Lost in spatial translation – A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia

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Abstract:

Spatial disorientation is a prominent feature of early Alzheimer's disease (AD) attributed to degeneration of medial temporal and parietal brain regions, including the retrosplenial cortex. By contrast, frontotemporal dementia (FTD) syndromes show generally intact spatial orientation at presentation. However, currently no clinical tasks are routinely administered to objectively assess spatial orientation in these neurodegenerative conditions. In this study we investigated spatial orientation in 58 dementia patients and 23 healthy controls using a novel virtual supermarket task as well as voxel-based morphometry. We compared performance on this task with visual and verbal memory function, which has traditionally been used to discriminate between AD and FTD. Participants viewed a series of videos from a first person perspective travelling through a virtual supermarket and were required to maintain orientation to a starting location. Analyses revealed significantly impaired spatial orientation in AD, compared to FTD patient groups. Spatial orientation performance was found to discriminate AD and FTD patient groups to a very high degree at presentation. More importantly, integrity of the retrosplenial cortex was identified as a key neural correlate of orientation performance. These findings confirm the notion that i) it is feasible to assess spatial orientation objectively via our novel Supermarket task; ii) impaired orientation is a prominent feature that can be applied clinically to discriminate between AD and FTD and iii) the retrosplenial cortex emerges as a critical biomarker to assess spatial orientation deficits in these neurodegenerative conditions.

Keywords: orientation, retrosplenial cortex, Alzheimer's disease, frontotemporal dementia

1. Introduction

Spatial and temporal disorientation is a well-documented early symptom of Alzheimer's disease (AD) (Hornberger, Piguet, Graham, Nestor, & Hodges, 2010; Pai & Jacobs, 2004; Pengas et al., 2010; Yew, Alladi, Shailaja, Hodges, & Hornberger, 2013). For patients diagnosed with one of the frontotemporal dementia (FTD) syndromes, however, orientation is reported to be relatively intact (Bellassen, Igloi, de Souza, Dubois, & Rondi-Reig, 2012; Pengas et al., 2010; Yew et al., 2013). This raises the question of whether orientation can be used as a discriminant of AD and FTD, in particular, between AD and the behavioural variant of FTD (bvFTD), where significant memory impairment in a subset of bvFTD patients can lead to diagnostic uncertainty (Hornberger et al., 2010).

Spatial navigation in general has been well studied in dementia patients including mild cognitive impairment (MCI), the prodromal stage of AD (for a review see Serino, Cipresso, Morganti, & Riva, 2014). Investigations of orientation in dementia patients, however, have been limited, given the lack of suitable, and practical, tasks that can be easily utilised in a clinical setting. Orientation can be characterised as being either egocentric or allocentric; cognitive processes which are subserved by different brain regions. Egocentric spatial orientation (i.e., location of objects in relation to the self) has been suggested to be dependent on parietal cortices while allocentric spatial orientation (i.e., location of objects in relation to other objects) is critically dependent on medial temporal lobe structures, including the hippocampus (Burgess, Becker, King, & O'Keefe, 2001). Significant structural and metabolic changes are present in the parietal lobe and retrosplenial region (Brodmann Areas 29 and 30) in AD (Nestor, Fryer, Ikeda, & Hodges, 2003; Pengas, Hodges, Watson, & Nestor, 2010; Tan, Wong, Hodges, Halliday, & Hornberger, 2013), but not bvFTD (Irish, Piguet, Hodges, & Hornberger, 2014; Tan et al., 2013). Egocentric spatial orientation may be, therefore, a suitable measure to discriminate between the two conditions. The importance of the retrosplenial region for spatial orientation has been highlighted in a case report of a taxi driver who suffered focal left retrosplenial haemorrhage and immediately presented with selective egocentric spatial disorientation (Ino et al., 2007). Evidence from functional imaging studies further suggests that egocentric navigation is subserved by the parietal cortex and, in particular, the retrosplenial cortex (RSC) for heading direction (for a review see, Boccia, Nemmi, & Guariglia, 2014).

