) Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **56**, 1133-1142.

[45] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[46] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**, 1546-1554.

[47] Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* **21**, 1078-1085.

[48] Alladi S, Arnold R, Mitchell J, Nestor PJ, Hodges JR (2006) Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychol Med* **36**, 507-515.

[49] Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, Zamora D, Goodkind M, Bell K, Stern Y, Devanand DP (2006) Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* **63**, 916-924.

[50] Chan D, Anderson V, Pijnenburg Y, Whitwell J, Barnes J, Scahill R, Stevens JM, Barkhof F, Scheltens P, Rossor MN, Fox NC (2009) The clinical profile of right temporal lobe atrophy. *Brain* **132**, 1287-1298.

[51] Guariglia C (2007) Spatial working memory in Alzheimer's disease: A study using the Corsi block-tapping test. *Dement Neuropsychol* **1**, 392-395.

[52] Hartley T, Bird CM, Chan D, Cipolotti L, Husain M, Vargha-Khadem F, Burgess N (2007) The hippocampus is required for short-term topographical memory in humans. *Hippocampus* **17**, 34-48.

[53] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[54] Nelson HE, O'Connell A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex* **14**, 234-244.

[55] Rey A (1941) L'examen psychologique dans le cas d'encéphalopathie traumatique. *Arch Psychol* **28**, 286-340.

[56] Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P (1994) Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* **5**, 266-281.

[57] Osterrieth PA (1944) Filetest de copie d'une figure complexe: Contribution a l'etude de la perception et de la memoire. *Arch Psychol* **30**, 286-356.

[58] Warrington EK, James M (1991) (Thames Valley Test Company, Bury St Edmunds).

[59] Riddoch JM, Humphreys GW (1993) *Birmingham Object Recognition Battery*, Psychology Press.

[60] Reitan RM (1958) Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Motor Skills* **8**, 271-276.

[61] McKenna P, Warrington EK (1980) Testing for nominal dysphasia. *J Neurol Neurosurg Psychiatry* **43**, 781-788.

[62] Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361-370.

[63] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17**, 37-49.

[64] Algase D, Son GR, Beel-Bates C, Song J, Lan Y, Beattie E, Leitsch S (2007) Initial psychometric evaluation of the Wayfinding Effectiveness Scale. *West J Nurs Res* **29**, 1015-1032.

[65] Mitchell J, Arnold R, Dawson K, Nestor PJ, Hodges JR (2009) Outcome in subgroups of mild cognitive impairment (MCI) is highly predictable using a simple algorithm. *J Neurol* **256**, 1500-1509.

[66] Ahmed S, Mitchell J, Arnold R, Nestor PJ, Hodges JR (2008) Predicting rapid clinical progression in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord* **25**, 170-177.

[67] Yamamoto R, Iseki E, Higashi S, Murayama N, Minegishi M, Sato K, Hino H, Fujisawa K, Kosaka K, Togo T, Katsuse O, Uchikado H, Furukawa Y, Yoshida M, Hashizume Y, Arai H (2009) Neuropathological investigation of regions responsible for semantic aphasia in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* **27**, 214-223.

[68] Sanders AE, Holtzer R, Lipton RB, Hall C, Verghese J (2008) Egocentric and exocentric navigation skills in older adults. *J Gerontol A Biol Sci Med Sci* **63**, 1356-1363.

[69] Rosenbaum RS, Gao F, Richards B, Black SE, Moscovitch M (2005) "Where to?" remote memory for spatial relations and landmark identity in former taxi drivers with Alzheimer's disease and encephalitis. *J Cogn Neurosci* **17**, 446-462.

[70] Nunn JA, Graydon FJ, Polkey CE, Morris RG (1999) Differential spatial memory impairment after right temporal lobectomy demonstrated using temporal titration. *Brain* **122**(Pt 1), 47-59.

[71] Smith ML, Milner B (1989) Right hippocampal impairment in the recall of spatial location: encoding deficit or rapid forgetting? *Neuropsychologia* **27**, 71-81.

[72] Doeller CF, King JA, Burgess N (2008) Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proc Natl Acad Sci U S A* **105**, 5915-5920.

