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Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia

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Semantic dementia is a progressive neurodegenerative condition characterized by the profound and amodal loss of semantic memory in the context of relatively preserved episodic memory. In contrast, patients with Alzheimer's disease typically display impairments in episodic memory, but with semantic deficits of a much lesser magnitude than in semantic dementia. Our understanding of episodic memory retrieval in these cohorts has greatly increased over the last decade, however, we know relatively little regarding the ability of these patients to imagine and describe possible future events, and whether episodic future thinking is mediated by divergent neural substrates contingent on dementia subtype. Here, we explored episodic future thinking in patients with semantic dementia ($n = 11$) and Alzheimer's disease ($n = 11$), in comparison with healthy control participants ($n = 10$). Participants completed a battery of tests designed to probe episodic and semantic thinking across past and future conditions, as well as standardized tests of episodic and semantic memory. Further, all participants underwent magnetic resonance imaging. Despite their relatively intact episodic retrieval for recent past events, the semantic dementia cohort showed significant impairments for episodic future thinking. In contrast, the group with Alzheimer's disease showed parallel deficits across past and future episodic conditions. Voxel-based morphometry analyses confirmed that atrophy in the left inferior temporal gyrus and bilateral temporal poles, regions strongly implicated in semantic memory, correlated significantly with deficits in episodic future thinking in semantic dementia. Conversely, episodic future thinking performance in Alzheimer's disease correlated with atrophy in regions associated with episodic memory, namely the posterior cingulate, parahippocampal gyrus and frontal pole. These distinct neuroanatomical substrates contingent on dementia group were further qualified by correlational analyses that confirmed the relation between semantic memory deficits and episodic future thinking in semantic dementia, in contrast with the role of episodic memory deficits and episodic future thinking in Alzheimer's disease. Our findings demonstrate that semantic knowledge is critical for the construction of novel future events, providing the necessary scaffolding into which episodic details can be integrated. Further research is necessary to elucidate the precise contribution of semantic memory to future thinking, and to explore how deficits in self-projection manifest on behavioural and social levels in different dementia subtypes.

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Abbreviation: VBM = voxel-based morphometry

Introduction

The study of patients with semantic dementia and Alzheimer's disease has proved illuminating for our understanding of the episodic and semantic declarative memory systems (Hodges and Graham, 2001; Nestor *et al*., 2006; Patterson *et al*., 2007). Whereas semantic dementia is characterized by the profound and amodal loss of conceptual knowledge in the context of relatively preserved recent episodic memory (Adlam *et al*., 2009; Mion *et al*., 2010), the clinical picture of Alzheimer's disease is dominated by episodic memory deficits in the context of milder semantic problems (Hodges and Patterson, 1995; Xie *et al*., 2010). Our conception of the episodic memory system, however, has undergone a radical revision over the past 5 years, with a shift from a past-oriented system to one that appears equally relevant for future-oriented thought (Schacter *et al*., 2007). Although significant advances have been made in understanding the component processes of this future-oriented system in healthy individuals (D'Argembeau *et al*., 2010; Addis *et al*., 2011), few corroborative human lesion studies exist.

A central principle underlying current theories of episodic future thinking is that past autobiographical retrieval is crucial for the construction and elaboration of future events (Addis and Schacter, 2008; Szpunar and McDermott, 2008). Parallel processes working in concert are posited to create a flexible and highly adaptive system capable of past and future mental time travel (Buckner and Carroll, 2007; Schacter and Addis, 2007*a*, *b*). If episodic future thinking relies on the extraction and flexible recombination of episodic details from past events (Schacter and Addis, 2007*a*, *b*), it follows that damage to the episodic memory system should impair the ability to imagine events in the future. This hypothesis has been confirmed in a number of clinical cohorts in which the capacity to remember the past is compromised, such as mild cognitive impairment (Gamboz *et al*., 2010), mild Alzheimer's disease (Addis *et al*., 2009*b*), amnesic patients with medial temporal lobe damage (Tulving, 1985; Hassabis *et al*., 2007*b*; Race *et al*., 2011) and developmental amnesia (Kwan *et al*., 2010). Importantly, common to all patient groups studied is the finding that difficulties in retrieving past memories in turn manifest in an impaired capacity to imagine the future. This finding has been interpreted as supporting a shared biological substrate for past and future aspects of mental time travel, and has led to the theoretical prominence of medial temporal lobe structures, particularly the hippocampus, in the simulation of personal future events (Okuda *et al*., 2003; Rosenbaum *et al*., 2005; Addis *et al*., 2007, 2009*a*; Szpunar *et al*., 2007; Addis and Schacter, 2008; Andelman *et al*., 2010), as well as a key role in the imagining of fictitious experiences (Hassabis *et al*., 2007*a*; Summerfield *et al*., 2009, 2010).

A number of challenging issues, however, remain. Critically, hippocampal damage and/or the loss of episodic memory does not always compromise the imagining of new experiences. A recent study showed that a group of patients with hippocampal damage could imagine the future (Squire *et al*., 2010), however, it is notable that the episodic memory loss in this group was only mild (Maguire and Hassabis, 2011). Moreover, a series of studies on developmental amnesics with hippocampal damage reported that these patients demonstrated intact construction of imagined experiences despite experiencing significant deficits in autobiographical memory (Maguire *et al*., 2010*b*; Cooper *et al*., 2011; Hurley *et al*., 2011). Such results may represent a difficulty for the idea that the capacity for imagining new experiences is solely contingent on the extraction of episodic details from the past. Maguire and colleagues (2010*b*) suggest that the preserved imagination abilities of some patients on their scene construction task may be mediated by intact semantic knowledge. This possibility is intriguing if we consider other forms of future thinking, such as the imagining of non-personal, or semantic, information. Indeed, evidence from amnesic patient D.B. suggests that the profound loss of episodic memory does not preclude the ability to conceive of non-episodic events that pertain exclusively to the public (semantic) domain (Klein *et al*., 2002).

Germane to the debate on the contribution of semantic memory to episodic future thinking is the fact that retrieval of past events inevitably draws on non-episodic elements, such as personal semantics, or more general conceptual knowledge (Levine *et al*., 2002; Gilboa, 2004). This position is supported by recent evidence, which showed that a network of regions in the left temporal and parietal heteromodal cortex activates when healthy individuals engage in internal mentation such as episodic and autobiographical retrieval, prospection and planning, creativity and problem-solving (Buckner *et al*., 2008), as well as semantic processing (Binder *et al*., 2009). Accordingly, the retrieval of conceptual knowledge has been posited as a central process shared across such cognitive functions as episodic memory, scene construction and self-knowledge tasks (Binder and Desai, 2011). If semantic memory forms a critical component of past episodic retrieval (Levine, 2004; Greenberg and Verfaellie, 2010), and underlies much of internally driven cognition (Binder *et al*., 2009), it follows that the construction and elaboration of fictitious scenes, and personal future events, should also draw on semantic knowledge (Irish *et al*., 2012).