The specialised role of the RSC in orientation during spatial navigation has been consistently demonstrated across functional neuroimaging studies (Baumann & Mattingley,

2010; Epstein, Parker, & Feiler, 2007; Iaria, Chen, Guariglia, Ptito, & Petrides, 2007; Marchette, Vass, Ryan, & Epstein, 2014). The RSC is the gateway to key occipital, temporal, and parietal lobe structures responsible for processing visual information, constructing an internal model of the environment (allocentric framework) and updating directional information based on movement from the motor system, respectively (Vann, Aggleton, & Maguire, 2009). Consequently, the RSC acts as a neural hub for the integration and processing of egocentric, allocentric and visual information necessary to orientate oneself within an environment (Epstein & Vass, 2013; Vann et al., 2009). Functional imaging studies have consistently shown activity in the RSC in healthy young participants during tasks involving orientation within a learnt virtual environment, when making judgements of relative direction (Baumann & Mattingley, 2010; Epstein et al., 2007; Marchette et al., 2014), and also during active navigation using landmarks as reference (Iaria et al., 2007). Multi-voxel pattern analysis carried out by Marchette and colleagues (2014) indicated that the location of environmental features, in addition to directional information, is encoded within the neural activity elicited by the RSC.

While the aforementioned studies have implemented behavioural tasks that excel in evoking RSC involvement, assessment of orientation is predicated on the accurate acquisition and formation of an internal representation of a new experimental environment and landmarks (with the exception of Epstein et al., 2007), a process which is critically dependent on the hippocampus (Boccia et al., 2014; Ekstrom et al., 2003; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012; Iaria et al., 2007). In patients with episodic memory deficits (i.e., compromised hippocampal function) both the time required, and demands of the initial learning phase would be significantly increased, reducing efficacy in a clinical setting. To our knowledge, the current most ecologically valid assessment of orientation in memory impaired patients involve topographical map assessments of landmarks within a patient's local city or surrounding locale (Campbell, Hepner, & Miller, 2014; Pai & Yang, 2013), similar to that implemented by Epstein and colleagues (2007). These tasks, however, are limited to participants familiar with specific environments (i.e. downtown Sydney), but can be overcome as in the case of the personalised versions used by Pai and Yang (2013), where they targeted unique landmarks near each participant's residence. Therefore, a spatial orientation task that does not require prior training and widely applicable to objectively assess memory impaired patients is necessary.

In the current study, we utilised a virtual supermarket environment that does not require prior learning of a spatial layout to assess spatial orientation in AD and FTD. Participants

viewed the environment from a first person perspective and maintained spatial orientation using an egocentric frame of reference. Spatial orientation performance was, therefore, dependent on two variables: i) incidental formation of a working egocentric representation of the environment, and ii) updating egocentric memory in response to movement through the environment (Land, 2014). AD, and FTD patients diagnosed with the behavioural (bvFTD) or semantic (SD) variants were tested – both have shown to have hippocampal but not RSC atrophy. We aimed to assess: i) the clinical applicability of the virtual supermarket task in these patient cohorts, ii) sensitivity of spatial orientation as a diagnostic discriminant between AD and bvFTD, and iii) neural correlates of spatial orientation in AD. We hypothesized that while orientation is dependent on memory processes, the retrosplenial region would be critical for egocentric spatial orientation, such that spatial orientation would be associated with reduced structural integrity of the RSC.

2. Methods

2.1. Participants

Fifty eight dementia patients (20 AD; 24 bvFTD; 14 SD) and 23 age- and education-matched healthy controls were recruited from the Sydney frontotemporal dementia research group (FRONTIER) database. All participants were assessed at the FRONTIER clinic located at Neuroscience Research Australia, Sydney. Study approval was provided by the South Eastern Sydney Local Health District Human Research Ethics Committee. All participants provided signed consent for neuropsychological assessment and neuroimaging prior to testing. Patient cohorts were matched for disease duration and clinical disease severity. All dementia patients fulfilled international consensus criteria for AD (McKhann et al., 2011), bvFTD (Rascovsky et al., 2011), and SD (Gorno-Tempini et al., 2011). Clinical diagnoses were established by consensus among senior neurologist, occupational therapist and neuropsychologist, based on a clinical interview, comprehensive neuropsychological assessment, and evidence of brain atrophy on structural neuroimaging. All bvFTD patients showed disease progression as well as atrophy on scans to exclude any phenocopy cases (Kipps, Hodges, & Hornberger, 2010). Participant demographics and clinical characteristics are provided in Table 1.

