Scene construction impairments in Alzheimer's disease – a unique role for the posterior cingulate cortex

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Abstract

Episodic memory dysfunction represents one of the most prominent and characteristic clinical features of patients with Alzheimer's disease (AD), attributable to the degeneration of medial temporal and posterior parietal regions of the brain. Recent studies have demonstrated marked impairments in the ability to envisage personally relevant events in the future in AD. It remains unclear, however, whether AD patients can imagine fictitious scenes free from temporal constraints, a process that is proposed to rely fundamentally upon the integrity of the hippocampus. The objective of the present study was to investigate the capacity for atemporal scene construction, and its associated neural substrates, in AD. Fourteen AD patients were tested on the scene construction task and their performance was contrasted with 14 age- and education-matched healthy older Control participants. Scene construction performance was strikingly compromised in the AD group, with significant impairments evident for provision of contextual details, spatial coherence, and the overall richness of the imagined experience. Voxel-based morphometry analyses based on structural MRI revealed significant associations between scene construction capacity and atrophy in posterior parietal and lateral temporal brain structures in AD. In contrast, scene construction performance in Controls was related to integrity of frontal, parietal, and medial temporal structures, including the parahippocampal gyrus and posterior hippocampus. The posterior cingulate cortex emerged as the common region implicated for scene construction performance across participant groups. Our study highlights the importance of regions specialised for spatial and contextual processing for the construction of atemporal scenes. Damage to these regions in AD compromises the ability to construct novel scenes, leading to the recapitulation of content from previously experienced events.

Keywords: Imagination; hippocampus; episodic memory; future thinking; autobiographical memory.

1. Introduction

Episodic memory facilitates the recollection of richly detailed and evocative experiences from the past, located within a unique spatiotemporal framework (Tulving, 2002). The retrieval of multifaceted past events involves multi-modal sensory-perceptual details (Conway, 2001), semantic representations (Irish and Piguet, 2013), emotional connotations (Holland and Kensinger, 2010) and visual imagery (Greenberg and Rubin, 2003), integrated within a personally relevant setting (Conway et al., 2004). Neuroimaging studies consistently identify a distributed set of brain regions which support the retrieval of episodic memories from the past (Cabeza and St Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). This "core network" comprises the medial temporal lobes including the hippocampus, as well as frontopolar, lateral temporal, posterior parietal, and occipital cortices (Spreng et al., 2009).

Of particular interest in this regard, is the well-established view that episodic memory is a constructive rather than reproductive endeavour (Bartlett, 1932; Schacter et al., 1998). Functional neuroimaging studies in healthy individuals have revealed striking similarities between the recruitment of brain regions supporting episodic retrieval and those implicated in future-oriented thinking (Addis et al., 2007; Botzung et al., 2008; Szpunar et al., 2007) suggestive of a common neural substrate subtending past and future modes of thought (Schacter et al., 2007). Interestingly, the same neural network has also been shown to robustly activate when healthy individuals construct fictitious scenes devoid of temporal connotations in their mind's eye (Hassabis et al., 2007a; Summerfield et al., 2010).

The study of patients with AD affords a compelling view of the cognitive architecture of the brain when distinct neurocognitive processes begin to degrade in a systematic and coordinated manner (Irish et al., 2012c). Episodic memory dysfunction represents a hallmark feature of this patient group, in light of the characteristic medial temporal lobe degeneration

evident from an early stage in the pathological process (Braak and Braak, 1991). An amnestic profile predominates whereby AD patients exhibit anterograde episodic memory difficulties concerning the encoding and retrieval of recent experiences, irrespective of task modality (de Toledo-Morrell et al., 2000; McKhann et al., 2011). Retrograde memory impairments are also prominent, manifesting in pronounced autobiographical memory dysfunction (Barnabe et al., 2012; Irish et al., 2011a; Irish et al., 2011b), which is significantly associated with the degree of medial and lateral temporal lobe atrophy (Gilboa et al., 2005). In parallel with these characteristic impairments in episodic and autobiographical memory, patients with AD display marked difficulties with spatial navigation and orientation, attributable to the degeneration of the posterior hippocampus and retrosplenial/posterior cingulate cortex (Pengas et al., 2012; Tu et al., 2015).

While episodic dysfunction for the past represents the prototypical cognitive complaint in AD, converging evidence points to profound disturbances when AD patients attempt to envisage the future (Addis et al., 2009; El Haj et al., 2015; Irish et al., 2012a, b; reviewed by Irish and Piolino, 2015). Importantly, parallel deficits across past and future contexts have been observed, encompassing not only the provision of contextual details but also the subjective phenomenological experience (El Haj et al., 2015; Irish et al., 2012b). Similarly, the number of self-defining memories and the quality of the autonoetic experience appears comparably affected across past and future contexts in AD (El Haj et al., 2015). Atrophy in the posterior cingulate cortex has been shown to correlate strongly with impairments in autobiographical retrieval of the past and the capacity to simulate the future in AD (Irish et al., 2012a; Irish et al., 2013). As such, similarities in performance across past and future contexts in AD is reflected on the neuroanatomical level.

One area that has not been investigated to date concerns the capacity for patients with AD to imagine fictitious scenes that are devoid of temporal connotations. Scene construction refers to the process of mentally generating and maintaining a coherent and complex scene, the product of which can later be manipulated and visualised (Hassabis and Maguire, 2007), and depends critically upon the integrity of a "core" network comprising the medial temporal lobes, including the hippocampus and parahippocampal cortex, as well as posterior parietal regions such as the retrosplenial cortex and precuneus (Hassabis et al., 2007a; Hassabis et al., 2007b; Summerfield et al., 2010). Scene construction is argued to provide the essential foundation to support an array of complex higher-order processes including autobiographical memory, future thinking, spatial navigation, and potentially dreaming and mind-wandering (Hassabis and Maguire, 2007; Mullally and Maguire, 2014).

Studies of scene construction in clinical populations have proved particularly illuminating in this regard. Hassabis and colleagues demonstrated that patients with selective bilateral hippocampal damage are unable to construct fictitious atemporal scenes, with the spatial coherence of the imagined scenes severely compromised (Hassabis et al., 2007b). Subsequent studies have replicated this finding of imagination deficits in cohorts with medial temporal lobe damage (Andelman et al., 2010; Mullally et al., 2012b; Race et al., 2011; but see Squire et al., 2010), with the observation that integrity of the right hippocampus may be critical for mental simulation and future thinking (Mullally et al., 2012a; Mullally et al., 2014).

