Preservation of episodic memory in semantic dementia: the importance of regions beyond the medial temporal lobes

Muireann Irish[a,b,c], Steffie Bunk[b], Sicong Tu[b,c,d], Jody Kamminga[b], John R. Hodges[b,c,d], Michael Hornberger[c,e], Olivier Piguet[b,c,d]

[a] School of Psychology, the University of New South Wales, Sydney, Australia.

[b] Neuroscience Research Australia, Randwick, Sydney, Australia.

[c] Australian Research Council Centre of Excellence in Cognition and its Disorders, Sydney, Australia.

[d] School of Medical Sciences, the University of New South Wales, Sydney, Australia.

[e] Norwich Medical School, University of East Anglia, Norwich, United Kingdom.

Corresponding author: Dr. Muireann Irish

Neuroscience Research Australia

P.O. Box 1165,

Randwick, Sydney

Australia, NSW 2031

Tel: +61 2 9399 1602

Fax: +61 2 9399 1047

Email: m.irish@neura.edu.au

Word count: 6334 (excluding figures, tables, references)

Abstract

Episodic memory impairment represents one of the hallmark clinical features of patients with Alzheimer's disease (AD) attributable to the degeneration of medial temporal and parietal regions of the brain. In contrast, a somewhat paradoxical profile of relatively intact episodic memory, particularly for non-verbal material, is observed in SD, despite marked atrophy of the hippocampus. This retrospective study investigated the neural substrates of episodic memory retrieval in 20 patients with a diagnosis of SD and 21 disease-matched cases of AD and compared their performance to that of 35 age- and education-matched healthy older Controls. Participants completed the Rey Complex Figure and the memory subscale of the Addenbrooke's Cognitive Examination-Revised as indices of visual and verbal episodic recall, respectively. Relative to Controls, AD patients showed compromised memory performance on both visual and verbal memory tasks. In contrast, memory deficits in SD were modality-specific occurring exclusively on the verbal task. Controlling for semantic processing ameliorated these deficits in SD, while memory impairments persisted in AD. Voxel-based morphometry analyses revealed significant overlap in the neural correlates of verbal episodic memory in AD and SD with predominantly anteromedial regions, including the bilateral hippocampus, strongly implicated. Controlling for semantic processing negated this effect in SD, however, a distributed network of frontal, medial temporal, and parietal regions was implicated in AD. Our study corroborates the view that episodic memory deficits in SD arise very largely as a consequence of the conceptual loading of traditional tasks. We propose that the functional integrity of frontal and parietal regions enables new learning to occur in SD in the face of significant hippocampal and anteromedial temporal lobe pathology, underscoring the inherent complexity of the episodic memory circuitry.

Keywords: Alzheimer's disease, hippocampus, posterior cingulate cortex, angular gyrus, semantic memory, prefrontal cortex.

1. Introduction

Semantic dementia (SD), also referred to as the semantic variant of primary progressive aphasia (Gorno-Tempini, et al., 2011), is characterised by the progressive and amodal deterioration of the conceptual knowledge base (Hodges & Patterson, 2007). The hallmark and most prominent presenting complaint in SD pertains to a "loss of memory for words" (Thompson, Patterson, & Hodges, 2003), manifesting in striking alterations in naming and comprehension, in the context of relatively fluent and grammatically correct speech. This loss of semantic knowledge occurs irrespective of modality and has been attributed to the degeneration of a central amodal semantic hub in the brain (Patterson, Nestor, & Rogers, 2007).

From a neural perspective, SD offers a compelling window into the neurocognitive architecture of the brain in relation to the coordinated and systematic degeneration of the semantic memory system (Irish, Piguet, & Hodges, 2012). The neuroanatomical signature of this syndrome is the progressive degeneration of the anterior temporal lobes, most severe on the ventral surface, encompassing the anterior fusiform gyrus, temporal pole, and perirhinal cortex, as well as medial temporal lobe (MTL) structures including the anterior hippocampus (Chan, et al., 2001; Galton, et al., 2001; Mion, et al., 2010). In most cases, initial atrophy is lateralised predominantly to the left hemisphere with progressive involvement of the contralateral hemisphere, producing bilateral temporal lobe insult over time (Irish, Hodges, & Piguet, 2014; Mion, et al., 2010).

Despite phenotypic alterations in semantic processing, patients with SD display an array of relatively preserved cognitive functions. For example, topographical orientation, visuospatial ability, non-verbal problem-solving, phonology, and working memory can all be remarkably preserved, even with advancing disease severity (Crutch & Warrington, 2002; Green & Patterson, 2009; reviewed by Hodges & Patterson, 2007; Pengas, Patterson, et al., 2010). The integrity of episodic memory is particularly noteworthy in this regard. While many patients with SD complain of memory impairment, this in fact does not reflect a true amnesia (Hodges & Patterson, 2007). A large corpus of research now demonstrates the striking preservation of episodic memory in SD, particularly when non-verbal tasks are employed (Bozeat, Gregory, Ralph, & Hodges, 2000; Maguire, Kumaran, Hassabis, & Kopelman, 2010). Clinically and anecdotally, SD patients display a relative preservation of day-to-day episodic memory, showing an intact capacity to encode and retrieve the "what", "where", and "when" of recent

events (Adlam, Patterson, & Hodges, 2009), as well as the detailed recollection of recent autobiographical experiences (Irish, Addis, Hodges, & Piguet, 2012; Irish, et al., 2011; McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Piolino, et al., 2003). Accruing evidence also suggests that patients with SD can learn and retain new verbal and non-verbal information, even in the face of severe degradation of semantic information regarding the studied items (reviewed by Graham, Patterson, & Hodges, 1999; Savage, Ballard, Piguet, & Hodges, 2013).

At first glance, the relative preservation of episodic memory in the context of profound semantic memory disruption in SD appears to support the classic fractionation of episodic and semantic memory as functionally distinct neurocognitive systems with relatively little overlap (Tulving, 1972). On close inspection, however, a paradox becomes apparent when we consider that SD patients display a relatively intact capacity for new learning and episodic retrieval in the context of marked hippocampal atrophy. Converging evidence reveals that the hippocampus is unequivocally involved in the SD pathological process and atrophy in this region can even surpass that typically seen in AD (Chan, et al., 2001; Davies, Graham, Xuereb, Williams, & Hodges, 2004; La Joie, et al., 2013), yet SD patients display substantially intact episodic memory (reviewed by Hodges & Patterson, 2007). The disease syndromes differ, however, in terms of the rostral-caudal gradient of hippocampal atrophy, with anterior portions most affected in SD versus predominantly posteromedial involvement in AD (Ranganath & Ritchey, 2012). This rostral-caudal gradient may be pivotal given that recent studies have highlighted the contribution of parietal regions, notably that of the posterior cingulate cortex, in the genesis of episodic memory impairments in AD (Frisch, et al., 2013; Irish, Hodges, & Piguet, 2013; Irish, Piguet, Hodges, & Hornberger, 2014; Nestor, Fryer, & Hodges, 2006).

A recent study has pointed to the hippocampus as occupying a critical nexus between functional brain networks that are differentially impacted by the SD and AD pathological process despite quantitatively comparable hippocampal atrophy in both patient groups (La Joie, et al., 2014). This study revealed that connectivity between the hippocampus and a largely posterior brain network, known to be vulnerable in AD, was exclusively related to episodic memory functioning in healthy individuals (La Joie, et al., 2014), further underscoring the need to consider regions beyond the hippocampus in supporting successful episodic memory retrieval (Rugg & Vilberg, 2013). As such, the relative preservation of episodic memory in SD likely reflects the sparing of regions beyond the MTL (Tan, et al.,

2014), with parietal structures, such as the posterior cingulate cortex, of particular interest in this regard (Nestor, et al., 2006).