Briefly, AD patients presented predominantly with significant episodic memory impairment with preserved social behaviour. BvFTD patients demonstrated changes in social functioning, loss of insight, disinhibition and increased apathy. SD patients were predominantly left lateralised (3 right) and showed loss of general conceptual knowledge in the form of significant naming and comprehension impairment. Exclusion criteria for all

participants included prior history of mental illness, head injury, movement disorders, alcohol and drug abuse, limited English proficiency, and, for controls, presence of abnormality on MRI.

Participants were administered a battery of cognitive tests to assess overall cognitive function, verbal and visual memory, and working memory. This assessment included: Addenbrooke's Cognitive Examination-Revised (ACE-R), Rey Auditory Verbal Learning Test (RAVLT), Rey Complex Figure Test (RCFT), and Digit Span. For a brief description of cognitive tasks see Supplementary Table 1.

2.2. Virtual supermarket task

Spatial orientation was assessed using an ecological virtual supermarket environment. The layout of the virtual environment did not include any notable landmarks and any spatial representation was acquired through incidental encoding during test trials. A total of 14 video trials (2 sections of 7 videos) were created from an English version of the 'Virtual Supermarket' (Waterlander, Scarpa, Lentz, & Steenhuis, 2011) based on Australian and New Zealand supermarkets. Videos were presented from a first person perspective and participants were taken to set locations throughout the supermarket, which involved moving while making a series of 90 degree turns (Fig. 1). Participants were asked to imagine that they were standing behind a trolley and pushing it to different locations of the supermarket. At the end of each trial, participants had to indicate the direction of the starting location. All trials began at the same location, but followed different routes to reach a different end point in each trial. Each trial within each section was standardised for length and number of turns (Section 1: 20 s, 3 turns; Section 2: 40 s, 5 turns). For all participants, Section 1 was administered first, followed by Section 2. No feedback was provided during test trials.

Prior to testing, participants were instructed they would be viewing a number of short videos that involved moving to different locations of a supermarket. After arriving at the new location, they would be required to make a decision about the direction of the original starting location. Participants were explicitly told they would start from the same starting location across trials and asked to keep track of the direction of the starting location throughout the videos. At the end of each trial, participants are shown a snapshot of the final location and cued by the onscreen text ("In which direction is the starting location?") to provide a response (Fig. 1). Critically, correct directional responses could not be made from only viewing the final screenshot. The task itself does not require any training component to successfully complete test trials and limits prior participant exposure of the supermarket

layout to a brief practice trial. A practice video trial (10 s, 2 turns), was given at the start of testing to introduce participants to the virtual supermarket environment and make sure task instructions were well understood. In particular, the practice trial aimed to make clear that the direction, not path taken, of the starting location from the final location was requested.

Participants were made aware that only a general direction that involved a distinction on two principal components (i.e., left/right and front/behind) was required. In most cases, participants spontaneously pointed to a particular direction. Some patients, however, required direct prompts by the task administrator (i.e., 'Is the starting location to the left or right of where you are now?'; 'Is the starting location in front of or behind where you are now?'). Segregating responses in this manner allowed for better comprehension and accurate responding from patients with greater generalised cognitive impairment. Previous versions of the task attempted using a circular illustration representing a 360° field of view segmented into 4 quartered sections (i.e., left/front; right/front; right/behind; left/behind) for responding. While elderly control participants had no difficulty responding in this manner, a number of patients showed confusion leading to inaccurate responding. Spatial orientation performance in the current version of the task was scored on individual directional components (L/R; F/B) as well as on an overall score, which required a correct response on both directional components. Each directional component, and overall performance, in Sections 1 and 2 were analysed independently. Overall performance was, however, the key variable of interest.