While a central role has been ascribed to the hippocampus in supporting scene construction, mounting evidence also points to the fundamental contribution of posterior parietal regions. Functional neuroimaging studies reliably implicate the retrosplenial cortex, posterior cingulate cortex, and precuneus when healthy individuals mentally construct atemporal scenes (Hassabis et al., 2007a; Summerfield et al., 2010). Moreover, a recent fMRI study in the developmental amnesic patient Jon reveals that he can construct fictitious scenes by

engaging many of the core regions of the scene construction network, including the retrosplenial and posterior cingulate cortices (Mullally et al., 2014). The importance of the posterior regions for atemporal imagination is underscored by the finding of grossly impaired scene construction in patients with posterior parietal lesions (Berryhill et al., 2010). As such, it appears that damage to any of the key nodes of the scene construction network precludes the capacity to construct spatially contiguous scenes.

To date, no study to our knowledge, has investigated the capacity to construct fictitious scenes devoid of temporal constraints in AD. This lack of research is somewhat surprising, given that key medial temporal and posterior parietal regions of the core network mediating scene construction are known to harbour significant pathology from early in the disease course in AD (Buckner et al., 2005). The objectives of the present study were twofold. Firstly, we sought to investigate the capacity for scene construction in a well-characterised cohort of AD patients, to determine whether deficits in imagination extend to atemporal forms. Secondly, we wished to elucidate the neural correlates of scene construction impairments in AD, to clarify which regions of the brain must be functional to support atemporal forms of imagination. We predicted that atemporal scene construction would be significantly compromised in AD relative to healthy older Controls, attributable primarily to hippocampal and posterior parietal degeneration characteristic of this disease.

2. Materials and Methods

2.1 Participants

Fourteen patients with Alzheimer's disease (AD) and 14 age- and education-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia (NeuRA), Sydney. All dementia patients met the relevant clinical diagnostic criteria for AD, displaying

significant episodic memory loss, cognitive dysfunction in at least one additional domain, and evidence of functional decline (McKhann et al., 2011). Clinical diagnoses were established by multidisciplinary consensus among a senior neurologist, clinical neuropsychologist, and occupational therapist based on extensive clinical investigations, cognitive assessment, informant report of activities of daily living, and structural neuroimaging.

Healthy controls were recruited from the NeuRA research volunteer panel and local community clubs. All controls scored 0 on the Clinical Dementia Rating scale (CDR) (Morris, 1997), and 88 or above on the Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi et al., 2006). Exclusion criteria for all participants included prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease, alcohol and other drug abuse, and limited English proficiency.

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales Human Research Ethics Advisory panel D. All participants, or their person responsible, provided written informed consent. Participants volunteered their time and were reimbursed for travel costs.

2.2 Behavioural testing

2.2.1 General cognitive screening

Participants completed a comprehensive battery of neuropsychological tests. The ACE-R was administered as a general measure of global cognitive functioning, Episodic memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) to measure

delayed verbal episodic recall; 3 minute recall of the Rey Complex Figure (RCF) (Rey, 1941) as an index of non-verbal episodic retrieval; Part A of the Doors and People Test (Baddeley et al., 1994) to measure non-verbal episodic recognition. Executive function was assessed using the Trail Making Test (Parts B-A) (Reitan, 1958) and the Digit Span task (Wechsler, 1997). Finally, verbal semantic processing was measured using letter fluency (F, A, S) (Strauss et al., 2006), and the Naming and Comprehension subtests from the Sydney Language Battery (SydBat) (Savage et al., 2013).

2.3 Assessment of scene construction

The capacity to imagine fictitious scenes was measured using the Scene Construction task developed by Hassabis et al. (2007b). To avoid fatigue in the AD participants, we shortened the test by constraining our focus to seven atemporal scenes (Beach, Museum, Pub, Ship, Market, Forest, Castle). In keeping with the original test protocol, the requirements of the scene construction task were explained to participants and examples were provided. A short description of each scenario was then read aloud and participants were instructed to imagine and describe the scenario in as much detail as possible. The scenario description was printed on a card and placed in front of participants to act as a reminder, if necessary. Importantly, participants were instructed not to recount an actual memory, but rather were required to construct something new. Participants provided their description of each scene uninterrupted until they reached a natural end to their narrative. Then, general probes were provided to elicit further details. Following the description of each scene, participants rated their constructions in terms of perceived salience, sense of presence, difficulty, and the degree to which the imagined scene resembled a past memory. Further, participants were required to indicate which qualitative statements accurately described the spatial properties of their

construction (Spatial Coherence). The test session lasted approximately 40 minutes. All interviews were digitally recorded for subsequent transcription and scoring.

The original scoring protocol developed by Hassabis et al. (2007b) was used to segment the scene construction narratives into a set of content statements. Content statements were then assigned to one of four categories; Entities Present, Spatial References, Sensory Descriptions, and Thoughts/Emotions/Actions. The scoring for each content category was capped at 7 points, leading to a maximum Total Content score of 28. The Spatial Coherence index reflected the degree to which participants rated their imagined scene as spatially contiguous and ranged from -6 (completely fragmented) to +6 (completely integrated). An objective quality judgement was conferred by the scorer to indicate how well the description of the scene evoked a vivid mental picture in their mind's eye, ranging from 0 (no mental image) to 10 (extremely vivid mental picture). SH scored all scene construction data and was blind to group membership and study objectives. To ensure consistency in scoring, an independent rater (MI) scored a subset of constructed scenes (4 AD and 4 Controls x 7 scenes per person = 56 scenes). Overall, inter-rater reliability was very high for Total Content (Cronbach's alpha = .979) and the quality judgment (Cronbach's alpha = .923).

A composite score, the Experiential Index, was generated from the four subcomponents of the scene construction task: Total Content, Participant Ratings (sense of presence, perceived salience), Spatial Coherence index, and objective Quality Judgment (see Hassabis et al., 2007b). The Experiential Index reflects the richness of the imagined experience ranging from 0 (not experienced at all) to 60 (extremely richly experienced).

2.4 Statistical analyses

Cognitive data were analysed using IBM SPSS Statistics (Version 21.0). Multivariate analyses of variance (MANOVA) were used to explore main effects of Group (Controls, AD) for all general cognitive tests and performance on the Scene Construction task. Chi-squared tests (X^2), based on the frequency patterns of dichotomous variables (e.g., sex), were also used. Finally, Spearman rank correlations were run to investigate the relationship between performance on the scene construction task and neuropsychological variables of interest.

2.5 Image acquisition

Participants underwent whole-brain T1-weighted images using a 3T Philips MRI scanner with standard quadrature head coil (8 channels). The 3D T1-weighted images were acquired using the following sequences: coronal orientation, matrix 256 x 256, 200 slices, 1 x 1 mm in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8ms, flip angle α = 19º. MRI structural scans were not available for 1 Control participant.