While a number of studies have differentiated between SD and AD in terms of the underlying neural regions affected (e.g., La Joie, et al., 2014; Nestor, et al., 2006) no study to date, to our knowledge, has directly contrasted the neural substrates of episodic memory performance in these groups. This lacuna is somewhat surprising given the unresolved paradox of substantially preserved episodic memory despite striking hippocampal atrophy in SD. As such, it remains unclear which regions mediate successful anterograde episodic memory in this syndrome. The objective of this study was to determine the neural substrates of episodic memory performance, across visual and verbal domains, in SD in contrast with disease-matched cases of AD. By incorporating structural neuroimaging analyses, we sought to clarify how changes in grey matter intensity are differentially associated with verbal versus visual aspects of episodic memory.

In line with the characteristic deficits observed in SD, we predicted significant episodic memory impairments exclusively in the verbal domain, in the context of relatively intact visual memory. In contrast, in AD, we predicted widespread episodic memory deficits irrespective of modality. On a neural level, we predicted an anterior-posterior dissociation in terms of the neural correlates of episodic memory dysfunction in SD and AD, respectively. While the hippocampus was expected to be significantly implicated irrespective of patient group for verbal memory, we hypothesised that the integrity of posterior parietal regions would be a crucial determinant of non-verbal episodic memory performance in SD.

2. Methods and Materials

2.1 Participants

A retrospective study of 76 participants who attended FRONTIER, the frontotemporal dementia clinic at Neuroscience Research Australia (NeuRA) in Sydney, was undertaken. Twenty individuals meeting current clinical diagnostic criteria for semantic dementia (SD; Gorno-Tempini, et al., 2011) and 21 individuals diagnosed with clinically probable Alzheimer's disease (AD; McKhann, et al., 2011) were identified as suitable for inclusion in the study. Clinical diagnosis of patients was established by multidisciplinary consensus among senior neurologist (JRH), neuropsychologist and occupational therapist based on extensive clinical investigations, cognitive assessment, informant interviews, and evidence of atrophy on structural neuroimaging. Briefly, SD patients presented with marked and progressive loss of word meaning, with significant impairments in naming and comprehension, and predominantly left-lateralised atrophy on structural MRI. SD cases presenting with right dominant anterior temporal lobe atrophy profiles were not included in this study. In contrast, AD patients displayed significant episodic memory loss and disorientation to time and place, in the context of relatively preserved behaviour and personality.

Thirty five healthy older control participants were recruited from local community groups and the NeuRA volunteer research panel. 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, Dawson, Mitchell, Arnold, & Hodges, 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.

Ethical approval for this study was obtained from the South Eastern Sydney Local Area Health and University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

2.2 General cognitive assessment

Participants completed a standard battery of neuropsychological tests. Global cognitive functioning was assessed using the ACE-R (Mioshi et al., 2006), which is a sensitive and specific tool to detect cognitive impairment in dementia and comprises subscales assessing attention and orientation, memory, fluency, language, and visuospatial function. Basic attention and working memory was assessed using Digit Span (Wechsler, 1997). Psychomotor speed and mental flexibility were measured using the Trail Making Test Parts A and B (Reitan, 1958), respectively. A Trails B-A difference score was computed to reflect capacity for set-switching and divided attention. The Naming, Comprehension, and Semantic Association subscales of the Sydney Language Battery (SydBAT; Savage, Hsieh, et al., 2013) were administered as indices of semantic processing, while verbal fluency was assessed using the Letter Fluency task (F,A,S; Strauss, Sherman, & Spreen, 2006). Finally, the copy score of the Rey Complex Figure (Rey, 1941) was used as an index of visuospatial ability.

Carers of patients rated their behavioural changes on the Cambridge Behavioural Inventory (CBI; Wedderburn, et al., 2008). Finally, the functional status of patients was determined using the Frontotemporal Dementia Rating Scale (FRS; Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) which is a dementia staging tool sensitive to change in functional ability.

2.3 Assessment of Episodic Memory

In keeping with previous studies of episodic memory dysfunction in dementia syndromes (e.g., Irish, Piguet, et al., 2014; Pennington, Hodges, & Hornberger, 2011), participants completed visual and verbal episodic memory tests.

Visual episodic memory was assessed using the delayed recall subscale of the Rey Complex Figure (RCF). Participants are required to copy a complex design as accurately as possible and, following a 3-minute delay, must reproduce the figure from memory. The maximum score for the copy and recall trials is 36 points. A percentage retained score was computed (recall/copy score * 100) to control for general executive and visuospatial processes. A recognition subtest is available for the RCF task, however this component was not administered in the current study.

Verbal episodic memory was assessed using aspects of the memory subscale of the ACE-R, including verbal recall of 3 words (max score: 3), immediate recall of a name and address (max score: 7), delayed recall of the name and address after a 15-minute interval (max score:

7), leading to a total maximum score of 17 points. This score was transformed into a percentage retained score (i.e., ACE-R memory performance = score/17 * 100), to allow direct comparison with the visual episodic memory score.

2.4 Statistical analyses

Cognitive data were analysed using IBM SPSS Statistics (Version 22). Multivariate analyses of variance (MANOVA) were run to investigate main effects of group (AD, SD, Controls) across each of the background neuropsychological tests. For the experimental measures of episodic memory, repeated measures ANOVAs were run to explore main effects of modality (Verbal, Visual). Sidak post hoc tests were used to explore main effects of group for all variables of interest. Chi-squared tests (X^2), based on the frequency patterns of dichotomous variables (e.g., sex), were also used. Data were missing for 3 AD patients on the RCF memory task (Table 1) and were imputed using mean substitution.

2.5 Image acquisition

Participants underwent whole-brain T_1 and serial diffusion weighted imaging using a 3T Philips MRI scanner with standard quadrature head coil (eight channels). Structural T_1-weighted images were acquired using the following sequences: coronal orientation, matrix 256 x 256, 200 slices, 1 mm^2 in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8 ms, flip angle $\alpha = 19°$. Structural MRI data were analysed with FSL-VBM, a voxel-based morphometry (VBM) analysis (Ashburner and Friston, 2000; Mechelli et al., 2005) using the FSL-VBM toolbox from the FMRIB software package (http://www.fmrib.ox.ac.uk/fsl/fslvbm) (Smith et al., 2004). All scans were examined by a neuroradiologist for structural abnormalities; none were reported for control participants. Prior to analyses, all participant scans were visually inspected for significant head movements and artefacts. Structural scans were not available for 7 participants (AD: 2; SD: 4; Controls: 1).

2.6 Voxel-based morphometry analysis

Voxel-based morphometry (VBM) using structural MRI data was used to identify grey matter

volume changes across groups on a voxel-by-voxel basis. Briefly, structural images were extracted using the FSL brain extraction tool (Smith, 2002). Tissue segmentation was then carried out on the brain extracted images using FMRIB's Automatic Segmentation Tool (FAST; Zhang et al., 2011). The resulting grey matter partial volumes were aligned to the Montreal Neurological Institute standard space (MNI152) using the FMRIB non-linear registration approach (FNIRT; Andersson et al., 2007a, b) using a b-spline representation of the registration warp field (Rueckert et al., 1999). A study-specific template was created from the resulting images, combining AD, SD and Controls 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, to correct for local expansion or contraction. Finally, the modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

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. In the first step, differences in cortical grey matter intensities between patients (SD and AD) and Controls were assessed. Clusters from the group atrophy analyses were extracted using the threshold-free cluster enhancement method (tfce) and corrected for Family-Wise Error (FWE) at $p < .001$.