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2.3. Statistical Analyses

Differences in participant group demographics, performance on standard cognitive tests were assessed using one-way analysis of variance (ANOVA).Orientation performance on the experimental task were assessed using multivariate analysis of covariance (MANCOVA) and two-tailed post hoc multiple comparisons to compare spatial orientation performance between groups while taking into account degree of memory impairment on standard cognitive tests in SPSS 21.0 (IBM Corp., Armonk, NY).

A composite memory score was created by averaging performance on the memory component of the ACE-R and delayed recall components on the RAVLT and RCFT as a percentage of the total score. For participants with missing assessments, a composite score was calculated if performance on at least 2 of the 3 memory components were available. Composite memory performance was compared with averaged overall spatial orientation performance on Sections 1 and 2 of the experimental task using logistic regression. Receiver operating characteristic (ROC) curves of sensitivity and specificity were also calculated using

the method by DeLong et al. (1988) in MedCalc for Windows, version 14.8.1 (MedCalc Software, Ostend, Belgium). In all analyses, p values < .05 were considered statistically significant.

2.4. Imaging Acquisition

Whole-brain structural T1 images were acquired for all participants using a 3T Philips MRI scanner with standard quadrature head coil (eight channels). Structural T1 scans were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, 1mm isotropic, TE/TR = 2.5/5.4 ms, flip angle $\alpha = 8°$. Prior to analyses, all participant scans were visually inspected for significant head movements and artefacts, and excluded from imaging analyses. Scans were missing from 7 control participants. Imaging analyses included MRI data from 16 AD, 18 bvFTD, 12 SD and 15 control participants. All scans were examined by a radiologist for structural abnormalities.

2.5. Imaging Analyses

Voxel-based morphometry (VBM) was conducted on whole-brain T1-weighted scans, using the VBM toolbox in FMRIB's Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). First, the brain was extracted from each scan using FSL's BET algorithm with a fractional intensity threshold of 0.22 (Smith, 2002). Each scan was visually checked following brain extraction to ensure no brain matter was excluded, and no non-brain matter was included. A study specific template of grey matter was generated from 12 scans from each participant cohort. An equivalent number of scans from each cohort were used to create the template, avoiding potential bias towards any single group's topography during registration. Template scans were then registered to the Montreal Neurological Institute (MNI) standard brain (MNI 152) using non-linear b-spline representation of the registration warp field, resulting in a study-specific grey matter template at 2 mm^3 resolution in MNI standard space. Simultaneously, participant brain-extracted scans were processed with the FMRIB's Automatic Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001), via a hidden Markov random field model and an associated Expectation-Maximization algorithm, segmenting brain tissue into CSF, grey matter and white matter. The FAST algorithm also corrected scans for spatial intensity variations such as bias field or radio-frequency inhomogeneities, resulting in partial volume maps. The following step saw grey matter partial volume maps then non-linearly registered to the study-specific template via b-spline representation of the registration warp. These maps were then modulated by dividing by the Jacobian of the warp field, to correct for any

contraction/enlargement caused by the non-linear component of the transformation. After normalisation and modulation, grey matter maps were smoothed using an isotropic Gaussian kernel (sigma = 3 mm).

Statistical analysis was performed with a voxel-wise general linear model. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). TFCE is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold. Instead, it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. We employed permutation-based non-parametric testing with 5000 permutations (Nichols & Holmes, 2002).

Comparisons of whole-brain grey matter integrity were carried out between each patient group and controls, as well as between AD and bvFTD cohorts. Reported clusters are corrected for multiple comparisons via Family-wise Error (FWE) and tested for significance at $p < .005$. Talairach and Harvard-Oxford Cortical/Subcortical Atlases were used as references to identify brain structures comprising significant clusters. A mask of the RSC (Brodmann areas 29, 30) was manually traced on the MNI 152 standard brain and used to calculate each participant's grey matter volume in this region. Whole-brain and RSC grey matter were correlated with averaged overall orientation performance across Sections 1 and 2.