Semantic dementia provides an ideal test bed to explore the role of semantic memory in episodic future thinking. It is a neurodegenerative brain disorder within the frontotemporal dementia spectrum (Neary *et al*., 1998; Gorno-Tempini *et al*., 2011) that is characterized by the profound cross-modal loss of semantic knowledge (Bozeat *et al*., 2000; Mion *et al*., 2010), involving the comprehension of words and related semantic processing (Snowden *et al*., 1989), with retained fluency, phonology and syntax (Kertesz *et al*., 2010). Despite their severe degradation of semantic knowledge, patients with semantic dementia demonstrate a range of well-preserved cognitive abilities including relatively spared recent episodic memory (Graham and Hodges, 1997;

Adlam *et al*., 2009; Irish *et al*., 2011*a*; but see McKinnon *et al*., 2006; Maguire *et al*., 2010*a*). From a neural standpoint, semantic dementia is typified by the progressive degeneration of the anterior temporal lobes (Hodges and Patterson, 2007), which is most severe on the ventral surface, including the anterior temporal fusiform gyrus, temporal pole, anterior hippocampus and amygdala (Chan *et al*., 2001; Galton *et al*., 2001; Davies *et al*., 2004; Whitwell *et al*., 2005; Mion *et al*., 2010).

The emerging evidence suggests considerable overlap between episodic and semantic representations and the likely pivotal role of semantic memory in self-projective tasks (Binder and Desai, 2011; Irish *et al*., 2012). Here, we sought to investigate the underlying mechanisms and neural correlates of constructive simulation across episodic (autobiographical) and semantic domains in semantic dementia and to contrast their performance with the classic amnestic profile of Alzheimer's disease. In doing so, we aimed to determine the relative contribution of semantic and episodic memory to constructive simulation of past and future, personal and non-personal events and to identify the brain regions that support these distinct forms of self-projection.

Based on the contrasting clinical profiles and locus of neural atrophy in semantic dementia and Alzheimer's disease, we hypothesized that differential performance would be evident according to temporal condition (past/future) and information type (episodic/semantic) contingent on patient group. For patients with Alzheimer's disease, we hypothesized that concordant deficits would be evident across past and future episodic conditions, in keeping with medial temporal lobe damage, the classic amnestic profile of Alzheimer's disease and previously reported deficits in episodic future thinking (Addis *et al*., 2009*b*). For semantic dementia, we had two hypotheses. If the capacity for episodic future thinking depends solely on the extraction of past episodic details, then the relative preservation of recent episodic memory in semantic dementia would permit the simulation of future events. Conversely, if semantic memory is a necessary component of all internally-driven complex cognitive functions (Binder *et al*., 2009), including episodic future thinking, then the amodal semantic knowledge loss evident in semantic dementia would impair the constructive simulation of novel episodic future events and semantic future scenarios. Finally, we were interested in determining whether distinct patterns of atrophy in each patient group are associated with deficits in episodic and semantic future thinking.

Methods

Participants

In total, 22 patients with dementia (semantic dementia = 11; Alzheimer's disease = 11) and 10 older education-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All dementia patients met relevant clinical diagnostic criteria (McKhann *et al*., 1984; Neary *et al*., 1998; Gorno-Tempini *et al*., 2011). Diagnosis was established by consensus among a senior neurologist, neuropsychologist and occupational therapist based on extensive clinical investigations, cognitive assessment and evidence of atrophy on structural brain neuroimaging. Briefly, the patients with semantic dementia exhibited progressive loss of word meaning manifesting in impaired naming and comprehension, prosopagnosia and/or associative agnosia, in the context of relatively spared everyday memory. Patients with Alzheimer's disease displayed significant episodic memory loss, with preserved behaviour and personality. Healthy controls were patients' family and friends, and individuals from local community clubs. All controls scored 0 on the Clinical Dementia Rating scale (Morris, 1997), and 85 or above on the Addenbrooke's Cognitive Examination-Revised (Mioshi *et al*., 2006). Exclusion criteria included prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease, alcohol and other drug abuse and limited English proficiency. Ethical approval for this study was obtained from the Southern Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

General cognitive screening

Participants were assessed with the following neuropsychological tests: Addenbrooke's Cognitive Examination-Revised as a general measure of global cognitive functioning, verbal letter fluency (F, A, S; Strauss *et al*., 2006), the Rey Auditory Verbal Learning Task (Schmidt, 1996) as an index of episodic encoding and retrieval, the Rey Complex Figure (Meyers and Meyers, 1995) and the Doors Part A subscale of the Doors and People test (Baddeley *et al*., 1994) to assess non-verbal episodic memory, and the Trail Making Test (Parts B-A; Reitan, 1958) as an index of executive function. Due to the heavy semantic loading of the Rey Auditory Verbal Learning Task, patients with semantic dementia were not assessed on this measure. Verbal semantic performance was assessed using a measure of Naming and Comprehension adapted from the Repeat and Point test (Hodges *et al*., 2008).

Episodic past and future thinking

The construction of autobiographical past and future events was probed using a procedure based on that of Addis *et al*. (2008). This past–future task was modified for use in the present patient cohort by limiting the trials to three per condition, and on each trial presenting both a cue word and a corresponding image. Six nouns (Apple, Baby, Car, Oven, Toy, Wine) were randomly selected from the Clark and Paivio (2004) extended norms. All stimuli were high in concreteness (mean = 6.91 $\pm$ 0.14), imageability (mean = 6.58 $\pm$ 0.25) and Thorndike–Lorge frequency (mean = 1.77 $\pm$ 0.20). The stimuli were randomly assigned to two separate lists (n = 3 stimuli per list). Analysis of variance (ANOVA) confirmed that the two stimulus lists did not differ in terms of concreteness, imageability and Thorndike–Lorge frequency. Each participant completed three past and three future trials. Temporal conditions were blocked so that all events for one condition were completed prior to moving to the other temporal direction. This blocked procedure was adopted to reduce cognitive load on patients and facilitate their understanding of the instructions for each condition. For each trial, the stimuli lists were randomized, as was the order of temporal condition, leading to four counterbalanced versions of the task. Within each stimulus list, the order of cue words was also randomized.