Next, correlations between performance on episodic memory tests and regions of grey matter atrophy were investigated in each patient group combined with Controls by including the episodic memory performance scores as covariates in separate general linear models. Patients were combined with Controls to increase the statistical power to detect brain-behaviour relationships across the entire brain by achieving greater variance in behavioural scores (Sollberger et al., 2009; Irish et al., 2012). For statistical power, a covariate only statistical model with a positive [1] t-contrast was used, providing an index of association between grey matter intensity and performance on the episodic memory measures. Two separate models were created to investigate the neural substrates of Visual and Verbal memory. Age was included as a nuisance variable in the atrophy and covariate analyses. 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

An overlap analysis was conducted to determine the neural regions commonly implicated in episodic memory dysfunction in AD and SD. The statistical maps generated in the covariate whole-brain analyses were scaled using a threshold of $p < .001$. These scaled contrasts were multiplied to create an inclusive, or overlap, mask across groups. To identify the regions uniquely implicated in each patient group separately, the same procedure was adopted however each scaled image was subsequently multiplied by the inverse of the other, to create an exclusive mask for each patient group (see also Irish, Piguet, et al., 2014). Clusters from the covariate analyses were extracted at $p < .001$ uncorrected. To reduce the potential for false positive results, a cluster extent threshold of 150 contiguous voxels was employed.

3. Results

3.1 Demographics

The participant groups did not differ significantly in terms of age ($p = .150$), years in education ($p = .197$), and sex distribution ($p = .917$). In addition, the AD and SD patient groups were matched for disease duration (months elapsed since onset of symptoms, $p = .647$), ratings of severity on the CDR-FTD sum of boxes ($p = .574$), and overall level of functional impairment ($p = .444$) with both groups presenting as "moderately impaired". Carers of AD and SD patients provided comparable ratings for overall behavioural changes ($p = 1.000$) on the CBI.

3.2 Global cognitive function

Neuropsychological testing revealed cognitive profiles characteristic of each patient group (Table 1). Briefly, both patient groups were significantly impaired relative to Controls on the cognitive screening test (ACE-R, $p < .0001$), but did not differ significantly from each other in terms of cognitive decline ($p = .543$). AD patients displayed marked deficits in comparison to Controls across all ACE-R subscales (all p values $< .0001$), and disproportionately poorer performance on the attention ($p = .001$) and visuospatial ($p < .0001$) subscales relative to SD. In contrast, SD patients showed significant impairments across all ACE-R subscales with the exception of the visuospatial subscale ($p = .838$).

On other cognitive tests, attention and executive function were significantly compromised in AD with respect to Controls (Digit Span Total, Trails A, Trails B-A, all *p* values < .0001) and SD patients (Digit Span Total, $p = .001$; Trails A, $p < .0001$; Trails B-A, $p = .002$). In contrast, SD patients demonstrated relatively intact attention and working memory capacity relative to Controls (Digit Span Total, $p = .130$; Trails A, $p = .971$; Trails B-A, $p = .058$). Semantic processing was significantly affected in both patient groups with respect to Controls (Letter fluency, Naming, Comprehension, Semantic Association, all *p* values < .0001); however, SD patients were disproportionately impaired on all of these measures relative to AD patients (all *p* values < .0001). Finally, marked deficits in visuospatial functioning were observed in the AD group relative to Controls (RCF copy, $p < .0001$) and SD patients ($p < .0001$) with SD patients scoring in line with Controls on the RCF copy ($p = .924$).

INSERT TABLE 1 AROUND HERE.

3.3 Episodic memory performance

Figure 1a displays the mean performance of participants on the verbal and visual episodic memory tasks. A repeated measures ANOVA was run to investigate the influence of modality (Visual, Verbal) on recall performance. A significant main effect of group was found ($F(2, 73) = 63.565$, $p < .0001$), as well as a significant main effect of modality ($F(1, 73) = 37.409$, $p < .0001$). A significant group x modality interaction ($F(2, 73) = 17.165$, $p < .0001$) was also present.

The group x modality interaction reflected the fact that while AD patients scored significantly lower than Controls on both visual ($p < .0001$) and verbal ($p < .0001$) measures of episodic recall, SD patients only showed compromised performance on the verbal task ($p < .0001$), scoring in line with Controls for visual recall ($p = .550$). SD patients demonstrated significantly higher performance across visual ($p = .008$) and verbal ($p = .001$) domains relative to the AD group.

Within patient group analyses revealed further dissociations between visual and verbal episodic recall. For Controls, verbal recall was significantly higher when compared to visual retrieval ($p < .0001$). This verbal > visual effect was also suggested in the AD group ($p =$

.057). In the SD group, however, no significant differences were evident between the visual and verbal subscales, reflecting the loss of the verbal dominance effect (p = .543).

INSERT FIGURE 1 AROUND HERE.

3.3.1 Controlling for semantic processing

To establish whether verbal recall deficits were driven primarily by semantic processing impairments characteristic of SD, we re-ran the analyses including semantic Naming performance as a covariate.

Figure 1b displays the estimated marginal means for visual and verbal episodic recall controlling for semantic naming performance. The overall main effect of group persisted (F(2, 72) = 48.094, p < .0001), however no main effect of Modality was evident (p = .481). A significant modality by group interaction was also observed (F(2, 72) = 4.477, p = .015). Sidak post hoc tests revealed significant episodic memory deficits in the AD group across visual (p = .014) and verbal (p < .0001) domains relative to Controls. SD patients, however, were now found to score in line with Controls for both visual (p = .899) and verbal (p = .229) domains, and outperformed their AD counterparts irrespective of modality (visual: p = .016; verbal: p < .0001). As such, controlling for semantic processing served to ameliorate episodic memory performance in the SD group, suggesting that conceptual processing deficits represent the chief neurocognitive mechanism driving episodic recall difficulties in SD.

In summary, episodic memory deficits that arise in SD appear to be primarily mediated by the conceptual loading of the to-be-remembered stimuli. When conceptually meaningful information is presented, SD patients display compromised recall performance comparable to that observed in AD. These deficits, however, are ameliorated when semantic processing impairments are controlled for. In contrast, when information is presented in a non-meaningful manner, SD patients perform in line with Control participants, and score significantly higher than their AD counterparts.

3.3.2 Controlling for encoding-related processes

To investigate whether verbal encoding-related processes impact verbal memory performance in SD, we further constrained our focus to the name and address subcomponent of the verbal memory measure and calculated a percentage retained score (delayed recall/initial encoding score * 100). This score provided an index of verbal delayed recall adjusting for verbal encoding-related processes across the groups. An overall main effect of group was evident ($F(2, 73) = 69.638$, $p < .0001$) with both patient groups scoring significantly lower than Controls (all p values < .0001). In addition, SD patients tended to score higher in comparison with AD patients for this measure ($p = .053$).

Finally, we controlled for semantic processing on the adjusted verbal delayed recall score and found that the overall group effect persisted ($F(2, 72) = 40.089$, $p < .0001$) with AD patients scoring significantly lower than Controls ($p < .0001$). The verbal memory deficit, however, was no longer present in the SD group ($p = .061$).