3. Results

3.1. Demographics and Cognitive Testing

Participant cohorts were well matched for demographic variables, and patient groups were matched for disease duration and disease severity (Table 1; all p values > .1). ANOVA of participant groups' performance across standard cognitive tests revealed significant group differences for all components (all p values < .003). In the two groups of interest, bvFTD showed a better cognitive profile than AD on the ACE-R screening of general cognition (all p values < .01), verbal memory (RAVLT: T1-5, 30 min delay; all p values < .003), and visual memory (RCFT: Delayed; $p = .009$). The two patient groups, however, did not differ on working memory as indicated by the Digit Span forwards ($p > .7$) and backwards ($p > .4$). Importantly, all aspects of episodic memory in bvFTD patients were significantly impaired compared to controls (Supplementary Table 2; all p values < .02).

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3.2. Spatial Orientation Performance

Spatial orientation was scored for correct response on the two directional components (front/back and left/right). Overall performance required correct judgement of orientation on both directional components (Fig. 2). MANCOVA was performed using memory performance on the ACE-R as a covariate for spatial orientation performance. After taking into account differences in general memory function, significant group differences were present for overall and individual components of orientation performance on sections 1 and 2 (all p-values < .03). Post-hoc contrasts indicated orientation performance remained significantly different between AD and bvFTD patient groups on all components (all p-values < .03), except for front/back responses in section 1 ($p = .34$). Control and FTD patient groups (bvFTD and SD) did not show any significant difference on task components (all p-values < .09).

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3.3. Memory and Orientation as Diagnostic Predictors of AD and bvFTD

Sensitivity and specificity of spatial orientation and memory performance in AD and bvFTD were compared using logistic regression and ROC curves. A composite memory score (ACE-R: memory; RAVLT: 30 min delay; RCFT: delayed) and Total Orientation (Sections 1 and 2) were used as predictors. Logistic regression indicated that the regression model based on memory and orientation predictors was statistically significant, $x^2(2) = 28.842$, $p < .001$. The model explained 85.9% (Nagelkerke R^2) of variance in AD and bvFTD patients and correctly classified 92.7% of patients (17 out of 18 AD; 21 out of 23 bvFTD) into their respective cohorts. Furthermore, total spatial orientation held a similar level of predictive power ($e^{\beta} = 1.101$; 95% CI, 1.001 to 1.210; $p < .05$) as memory ($e^{\beta} = 1.212$; 95% CI, .984 to 1.491; $p = .07$). Tests of collinearity between predictors indicated that multicollinearity was not a concern (Tolerance = .88, VIF = 1.14).

ROC curves were computed for memory and orientation predictors in diagnosing AD and bvFTD patients (Fig. 3). Area under the curve (AUC) values indicated memory (AUC = 0.918, SE = 0.052; 95% CI, 0.751 to 0.988) and total orientation (AUC = 0.905, SE = 0.054; 95% CI, 0.734 to 0.983) had a similar level of diagnostic accuracy. Pairwise comparison of memory and orientation ROC curves revealed no significant difference between the two predictors ($p = .87$).

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3.4. Structural Imaging Results

Whole-brain grey matter integrity was examined using VBM to compare patient cohorts with healthy controls (Supplementary Table 3; Supplementary Fig. 1). The pattern of atrophy present in each patient group was consistent with previous reports in the literature (Irish et al., 2014; Rohrer et al., 2008). Briefly, AD patients showed temporal and parietal lobe atrophy. In particular, grey matter integrity was reduced in the retrosplenial region as well as bilateral hippocampi. In bvFTD patients, only clusters in the medial prefrontal cortex was found to significantly differ, compared to controls, after thresholding. In SD patients, atrophy was found in the left medial prefrontal cortex and temporal lobes. Notably, SD patients also showed significant bilateral atrophy in the hippocampus, with greater atrophy in the left hippocampus, due to the inclusion of both left and right lateralised SD cases.