Prior to commencing the task, detailed instructions were read aloud to participants specifying that they would be asked to remember specific events in their lives from the past year, and to imagine possible one-off events that could happen in their lives in the next year. To ensure that these events were autobiographical in nature, participants

were instructed that they should feature directly in the event and not merely describe an event happening to another person. Participants were then shown the instructions 'Recall an event from the past year . . . A specific event that happened on one particular day' for the past condition, and 'Imagine a future event in the next year . . . A specific event that happens on one particular day' for the future condition. Participants were shown the cue word accompanied by a corresponding visual image along with the task instruction 'Recall past event . . . within the last year' for the past condition or 'Imagine future event . . . within the next year' for the future condition. Participants were instructed to generate as much detail as possible about the event in response to the cues. The event generated did not strictly have to involve the cued object, and participants were encouraged to freely associate to generate a specific event. Events were required to be spatiotemporally specific, occurring over minutes and hours but not longer than 1 day (Levine *et al.*, 2002). Future events were required to be plausible given the participant's current plans and not previously experienced by the participant. The cues and instructions remained on the screen until the participant reached a natural end. Then, specific probes of the Autobiographical Interview (Levine *et al.*, 2002), targeting five discrete categories (event, time, place, perceptual, emotion/thought details) were provided to elicit further details. No time limit was imposed. The description of each event typically took 3–5 min.

Scoring of past and future events

The interview lasted for ~30 min and responses were recorded using a digital recorder for later transcription and scoring. The standardized scoring procedure of the Autobiographical Interview (Levine *et al.*, 2002) was used to score each event. Transcripts of each event (following specific probes) were segmented into informational bits or details. Each detail was classified as 'internal' or 'external'. Details were labelled as internal if they were directly related to the main episode being described and were located within a specific spatiotemporal context. Otherwise, details were labelled as external if they consisted of tangential details or details unrelated to the main event, repetitions, semantic facts or metacognitive statements. Details from each category were summed to form internal and external composite scores.

Semantic past and future thinking

The 'Known' (semantic) subscale of the Memory and Temporal experience questionnaire (Klein *et al.*, 2002) was used to probe past semantic retrieval and future semantic thinking. Participants were asked seven questions regarding non-personal events over the past 10 years and future 10 years, across the following domains; politics, community issues, national issues, medical breakthroughs, issues for the planet, advances in technology and environmental issues. For example, a past semantic question would be as follows, 'Can you tell me what have been the greatest advances in technology over the last ten years?' The corresponding future subscale asked the same questions but with regard to the next 10 years, for example 'Can you tell me what you think will be the greatest advances in technology in the next ten years?' One point was awarded for each category if the participant could provide two or more plausible responses, leading to a possible maximum score of 7 points for each temporal condition. To increase the variation in scores across groups, scores were scaled to a maximum of 10 points.

Behavioural analyses

Data were analysed using PASW® Statistics (Version 18.0.0). Suitability of variables for parametric analyses was determined using Kolmogorov–Smirnov tests. Repeated-measures ANOVA with Sidak *post hoc* tests were used to investigate main effects of group (controls, semantic dementia, Alzheimer's disease) and condition (past, future), as well as group × condition interactions, for internal details and semantic information. The rationale for using Sidak modification of the traditional Bonferroni *post hoc* test is that the statistical power of the analyses is not affected, while the flexibility of the original Bonferroni method is maintained (Keppel and Wickens, 2004). Confidence intervals of 95% (95% CI) were calculated for all significant differences. Chi-squared tests (χ^2), based on the frequency patterns of dichotomous variables, were also used. One-tailed Pearson *R* correlations were used to investigate the relationship between experimental variables and performance on neuropsychological tests of episodic memory and semantic processing.

Image acquisition

Voxel-based morphometry (VBM) was used to identify grey matter intensity changes across groups on a voxel-by-voxel basis using structural MRI data. Briefly, all patients and controls underwent whole-brain T_1-weighted images using a 3T Philips MRI scanner with standard quadrature head coil (eight channels). The 3D T_1-weighted images were acquired using the following sequences: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm^2 in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8 ms, flip angle $\alpha = 19^\circ$.

Data preprocessing

MRI data were analysed with FSL (Functional MRI of the Brain Software Library)-VBM, (Ashburner and Friston, 2000; Mechelli *et al.*, 2005) using the toolbox from the FMRIB software package (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html; Smith *et al.*, 2004). Briefly, structural images were extracted using the brain extraction tool (BET) (Smith, 2002). Tissue segmentation was then carried out on the brain extracted images using FMRIB's Automatic Segmentation Tool (FAST) (Zhang *et al.*, 2001). The resulting grey matter partial volumes were then aligned to the Montreal Neurological Institute standard space (MNI152) using the FMRIB Non-linear Image Registration Tool (FNIRT) (Andersson *et al.*, 2007*a*, *b*), which uses 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 non-linearly. The registered partial volume maps were then modulated by dividing by the Jacobian of the warp field. This was to correct for local expansion or contraction. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

Voxel-based morphometry analysis

A voxel-wise general linear model was applied to investigate grey matter intensity differences via permutation-based non-parametric testing (Nichols and Holmes, 2002) with 5000 permutations per contrast. Differences in cortical grey matter intensities between patients (semantic dementia and Alzheimer's disease) and controls were assessed using *t*-tests. Next, correlations between the total number of internal details generated for past and future conditions and regions of

grey matter atrophy were investigated in patients with semantic dementia and patients with Alzheimer's disease combined with controls. This procedure has been adopted in previous studies including patients with semantic dementia and patients with Alzheimer's disease (Sollberger *et al*., 2009) to achieve greater variance in behavioural scores, and therefore increase the study's statistical power to detect brain–behaviour relationships across the entire brain. Given the significant temporal lobe atrophy typically seen in semantic dementia (Mion *et al*., 2010), all behavioural results were plotted to ensure that the distribution of scores was not bimodal. As a final check, the correlations between episodic future thinking performance and grey matter intensity for the key regions of interest were plotted to ensure that the data were normally distributed (Supplementary material). For further statistical power, a covariate-only statistical model with a [1] *t*-contrast was used, providing an index of association between decreasing grey matter intensity and lower scores on the experimental measures.

Results were significant for $P < 0.001$, uncorrected for multiple comparisons, including age as a covariate. Anatomical locations of significant results were overlaid on the Montreal Neurological Institute standard brain, with maximum coordinates provided in Montreal Neurological Institute stereotaxic space. Anatomical labels were determined with reference to the Harvard–Oxford probabilistic cortical atlas.

Results

Clinical characteristics

Demographics and general cognitive scores are summarized in Table 1. The groups were matched for years of education but not age, controls being on average 7.1 years older than patients with semantic dementia [$F(2, 29) = 4.122$, $P = 0.027$]. Age was controlled for in all subsequent analyses. Sex was not evenly distributed between the groups, as the male:female ratio was higher in the patient groups compared with the control group [χ^2 (2) = 7.536, $P = 0.023$]. A univariate ANOVA revealed no significant differences for disease duration or general cognitive functioning between the patient groups.

Cognitive screening

General cognitive testing revealed profiles typical of the two dementia syndromes. In semantic dementia, disproportionate deficits on semantic tasks (Naming and Comprehension) were evident, in the context of relatively preserved executive function (Trails, Letter Fluency) and episodic memory (Rey Complex Figure recall; Doors). In contrast, episodic memory was impaired in Alzheimer's disease across verbal (Rey Auditory Verbal Learning Task) and non-verbal domains (Rey Complex Figure recall; Doors), with additional deficits evident for executive function (Trails), mild semantic problems (Naming) and relatively preserved Comprehension.