2.6 Voxel-based morphometry analysis

Three-dimensional T1-weighted sequences were analysed with FSL-VBM, a voxel-based morphometry analysis (Ashburner and Friston, 2000; Mechelli et al., 2005) using the FSL-VBM toolbox from the FMRIB software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM/UserGuide) (Smith et al., 2004). The VBM technique was used to identify grey matter density changes across groups on a voxel-by-voxel basis. Briefly, structural MR images were extracted using the brain extraction tool (BET) (Smith, 2002), following which, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang et al., 2001). The FMRIB non-linear

registration approach (FNIRT) (Andersson et al., 2007a, 2007b) was then used to align the resulting grey matter partial volumes to the Montreal Neurological Institute standard space (MNI152), using a b-spline representation of the registration warp field (Rueckert et al., 1999). A study-specific template was created using the resulting images, to which the native grey matter images were re-registered nonlinearly. To correct for local expansion or contraction, the registered partial volume maps were modulated by dividing by the Jacobian of the warp field. Finally, the modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3mm.

An unbiased whole-brain general linear model was employed to investigate grey matter intensity differences via permutation-based non-parametric testing (Nichols and Holmes, 2002) with 10,000 permutations per contrast. Differences in cortical grey matter intensities between AD patients and Controls were assessed using regression models with separate directional contrasts (i.e., t-tests). Age was included as a nuisance variable in the atrophy analysis. Clusters were extracted using the threshold-free cluster enhancement and corrected for False Discovery Rate at $p < .05$.

Next, correlations between the Experiential Index of the scene construction task and regions of grey matter intensity were investigated in each participant group separately. The Experiential Index was chosen as the key outcome measure as it reflects the overall richness and coherence of the constructed scene (Hassabis et al., 2007b). For additional statistical power, a covariate-only statistical model was employed. A positive t-contrast was used in the covariate model, providing an index of association between grey matter volume and scene construction scores. Anatomical locations of significant results were overlaid on the MNI standard brain, with maximum coordinates provided in MNI stereotaxic space. Anatomical labels were determined with reference to the Harvard-Oxford probabilistic cortical atlas. For all covariate analyses, clusters were corrected for False Discovery Rate at $p < .05$. To further

reduce the potential for false positive results, a cluster threshold of 50 contiguous voxels was employed. For illustrative purposes, correlations were run between the Experiential Index and grey matter intensity for key regions of interest to emerge as significant from the covariate analyses in each participant group.

Finally, an overlap analysis was conducted using the results from the covariate analyses to identify common grey matter regions implicated in scene construction performance across the groups. The scaled contrasts of the statistical maps generated from the AD and Control covariate analyses were multiplied to create an inclusive, or overlap, mask across groups.

3. Results

3.1 Demographics

Participants were matched for age ($F(1, 26) = 1.182$, $p = .287$) and years in education ($F(1, 26) = 3.016$, $p = .094$). Chi-squared tests revealed no difference in sex distribution between the groups ($p = .445$) (Table 1).

3.2 General cognitive functioning

Neuropsychological testing revealed a characteristic profile of deficits in the AD group relative to Controls (Table 1). AD patients showed global cognitive impairment on the ACE-R screening tool ($F(1, 26) = 20.049$, $p < .0001$), and presented in the mild to moderate stages of the disease (ACE-R total score range: 89-62). Prominent impairments in episodic memory were evident in the AD group for recall of verbal (RAVLT: $F(1, 24) = 225.238$, $p < .0001$) and non-verbal (RCF: $F(1, 23) = 33.970$, $p < .0001$) information, as well as visual episodic

recognition (Doors A: $F(1, 20) = 46.342$, $p < .0001$). Further deficits in semantic processing (Naming: $F(1, 24) = 19.592$, $p = .001$; Comprehension: $F(1, 23) = 16.835$, $p < .0001$) and verbal fluency ($F(1, 20) = 10.757$, $p = .004$) were observed. Finally, AD patients displayed significant executive dysfunction relative to Controls (Digit span total: $F(1,25) = 23.568$, $p < .0001$; Trails B-A $F(1, 20) = 6.258$, $p = .021$).

INSERT TABLE 1 AROUND HERE

3.3 Scene Construction Performance

3.3.1 Experiential Index

The key result, illustrated in Figure 1, was that AD patients displayed marked impairments in the ability to imagine spatially coherent scenes on the scene construction task relative to Controls. Firstly, the overall ability to imagine new experiences was ascertained using the Experiential Index, a composite score of all subcomponents of the scene construction task. AD patients scored significantly lower than controls on the Experiential Index ($F(1, 26) = 71.420$, $p < .0001$), indicating that the capacity to imagine new experiences in rich detail is grossly impaired in AD.

INSERT FIGURE 1 AROUND HERE.

3.3.2 Total Content

Looking at each of the main subcomponents of the scene construction task in turn revealed important group differences (Table 2). AD patients displayed marked deficits in the provision of contextual details for the imagined scenes (Total Content: $F(1, 26) = 43.839$; $p < .0001$). This disruption of content occurred irrespective of detail subcategory, with AD patients providing significantly lower levels of detail for Spatial References ($p < .0001$), Entities Present ($p < .0001$), Sensory Descriptions ($p = .001$) and Thought/Emotions/Actions ($p < .0001$) (see Figure 2 for representative examples of scene construction narratives).

INSERT FIGURE 2 AROUND HERE.

3.3.3 Spatial Coherence

Analysis of the Spatial Coherence index, which represents the degree to which the imagined experiences are bound within a coherent spatial context, also revealed a significant group effect ($F(1, 26) = 7.819$, $p = .010$). This group difference reflected the fact that AD patients rated their imagined scenarios as fragmented and lacking in coherence, resembling a collection of disparate images rather than a fully integrated visual scene.

3.3.4 Quality Judgment

The Quality Judgment provides an objective measure of the overall quality of the imagined scenes. AD patients' constructions were judged to be significantly poorer in quality than those of Controls ($F(1, 26) = 221.663$, $p < .0001$) failing to evoke a rich visual image in the mind's eye of the rater.

INSERT TABLE 2 AROUND HERE.

3.3.5 Participant ratings

Interestingly, the subjective experiential ratings failed to discriminate between the two participant groups. AD patients did not differ from Controls in terms of their subjective feeling of presence in the imagined scene (p = .387) or their perceived salience of the imagined experiences (p = .323) (see Table 2). Importantly, AD patients did not judge the scene construction task to be more difficult than Controls (AD mean = 2.3; Control mean = 2.1; p = .349).

Finally, the degree to which the imagined new experiences resembled previously experienced events was explored. A significant group difference was found for ratings of similarity to past memories ($F(1, 26) = 22.403$, $p < .0001$) with AD patients tending to rate their imagined experiences as "similar to past memories" (AD mean = 2.4) whereas Controls rated their experiences as only reminding them of elements of a few memories (Control mean = 3.2).