[73] Fanselow MS, Dong HW Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* **65**, 7-19.

[74] Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Cipolotti L, Rossor MN (2001) Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* **49**, 433-442.

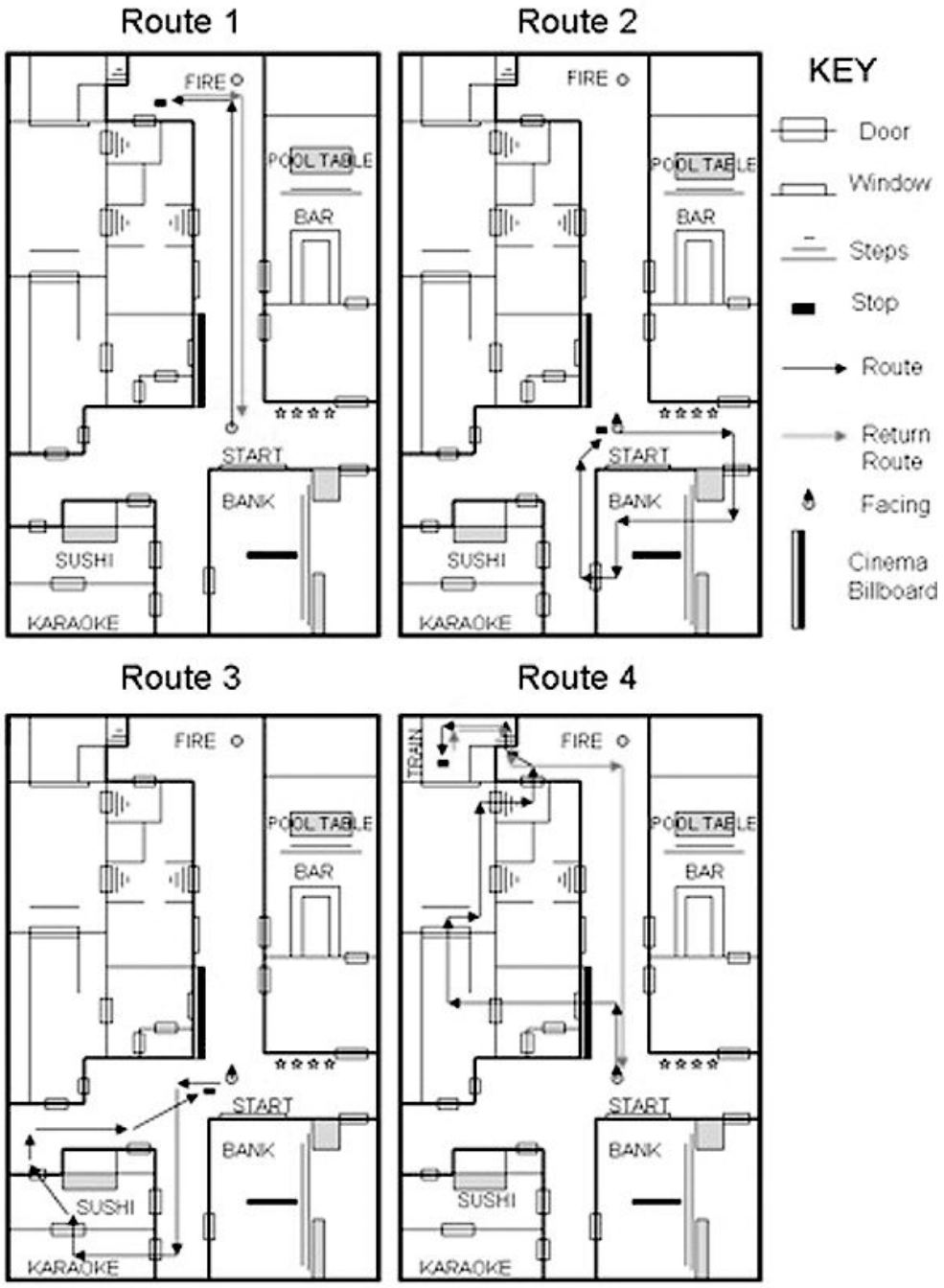
[75] Davies RR, Graham KS, Xuereb JH, Williams GB, Hodges JR (2004) The human perirhinal cortex and semantic memory. *Eur J Neurosci* **20**, 2441-2446.