3.4 Voxel-based morphometry group analysis

3.4.1 Patterns of grey matter atrophy

Figure 2 and Table 2 show the patterns of grey matter intensity decrease in AD (A) and SD (B) participants relative to Controls. AD patients showed widespread grey matter intensity decrease in bilateral medial temporal, frontal, parietal and occipital regions of the brain, including the frontopolar and frontoinsular cortices, the lateral temporal cortices as well as medial temporal structures including the hippocampus, amygdala, and thalamus bilaterally. Atrophy also extended posteriorly to include the bilateral angular and supramarginal gyrus, the precuneus and posterior cingulate cortices, as well as the lateral occipital cortices and occipital poles.

SD patients displayed characteristic grey matter intensity loss predominantly in bilateral anteromedial temporal regions including the temporal fusiform cortex, temporal poles, parahippocampal gyrus, amygdala, hippocampus, and extending to include the bilateral frontoinsular cortices, and OFC. While atrophy was present in both hemispheres in SD, the left-side was disproportionately affected relative to the right-side.

A direct comparison of the AD and SD groups revealed that SD patients showed significantly more grey matter atrophy in anteromedial temporal regions of the brain relative to AD

patients (Figure 2C). The regions disproportionately affected in SD relative to AD included the left temporal fusiform cortex, left temporal pole, left OFC, left amygdala, left hippocampus, and left inferior, middle and superior temporal gyri. The reverse contrast revealed that AD patients harboured significantly more atrophy relative to SD patients in the precuneus, the superior parietal lobule, and the occipital cortex bilaterally (Figure 2D). These patterns of atrophy are consistent with previous reports in AD (Whitwell, et al., 2007) and SD (Mion, et al., 2010).

INSERT TABLE 2 AROUND HERE.

INSERT FIGURE 2 AROUND HERE.

3.4.2 Neural correlates of episodic recall performance by modality

Figure 3 and Table 3 show the significant regions to emerge from the covariate analyses investigating verbal (Figure 3A) and visual (Figure 3B) episodic recall in AD and SD (see also Supplementary Figures 1 and 2).

For verbal recall, regions implicated irrespective of diagnosis included the bilateral anterior temporal fusiform cortex, bilateral temporal pole, bilateral orbitofrontal cortices, bilateral lateral temporal cortex, bilateral parahippocampal gyrus, bilateral amygdala, bilateral hippocampus, and the left lateral occipital cortex.

The exclusive masking technique revealed that regions implicated for verbal recall solely in AD included bilateral posterior inferior temporal gyrus, bilateral parietal operculum cortex, bilateral supramarginal gyrus, bilateral angular gyrus, prefrontal regions including the bilateral medial prefrontal cortex, bilateral frontal pole, the bilateral posterior hippocampus, and bilateral precuneus and posterior cingulate cortices.

For SD patients, the regions exclusively implicated in verbal episodic recall performance were the bilateral anterior temporal fusiform cortices, bilateral temporal poles, bilateral parahippocampal gyrus, bilateral orbitofrontal cortices, bilateral hippocampus, and right amygdala.

****INSERT FIGURE 3 AROUND HERE****.

****INSERT TABLE 3 AROUND HERE****.

For visual recall, regions in the parietal lobes, including the left supramarginal gyrus and the left superior parietal lobule, were exclusively implicated in AD. In contrast, no significant clusters emerged in the SD group analyses, reflecting the fact that SD patients scored in line with Controls for visual recall.

3.4.3 Controlling for semantic processing

Finally, given that semantic processing impairments were found to significantly drive verbal episodic memory impairment in SD, we re-ran the verbal recall covariate analyses with semantic Naming including in the model. Figure 4 and Table 4 display the significant regions to emerge from the analyses in AD and SD participants (see also Supplementary Figure 3).

No significant regions of overlap were identified across participant groups. Exclusive masking revealed no significant clusters in the SD group. In contrast, hallmark regions of the episodic memory network were implicated in the AD group, including right frontopolar and orbitofrontal cortices, lateral and medial temporal regions including the bilateral hippocampus, bilateral occipital cortices, as well as significant parietal involvement including the bilateral angular gyrus, left supramarginal gyrus, bilateral superior parietal lobule, bilateral precuneus cortex, and the left posterior cingulate cortex.

****INSERT FIGURE 4 AROUND HERE****.

****INSERT TABLE 4 AROUND HERE****.

4. Discussion

The objective of this study was to investigate episodic memory performance across verbal and non-verbal domains in SD and AD, and to identify the neural substrates that are essential

for successful episodic memory retrieval in each group. At first glance, our findings suggest that episodic memory deficits in SD arise very largely as a consequence of the modality of testing, and manifest prominently in the verbal domain. Importantly, however, only the verbal, but not the visual, episodic stimuli were meaningful. A more parsimonious interpretation, therefore, is that episodic memory deficits in SD reflect the conceptual load of traditional neuropsychological tests rather than a simple modality effect. In contrast, patients with AD display amodal episodic memory deficits, irrespective of the conceptual load of the stimuli, attributable to the degeneration of frontal, medial temporal, and parietal nodes of the classic episodic memory network. Our findings underscore the importance of regions beyond the medial temporal lobes in modulating relatively successful episodic memory retrieval in SD when the conceptual loading of stimuli is controlled for.

Recent studies have highlighted the apparent paradox of episodic memory performance in SD, whereby everyday memory is relatively preserved (Adlam, et al., 2009; Irish, et al., 2011) despite severe hippocampal atrophy often comparable to, or even greater than, that typically observed in AD (Chan, et al., 2001; Davies, et al., 2004; Galton, et al., 2001; La Joie, et al., 2013; Nestor, et al., 2006). While the hippocampus arguably occupies a crucial node in the classic episodic memory network (reviewed by Dickerson & Eichenbaum, 2010), our findings suggest that the hippocampal atrophy found in SD does not, by default, give rise to a global amnestic profile. Our SD patients displayed striking anteromedial temporal lobe atrophy, with significantly greater left hippocampal insult relative to the AD comparison group yet episodic memory performance differed markedly contingent on the domain of testing. Notably, SD patients' episodic memory deficits were confined to the verbal domain. Importantly, however, the verbal memory task was distinct from the non-verbal condition in that the verbal stimuli were imbued with conceptual meaning. Not surprisingly then, these verbal episodic memory deficits were ameliorated in the SD group after controlling for semantic processing capacity. Our findings corroborate the proposal that verbal memory dysfunction in SD arises very largely as a consequence of the conceptual knowledge demands inherent in traditional verbal tasks of episodic memory (Graham, Patterson, Powis, Drake, & Hodges, 2002; Hodges & Patterson, 2007).