Episodic past and future thinking

The key result, illustrated in Fig. 1, was that differential patterns emerged for the generation of past and future internal details in the groups with semantic dementia and Alzheimer's disease. An overall main effect of group was found [$F(2,28) = 13.182$, $P < 0.0001$], with controls providing more internal details than the patient groups. This group effect was qualified by a significant condition × group interaction [$F(2,28) = 9.847$, $P = 0.001$]. *Post hoc* comparisons revealed that in the past condition, whereas patients with Alzheimer's disease recalled significantly fewer past

Table 1 Demographic and clinical characteristics of study cohort

Demographics and cognitive tests	Semantic dementia (*n* = 11)	Alzheimer's disease (*n* = 11)	Controls (*n* = 10)	*F*-test	*Post hoc* test
Sex (M:F)	10:1	9:2	4:6	*	
Age (years)	62.1 (5.5)	64.6 (6.1)	69.2 (5.6)	*	Controls > semantic dementia
Education (years)	12.9 (3.6)	11.4 (3.9)	12.7 (1.5)	NS	NS
Disease duration (months)	58.0 (23.8)	51.9 (26.7)	NA	NS	NS
Addenbrooke's Cognitive Examination-Revised (100)	57.9 (13.7)	70.2 (14.1)	93.0 (3.8)	***	Patients < controls semantic dementia = Alzheimer's disease
Rey Auditory Verbal Learning Task (15)	NA	2.4 (2.8)	10.6 (2.1)	***	Alzheimer's disease < controls
Rey Complex Figure, 3 min recall (36)	15.7 (6.3)	4.7 (4.7)	14.3 (6.0)	**	Alzheimer's disease < controls Alzheimer's disease < semantic dementia
Doors Part A (12)	8.4 (2.7)	7.4 (2.4)	11.0 (1.2)	**	Alzheimer's disease < controls
Naming (30)	4.9 (3.5)	19.3 (4.6)	24.8 (2.2)	***	Patients < controls semantic dementia < Alzheimer's disease
Comprehension (30)	15.5 (4.9)	25.1 (4.1)	28.1 (2.1)	***	Semantic dementia < controls
Letter fluency	23.7 (11.7)	27.8 (19.0)	44.0 (13.1)	NS	NS
Trail Making Test Part B-A (s)	59.7 (32.0)	119.2 (67.8)	49.7 (17.4)	*	Alzheimer's disease < controls

Maximum score for each test in brackets where applicable. Rey Complex Figure data available for 10 patients with semantic dementia and 10 with Alzheimer's disease. Doors Part A data available for eight patients with semantic dementia. Trail Making test available for seven patients with semantic dementia, and nine with Alzheimer's disease. Letter fluency available for 10 patients with Alzheimer's disease and nine with semantic dementia. Rey Auditory Verbal Learning Task not assessed in semantic dementia and two patients with Alzheimer's disease. Age included as a covariate in all between group comparisons.
*$P < 0.05$; **$P < 0.005$; ***$P < 0.0001$. Standard deviation given in bracket for semantic dementia, Alzheimer's disease and controls. NA = not applicable; NS = not significant.

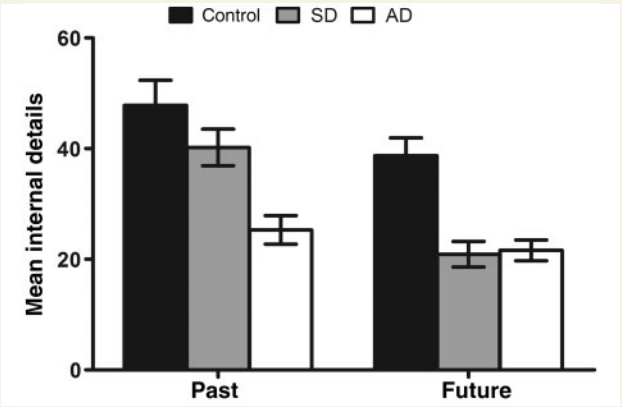

Figure 1 Bar chart showing the average number of internal (episodic) details generated following probing across participant groups; controls, semantic dementia (SD), and Alzheimer's disease (AD) on past and future conditions. Error bars indicate standard error of the mean.

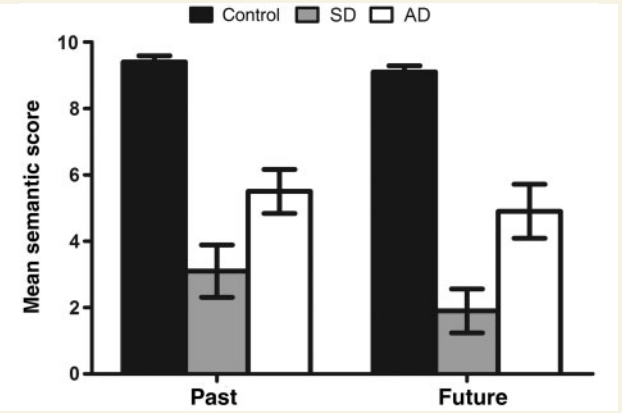

Figure 2 Bar chart showing scores from the semantic subscale of Klein *et al.*'s (2002) Memory and Temporal Experience questionnaire across all three groups; controls, semantic dementia (SD), and Alzheimer's disease (AD). Error bars indicate standard error of the mean.

internal details than controls ($P < 0.0001$, mean difference = 24.5, 95% CI 11.2–37.8), importantly, patients with semantic dementia scored at control levels ($P = 0.183$) and recalled significantly more internal details than patients with Alzheimer's disease ($P = 0.029$, mean difference = 13.7, 95% CI 1.2–26.3). For future internal details, however, patient groups were equally impaired relative to controls (semantic dementia: mean difference = 19.7, 95% CI 9.5–30.0; Alzheimer's disease: mean difference = 18.2, 95% CI 8.7–27.7). Moreover, this interaction reflected the fact that both controls and patients with semantic dementia demonstrated a past > future effect (controls: $P = 0.001$, mean difference = 9.8, 95% CI 4.3–15.4; semantic dementia: $P < 0.0001$, mean difference = 18.8, 95% CI 13.6–23.9), whereas the group with Alzheimer's disease performed equally poorly in the two conditions ($P = 0.154$).

The number of external details generated for past and future conditions was similar across the groups, indicating that verbal output did not differ significantly between the groups. Sex and age did not exert a significant effect for any of the experimental variables.

Retrieval and constructive simulation of personally relevant events was differentially affected contingent on dementia group. Despite a relative preservation of recent episodic memory in semantic dementia, significant deficits in the construction of future episodes were evident. In contrast, patients with Alzheimer's disease showed parallel deficits across both past and future episodic conditions.