3.3.6 Relationship between scene construction performance and neuropsychological tests

Spearman rank correlations were run to investigate the potential relationship between scene construction performance and the domains of episodic memory, semantic processing, attention/executive function, and language. No significant associations were found between Experiential Index scores on the scene construction task and performance across each of the

background neuropsychological tests for AD patients or Control participants (all *p* values > .1, Table 3).

INSERT TABLE 3 AROUND HERE

Finally, to ensure that scene construction deficits were not primarily attributable to a general decline in language, we conducted an analysis of covariance (ANCOVA) with letter fluency and ACE-R Language subscales scores as covariates. Significant group differences persisted for the Experiential Index ($F(1, 18) = 22.718$, $p < .0001$) indicating that a broader language impairment cannot account for the marked impairments in scene construction demonstrated by AD patients.

3.4 Voxel-based morphometry analyses

3.4.1 Atrophy analyses

Compared to Controls, AD patients displayed significant grey matter intensity decrease in a distributed set of frontal, lateral and medial temporal, and posterior parietal brain regions. Significant atrophy was evident in medial temporal lobe regions including the bilateral hippocampi, amygdalae, and parahippocampal gyri, extending to the left lateral temporal cortices. The bilateral frontal poles, inferior frontal gyri, and medial prefrontal cortices were also affected, as were posterior regions including the bilateral angular gyri, bilateral supramarginal gyri, and bilateral lateral occipital cortices (Table 4). These patterns of atrophy are consistent with previous reports in AD (Karas et al., 2010).

INSERT TABLE 4 AROUND HERE.

3.4.2 Grey matter correlates of scene construction performance

Figure 3 displays the results from the covariate analyses investigating the association between Experiential Index scores and grey matter intensity in the brain in each participant group.

For AD patients, the capacity to envisage spatially coherent atemporal scenes was significantly associated with integrity of the left posterior cingulate cortex and precuneus, the left inferior temporal gyrus, and the right supramarginal gyrus (Figure 3, Table 5). In contrast, for healthy older Controls, Experiential Index scores were significantly associated with integrity of a distributed network including the bilateral parahippocampal gyri, left posterior hippocampus, left posterior cingulate and precuneus, the left supramarginal and angular gyrus, the left superior frontal gyrus, left frontal pole, and left medial prefrontal cortex (Figure 3, Table 5).

INSERT FIGURE 3 AROUND HERE.

INSERT TABLE 5 AROUND HERE.

Finally, grey matter intensity values for each participant were extracted at the peak coordinate for key regions to emerge as significant from the covariate analyses (posterior cingulate cortex; parahippocampal gyrus/hippocampus). The relationship between grey matter integrity of these regions and scene construction performance were explored using Spearman rank correlations. The r correlation coefficients were then converted to z scores using Fisher's transformation to compare the magnitude of the relationship between these key brain regions and scene construction performance between the groups. Integrity of the

posterior cingulate cortex correlated with Experiential Index scores in the AD (r = .586, p = .03) and Control (r = .791; p = .002) groups (Figure 4A) with no difference in the magnitude of this correlation between the groups (z = 0.92, p = .358). In contrast, integrity of the left parahippocampal gyrus/hippocampus was found to correlate robustly with scene construction performance in Controls (r = .861, p < .001), yet this relationship was absent in the AD group (r = -.269, p =.346) (z = 3.6; p < .001) (Figure 4B).

INSERT FIGURE 4 AROUND HERE.

Finally, to identify the regions significantly associated with scene construction performance in both the AD and Control groups, we conducted an overlap analysis based on the statistical maps generated from the covariate analyses. This analysis revealed that the common structure implicated in scene construction performance across AD and Control groups was the posterior cingulate cortex (MNI coordinates: x = -2, y = -38, z = 24; Figure 5).

INSERT FIGURE 5 AROUND HERE.

4. Discussion

This study represents the first investigation of atemporal scene construction, and its associated neural correlates, in Alzheimer's disease (AD). Marked impairments in the capacity to construct spatially coherent scenes were evident in AD, attributable to damage to posterior parietal and lateral temporal regions in the brain. In contrast, integrity of a distributed network comprising frontal, parietal, and medial temporal lobe structures including the parahippocampal gyrus and posterior hippocampus were associated with intact

performance in Controls. An overlap analysis revealed that the posterior cingulate cortex was commonly implicated in scene construction performance in both AD and Control groups. Here we discuss the implications of our findings for current models of memory and imagination, as well as in the context of the characteristic deficits typically observed in AD.

The most important finding arising from this study is the observation of striking alterations in scene construction processes in AD, converging with previous reports of imagination difficulties in patients with medial temporal lobe damage (Andelman et al., 2010; Hassabis et al., 2007b; Klein et al., 2002; Race et al., 2011). Importantly, these deficits encompassed not only the provision of contextual details but also the ability to integrate these details into a spatially coherent whole in the mind's eye. As such, AD patients tended to provide overgeneral fragmented descriptions which largely recapitulated events that had previously transpired. Given the cross-sectional nature of this study, it remains difficult to disentangle the interplay between impaired scene construction performance and overall episodic memory integrity in AD. Our correlation analyses failed to reveal a significant relationship between scene construction performance and standard neuropsychological tests of episodic memory retrieval however, our relatively small sample size may have limited our power to detect significant associations in this regard. Notably, in a previous study we documented a significant relationship between episodic memory integrity and the ability to envisage plausible future events in AD (Irish et al., 2012a), in line with current theories emphasising a fundamental role for episodic memory in the constructive simulation of future events (Schacter et al., 2007). It may be that traditional lab-based episodic memory paradigms fail to capture the complexity of the type of contextual recall that is essential for performance on the scene construction task. Given that AD patients tended to draw upon overgeneral memories from their past, it would be interesting to explore the potential relationship between

semanticized aspects of autobiographical memory retrieval and the provision of content during scene construction.

Neuroimaging covariate analyses revealed that the degeneration of posterior parietal and lateral temporal structures underpins scene construction impairments in AD. Indeed, the posterior cingulate cortex (PCC) emerged as the sole region common to scene construction performance in AD patients and healthy Controls. Our finding of significant posterior cingulate/precuneus involvement in the construction of atemporal scenes in AD converges with previous studies investigating lab-based episodic memory (Irish et al., 2014), autobiographical memory and episodic future thinking (Irish et al., 2012a; Irish et al., 2013) in this syndrome. The posterior cingulate cortex represents a particularly interesting convergence zone in the brain as it occupies a crucial node in the core autobiographical memory network (Svoboda et al., 2006), and represents a "hub" within the brain's default mode network (Andrews-Hanna et al., 2010). Moreover, the PCC has been implicated across an array of memory-based construction/simulation functions such as autobiographical memory, episodic future thinking, and scene construction (Andrews-Hanna et al., 2010). Damage to the PCC in AD most likely reflects the degeneration of a broader posteromedial network, in which functional connectivity between the PCC and hippocampus is compromised (La Joie et al., 2014). Of note, a recent resting-state functional connectivity study points to disrupted connectivity between the PCC and MTL in medial temporal lobe amnesics (Hayes et al., 2012) suggesting that, in addition to structural anomalies in the MTL, functional aberrations across large-scale brain networks likely modulate memory-based construction/simulation deficits in these syndromes.