In contrast, on a non-verbal, and non-meaningful, test of episodic memory, SD patients performed in line with Control participants, supporting extensive work demonstrating that patients with SD exhibit relatively preserved episodic memory for non-verbal stimuli even when they are unable to comprehend these items (Graham, Simons, Pratt, Patterson, &

Hodges, 2000; Simons, et al., 2002). These findings reinforce the view that, in the absence of meaningful semantic input, SD patients can harness perceptual information in the service of episodic remembering (Graham, et al., 2000; Simons, et al., 2002). This proposal elegantly accounts for the finding of compromised verbal recall in SD given that perceptual information is far less useful in discriminating between words than pictures (Simons, et al., 2002). Interestingly, interactive processing between perceptual and conceptual information has been demonstrated whereby degraded conceptual knowledge about real objects impedes the ability to recognise an object as belonging in the same class as another instance (Ikeda, Patterson, Graham, Ralph, & Hodges, 2006). Ikeda et al. (2006) argued that the conceptual degradation characteristically seen in SD increases the salience of the specific perceptual features of objects leading to impairments in episodic recognition when attributes such as colour, angle of view, or exemplar are varied. Successful recall performance on the Rey Complex Figure task therefore likely reflects intact perceptual processing in SD. Our results complement previous findings of impaired non-verbal episodic memory in SD in situations where successful performance relies upon the use of conceptual knowledge (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Patterson, et al., 2006). We suggest that future studies contrasting the retrieval of real versus non-real objects (i.e., conceptually loaded versus non-meaningful stimuli) will be crucial to further elucidate the potential interplay between conceptual and perceptual routes of learning (see Simons, et al., 2002).

Our voxel-based morphometry analyses revealed important insights into the underlying brain regions that are differentially associated with episodic memory performance in each dementia syndrome. Striking commonalities were observed in terms of the neural correlates of verbal episodic memory dysfunction in SD and AD, with anteromedial structures including the bilateral temporal poles, bilateral lateral temporal cortices, bilateral orbitofrontal cortex, and bilateral hippocampus significantly involved irrespective of patient group. At first glance, this pattern of results seems to implicate the hippocampus in the genesis of episodic memory dysfunction in SD. Importantly, however, this verbal episodic memory effect was negated when we covaried for semantic processing, and the hippocampus was no longer involved in the SD group. By contrast, verbal memory deficits persisted strongly in AD, reflecting the degeneration of the classic episodic memory network including frontal, lateral and medial temporal, parietal and occipital regions. Importantly, bilateral posterior hippocampal and parietal regions emerged as significant neural correlates in the AD group including the supramarginal gyrus, angular gyrus, precuneus cortex and posterior cingulate cortex.

Previous studies have highlighted the breakdown of a distributed neural network subtending episodic memory deficits in AD, drawing attention towards the pivotal role of posterior parietal structures in the origins of episodic memory dysfunction in this syndrome (Frisch, et al., 2013; Irish, Piguet, et al., 2014). Atrophy in the posterior cingulate cortex has been heralded as critical in differentiating between SD and AD patients (Nestor, et al., 2006) with the proposal that integrity of this region holds the key to relatively intact episodic memory performance in SD well into the disease course (Nestor, et al., 2006; Pengas, Hodges, Watson, & Nestor, 2010; Pengas, Patterson, et al., 2010). Thus the observation of relatively preserved capacity for new episodic learning in SD (Adlam, et al., 2009; Savage, Ballard, et al., 2013), despite striking anteromedial temporal lobe atrophy, can therefore potentially be reconciled by considering the involvement of these relatively preserved parietal structures (see also Hodges & Patterson, 2007).

Our findings resonate strongly with a recent study which dissociated between SD- (anteromedial) versus AD- (posterior medial) vulnerable brain networks with the hippocampus representing an anchor point, or "crossroads", between these functional networks (La Joie et al., 2014). Notably, the crucial determinant of episodic memory performance in healthy individuals was found to relate to connectivity between the hippocampus and posterior parietal regions including the precuneus/posterior cingulate cortex, and the angular gyrus. Our voxel-based morphometry findings map remarkably well onto those reported by La Joie et al. (2014) and confirm the role of parietal brain structures in the origins of episodic memory dysfunction in AD. It is notable that many of the core regions implicated in memory dysfunction in AD can be subsumed under the posterior medial cortical memory system proposed by Ranganath and Ritchey (2012). This putative memory system comprises an extended network of largely posterior brain regions including the posterior cingulate cortex, precuneus, angular gyrus, retrosplenial and parahippocampal cortices, as well as the medial prefrontal cortex, with dense anatomical connections to subregions of the hippocampal formation. Collectively, these brain regions facilitate the construction and application of spatiotemporally specific schemas, which are posited to underpin a range of constructive endeavours such as remembering the past, simulating the future, and spatial memory (Ranganath & Ritchey, 2012). In support of this hypothesis, mounting evidence confirms that damage to key nodes of this posterior medial memory system gives rise to a host of phenotypic impairments in AD in such domains as autobiographical memory (Irish, Addis, et al., 2012; reviewed by Irish & Piguet, 2013),

episodic future thinking (Irish, et al., 2013; reviewed by Irish & Piolino, 2015), scene construction (Irish, et al., 2015), and spatial memory (Pengas, Patterson, et al., 2010; Tu, et al., 2015). As such, the pervasive memory deficits in AD can be understood in terms of the disruption of a broader posterior medial memory system, in which connectivity between subregions of the hippocampus extending to parietal brain structures such as the retrosplenial cortex and posterior cingulate cortex, are the crucial determinants of episodic memory performance. Where SD is concerned, functional integrity of this posteromedial memory system may hold the key to understanding the relative preservation of episodic memory in this syndrome (La Joie, et al., 2014).

Recent fMRI studies have begun to shed light upon the brain regions which must be functional to support episodic memory processes in SD. Maguire et al. (2010) conducted a longitudinal fMRI study of autobiographical memory in a case of SD, patient A.M., and revealed a relative preservation of autobiographical retrieval in the face of marked semantic difficulties. Despite significant hippocampal volume loss, A.M. was found to activate residual hippocampal and neocortical tissue during autobiographical recollection. Moreover, compensatory up-regulation of core brain regions within the episodic memory network was found, with significant activation observed in the ventromedial and ventrolateral prefrontal cortices, right temporal neocortex, and the precuneus bilaterally (Maguire, et al., 2010). This up-regulation of crucial regions within the episodic memory network has been confirmed in more recent studies exploring autobiographical memory (Viard, et al., 2013) and episodic future thinking (Viard, et al., 2014) in case series of SD. As such, compensatory activations in frontal and parietal regions of the episodic memory network may, in part, account for the phenomenon of relatively spared episodic memory in the face of severe atrophy of medial and lateral temporal lobe structures in SD. Future studies teasing apart the functional contributions of specific regions in the frontal, medial temporal and parietal lobes will be of particular interest in this regard.

A number of methodological issues warrant consideration in the current context. The assessment of verbal episodic memory using traditional neuropsychological tests such as the Rey Auditory Verbal Learning Task is severely hampered by the profound semantic impairments seen in SD. As this was a retrospective study, we used the memory subscale of the ACE-R screening tool as a surrogate measure of verbal memory performance collected as part of the routine clinical assessment in the FRONTIER clinic. Given this retrospective approach, our measures of verbal and visual episodic memory invariably present with certain

limitations. For example, the verbal score comprises both encoding and delayed retrieval processes. Importantly, however, a separate analysis controlling for verbal encoding-related processes revealed the same overall pattern of results. Similarly, the visual measure probes retrieval of a non-semantic object, which was essential to allow us to dissociate the contribution of semantic associations from perceptual aspects. Nevertheless, future prospective studies of episodic memory in these syndromes will benefit from including counterbalanced conditions manipulating the conceptual loading of verbal (e.g., words versus non-words) and visual (real versus non-real objects) stimuli. Our study was cross-sectional in nature and as such it will be important to clarify the fate of episodic memory in SD with advancing disease severity, to determine whether episodic memory for non-conceptual material ultimately becomes compromised, and which neural regions are implicated in such deficits. Our grey matter voxel-based morphometry covariate results did not survive conservative correction for multiple comparisons (i.e., Family-Wise Error) and were therefore reported uncorrected using a stringent threshold of $p < .001$. To guard against the potential for false positive results, however, we applied strict cluster extent thresholds in the covariate analyses. Given our sample size, the application of stringent cluster extent thresholds, and our *a priori* hypothesis, we are confident that our results do not represent false positive findings. As discussed, future studies incorporating task-based fMRI assessment of episodic memory performance in SD will be crucial to explore the capacity for compensatory up-regulation of frontal and parietal cortices during episodic retrieval. In addition, we suggest that the inclusion of resting-state functional connectivity metrics will illuminate how alterations in functional connectivity between anteromedial and posteromedial brain networks differentially disrupt episodic and semantic memory performance in the dementias, building on the recent findings of La Joie et al. (2014).