[76] Nestor PJ, Fryer TD, Hodges JR (2006) Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage* **30**, 1010-1020.

[77] Acosta-Cabronero J, Williams GB, Pereira JM, Pengas G, Nestor PJ (2008) The impact of skull-stripping and radio-frequency bias correction on grey-matter segmentation for voxel-based morphometry. *Neuroimage* **39**, 1654-1665.

[78] Nestor PJ, Fryer TD, Smielewski P, Hodges JR (2003a) Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol* **54**, 343-351.

**Appendix A: The VRLT route plans**



**Appendix B: Modified Way-finding Effectiveness Scale (Family Member)**

A. When your family member changes location inside or outside the house, does your family member need physical assistance?

Yes ( ) No ( )

If yes, what kind of physical assistance does your family member need? (Check all that apply).

1. Cane ( )
2. Walker ( )
3. Wheelchair ( )
4. Other _____

B. When your family member changes location inside or outside the house, does your family member need assistance to find a destination?

Yes ( ) No ( )

If yes, what kind of physical assistance does your family member need? (Check all that apply).

1. Verbal direction ( )
2. Written direction ( )
3. Maps ( )
4. Transportation ( )
5. Other _____

To what extent do the following describe your family member?
Answer by thinking of your family member's **present behavior.**

| Statement | 5 never/ unable | 4 seldom | 3 some-times | 2 usually | 1 always |
|---|---|---|---|---|---|
| 1. He/she could locate any room in his/her current residence. | | | | | |
| 2. He/she can find his/her way around area of residence, if the route and destination were familiar. | | | | | |
| 3. He/she can find his/her way to near places, if the route and destination were familiar. | | | | | |
| 4. He/she can find his/her way to distant places, if the route and destination were familiar. | | | | | |
| 5. He/she can find his/her way to near but unfamiliar places. | | | | | |
| 6. He/she can find his/her way to distant places, even if the route and destination were unfamiliar. | | | | | |
| 7. He/she relies on maps when heading for a familiar destination. | | | | | |
| 8. He/she heads in the wrong direction for a familiar route. | | | | | |
| 9. He/she heads in the wrong direction to an unfamiliar location. | | | | | |
| 10. You would be worried that they would be lost if he/she were to go out alone. | | | | | |
| 11. He/she has been lost and required help to find way. | | | | | |
| 12. He/she has been escorted home by others | | | | | |
| 13. He/she can detect when "off course" to a familiar location. | | | | | |
| 14. He/she can compensate without requesting assistance once "off course" to a familiar location. | | | | | |
| 15. He/she can compensate for a forced detour when traveling to a familiar location. | | | | | |
| 16. He/she can detect when "off course" to an unfamiliar location. | | | | | |
| 17. He/she can compensate without requesting assistance once "off course" to an unfamiliar location. | | | | | |

18. Can he/she give clear and accurate instructions of a route to another person?
Check *one* (most appropriate) statement:
1 = Perfect instructions ( )
2 = Mostly correct information ( )
3 = Some correct information ( )
4 = Attempts but is very inaccurate ( )
5 = Not at all ( )

19. How far away from home do they ever venture *alone*? Check *one* (most appropriate) statement:
1 = Drives on motorways and/or to other towns ( )
2 = Drives a set route only (e.g. from house to shops) ( )
3 = Walks or cycles long distances from home ( )
4 = Walks to local area only (e.g. the local shops) ( )
5 = Never unescorted outside of home ( )

20. If you feel, that he/she *does* have some way-finding difficulties, when did you notice the *first* signs of such problems? Please write down the duration of time, in months or years (write 0 if none) of way-finding difficulties: _____months/years ago (delete as appropriate).

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Supplementary Data

# Lost and Found: Bespoke Memory Testing for Alzheimer's Disease and Semantic Dementia

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## 1. Introduction

The effect of potential confounding factors, such as mood, sex, age and educational achievement was examined.