VBM analyses were also conducted between AD and FTD patient groups (Table 2). Findings indicated AD patients showed significantly greater atrophy in medial parietal and retrosplenial regions, compared to bvFTD patients (Fig. 4A). Similarly, compared to SD, AD patients showed greater atrophy in medial parietal and right lateral parietal lobe regions. Reported clusters were corrected for multiple comparisons using family-wise error correction and significant at $p < .005$.

In AD, total orientation (Sections 1 and 2) performance was correlated with whole-brain grey matter integrity to determine the neural correlates of their impaired performance (Fig. 4B). Orientation performance was found to correlate with the retrosplenial region (Brodmann areas 23, 29, 30; MNI co-ordinates: 6, -46, 24) as well as the left lingual gyrus (MNI co-ordinates: -14, -66, -6). Whole brain volume did not show a significant correlation with orientation performance.

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4. Discussion

The current study demonstrated that spatial orientation can be used to discriminate between AD and bvFTD beyond their memory impairment. The virtual supermarket task was successfully used to assess spatial orientation in amnesic dementia patient populations with hippocampal atrophy. Notably, orientation was impaired in AD, but relatively intact in FTD patient groups, even after accounting for differences in performance on episodic memory tasks. Orientation performance showed the same level of diagnostic sensitivity as standardised measures of episodic memory. This finding is consistent with surrogate reports

of temporal and spatial disorientation in everyday life during the early stages of AD (Kwok, Yuen, Ho, & Chan, 2010; Pai & Jacobs, 2004), but not in FTD, and formally addressed orientation performance beyond the context of a general screening of cognition or clinical interview.

The ability to orient ourselves to topographical features within our immediate environment requires an internal working representation (egocentric memory) of objects relative to head and body orientation (Land, 2014). A key feature of this internal model of the outside world is the ability to continually update the directional relationship between external objects and the self. Our experimental task aimed to mimic this process by engaging participants within the context of a novel, but familiar, supermarket shopping scenario whereby they were taken to various locations within the store, while having to maintain and update the directional relationship to the starting location. The task aimed to engage egocentric memory with a relatively low allocentric spatial map contribution of the supermarket environment, which is suggested to be formed and stored in the hippocampus and medial temporal cortices (Burgess et al., 2001; Burgess, 2006; Byrne, Becker, & Burgess, 2007). Egocentric and allocentric representations are complementary processes for navigating the real world and information from each framework freely updates the other (Burgess, 2006; Land, 2014; Vann et al., 2009). Here, however, reduced integrity of parietal, rather than temporal lobe, structures was associated with impaired orientation performance in AD patients, which would support the view that the experimental task is assessing egocentric memory.

A number of virtual reality tasks based on route learning and hidden goal paradigms have previously been developed to assess egocentric and allocentric spatial processing in AD and MCI (Serino et al., 2014). Findings indicate deficits in allocentric and egocentric spatial representations (Bellassen et al., 2012; Jheng & Pai, 2009; Laczo et al., 2012; Morganti, Stefanini, & Riva, 2013; Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012; Weniger, Ruhleder, Lange, Wolf, & Irle, 2011; although see Burgess, Trinkler, King, Kennedy, & Cipolotti, 2006). To our knowledge, however, the only study that has applied this to AD and FTD patient cohorts is the study by Bellassen and colleagues (2012) using the ‘Starmaze’ (Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010). The Starmaze comprises 5 alleyways branching from a pentagonal centre, and assessed participant’s ability to learn and actively navigate specific routes (egocentric), as well as their ability to trace routes on a map layout (allocentric). In healthy young participants, performance on the Starmaze primarily elicits activity in the hippocampus (Igloi et al., 2010). Deficits in egocentric and allocentric route recall were observed in the AD and amnesic MCI groups, while the FTD patient group

performed at the same level as age matched controls for both conditions. Similar to existing spatial navigation tasks in AD, performance on the Starmaze is predicated on a successful learning phase and aims to assess degradation in hippocampal-dependent memory processes, in accordance with the diagnostic criteria for early detection of AD (Dubois et al., 2010). In the current virtual supermarket task our objective was to engage parietal rather than traditional temporal lobe memory structures, such as the hippocampus, within a familiar but novel environment. A key difference, compared to the Starmaze, being the absence of a learning component as well as active navigation within a virtual environment, which amnesic patients and those presenting with apraxia can find challenging.