5. Conclusions

In summary, this is the first study to directly contrast the neural correlates of verbal and non-verbal episodic memory performance in the dementia syndromes of SD and AD. Despite severe hippocampal atrophy, patients with SD appear remarkably adept at encoding and retrieving episodic information, particularly when this information is presented in a non-conceptually driven manner. Our findings build upon a growing body of work pointing to relatively spared episodic memory in this syndrome, and point to the importance of

considering the functional integrity of structures in the frontal and parietal lobes as key mediators of successful episodic memory performance.

Acknowledgements

The authors are grateful to the patients and their families for their continued support of our research. This work was supported by funding to ForeFront, a collaborative research group dedicated to the study of frontotemporal dementia and motor neuron disease, from the National Health and Medical Research Council (NHMRC) (APP1037746) and the Australian Research Council (ARC) Centre of Excellence in Cognition and its Disorders Memory Node (CE11000102). ST is supported by an Alzheimer's Australia Dementia Research Foundation postgraduate award and a National Health and Medical Research Council postgraduate award. SB is supported by an International Internship award from the Dutch Alzheimer Association, Alzheimer Nederland. OP is supported by an NHMRC Senior Research Fellowship (APP1103258). MI is supported by an ARC Discovery Early Career Researcher Award (DE130100463). These funding sources had no involvement in the study design, collection, analysis and interpretation of data, writing the manuscript, and in the decision to submit the manuscript for publication. The authors report no conflict of interest.

References:

Adlam, A., Patterson, K., & Hodges, J. R. (2009). “I remember it as if it were yesterday”: Memory for recent events in patients with semantic dementia. *Neuropsychologia, 47*, 1344-1351.

Bozeat, S., Gregory, C. A., Ralph, M. A., & Hodges, J. R. (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry, 69*, 178-186.

Bozeat, S., Lambon Ralph, M. A., Patterson, K., Garrard, P., & Hodges, J. R. (2000). Non-verbal semantic impairment in semantic dementia. *Neuropsychologia, 38*, 1207-1215.

Chan, D., Fox, N., Scahill, R., Crum, W., Whitwell, J., Leschziner, G., Rossor, A., Stevens, J., Cipolotti, L., & Rossor, M. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol, 49*, 433-442.

Crutch, S. J., & Warrington, E. K. (2002). Preserved calculation skills in a case of semantic dementia. *Cortex, 38*, 389-399.

Davies, R. R., Graham, K. S., Xuereb, J. H., Williams, G. B., & Hodges, J. R. (2004). The human perirhinal cortex and semantic memory. *Eur J Neurosci, 20*, 2441-2446.

Dickerson, B. C., & Eichenbaum, H. (2010). The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology, 35*, 86-104.

Frisch, S., Dukart, J., Vogt, B., Horstmann, A., Becker, G., Villringer, A., Barthel, H., Sabri, O., Muller, K., & Schroeter, M. L. (2013). Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration - a combined study of hypometabolism and atrophy. *PLoS One, 8*, e55251.

Galton, C., Patterson, K., Graham, K., Lambon-Ralph, M., Williams, G., Antoun, N., Sahakian, B., & Hodges, J. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology, 57*, 216-225.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76*, 1006-1014.

Graham, K. S., Patterson, K., & Hodges, J. R. (1999). Episodic memory: new insights from the study of semantic dementia. *Curr Opin Neurobiol, 9*, 245-250.

Graham, K. S., Patterson, K., Powis, J., Drake, J., & Hodges, J. R. (2002). Multiple inputs to episodic memory: words tell another story. *Neuropsychology, 16*, 380-389.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. (2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia, 38*, 313-324.

Green, H. A., & Patterson, K. (2009). Jigsaws-a preserved ability in semantic dementia. *Neuropsychologia, 47*, 569-576.

Hodges, J. R., & Patterson, K. (2007). Semantic dementia: a unique clinicopathological syndrome. *The Lancet Neurology, 6*, 1004-1014.

Ikeda, M., Patterson, K., Graham, K. S., Ralph, M. A., & Hodges, J. R. (2006). A horse of a different colour: do patients with semantic dementia recognise different versions of the same object as the same? *Neuropsychologia, 44*, 566-575.

Irish, M., Addis, D. R., Hodges, J. R., & Piguet, O. (2012). Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain, 135*, 2178-2191.

Irish, M., Halena, S., Kamminga, J., Tu, S., Hornberger, M., & Hodges, J. R. (2015). Scene construction impairments in Alzheimer's disease - A unique role for the posterior cingulate cortex. *Cortex, 73*, 10-23.

Irish, M., Hodges, J. R., & Piguet, O. (2013). Episodic future thinking is impaired in the behavioural variant of frontotemporal dementia. *Cortex, 49*, 2377-2388.

Irish, M., Hodges, J. R., & Piguet, O. (2014). Right anterior temporal lobe dysfunction underlies theory of mind impairments in semantic dementia. *Brain, 137*, 1241-1253.
Irish, M., Hornberger, M., Lah, S., Miller, L., Pengas, G., Nestor, P. J., Hodges, J. R., & Piguet, O. (2011). Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia, 49*, 2694-2702.
Irish, M., & Piguet, O. (2013). The pivotal role of semantic memory in remembering the past and imagining the future. *Front Behav Neurosci, 7*, 27.
Irish, M., Piguet, O., & Hodges, J. R. (2012). Self-projection and the default network in frontotemporal dementia. *Nat Rev Neurol, 8*, 152-161.
Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2014). Common and unique grey matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. *Human Brain Mapping, 35*, 1422-1435.
Irish, M., & Piolino, P. (2015). Impaired capacity for prospection in the dementias - Theoretical and clinical implications. *Br J Clin Psychol*.
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., & Chetelat, G. (2014). Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks. *Neuron, 81*, 1417-1428.
La Joie, R., Perrotin, A., de La Sayette, V., Egret, S., Doeuvre, L., Belliard, S., Eustache, F., Desgranges, B., & Chetelat, G. (2013). Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia. *Neuroimage Clin, 3*, 155-162.
Maguire, E. A., Kumaran, D., Hassabis, D., & Kopelman, M. D. (2010). Autobiographical memory in semantic dementia: A longitudinal fMRI study. *Neuropsychologia, 48*, 123-136.
McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). 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*, 263-269.
McKinnon, M., Black, S., Miller, B., Moscovitch, M., & Levine, B. (2006). Autobiographical memory in semantic dementia: Implications for theories of limbic-neocortical interaction in remote memory. *Neuropsychologia, 44*, 2421-2429.
Mion, M., Patterson, K., Acosta-Cabronero, J., Pengas, G., Izquierdo-Garcia, D., Hong, Y. T., Fryer, T. D., Williams, G. B., Hodges, J. R., & Nestor, P. J. (2010). What the left and right anterior fusiform gyri tell us about semantic memory. *Brain, 133*, 3256-3268.
Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry, 21*, 1078-1085.
Mioshi, E., Hsieh, S., Savage, S., Hornberger, M., & Hodges, J. R. (2010). Clinical staging and disease progression in frontotemporal dementia. *Neurology, 74*, 1591-1597.
Morris, J. (1997). Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International psychogeriatrics, 9*, 173-176.
Nestor, P. J., Fryer, T. D., & Hodges, J. R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage, 30*, 1010-1020.
Patterson, K., Lambon Ralph, M. A., Jefferies, E., Woollams, A., Jones, R., Hodges, J. R., & Rogers, T. T. (2006). "Presemantic" cognition in semantic dementia: six deficits in search of an explanation. *J Cogn Neurosci, 18*, 169-183.
Patterson, K., Nestor, P., & Rogers, T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience, 8*, 976-987.