Semantic past and future thinking

Performance on the semantic experimental tasks is illustrated in Fig. 2. An overall main effect of group was found [$F(2,27) = 25.556$, $P < 0.0001$]. Patients with Alzheimer's disease showed impairments across past ($P < 0.0001$, mean difference = 4.0, 95% CI 1.8–6.2) and future conditions ($P = 0.011$, mean difference = 4.2, 95% CI 1.9–6.5) when compared with controls. Similarly, patients with semantic dementia showed parallel impairments across semantic past ($P < 0.0001$, mean difference = 6.4, 95% CI 4.1–8.6) and future conditions ($P < 0.0001$, mean difference = 7.2, 95% CI 4.7–9.6) in comparison with controls. Additionally, patients with semantic dementia were impaired with respect to patients with Alzheimer's disease across semantic past ($P = 0.028$) and future ($P = 0.008$) conditions.

For retrieval and simulation of semantic, non-personal information, similar profiles of performance were evident in semantic dementia and Alzheimer's disease. Both patient groups showed impairments in the retrieval and future simulation of semantic information. The semantic deficits exhibited by patients with semantic dementia, however, were significantly more pronounced than those displayed by the group with Alzheimer's disease.

Correlations between experimental variables and standardized tests

The semantic dementia group showed a specific impairment of episodic future thinking in the context of preserved episodic and impaired semantic memory, whereas the group with Alzheimer's disease showed deficits in episodic future thinking in the context of episodic and mild semantic memory impairment. Correlational analyses revealed group differences in the pattern of associations between episodic and semantic memory abilities and episodic future thinking (Table 2). In Alzheimer's disease, episodic future thinking correlated with the retrieval of past episodic internal details and performance on a standardized test of episodic memory (Doors Part A), but with none of the measures of semantic knowledge. In semantic dementia, episodic future thinking was related to retrieval of past episodic and semantic information, generation of future semantic information and a measure of semantic knowledge (naming), but not with a measure of non-verbal episodic memory.

Deficits in episodic and semantic future thinking appear to be mediated by different underlying mechanisms contingent on patient group. Whereas integrity of episodic memory was significantly related to episodic future thinking deficits in Alzheimer's

Table 2 Pearson correlations between episodic future thinking performance and standardized tests of episodic and semantic memory

	Group	Internal past details	Semantic Past	Semantic future	Naming[a]	Doors part A
Internal future details	Semantic dementia	0.611*	0.595*	0.756**	0.502*	0.060
	Alzheimer's disease	0.760**	0.437	0.239	−0.093	0.517*
	Controls	0.793**	0.096	0.439	−0.391	−0.133

*$P < 0.05$, **$P < 0.005$.
a For Naming $P = 0.058$.

Table 3 Voxel-based morphometry results showing regions of significant grey matter intensity decrease for the contrasts of semantic dementia and Alzheimer's disease patient groups with controls

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	y	z
Controls versus semantic dementia	Temporal fusiform cortex, parahippocampal gyrus, hippocampus, amygdala, temporal pole	L	8955	−28	12	−30
	Temporal fusiform cortex extending into temporal pole, parahippocampal gyrus and posterior hippocampus	R	4333	32	−4	−50
	Anterior supramarginal gyrus	R	143	66	−28	38
	Posterior supramarginal gyrus	L	116	−48	−48	36
	Temporo-occipital inferior temporal gyrus	L	93	−50	−58	−8
	Postcentral gyrus	L	86	−34	−32	64
Controls versus Alzheimer's disease	Insular cortex	L	725	−26	22	0
	Anterior parahippocampal gyrus	R	270	16	−2	−20
	Frontal pole	L	265	−10	58	−12
	Postcentral gyrus	R	250	64	−18	28
	Angular gyrus	L	224	−52	−54	30
	Anterior inferior temporal gyrus	L	208	−48	−8	−40
	Superior frontal gyrus	L	186	−20	22	40
	Temporal pole	L	164	−36	10	−42
	Angular gyrus	R	127	60	−48	42
	Anterior hippocampus	L	123	−28	−12	−16
	Frontal pole	R	120	8	66	2
Alzheimer's disease versus semantic dementia	Temporal fusiform cortex, parahippocampal gyrus, temporal pole, anterior hippocampus, amygdala, posterior parahippocampal gyrus, temporo-occipital fusiform cortex	L	5949	−32	−10	−50
	Anterior temporal fusiform cortex, anterior parahippocampal gyrus, temporal pole, anterior hippocampus, amygdala	R	1477	24	2	−48
	Anterior inferior temporal gyrus, anterior middle temporal gyrus	R	104	52	0	−36

Age included as a covariate in all contrasts. Semantic dementia versus Alzheimer's disease contrast did not produce clusters of at least 80 contiguous voxels at $P < 0.001$. All clusters reported $t > 3.97$. L = left; R = right; MNI = Montreal Neurological Institute.

disease, semantic processing was significantly related to episodic future thinking deficits in semantic dementia. These correlations suggest that fundamentally different component processes contribute to future thinking in each patient type.

Voxel-based morphometry group analysis

Patterns of atrophy

Compared with controls, patients with semantic dementia showed significant atrophy in the anterior temporal lobes bilaterally, with greatest atrophy present in the left hemisphere (Table 3 and Fig. 3). In contrast, widespread patterns of atrophy were evident in the group with Alzheimer's disease relative to controls, involving the medial and lateral temporal lobes including the left hippocampus and insular cortex, bilateral frontal poles and posterior brain regions, notably the angular gyrus bilaterally.

Direct comparison of the patients with semantic dementia and patients with Alzheimer's disease revealed greater atrophy in the temporal lobes, including the bilateral anterior and posterior temporal fusiform cortex, parahippocampal gyrus, anterior hippocampus and amygdala in the semantic dementia group, more pronounced on the left side. These patterns of atrophy are

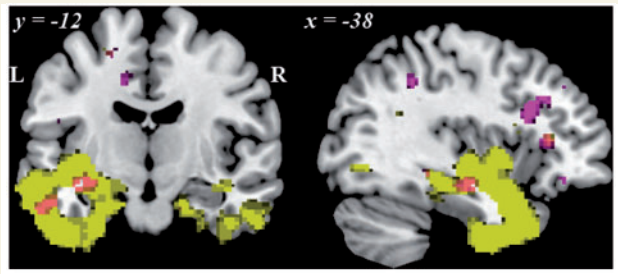

Figure 3 VBM analyses showing brain areas of decreased grey matter intensity in semantic dementia compared with Control participants (yellow), and in Alzheimer's disease compared with Control participants (pink). Coloured voxels show regions that were significant in the analysis with $P < 0.001$ uncorrected for all contrasts, with a cluster threshold of 80 contiguous voxels. All clusters reported $t > 3.97$. Clusters are overlaid on the Montreal Neurological Institute standard brain. Montreal Neurological Institute coordinates: $x = -38$, $y = -12$, $z = -14$.

consistent with previous reports in semantic dementia (Rosen *et al.*, 2002; Mion *et al.*, 2010) and in Alzheimer's disease (Karas *et al.*, 2004; Dickerson *et al.*, 2009). All thresholds reported are uncorrected at the $P < 0.001$ level.