The notion of using orientation as a diagnostic marker between AD and bvFTD patients has previously been raised and cursorily examined using a subcomponent of the ACE-R screening of general cognition in dementia patients in previous work by our group (Hornberger et al., 2010; Yew et al., 2013). Temporal and geographical orientation was assessed using subcomponents of the ACE-R screening of general cognition by evaluating patients on their knowledge of the current time (i.e. day, date, month, year, season) and location (i.e. building, floor, town, state, country). The study by Yew and colleagues (2013) found orientation was impaired in AD while bvFTD performed at the same level as controls, and furthermore, that orientation was more sensitive at discriminating the two patient populations than the memory component of the ACE-R screening. The supermarket task provides an approach to assess orientation while minimising episodic memory contributions. Our results indicated that consideration of orientation performance complements standardised measures of episodic recall to improve diagnostic accuracy between AD and bvFTD.

Structural neuroimaging revealed AD patients had the characteristic pattern of grey matter atrophy, involving bilateral hippocampi, and temporal and parietal lobe regions (Irish et al., 2014). Structural integrity of the hippocampus, however, did not differ between AD and FTD groups. Hippocampal atrophy has previously been reported in neuroimaging studies of FTD (de Souza et al., 2013; Hornberger et al., 2012; Moller et al., 2014; Rohrer et al., 2008; Tan et al., 2014). Furthermore, for AD and bvFTD pathology, specifically, hippocampal volume has been shown to be a poor diagnostic marker at post-mortem (Hornberger et al., 2012). Analyses indicated that the impaired spatial orientation performance observed in AD was related to reduced grey matter volume in the left lingual gyrus and retrosplenial region of the posterior cingulate. This finding is consistent with the view that the RSC plays a central role in spatial navigation (for a review see Vann et al., 2009). The RSC is suggested to act as a hub for the integration and translation of different frameworks (i.e., visual information from

the occipital cortex; body orientation from the parietal cortex [egocentric]; spatial map of the environment from the hippocampus [allocentric]) and holds reciprocal anatomical connections with the occipital and parietal cortices, and the hippocampal formation (Burgess et al., 2001; Burgess, 2006; Byrne et al., 2007; Vann et al., 2009). Functional imaging studies in humans consistently elicit strong activation in the RSC when navigating through familiar environments (Vann et al., 2009). In particular, studies by Spiers and Maguire (2006), and Baumann and Mattingley (2010), both observed strong activation of the RSC during retrieval of directional information from topographical representations during spatial navigation tasks. Notably, the study by Baumann and Mattingley (2010) utilised a virtual environment stripped of all environmental cues creating an immediate sense of disorientation. Participants were extensively trained to locate and navigate to specific stimuli and later exposed to paired stimuli images representing either the same or different heading directions at test. Retrieval of heading direction was found to activate the retrosplenial region for both conditions, but significantly higher when paired stimuli represented different heading directions.