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

Pengas, G., Patterson, K., Arnold, R. J., Bird, C. M., Burgess, N., & Nestor, P. J. (2010). Lost and found: bespoke memory testing for Alzheimer's disease and semantic dementia. *J Alzheimers Dis, 21*, 1347-1365.

Pennington, C., Hodges, J. R., & Hornberger, M. (2011). Neural correlates of episodic memory in behavioural variant frontotemporal dementia. *Journal of Alzheimer's disease, 24*, 261-268.

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De La Sayette, V., & Eustache, F. (2003). Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. *Brain, 126*, 2203-2219.

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci, 13*, 713-726.

Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique. *Archives de Psychologie, 28*, 215-285.

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol, 23*, 255-260.

Savage, S. A., Ballard, K. J., Piguet, O., & Hodges, J. R. (2013). Bringing words back to mind - Improving word production in semantic dementia. *Cortex, 49*, 1823-1832.

Savage, S. A., Hsieh, S., Leslie, F., Foxe, D., Piguet, O., & Hodges, J. R. (2013). Distinguishing Subtypes in Primary Progressive Aphasia: Application of the Sydney Language Battery. *Dement Geriatr Cogn Disord, 35*, 208-218.

Simons, J. S., Verfaellie, M., Galton, C. J., Miller, B. L., Hodges, J. R., & Graham, K. S. (2002). Recollection-based memory in frontotemporal dementia: implications for theories of long-term memory. *Brain, 125*, 2523-2536.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*: Oxford University Press, USA.

Tan, R. H., Wong, S., Kril, J. J., Piguet, O., Hornberger, M., Hodges, J. R., & Halliday, G. M. (2014). Beyond the temporal pole: limbic memory circuit in the semantic variant of primary progressive aphasia. *Brain, 137*, 2065-2076.

Thompson, S. A., Patterson, K., & Hodges, J. R. (2003). Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. *Neurology, 61*, 1196-1203.

Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial translation - A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex, 67*, 83-94.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory.* (pp. 381-403). New York: Academic Press.

Viard, A., Desgranges, B., Matuszewski, V., Lebreton, K., Belliard, S., de La Sayette, V., Eustache, F., & Piolino, P. (2013). Autobiographical memory in semantic dementia: New insights from two patients using fMRI. *Neuropsychologia*.

Viard, A., Piolino, P., Belliard, S., de La Sayette, V., Desgranges, B., & Eustache, F. (2014). Episodic future thinking in semantic dementia: a cognitive and FMRI study. *PLoS One, 9*, e111046.

Wechsler, D. (1997). *Wechsler Memory Scale - Third edition: Administration and Scoring Manual.* San Antonio, TX: Psychological Corporation.

Wedderburn, C., Wear, H., Brown, J., Mason, S. J., Barker, R. A., Hodges, J. R., & Williams-Gray, C. (2008). The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. *Journal of Neurology, Neurosurgery and Psychiatry, 79*, 500-503.

Whitwell, J. L., Przybelski, S. A., Weigand, S. D., Knopman, D. S., Boeve, B. F., Petersen, R. C., & Jack, C. R., Jr. (2007). 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain, 130*, 1777-1786.

Figure Legends

Figure 1. Episodic memory performance across visual and verbal modalities in Alzheimer's disease (AD), semantic dementia (SD), and Control participants. Panel A represents percentage correct performance on the episodic memory tasks. Panel B displays the estimated marginal means for episodic memory performance controlling for semantic processing. Error bars represent standard error of the mean. *$p < .05$; **$p < .0001$ denote group differences relative to Control performance.

Figure 2. Voxel-based morphometry analyses showing regions of decreased grey matter intensity in (A) AD patients in comparison with Controls (MNI coordinates: $x = -14$, $y = -10$), (B) SD patients in comparison with Controls ($x = -14$, $y = -10$), (C) SD patients relative to AD patients ($x = -26$, $y = -8$), and (D) AD patients relative to SD patients ($x = 2$, $y = -70$). Coloured voxels show regions that were significant in the analyses at $p < .001$ corrected for Family-Wise Error using the threshold-free cluster enhancement method (tfce). Clusters are overlaid on the Montreal Neurological Institute standard brain. Age is included as a covariate in the analyses. L = Left.

Figure 3. Voxel-based morphometry covariate analyses showing brain regions which correlate significantly with (A) verbal (MNI coordinates: $x = -24$, $y = -26$) and (B) visual ($x = -38$, $y = -24$) episodic memory recall performance. Coloured voxels show regions that were significant in the analyses at $p < .001$ uncorrected. All clusters reported $t > 3.7$. Clusters are overlaid on the Montreal Neurological Institute standard brain. Age is included as a covariate in the analyses. Red clusters = regions commonly implicated across dementia syndromes; green clusters = regions exclusively implicated in AD; yellow clusters = regions exclusively implicated in SD. L = Left.

Figure 4. Voxel-based morphometry covariate analyses showing brain regions which correlate significantly with verbal recall performance, controlling for semantic processing in (A) AD and (B) SD participants (MNI coordinates: $x = -14$, $y = -36$). Coloured voxels show regions that were significant in the analyses at $p < .001$ uncorrected. All clusters reported $t > 3.7$. Clusters are overlaid on the Montreal Neurological Institute standard brain. Semantic Naming and age are included as covariates in the analyses. Green clusters = regions exclusively implicated in AD; yellow clusters = regions exclusively implicated in SD. L = Left.