Neural correlates of past and future episodic thinking

Retrieval of past internal details for all participants (controls, Alzheimer's disease, semantic dementia) was associated with grey matter intensity of the left inferior temporal gyrus and left superior frontal gyrus (Table 4). For patients with Alzheimer's disease, when combined with controls, atrophy in the right frontal pole, right posterior cingulate and precuneus, and left inferior temporal and middle frontal gyri correlated significantly with impaired episodic retrieval. In contrast, for patients with semantic dementia, no significant correlations between grey matter density and past episodic retrieval were found. This finding is important as it indicates that the characteristic temporal lobe atrophy in the semantic dementia group does not, by default, correlate with all cognitive tasks administered to this group.

Different patterns of associations were observed between episodic future thinking performance and grey matter intensities (Table 4). For all participants combined, episodic future thinking significantly correlated with grey matter intensity in the left inferior and middle temporal gyrus, and the left precentral gyrus. For patients with semantic dementia combined with controls, episodic future thinking correlated with the left inferior temporal gyrus and to a much lesser extent with the right temporal pole (Fig. 4). In contrast, in patients with Alzheimer's disease combined with controls, atrophy in the left posterior cingulate cortex and precuneus, right posterior parahippocampal gyrus and the additional involvement of the left frontal pole, correlated with impaired episodic future thinking. For brevity, we discuss the implications of our findings with respect to the characteristic patterns of atrophy in each patient group.

Neural correlates of past and future semantic thinking

Across all participants, retrieval of semantic past information was associated with grey matter intensity of the left anterior inferior temporal gyrus, and the right temporal pole (Table 4). Considerable overlap was evident between these regions and those areas correlating with semantic future thinking, namely the left temporal lobes and right temporal pole, but with additional correlations in the left posterior temporal fusiform cortex. For patients with semantic dementia, compared with controls, impaired semantic past retrieval was associated with left temporal lobe atrophy, specifically the left anterior inferior temporal gyrus, and the left temporal pole. For future semantic thinking, however, the additional involvement of the right temporal pole was evident. In the Alzheimer's disease group, compared with controls, deficits in retrieval of semantic information also correlated with atrophy in the left anterior inferior temporal gyrus, as well as the left superior lateral occipital cortex, superior frontal gyrus and the left insular cortex. Similar regions were implicated in semantic future thinking in Alzheimer's disease with the additional involvement of the left angular gyrus.

Figure 5 shows the overlap between areas implicated in episodic future thinking and semantic future thinking in semantic dementia, and neuroanatomically distinct regions correlating with episodic future thinking and semantic future thinking in Alzheimer's disease.

Deficits in episodic and semantic future thinking appear to be associated with changes in distinct brain regions in semantic dementia and Alzheimer's disease. Episodic future thinking in semantic dementia was related to atrophy in the left anterior temporal lobe, whereas atrophy in the left posterior cingulate, right parahippocampal gyrus and left frontal pole significantly predicted episodic future thinking deficits in Alzheimer's disease. Left temporal lobe atrophy also significantly correlated with semantic future thinking deficits in semantic dementia, pointing to overlap in the neural substrates mediating these types of future-oriented thought.

Discussion

This study investigated the capacity for future-oriented thought across episodic and semantic domains in patients with semantic dementia and Alzheimer's disease, and has uncovered novel findings that bear relevance for current models of future thinking and have clinical implications. The most important finding arising from this study is the striking impairment of future thinking in semantic dementia that is as severe as that observed in Alzheimer's disease. Unlike patients with Alzheimer's disease, however, the episodic future thinking deficit in semantic dementia was evident despite a relative preservation of episodic memory for recent past events. Importantly, the profound semantic deficits characteristic of patients with semantic dementia did not preclude the ability to consciously retrieve recent past experiences, in keeping with recent observations in semantic dementia (Adlam *et al.*, 2009; Irish *et al.*, 2011*a*). In this group, however, it appears that the capacity to

Table 4 Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with episodic and semantic past and future thinking

	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Episodic past retrieval						
All participants	Posterior inferior temporal gyrus	L	87	−52	−26	−28
	Superior frontal gyrus	L	82	−24	16	40
Semantic dementia and controls	No clusters >80 voxels					
Alzheimer's disease and controls	Frontal pole	R	344	6	64	−18
	Posterior cingulate	R	194	6	−46	30
	Posterior inferior temporal gyrus	L	115	−50	−24	−30
	Posterior supramarginal gyrus	L	111	−58	−44	30
	Middle frontal gyrus	L	84	−26	14	40
Episodic future thinking						
All participants	Inferior temporal gyrus	L	381	−46	−8	−48
	Posterior middle temporal gyrus	L	165	−48	−28	−8
	Precentral gyrus	L	132	−24	−10	46
Semantic dementia and controls	Anterior inferior temporal gyrus	L	2114	−46	−8	−48
	Posterior inferior temporal gyrus	L	291	−56	−44	−12
	Temporal pole	R	170	22	8	−48
Alzheimer's disease and controls	Posterior cingulate/precuneus	L	127	−14	−34	40
	Posterior cingulate	L	94	−6	−40	32
	Posterior parahippocampal gyrus	R	89	28	−30	−18
	Frontal pole	L	80	−12	66	−12
Semantic past retrieval						
All participants	Anterior inferior temporal gyrus	L	1406	−48	−2	−46
	Temporal pole	R	114	44	12	−20
Semantic dementia and controls	Anterior inferior temporal gyrus	L	359	−40	−6	−44
	Temporal pole	L	227	−44	4	−26
Alzheimer's disease and controls	Superior lateral occipital cortex	L	580	−44	−64	18
	Anterior inferior temporal gyrus	L	172	−50	−2	−44
	Superior frontal gyrus	L	148	−20	12	42
	Insular cortex	L	134	−32	22	−2
	Posterior inferior temporal gyrus	L	126	−54	−26	−30
	Inferior frontal gyrus	L	121	−38	12	22
Semantic future thinking						
All participants	Anterior inferior temporal gyrus	L	2271	−44	0	−48
	Temporal pole	R	729	40	14	−38
	Posterior temporal fusiform cortex	L	103	−30	−30	−22
Semantic dementia and controls	Anterior inferior temporal gyrus	L	1853	−48	−2	−46
	Temporal pole	R	132	30	8	−30
Alzheimer's disease and controls	Anterior inferior temporal gyrus	L	262	−48	0	−44
	Angular gyrus	L	180	−54	−56	32
	Inferior frontal gyrus	L	168	−40	16	20
	Insular cortex	L	122	−32	22	−2

All results uncorrected at $P < 0.001$; only clusters with at least 80 contiguous voxels were included. All clusters reported $t > 3.97$. L = left; R = right; MNI = Montreal Neurological Institute.

retrieve past episodic details is not sufficient for the successful simulation of future events (see also Andelman *et al.*, 2010).