The PCC is implicated across a wide spectrum of cognitive processes and may support scene construction in a variety of ways. For example, this region has been implicated in the generation of visuospatial imagery (Cavanna and Trimble, 2006), the recollective aspect of episodic memory retrieval (Wagner et al., 2005), and in the invoking of self-referential processes when envisaging oneself across past and future contexts (Abraham et al., 2008; Northoff and Bermpohl, 2004). Functional neuroimaging studies of scene construction in healthy individuals have revealed that the precuneus and posterior cingulate cortex are differentially recruited during retrieval of real versus imaginary memories (Hassabis et al., 2007a), a finding which may reflect greater familiarity for the visual context for real memories versus more novel imaginary events (Hassabis and Maguire, 2009). Recruitment of midline posterior structures has been hypothesised to reflect the reactivation of familiar visuospatial contexts which facilitates the generation of a plausible future image (Szpunar et al., 2007). This position is supported by the finding that AD patients tend to recapitulate previously experienced events during future simulation rather than creating genuinely novel events (Irish et al., 2012b). In the context of scene construction, AD patients may rely upon a limited pool of overgeneral gist-based memories, which remain relatively intact in the early stages of the disease (Gallo et al., 2006) and serve as the most accessible form of information that is relevant to the event of interest (El Haj et al., 2015). In this vein, the degeneration of posterior parietal structures may disrupt the capacity for old/new detection, leading to the recasting of content from previously experienced events.

The left lateral temporal cortex was also implicated in scene construction performance in AD. This finding is notable given the well-established role of the left temporal cortices in semantic processing (Visser et al., 2010). Mounting evidence now points to the fundamental contribution of semantic memory for a range of constructive endeavours including

remembering the past (Greenberg and Verfaellie, 2010) and imagining the future (Duval et al., 2012; Irish et al., 2012a). In the context of atemporal scene construction, it has been suggested that intact semantic memory may facilitate the construction of scenes in patients with developmental amnesia (Hurley et al., 2011) and paediatric patients with hippocampal damage (Cooper et al., 2011). Semantic memory represents a suitable conduit for constructive endeavours given that it provides undifferentiated conceptual information that can be generalised across a range of contexts (Binder and Desai, 2011; Irish and Piguet, 2013). In particular, semantic memory may be critically required where novel scenes or events must be constructed, as evidence from patients with semantic dementia suggests that the loss of semantic memory disproportionally disrupts the novelty of future simulations (Irish et al., 2012a, b). While we did not find a relationship between neuropsychological assessments of semantic memory and scene construction performance in AD, our neuroimaging findings support current theories emphasising the importance of the semantic memory system in mediating complex constructive endeavours (Binder and Desai, 2011; Irish and Piguet, 2013; Mullally and Maguire, 2014). It may be that the lab-based tests of semantic processing used here do not adequately capture the specific mechanisms of semantic memory required for successful scene construction, and we suggest that future studies will be important to tease apart the contribution of semantic memory in this regard.

Turning our attention towards the healthy Control group, our neuroimaging findings revealed significant associations between a distributed network of regions comprising medial temporal structures, including the bilateral parahippocampal gyrus and left posterior hippocampus, along with prefrontal and posterior parietal regions such as the supramarginal and angular gyrus and performance on the scene construction task. We draw attention to the fact that these findings represent associations between scene construction scores and grey matter

intensity in the brain rather than functional activations in response to task performance. In addition, we note that our Controls performed almost at ceiling on this task, potentially reflecting the capped nature of the content scoring system. These caveats aside, the regions to emerge from our VBM analyses converge remarkably well with subregions of the construction system of the brain, a core network of regions that activates during the recall of recent episodic memories, recollection of previously imagined experiences, and the construction of novel scenarios (Hassabis et al., 2007a; Hassabis and Maguire, 2009). Our finding of significant left posterior hippocampal involvement in the construction of atemporal scenes resonates with functional neuroimaging studies in which the centrality of the hippocampus, albeit particularly on the right hand side, has been emphasised (Hassabis et al., 2007a; Mullally et al., 2012a; Mullally et al., 2014; Summerfield et al., 2010). Accordingly, it has been proposed that a unique contribution of the hippocampus is to provide a coherent spatial context as the foundation for an array of constructive endeavours including autobiographical memory, simulation of future events, spatial navigation, and prediction of the upcoming environment (reviewed by Mullally and Maguire, 2014). The fact that our analyses exclusively implicated the posterior hippocampus is noteworthy and likely reflects a functional subdivision in the hippocampus, by which the posterior portion is differentially involved in the retrieval of spatial information and the reinstatement of spatial contexts (reviewed by Nadel et al., 2013). It has been suggested that the posterior hippocampus provides the requisite spatial "backdrop" for the constructed scenes (Mullally et al., 2012a). In addition, the posterior hippocampus is densely connected to posterior midline regions via the retrosplenial cortex, and it has been proposed that the retrosplenial cortex makes a fundamental contribution to the processing of scenes by translating allocentric (hippocampally-mediated) representations into those that are egocentric (parietal cortically-based) (Vann et al., 2009). Finally, our finding of significant bilateral posterior

parahippocampal involvement underscores the fundamental contribution of this region to the construction of scenes, potentially by coding for the presence of space (Mullally and Maguire, 2011; Zeidman et al., 2012) or the processing of contextual associations (Aminoff et al., 2013).