While depression is associated with memory complaints, and is often the main alternative diagnosis with respect to isolated memory impairment, TM has been reported to be insensitive to depression [1], in contrast to conventional memory tests (e.g. word-list learning). Furthermore, patients with subjective memory complaints performed normally at the Four Mountains short-term TM test [2]. This suggests that clinical tests of TM may have a role in separating these groups.

There is debate in the literature with respect to the effect of sex in navigational ability. Some authors claim to find sex-specific differences [3,4] while others do not [5,6]. Others focus on the fact that men and women employ or favour different strategies with which to navigate [7], or even that other factors, such as previous experience (by men) of virtual environments [8] are driving such differences.

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## 2. Methods

An independent samples t-test of male versus female controls was performed for each TM task to look for any sex-specific differences in performance.

To assess potential relationships of age, intelligence and mood with TM, Pearson product-moment correlation coefficients (or Spearman's , if the data were not normally distributed) were performed in controls.

## 3. Results

### *3.1. Sex differences in TM performance*

Women performed less well in the HOT ($p = 0.0009$) but there was no difference in the VRLT, 4M-PP or the 4M-PM task (Supplemental Fig. 3). Therefore, the HOT results were re-analysed in a two-way ANOVA [Sex (2) x Subject Group (4)]. There was a significant effect of group [$F(3,80) = 14.18$, $p < 0.0001$] (which, as before, was driven only by AD impairment) and of Sex [$F(1,80) = 21.35$, $p < 0.0001$], with men outperforming women, but not a group by sex interaction [$F(3,80) = 0.85$, $p = 0.47$)].

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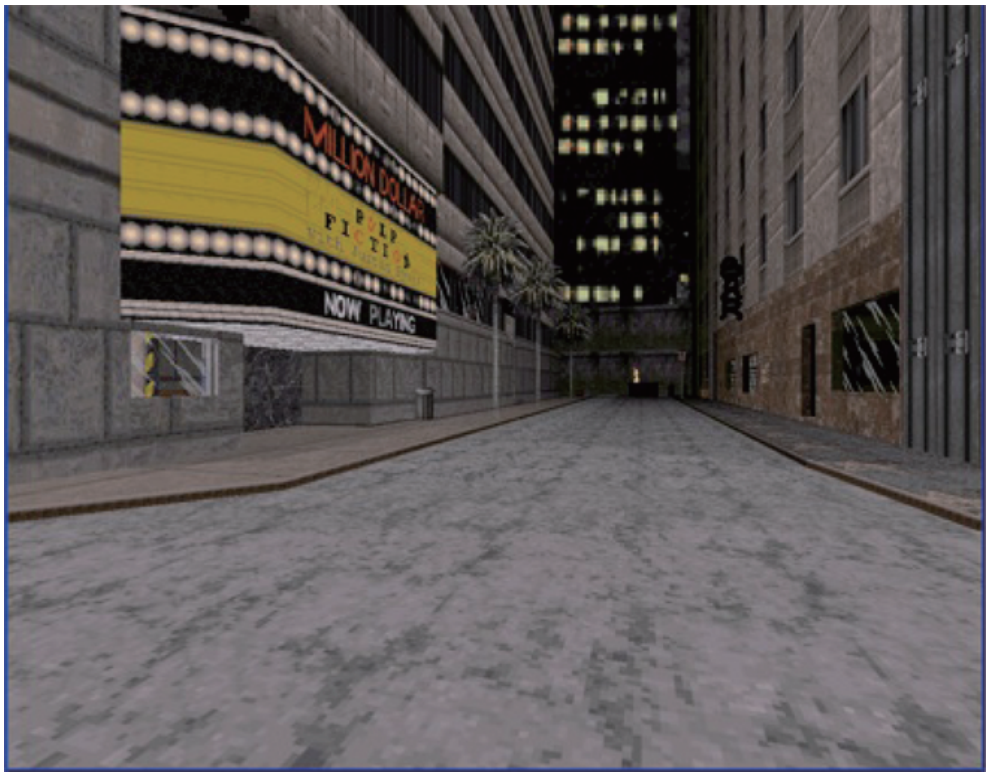



Supplemental Fig. 1. View of the cinema in the virtual town. This exact position and facing is the starting point for all tasks.