Our correlation analyses confirmed that episodic future thinking performance was related to different underlying mechanisms contingent on dementia subtype. In semantic dementia, episodic future thinking performance correlated chiefly with semantic knowledge disruption and retrieval of past episodic details. In contrast, only measures of episodic memory performance were found to correlate with episodic future thinking in Alzheimer's disease. These findings relate to the underlying deficits characteristic of each patient group, and were attributable to specific patterns of neural atrophy as demonstrated by VBM analyses. In semantic dementia, atrophy in the bilateral anterior temporal lobes, including the anterior inferior temporal gyrus and temporal pole, correlated with episodic future thinking performance, whereas, in Alzheimer's disease, the posterior cingulate, posterior parahippocampal gyrus and frontal pole correlated with episodic future thinking capacity. Critically, the left inferior temporal gyrus and temporal pole also correlated with performance on the semantic future thinking task in both patient groups, supporting the view that anterior temporal lobe regions underpin semantic representations (Visser *et al.*, 2010). Therefore, while divergent neural circuits underlie the capacity for episodic future thinking in

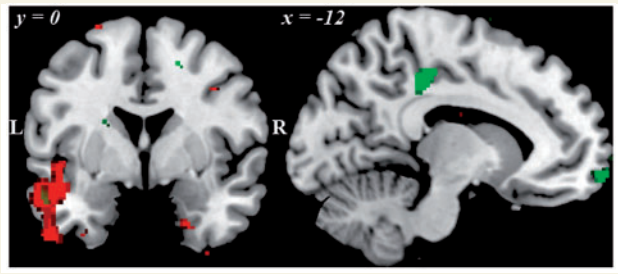

Figure 4 VBM analyses showing brain areas in which grey matter intensity correlates significantly with episodic future thinking in SD and Control participants (red), and in Alzheimer's disease and Control participants (green). Coloured voxels show regions that were significant in the analysis with $P < 0.001$ uncorrected with a cluster threshold of 80 contiguous voxels. All clusters reported $t > 3.97$. Clusters are overlaid on the Montreal Neurological Institute standard brain. Montreal Neurological Institute coordinates: $x = -12$, $y = 0$, $z = 5$.

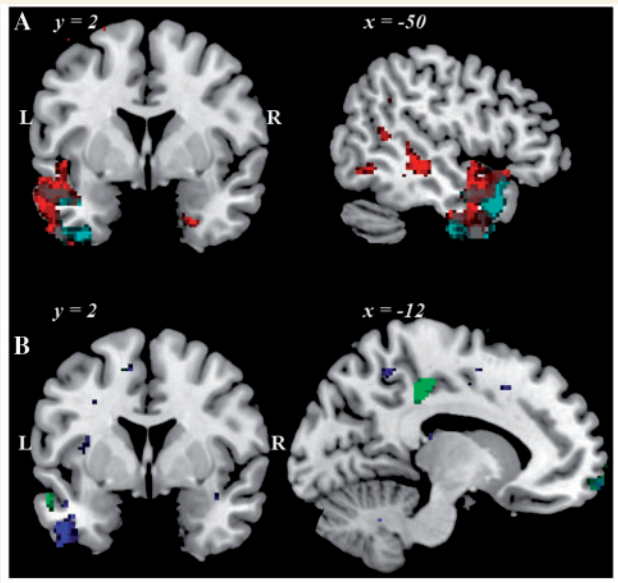

Figure 5 VBM analyses showing (**A**) overlap between brain areas in which grey matter intensity correlates significantly with episodic future thinking (red) and with semantic future thinking (light blue) in participants with semantic dementia and control participants (Montreal Neurological Institute coordinates: $x = -50$, $y = 2$, $z = -25$) and (**B**) separate regions in which grey matter intensity correlates with episodic future thinking (green) and semantic future thinking (dark blue) in participants with Alzheimer's disease and controls (Montreal Neurological Institute coordinates: $x = -12$, $y = 2$, $z = -29$). Coloured voxels show regions that were significant in the analysis with $P < 0.001$, uncorrected with a cluster threshold of 80 contiguous voxels. All clusters reported $t > 3.97$. Clusters are overlaid on the Montreal Neurological Institute standard brain.

semantic dementia and Alzheimer's disease, a common substrate for semantic future thinking is evident irrespective of dementia type.

From a theoretical perspective, our findings offer compelling evidence that the disintegration of the conceptual knowledge base in semantic dementia adversely affects the ability to imagine events in the future. Our findings corroborate those from a recent study investigating the link between the self and autobiographical memory in semantic dementia across past, present and future contexts, which also suggests that episodic memory alone may not be sufficient for envisioning the future (Duval *et al*., 2012). Duval and colleagues (2012) studied aspects of the structural and functional self by asking patients with semantic dementia to generate statements each beginning with 'I am', 'I was' and 'I will be' in response to the question 'Who am I?' and analysed the details provided by participants for the two most representative aspects of their self across past, present and future. Whereas recall of past self-representations was preserved, patients with semantic dementia demonstrated significant impairments when thinking about their possible future selves. Strikingly, patients with semantic dementia appeared unable to construct a self-image in the future condition or to provide relevant event details to support their future self-representations. Taken together, these results highlight the importance of personal semantic information for imagining the future self (Duval *et al*. 2012), and converge with our present findings to show the importance of the semantic memory system for future-oriented thought.

The demonstration that semantic memory contributes to the imagining of personal episodic future events, and future self-representations (Duval *et al*., 2012), represents an expansion to the current view of episodic future thinking which, to date, has focused primarily on the role of the medial temporal lobe and episodic memory (Schacter and Addis, 2007*a*, *b*; Race *et al*., 2011). Although our semantic dementia cohort exhibited significant bilateral hippocampal atrophy, anterior temporal lobe rather than medial temporal structures were found to correlate with their episodic future thinking performance. Structures within the medial temporal lobe are clearly vital for the extraction of past episodic details, and possibly also their successful recombination into a novel and spatially coherent simulation (Hassabis *et al*., 2007*a*; Addis and Schacter, 2008). Our findings suggest, however, that anterior temporal regions subserving the retrieval of semantic information are also crucial to episodic future simulation. The differences between episodic and semantic memory, and the methods used to assess these processes, are particularly relevant in this context. Episodic memory represents unique occurrences, located within a specific spatiotemporal framework, bearing emotional and self-referential connotations (Conway, 2009), and is typically imbued with autonoetic consciousness (Tulving, 1985; Irish *et al*., 2008). In contrast, semantic knowledge can be generalized to many different contexts (Mion *et al*., 2010), providing undifferentiated conceptual information that is likely to be drawn upon for the construction of future events (Binder and Desai, 2011). This type of information is particularly important for the simulation of truly novel events, that is, events for which no personal experience exists. Such novel event creation probably relies on general conceptual knowledge that can be harnessed irrespective of task demands, providing scaffolding into which specific episodic details can be integrated. Accordingly, the anterior temporal lobe atrophy seen in semantic dementia disrupts these amodal semantic representations, precluding the assembly of a coherent framework from which to construct detailed future simulations.