In addition to the contribution of medial temporal structures, our study reveals the importance of lateral parietal regions including the left angular gyrus and left supramarginal gyrus in supporting the construction of fictitious scenes. Posterior parietal activation during scene construction in healthy individuals has been previously documented (Hassabis et al., 2007a; Summerfield et al., 2010) and damage to posterior parietal cortices has been shown to manifest in scene construction impairments (Berryhill et al., 2010). The angular gyrus, in particular, has been proposed to represent a cross-modal integrative hub that is well positioned to subserve the convergence of multisensory information and to impart meaning to events within contextualised environments (Seghier, 2013). This region has further been posited to occupy a core node of a posterior medial cortical system which facilitates the construction and deployment of a "situation model" in which relationships between entities, outcomes and actions are represented (Ranganath and Ritchey, 2012). Finally, we observed significant associations between scene construction performance in Controls and grey matter integrity in frontal regions, including the superior frontal gyrus, frontal pole, and medial prefrontal cortex. Of particular relevance here is the medial prefrontal cortex, which has been proposed to represent an ancillary region that is co-opted into the core construction network contingent on task demands (Hassabis et al., 2007a). In this vein, recruitment of medial prefrontal regions may reflect demands placed upon self-referential processes as individuals attempt to distinguish between real and fictitious memories and to evaluate the "realness" of constructed scenes (Hassabis and Maguire, 2009; Summerfield et al., 2010).

A number of methodological limitations warrant consideration. While we have demonstrated that scene construction is markedly impaired in AD it remains unclear whether this represents the primary mechanism underlying a host of phenotypic impairments in this disorder. Moreover, given the co-occurrence of significant scene construction and episodic memory impairments in our AD sample, it is difficult to ascertain the relationship between these processes, leading to the proverbial "chicken and egg" problem. As such, whether scene construction deficits emerge secondary to, or in parallel with, changes in episodic memory remains to be elucidated. Related to this point, it is clear that the content of the scenes created by AD patients resemble previously experienced autobiographical events, suggesting that patients harness overgeneral gist-based memory to populate their constructions. It will therefore be important for future studies to tease apart the potential role of overgeneral autobiographical memories to the overall process of scene construction in AD. We suggest that future studies which differentially stress the construction of novel scenes (e.g., walking on the moon, swimming in Antarctica) will prove particularly interesting in this context, compelling participants to move beyond the provision of potentially routinized scripts or overgeneral autobiographical memories from the past. Within the limits of the current study, it was not possible to investigate how scene construction performance relates to other cognitive functions, such as autobiographical memory, future thinking, or spatial navigation, processes which have been proposed to hinge upon the capacity to construct spatially coherent scenes (Hassabis and Maguire, 2009; Mullally and Maguire, 2014) and to rely upon the integrity of a common core brain network (Spreng et al., 2009). Accordingly, it will be important for future studies to explore the potential interplay between scene construction deficits and the prototypical impairments of autobiographical and spatial memory, seen in AD. The contribution of mental imagery to scene construction deficits in AD also warrants

further study, given that patients with AD display significant difficulties on complex spatial mental imagery tasks, in the context of relatively preserved basic forms of mental imagery (Hussey et al., 2012). Similarly, we did not investigate the general narrative capacity of the AD cohort. Conflicting evidence exists regarding the relationship between constructive processes and general narrative ability (Gaesser et al., 2011; Race et al., 2011). Further, marked heterogeneity has been observed in the discourse patterns produced by AD patients, with one study revealing that over half of AD patients score at Control levels for discourse production related to picture-supported narratives (Duong et al., 2005). As such, it will be important for future studies to clarify the relationship between scene construction performance and narrative discourse in AD. Finally, our AD patients were in the mild to moderate stages of the disease and it remains unclear at what stage of the pathological process difficulties in scene construction manifest. To address this issue, we suggest that studies targeting the prodromal stage of Mild Cognitive Impairment, characterised by circumscribed MTL pathology, will provide important insights into the origin and evolution of scene construction dysfunction, and will serve to clarify the neurocognitive mechanisms driving such deficits. Functional activation studies of scene construction performance in healthy aging, MCI and AD will prove particularly informative in this regard, bridging voxel-based morphometry findings in patient populations with the extant fMRI literature in healthy individuals.

Conclusions

In conclusion, this study represents the first investigation of scene construction in patients with Alzheimer's disease. Our findings are notable in two respects. Firstly, we have confirmed that the capacity to construct spatially coherent scenes is grossly compromised in AD. Secondly, our neuroimaging analyses support current influential theories emphasising

the importance of the posterior hippocampus and neighbouring retrosplenial/posterior cingulate cortical regions in the generation of spatially coherent scenes (Mullally and Maguire, 2014; Vann et al., 2009). A question of paramount importance to address is whether scene construction dysfunction represents the core mechanism underlying a host of phenotypic impairments displayed by patients with AD and amnestic Mild Cognitive Impairment. We suggest that future studies investigating the potential relationship between scene construction processes and disparate cognitive functions essential for everyday adaptive functioning will prove particularly illuminating in this regard.

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References

Abraham A, Schubotz RI, and von Cramon DY. Thinking about the future versus the past in personal and non-personal contexts. *Brain Res*, 1233: 106-119, 2008.

Addis DR, Sacchetti DC, Ally BA, Budson AE, and Schacter DL. Episodic simulation of future events is impaired in mild Alzheimer's disease. *Neuropsychologia*, 47 (12): 2660-2671, 2009.

Addis DR, Wong AT, and Schacter DL. Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, 45 (7): 1363-1377, 2007.

Aminoff EM, Kveraga K, and Bar M. The role of the parahippocampal cortex in cognition. *Trends Cogn Sci*, 17 (8): 379-390, 2013.

Andelman F, Hoofien D, Goldberg I, Aizenstein O, and Neufeld M. Bilateral hippocampal lesion and a selective impairment of the ability for mental time travel. *Neurocase*, 16 (5): 426-435, 2010.

Andersson JLR, Jenkinson M, and Smith S. Non-linear optimisation. FMRIB Technical Report TR07JA1. University of Oxford FMRIB Centre: Oxford, 2007a.

Andersson JLR, Jenkinson M, and Smith S. Non-linear registration, aka Spatial normalisation. FMRIB Technical Report TR07JA2. University of Oxford FMRIB Centre: Oxford, 2007b.

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, and Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron*, 65 (4): 550-562, 2010.

Ashburner J, and Friston KJ. Voxel-based morphometry - the methods. *Neuroimage*, 11: 805-821., 2000.

Baddeley AD, Emslie H, and Nimmo-Smith I. *The Doors and People Test: a test of visual and verbal recall and recognition.* Bury St. Edmunds: Thames Valley Test Company, 1994.

Barnabe A, Whitehead V, Pilon R, Arsenault-Lapierre G, and Chertkow H. Autobiographical memory in mild cognitive impairment and Alzheimer's disease: A comparison between the Levine and Kopelman interview methodologies. *Hippocampus*, 22 (9): 1809-1825, 2012.

Bartlett FC. Remembering. Cambridge University Press: Cambridge, 1932.

Berryhill ME, Picasso L, Arnold R, Drowos D, and Olson IR. Similarities and differences between parietal and frontal patients in autobiographical and constructed experience tasks. *Neuropsychologia*, 48 (5): 1385-1393, 2010.