Human lesion studies also highlight selective topographical disorientation as a result of damage to the retrosplenial region (Ino et al., 2007; Osawa, Maeshima, & Kunishio, 2008; Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997; although see Maeshima et al., 2014). Patients with hippocampal lesions, however, demonstrate impaired spatial navigation, but a preserved sense of direction within a familiar environment (Spiers & Maguire, 2007). In the current study, SD patients with confirmed hippocampal atrophy showed well preserved orientation on the experimental task, while AD patients with atrophy in the medial parietal lobe and retrosplenial region were severely impaired. These behavioural findings in AD and SD are consistent with previous findings by Pengas and colleagues (2010) using a virtual route learning paradigm with active navigation in combination with a heading orientation test. AD patients proved to be significantly impaired on route learning as well as heading orientation while SD patients showed no significant differences in performance to controls. This same pattern of dissociation between AD, SD and age-matched control cohorts was observed for orientation performance in the current virtual supermarket task. Although Pengas and colleagues (2010) discuss studies in SD that have demonstrated atrophy in medial temporal lobe structures (Chan et al., 2001; Davies, Graham, Xuereb, Williams, & Hodges, 2004), the state of hippocampal atrophy in their patient cohorts is unclear. In the current study, AD and SD patient groups showed bilateral hippocampal atrophy compared to controls, but a direct contrast between AD and SD did not find any significant differences in

the structure. This further suggests atrophy in the parietal lobe, namely the retrosplenial region of the posterior cingulate underlies observed orientation deficits in AD.

Behavioural and structural imaging analyses confirmed that the virtual supermarket task is a suitable measure of spatial orientation, specific to expected AD pathology and accompanying disorientation. More importantly, in contrast to other tasks it is clinically feasible to use, as the total time taken for each section is only ~7 minutes in the dementia patients. Thus, inclusion of the Supermarket task in a clinical setting would allow more objective assessment of spatial orientation deficits instead of only relying on the generic orientation component in general cognitive screening tests. Some caveats, however, must be acknowledged. The supermarket environment (Waterlander et al., 2011) was designed to reflect an accurate representation of real-life supermarkets and in the current task was not stripped of these naturalistic features to increase understanding and engage dementia patients. Therefore, compared to other tasks, such as the 'tunnel task' whereby participants are also required to maintain orientation to a starting location within a topographically featureless tunnel environment (Schonebeck, Thanhauser, & Debus, 2001), the supermarket paradigm may not be seen as a "pure" cognitive assessment of spatial orientation. The task does, however, discriminate between AD and bvFTD patients within a clinical setting. Another issue is the extent to which orientation performance is dependent on memory function. We addressed this by including differences in general memory function as a covariate in our behavioural analyses, but the RSC which we identified as the key structure resulting in impaired orientation performance in AD is also involved in various memory processes, such as autobiographical memory retrieval (Vann et al., 2009). Another potential limitation is the lack of pathological confirmation in patients. Patients with AD and bvFTD can present with varying levels of memory impairment and the current findings will need to be replicated to confirm the efficacy of the supermarket task.

In conclusion, disorientation is a significant impairment present in AD, but relatively intact in FTD patients, which can be teased apart by assessing egocentric orientation. The neural correlates associated with impaired orientation in AD include occipital and parietal cortices, in particular the RSC.

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Legends:

Figure 1. Screenshots from an example trial from Section 1 (left) and spatial layout of the virtual supermarket (right). The video begins at the starting location and involves 3 x 90 degree turns to arrive at the final location. Participants were asked to respond with the direction to the starting location from the final location.

Figure 2. Participant spatial orientation performance on the virtual supermarket task. Percentage of correct (a) overall, (b) front/back and (c) left/right orientation response. * Indicates significance at $p < .05$.

Figure 3. ROC curve for memory and orientation performance in diagnosing AD and bvFTD patients.

Figure 4. Voxel-based morphometry analysis of structural grey matter in patient groups. (A) AD patients showed greater atrophy in medial parietal and retrosplenial cortices compared to FTD patients (bvFTD and SD), and greater atrophy in the right lateral parietal lobe compared to SD patients. (B) Total correct orientation performance correlated with the retrosplenial cortex and left lingual gyrus in AD patients. Clusters are corrected for multiple comparisons using family-wise error correction and significant at $p < .005$. Co-ordinates are provided in MNI standard space.

Table 1. Participant demographic characteristics and performance on standardised neuropsychological assessments.

Table 2. Voxel-based morphometry results showing regions of significant grey matter intensity differences between AD and FTD patient groups.