In keeping with the prevailing view on episodic future thinking, we also found evidence supporting the position that access to past episodic details is necessary for constructing future simulations (Schacter and Addis, 2007*a*, *b*). Specifically, the Alzheimer's disease group was significantly impaired at generating internal episodic details for both past and future episodic conditions in the context of mild semantic deficits. This finding of impaired episodic thinking across past and future conditions is concordant with a previous study in Alzheimer's disease (Addis *et al*., 2009*b*). Our Alzheimer's disease group displayed a distinct pattern of atrophy that correlated with their episodic future thinking deficits, including atrophy in the posterior cingulate, parahippocampal gyrus and frontal pole. Notably, these regions have been linked previously with episodic imagery, contextual detail and scene construction processes important to both past and future events (Fletcher *et al*., 1995; Bar and Aminoff, 2003; Okuda *et al*., 2003; Hassabis and Maguire, 2007; Hassabis *et al*., 2007*a*; Szpunar *et al*., 2009; Andrews-Hanna *et al*., 2010).

Midline brain structures may play a particularly crucial role in mediating self-referential thought (Northoff *et al*., 2006). This idea is further qualified by a recent study in healthy individuals, in which activity in the medial prefrontal cortex and posterior cingulate correlated significantly with participants' ratings of personal significance and affect (Andrews-Hanna *et al*., 2010). Taken together, these findings suggest that the characteristic patterns of atrophy in Alzheimer's disease disrupt the self-referential or autonoetic aspect of episodic thinking as has been demonstrated for retrieval of autobiographical events from across the lifespan (Irish *et al*., 2011*b*). The relationship between atrophy in the posterior cingulate and episodic future thinking performance in Alzheimer's disease is significant, adding to converging evidence that views the posterior cingulate as critical in the genesis of declarative memory problems in this patient cohort (Nestor *et al*., 2006; Irish *et al*., 2011*a*). Importantly, though our findings in Alzheimer's disease reinforce current thinking that loss of episodic memory can disrupt episodic future thinking (Tulving, 1985; Klein *et al*., 2002; Hassabis *et al*., 2007*b*; Kwan *et al*., 2010; Race *et al*., 2011), they nevertheless challenge the view that episodic future thinking deficits in Alzheimer's disease can be explained by medial temporal lobe damage alone.

By studying two dementia syndromes characterized by differential impairments in episodic and semantic memory, our findings indicate that if either episodic or semantic memory—and regions supporting these functions—are sufficiently compromised, the construction of future scenarios will be impaired. Of further interest, however, is the possibility that these distinct neurocognitive mechanisms contribute to different aspects of future thinking. For instance, even though patients with Alzheimer's disease and patients with semantic dementia produced a similar number of internal details for future events, the type of details produced, the spatial coherence (Hassabis and Maguire, 2007) and integration (Rosenbaum *et al*., 2009) of the scenarios may differ across groups. This question is intriguing in light of recent evidence showing that the content of episodic autobiographical memory varies considerably across dementia syndromes (Irish *et al*., 2011*a*). While the cross-modal semantic deficits in semantic dementia appear to impinge on the labelling of spatiotemporal and emotional details, patients with Alzheimer's disease, in contrast, show deficits in retrieving core event and emotional details (Irish *et al*., 2011*a*). This begs the question of whether parallel patterns in the production of internal details are evident for future simulations generated by each patient group (Supplementary material). Further, it will be important to establish which internal details are particularly vulnerable during the construction of future events in patients with semantic dementia, manifesting in the past > future effect observed here. Of note is our finding that patients with semantic dementia showed a strong tendency to 'recast' entire past experiences and imagine the event occurring again at a future time (80% of future episodic trials compared with 67% in Alzheimer's disease), despite specific instructions to generate novel events. We suggest that in semantic dementia, recasting of prior events occurs in the face of an inability to generate the conceptual framework for a novel future event, despite largely preserved episodic memory retrieval. Further research investigating the content of future simulations in dementia syndromes, and the recasting phenomenon in semantic dementia, is clearly warranted.

From a clinical standpoint, our results offer potential insights into the behavioural changes observed in semantic dementia. The profound deficits in simulating future events exhibited by patients with semantic dementia, despite a relative preservation of past episodic memory, suggest that other forms of self-projection, such as theory of mind, empathy and moral reasoning (Spreng *et al*., 2009), may also be compromised. Self-projection underlies many cognitive abilities that are essential for successful human interactions (Buckner and Carroll, 2007). This becomes particularly important given the pervasive lack of empathy commonly reported by caregivers of patients with semantic dementia (Mychack *et al*., 2001; Rankin *et al*., 2006). Whether such empathic deficits reflect a specific breakdown in self-projection, or are attributable to global deficits in general conceptual knowledge about social scenarios, remains unknown. Similarly, the contribution of the anterior temporal lobes in supporting successful social interactions remains to be fully explored (Olson *et al*., 2007).

In summary, the major finding of this study is that patients with semantic dementia exhibit profound deficits in the ability to imagine future events, despite a relative preservation of recent episodic memory. Using semantic dementia as a lesion model for semantic memory illuminates the importance of conceptual knowledge in the construction of future scenarios, an ability previously posited to depend exclusively on the integrity of the episodic memory system. The results from the group with semantic dementia stand in contrast to those observed in Alzheimer's disease, whereby parallel deficits across past and future episodic conditions are evident. Taken together, the present study highlights the differential involvement of medial and anterior temporal lobe structures in facilitating different forms of future thinking. Additional involvement of midline cortical regions such as the posterior cingulate, and the prefrontal cortex in Alzheimer's disease, points to the disruption of self-referential or autonoetic thought in this cohort, whereas erosion of the semantic memory system appears to be the primary contributing mechanism to future thinking deficits in semantic dementia. Importantly, our findings point towards

a critical role of the semantic memory system in supporting the simulation of future events, in concert with contributions from episodic memory. The next challenge lies in elucidating the precise contribution of the semantic memory system to the simulation of future events, and the clinical implications of such deficits in future thinking on behavioural and social levels in different patient groups.

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Supplementary material

Supplementary material is available at *Brain* online.

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