Binder JR, and Desai RH. The neurobiology of semantic memory. *Trends in Cognitive Sciences*, 15 (11): 527-536, 2011.

Botzung A, Denkova E, and Manning L. Experiencing past and future personal events: Functional neuroimaging evidence on the neural bases of mental time travel. *Brain Cogn*, 66 (2): 202-212, 2008.

Braak H, and Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, 82: 239-249, 1991.

Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, and Mintun MA. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci*, 25 (34): 7709-7717, 2005.

Cabeza R, and St Jacques P. Functional neuroimaging of autobiographical memory. *Trends Cogn Sci*, 11 (5): 219-227, 2007.

Cavanna AE, and Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 129 (Pt 3): 564-583, 2006.

Conway MA. Sensory–perceptual episodic memory and its context: Autobiographical memory. *Philosophical Transactions B*, 356 (1413): 1375-1384, 2001.

Conway MA, Singer JA, and Tagini A. The self and autobiographical memory: Correspondence and coherence. *Social Cognition*, 22 (5): 491-529, 2004.

Cooper JM, Vargha-Khadem F, Gadian DG, and Maguire EA. The effect of hippocampal damage in children on recalling the past and imagining new experiences. *Neuropsychologia*, 49 (7): 1843-1850, 2011.

de Toledo-Morrell L, Dickerson B, Sullivan MP, Spanovic C, Wilson R, and Bennett DA. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus*, 10 (2): 136-142, 2000.
Duong A, Giroux F, Tardif A, and Ska B. The heterogeneity of picture-supported narratives in Alzheimer's disease. *Brain Lang*, 93 (2): 173-184, 2005.
Duval C, Desgranges B, de La Sayette V, Belliard S, Eustache F, and Piolino P. What happens to personal identity when semantic knowledge degrades? A study of the self and autobiographical memory in semantic dementia. *Neuropsychologia*, 50 (2): 254-265, 2012.
El Haj M, Antoine P, and Kapogiannis D. Similarity between remembering the past and imagining the future in Alzheimer's disease: Implication of episodic memory. *Neuropsychologia*, 66: 119-125, 2015.
Gaesser B, Sacchetti DC, Addis DR, and Schacter DL. Characterizing age-related changes in remembering the past and imagining the future. *Psychol Aging*, 26 (1): 80-84, 2011.
Gilboa A, Ramirez J, Kohler S, Westmacott R, Black SE, and Moscovitch M. Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. *Hippocampus*, 15 (4): 535-550, 2005.
Greenberg DL, and Rubin DC. The neuropsychology of autobiographical memory. *Cortex*, 39 (4-5): 687-728, 2003.
Greenberg DL, and Verfaellie M. Interdependence of episodic and semantic memory: evidence from neuropsychology. *J Int Neuropsychol Soc*, 16 (5): 748-753, 2010.
Hassabis D, Kumaran D, and Maguire EA. Using imagination to understand the neural basis of episodic memory. *Journal of Neuroscience*, 27 (52): 14365-14374, 2007a.
Hassabis D, Kumaran D, Vann SD, and Maguire EA. Patients with hippocampal amnesia cannot imagine new experiences. *Proceedings of the National Academy of Sciences U S A*, 104 (5): 1726-1731, 2007b.
Hassabis D, and Maguire EA. Deconstructing episodic memory with construction. *Trends in Cognitive Sciences*, 11 (7): 299-306, 2007.
Hassabis D, and Maguire EA. The construction system of the brain. *Philos Trans R Soc Lond B Biol Sci*, 364: 1263-1271, 2009.
Hayes SM, Salat DH, and Verfaellie M. Default network connectivity in medial temporal lobe amnesia. *J Neurosci*, 32 (42): 14622-14629, 2012.
Holland AC, and Kensinger EA. Emotion and autobiographical memory. *Phys Life Rev*, 7 (1): 88-131, 2010.
Hurley NC, Maguire EA, and Vargha-Khadem F. Patient HC with developmental amnesia can construct future scenarios. *Neuropsychologia*, 49 (13): 3620-3628, 2011.
Hussey EP, Smolinsky JG, Piryatinsky I, Budson AE, and Ally BA. Using mental imagery to improve memory in patients with Alzheimer disease: trouble generating or remembering the mind's eye? *Alzheimer Dis Assoc Disord*, 26 (2): 124-134, 2012.
Irish M, Addis DR, Hodges JR, and Piguet O. Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain*, 135 (Pt 7): 2178-2191, 2012a.
Irish M, Addis DR, Hodges JR, and Piguet O. Exploring the content and quality of episodic future simulations in semantic dementia. *Neuropsychologia*, 50 (14): 3488-3495, 2012b.
Irish M, Hodges JR, and Piguet O. Episodic future thinking is impaired in the behavioural variant of frontotemporal dementia. *Cortex*, 49 (9): 2377-2388, 2013.
Irish M, Hornberger M, Lah S, Miller L, Pengas G, Nestor PJ, Hodges JR, and Piguet O. Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia*, 49 (9): 2694-2702, 2011a.
Irish M, Lawlor BA, O'Mara SM, and Coen RF. Impaired capacity for autonoetic reliving during autobiographical event recall in mild Alzheimer's disease. *Cortex*, 47 (2): 236-249, 2011b.
Irish M, and Piguet O. The pivotal role of semantic memory in remembering the past and imagining the future. *Front Behav Neurosci*, 7: 27, 2013.
Irish M, Piguet O, and Hodges JR. Self-projection and the default network in frontotemporal dementia. *Nat Rev Neurol*, 8 (3): 152-161, 2012c.