### *3.2. The effect of age*

Correlation analyses revealed a small but significant effect of age-related decline in performance of the 4M-PM task in controls ($p < 0.05$, Pearson R $= -0.38$). There was no relationship to age on the VRLT, HOT or 4M-PP task.

### *3.3. The effect of education*

There was no correlation between any of the TM tests and years of education.

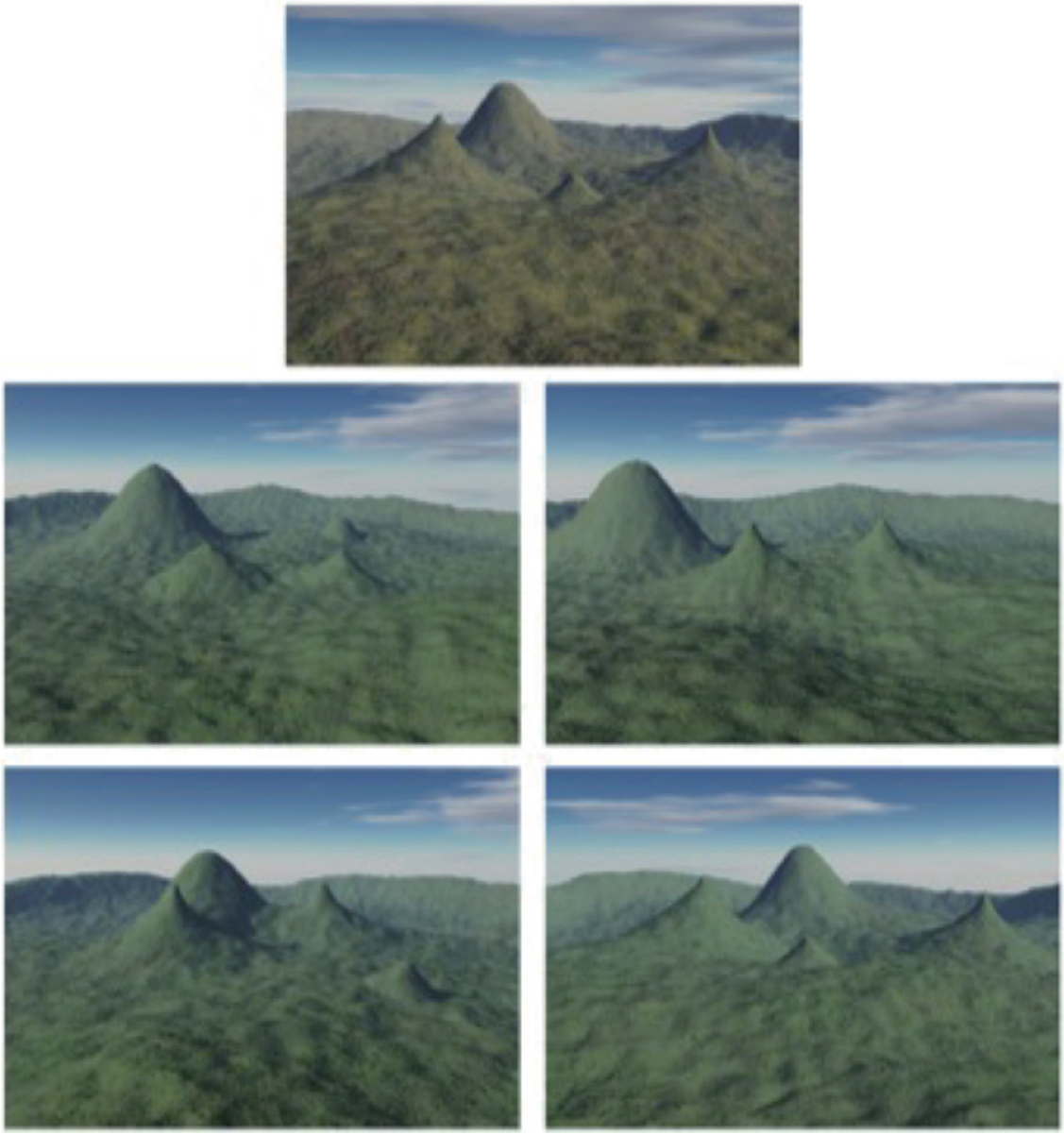
### *3.4. The effect of mood*

The 4M-PM test correlated weakly with the GDS (p(1-tailed) $= 0.03$, $= -0.34$) but not the HADS-Depression or Anxiety scores. There was no relationship of anxiety or depression with the 4M-PP, VRLT or HOT.

## 4. Discussion

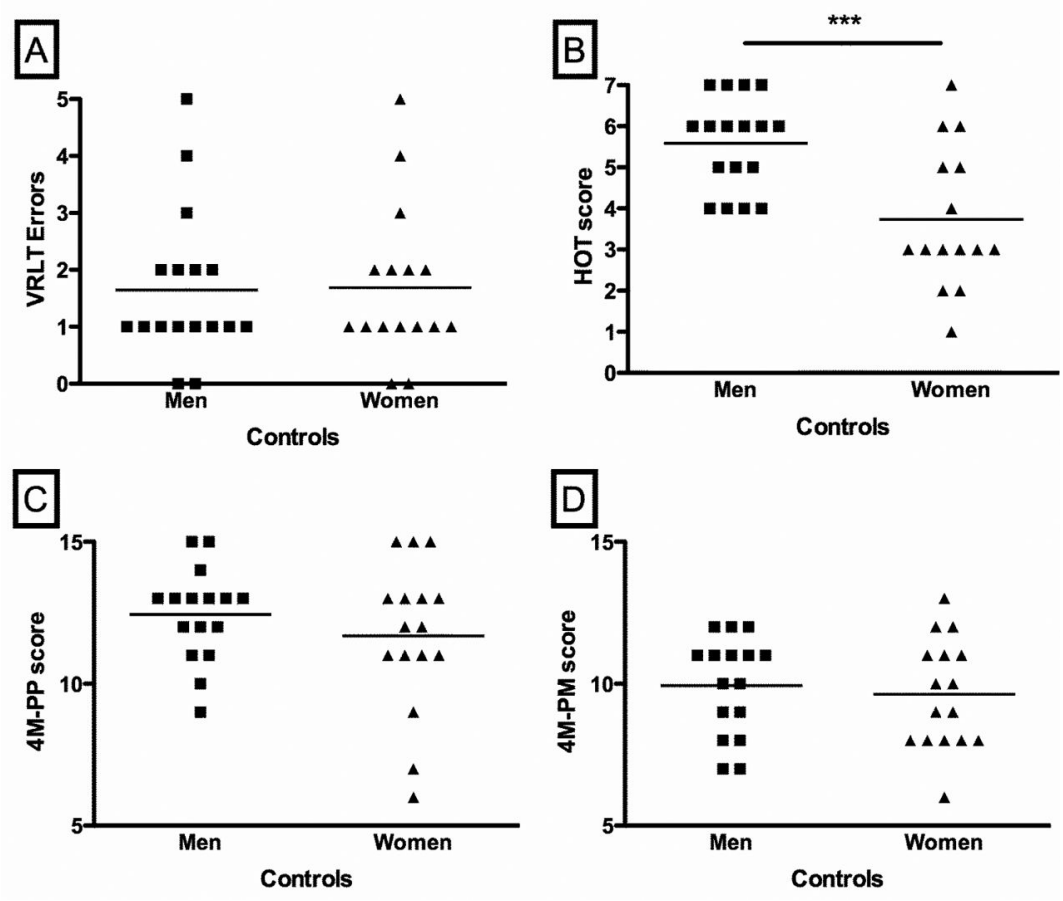
In this aged control cohort, TM performance was unrelated to education level, or anxiety. The 4M-PM correlated weakly with depressive symptoms (using the GDS but not HADS) and age; the VRLT, HOT and 4M-PP task did not. It is important to acknowledge, however, that the absence of correlation was with depressive symptoms in a dementia cohort; it does not necessarily follow that this would be the case where depression is severe and the primary diagnosis, as in the study by Gould et al. [9]. As this study aimed to examine TM performance in dementia, the controls' age range (59–79) was matched to that of the patient groups. As such, although the VRLT, HOT and 4M-PP test performance was independent of age in this control group, it is quite possible that there is an age effect over a wider range, as has been demonstrated in TM tasks when young versus aged healthy volunteers were contrasted [5,10]. Importantly for the current study's purpose, however, the tests remained stable in controls across the age range in which patients typically present with neurodegenerative dementias.