Irish M, Piguet O, Hodges JR, and Hornberger M. Common and unique grey matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. *Human Brain Mapping*, 35 (4): 1422-1435, 2014.
Irish M, and Piolino P. Impaired capacity for prospection in the dementias - Theoretical and clinical implications. *Br J Clin Psychol*, 2015.
Klein SB, Loftus J, and Kihlstrom JF. Memory and temporal experience: the effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. *Social Cognition*, 20 (5): 353-379, 2002.
La Joie R, Landeau B, Perrotin A, Bejanin A, Egret S, Pelerin A, Mezenge F, Belliard S, de La Sayette V, Eustache F, Desgranges B, and Chetelat G. Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks. *Neuron*, 81 (6): 1417-1428, 2014.
Maguire EA. Neuroimaging studies of autobiographical event memory. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 356 (1413): 1441-1451, 2001.
McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, and Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, 7 (3): 263-269, 2011.
Mechelli A, Price CJ, Friston KJ, and Ashburner J. Voxel-based morphometry of the human brain: methods and applications. *Curr Med Imaging Rev*, 1: 1-9, 2005.
Mioshi E, Dawson K, Mitchell J, Arnold R, and Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21 (11): 1078-1085, 2006.
Morris J. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International Psychogeriatrics*, 9 (S1): 173-176, 1997.
Mullally SL, Hassabis D, and Maguire EA. Scene construction in amnesia: an FMRI study. *J Neurosci*, 32 (16): 5646-5653, 2012a.
Mullally SL, Intraub H, and Maguire EA. Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. *Current Biology*, 22 (4): 261-268, 2012b.
Mullally SL, and Maguire EA. A new role for the parahippocampal cortex in representing space. *J Neurosci*, 31 (20): 7441-7449, 2011.
Mullally SL, and Maguire EA. Memory, Imagination, and Predicting the Future: A Common Brain Mechanism? *The Neuroscientist*, 20: 220-234, 2014.
Mullally SL, Vargha-Khadem F, and Maguire EA. Scene construction in developmental amnesia: an fMRI study. *Neuropsychologia*, 52: 1-10, 2014.
Nadel L, Hoscheidt S, and Ryan LR. Spatial cognition and the hippocampus: the anterior-posterior axis. *J Cogn Neurosci*, 25 (1): 22-28, 2013.
Nichols TE, and Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping*, 15: 1-25., 2002.
Northoff G, and Bermpohl F. Cortical midline structures and the self. *Trends in Cognitive Sciences*, 8 (3): 102-107, 2004.
Pengas G, Williams GB, Acosta-Cabronero J, Ash TW, Hong YT, Izquierdo-Garcia D, Fryer TD, Hodges JR, and Nestor PJ. The relationship of topographical memory performance to regional neurodegeneration in Alzheimer's disease. *Front Aging Neurosci*, 4: 17, 2012.
Race E, Keane MM, and Verfaellie M. Medial temporal lobe damage causes deficits in episodic memory and episodic future thinking not attributable to deficits in narrative construction. *J Neurosci*, 31 (28): 10262-10269, 2011.
Ranganath C, and Ritchey M. Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci*, 13 (10): 713-726, 2012.
Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and motor skills*, 8: 271-276, 1958.

Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique. *Archives de Psychologie*, 28: 215-285, 1941.
Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, and Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Transactions on Medical Imaging*, 18: 712-721, 1999.
Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, and Hodges JR. Distinguishing Subtypes in Primary Progressive Aphasia: Application of the Sydney Language Battery. *Dement Geriatr Cogn Disord*, 35 (3-4): 208-218, 2013.
Schacter DL, Addis DR, and Buckner RL. Remembering the past to imagine the future: the prospective brain. *Nature Reviews Neuroscience*, 8 (9): 657-661, 2007.
Schacter DL, Norman KA, and Koutstaal W. The cognitive neuroscience of constructive memory. *Annu Rev Psychol*, 49: 289-318, 1998.
Schmidt M. *Rey Auditory and Verbal Learning Test: A handbook*. Los Angeles: Western Psychological Services., 1996.
Seghier ML. The angular gyrus: multiple functions and multiple subdivisions. *The Neuroscientist*, 19 (1): 43-61, 2013.
Smith SM. Fast robust automated brain extraction. *Human Brain Mapping*, 17: 143-155, 2002.
Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, and Niazy RK. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23: S208-219., 2004.
Spreng RN, Mar RA, and Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J Cogn Neurosci*, 21 (3): 489-510, 2009.
Squire LR, van der Horst AS, McDuff SG, Frascino JC, Hopkins RO, and Mauldin KN. Role of the hippocampus in remembering the past and imagining the future. *Proceedings of the National Academy of Sciences U S A*, 107 (44): 19044-19048, 2010.
Strauss E, Sherman EMS, and Spreen O. *A compendium of neuropsychological tests: Administration, norms, and commentary*Oxford University Press, USA, 2006.
Summerfield JJ, Hassabis D, and Maguire EA. Differential engagement of brain regions within a 'core' network during scene construction. *Neuropsychologia*, 48 (5): 1501-1509, 2010.
Svoboda E, McKinnon MC, and Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*, 44 (12): 2189-2208, 2006.
Szpunar K, Watson J, and McDermott KB. Neural substrates of envisioning the future. *Proceedings of the National Academy of Sciences*, 104 (2): 642-647, 2007.
Tu S, Wong S, Hodges JR, Irish M, Piguet O, and Hornberger M. Lost in spatial translation - A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex*, 67: 83-94, 2015.
Tulving E. Episodic memory: from mind to brain. *Annual Review of Psychology*, 53: 1-25, 2002.
Vann SD, Aggleton JP, and Maguire EA. What does the retrosplenial cortex do? *Nat Rev Neurosci*, 10 (11): 792-802, 2009.
Visser M, Embleton KV, Jefferies E, Parker GJ, and Ralph MA. The inferior, anterior temporal lobes and semantic memory clarified: novel evidence from distortion-corrected fMRI. *Neuropsychologia*, 48 (6): 1689-1696, 2010.
Wagner AD, Shannon BJ, Kahn I, and Buckner RL. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci*, 9 (9): 445-453, 2005.
Wechsler D. *Wechsler Memory Scale - Third edition: Administration and Scoring Manual.* San Antonio, TX: Psychological Corporation, 1997.
Zeidman P, Mullally SL, Schwarzkopf DS, and Maguire EA. Exploring the parahippocampal cortex response to high and low spatial frequency spaces. *Neuroreport*, 23 (8): 503-507, 2012.
Zhang Y, Brady M, and Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, 20: 45-57, 2001.

Figure Legends

Figure 1. Experiential Index scores on the scene construction task for Alzheimer's disease and Control participants. Error bars represent the standard error of the mean.

Figure 2. Representative excerpts from (A) an Alzheimer's disease patient and (B) a Control participant describing the "Museum" scene on the scene construction task. Experimenter prompts are provided in italics.

Figure 3. Voxel-based morphometry analyses showing brain areas in which grey matter intensity correlates significantly with Experiential Index scores on the scene construction task for AD (green) and Control (red) participants. Coloured voxels show regions that were significant in the analyses at $p < .05$ corrected for False Discovery Rate with a cluster threshold of 50 contiguous voxels. All clusters reported $t > 3.8$. Clusters are overlaid on the Montreal Neurological Institute standard brain. L = Left.

Figure 4. Scatterplots showing relationship between grey matter intensity in: (A) left posterior cingulate cortex, and (B) left parahippocampal gyrus/posterior hippocampus for scene construction performance in Alzheimer's disease and Control participants.

Figure 5. Inclusive masking results showing overlap in brain regions associated with scene construction performance in Alzheimer's disease patients and Control participants. Clusters are overlaid on the Montreal Neurological Institute standard brain. L = Left. MNI coordinates: $x = -2$, $y = -38$, $z = 24$.