The was no sex difference in performance of the VRLT and Four Mountains tasks, but women were sig-



Supplemental Fig. 2. The Four Mountains Test. In the 4M-PP (control) condition, the target (top picture) was presented concurrently with four possible responses, whereas in the 4M-PM condition, the target was presented alone first and then hidden. The answer in this exemplar is the bottom right hand landscape.

nificantly worse than men at the HOT. Female controls were as good as males at learning routes in a virtual town, contrary to suggestions that men have an inherent advantage in virtual environments [8]. In the same environment, however, women were significantly less accurate at pointing to the direction of a landmark. Routes taken were often long, with multiple turns, so path integration, or tallying the number of turns taken, was not an efficient strategy; a more allocentric representation [11], including translation between allocentric and egocentric space, was necessary to perform this task accurately. It has been suggested [7], that women favour different strategies than men, e.g. that men use both landmarks and vectors to navigate whereas women favour mainly landmarks [8]. Thus a plausible explanation could be that there is a different weighting to certain strategies between the sexes in navigation (VRLT) but either is adequate for task success. If, however,




Supplemental Fig. 3. Gender differences in TM. ***, $p < 0.0001$.

one probes a specific determinant of task performance (in this case heading orientation), then sex differences emerge.

## References


[1] Ritter E, Despres O, Monsch AU, Manning L (2006) Topographical recognition memory sensitive to amnestic mild cognitive impairment but not to depression. *Int J Geriatr Psychiatry* **21**, 924-929.

[2] Bird CM, Chan D, Hartley T, Pijnenburg YA, Rossor MN, Burgess N (2009) Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. Hippocampus In press.

[3] Astur RS, Ortiz ML, Sutherland RJ (1998) A characterization of performance by men and women in a virtual Morris water task: a large and reliable sex difference. *Behav Brain Res* **93**, 185-190.

[4] Cushman LA, Duffy CJ (2007) The sex specificity of navigational strategies in Alzheimer disease. *Alzheimer Dis Assoc Disord* **21**, 122-129.

[5] Moffat SD, Kennedy KM, Rodrigue KM, Raz N (2007) Extrahippocampal contributions to age differences in human spatial navigation. *Cereb Cortex* **17**, 1274-1282.

[6] Schmitz S (1997) Gender-related strategies in environmental development: effects of anxiety on wayfinding in and representation of a three-dimensional maze. *Journal of Environmental Psychology* **17**, 215-228.

[7] Choi J, Silverman I (2002) The relationship between testosterone and route-learning strategies in humans. *Brain Cogn* **50**, 116-120.

[8] Maguire EA, Burgess N, O'Keefe J (1999) Human spatial navigation: cognitive maps, sexual dimorphism, and neural substrates. *Curr Opin Neurobiol* **9**, 171-177.

[9] Gould NF, Holmes MK, Fantie BD, Luckenbaugh DA, Pine DS, Gould TD, Burgess N, Manji HK, Zarate CA, Jr. (2007) Performance on a virtual reality spatial memory navigation task in depressed patients. *Am J Psychiatry* **164**, 516-519.

[10] Cushman LA, Stein K, Duffy CJ (2008) Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology* **71**, 888-895.

[11] Burgess N (2006) Spatial memory: how egocentric and allocentric combine. *Trends Cogn Sci* **10**, 551-557.