Table 1. Demographic and clinical characteristics of study samples[a,b,c]

	SD (n=20)	AD (n=21)	Controls (n=35)	Group effect	Post hoc test
Sex (M:F)	12:8	12:9	19:16	n/s	-
Age (years)	61.7 (4.8)	64.4 (6.7)	64.4 (4.8)	n/s	-
Education (years)	12.3 (2.1)	12.0 (3.4)	13.2 (2.3)	n/s	-
Disease duration (months)	56.2 (20.0)	52.7 (27.5)	-	n/s	-
CDR FTLD (24)	5.9 (3.2)	6.6 (3.3)	-	n/s	-
FRS Rasch logit score	1.0 (1.2)	0.6 (1.6)	-	n/s	-
CBI Total (%)	26.0 (15.1)	26.0 (15.6)	2.6 (2.6)	**	SD, AD > Controls SD = AD
ACE-R Total (100)	60.9 (13.2)	64.1 (9.3)	95.6 (3.0)	**	SD, AD < Controls SD = AD
ACE-R Attention (18)	16.1 (1.8)	13.7 (2.5)	17.8 (0.5)	**	SD, AD < Controls SD > AD
ACE-R Fluency (14)	4.4 (3.3)	6.5 (2.9)	12.5 (1.5)	**	SD, AD < Controls SD < AD
ACE-R Language (26)	12.3 (4.0)	20.8 (3.6)	25.3 (1.1)	**	SD, AD < Controls SD < AD
ACE-R Visuospatial (16)	15.1 (1.2)	11.5 (3.3)	15.5 (1.0)	**	SD, Controls > AD SD = Controls
Psychomotor Speed					
Trails A (sec)	35.5 (11.7)	103.1 (71.5)	31.3 (11.3)	**	SD, Controls < AD SD = Controls
Attention/Working Memory					
Digit Span Total (30)	17.0 (4.6)	12.0 (3.6)	19.4 (4.3)	**	SD, Controls > AD SD = Controls
Executive Function					
Trail Making Test B-A (sec)	67.0 (40.7)	115.0 (51.1)	43.3 (25.6)	**	SD, Controls < AD SD = Controls

Language					
Letter Fluency Total	23.4 (9.5)	23.6 (11.5)	45.5 (11.7)	**	SD, AD < Controls SD = AD
Semantic processing					
Naming (30)	5.7 (4.5)	19.4 (5.3)	27.0 (2.3)	**	SD, AD < Controls SD < AD
Comprehension (30)	18.4 (5.9)	24.9 (3.3)	29.2 (1.4)	**	SD, AD < Controls SD < AD
Semantic Association (30)	17.4 (6.0)	24.3 (2.3)	27.9 (1.6)	***	SD < AD < Controls
Visuospatial function					
RCF Copy (36)	31.8 (2.9)	16.5 (10.7)	32.8 (3.3)	**	SD, Controls > AD SD = Controls

[a] Maximum score for each test and standard deviations in brackets where applicable.

[b] SD = semantic dementia; AD = Alzheimer's disease; CDR FTLD = Frontotemporal Lobar Degeneration modified Clinical Dementia Rating; FRS = Frontotemporal Dementia Rating Scale, logit transformation (very mild: 5.39 to 4.12; mild: 3.35 to 1.92; moderate: 1.68 to -0.40; severe: -0.40 to -2.58; very severe: -3.09 to -4.99; profound: -6.66); CBI = Cambridge Behavioural Inventory; ACE-R = Addenbrooke's Cognitive Examination Revised; RCF = Rey Complex Figure test.

[c] CDR FTLD available for 15 SD and 15 AD cases. FRS Rasch available for 18 SD and 14 AD cases. CBI available for 19 SD cases and 32 Controls. Trails A available for 19 AD cases. Trail Making Test B-A available for 10 AD cases. Letter Fluency available for 16 SD and 17 AD cases. Semantic Association data available for 19 SD cases.

* $p < .05$; ** $p < .001$; n/s = non-significant; '-' = not applicable.

Table 2. Voxel-based morphometry results showing regions of grey matter intensity decrease in AD and SD patients relative to Controls (n = 69).

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
AD vs Controls	Temporal fusiform cortex, temporal pole, inferior temporal gyrus, parahippocampal gyrus, hippocampus, amygdala, thalamus, insular cortex, orbitofrontal cortex, medial PFC, anterior cingulate cortex, frontal pole, inferior frontal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum cortex, superior temporal gyrus, precuneus cortex, posterior cingulate cortex, lateral occipital cortex, occipital pole.	B	76,371	-28	-4	-52
SD vs Controls	Temporal fusiform cortex, temporal pole, orbitofrontal cortex, frontal pole, insular cortex, amygdala, hippocampus, parahippocampal gyrus, inferior/middle/superior temporal gyrus, angular gyrus, supramarginal gyrus.	L	22,126	-28	-4	-52
	Temporal fusiform cortex, temporal pole,	R	8,510	28	-2	-52

	orbitofrontal cortex, insular cortex, amygdala, hippocampus, parahippocampal gyrus, inferior/middle/superior temporal gyrus.					
SD vs AD	Temporal fusiform cortex, temporal pole, orbitofrontal cortex, insular cortex, amygdala, hippocampus, parahippocampal gyrus, inferior/middle/superior temporal gyrus.	L	6,162	-28	-10	-50
AD vs SD	Precuneus cortex, lateral occipital cortex, superior parietal lobule	B	1,718	-2	-74	46

MRI scans not available for 1 Control, 2 AD, and 4 SD participants. All clusters reported using threshold free cluster enhancement method and corrected for Family Wise Error (FWE) at $p < .001$. Age is included as a nuisance variable in all contrasts. All clusters reported at $t > 3.7$. L = Left; B = Bilateral; MNI = Montreal Neurological Institute.

Table 3. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that correlate with episodic recall performance by modality in AD and SD.

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Verbal						
Regions of overlap	Temporal fusiform cortex, temporal pole, orbitofrontal cortex, insular cortex, parahippocampal gyrus, amygdala, hippocampus	L	5,910	-32	-8	-50
	Temporal fusiform cortex, temporal pole, parahippocampal gyrus, amygdala, hippocampus, inferior temporal gyrus	R	1,859	26	-4	-50
	Orbitofrontal cortex, medial prefrontal cortex	L	278	-20	28	-24
	Inferior temporal gyrus (temporooccipital part), lateral occipital cortex	L	171	-46	-52	-20
Exclusive to AD	Inferior/middle/superior temporal gyrus (posterior), insular cortex, orbitofrontal cortex, bilateral medial prefrontal cortex, frontal pole, hippocampus (posterior), thalamus, postcentral gyrus, parietal operculum cortex, supramarginal gyrus,	R	14,977	58	-8	-40

	angular gyrus, superior parietal lobule, lateral occipital cortex, occipital pole					
	Inferior/middle/superior temporal gyrus (posterior), central opercular cortex, parietal operculum cortex, supramarginal gyrus, angular gyrus, lateral occipital cortex, occipital pole, bilateral precuneus, bilateral posterior cingulate cortex, hippocampus (posterior)	L	13,073	-54	-24	-32
	Superior frontal gyrus, middle frontal gyrus	L	565	-22	22	38
	Paracingulate gyrus	R	387	0	50	16
	Superior frontal gyrus	R	333	20	14	44
	Superior parietal lobule	R	325	36	-40	58
	Anterior cingulate gyrus, paracingulate gyrus	R	305	2	8	44
	Posterior cingulate cortex, precuneus cortex	L	296	-12	-30	36
	Cerebellum	R	291	42	-56	-60
	Cerebellum	L	190	-6	-86	-44
	Intracalcarine cortex, cuneal cortex	R	163	12	-86	12
Exclusive to SD	Temporal fusiform cortex (anterior), temporal pole, orbitofrontal cortex, putamen, insular cortex, parahippocampal	L	6,439	-28	-4	-52

	gyrus, hippocampus, temporal occipital fusiform cortex					
	Temporal fusiform cortex (anterior), inferior temporal gyrus, temporal pole, parahippocampal gyrus, amygdala, hippocampus (anterior), orbitofrontal cortex	R	2,700	30	-8	-50
Visual						
Exclusive to AD	Supramarginal gyrus, superior parietal lobule	L	551	-32	-48	34

MRI scans not available for 1 Control, 2 AD, and 4 SD participants. All clusters reported using voxel-wise contrasts and uncorrected at $p < .001$ and with a cluster extent threshold of 150 contiguous voxels. Age is included as a nuisance variable in all contrasts. All clusters reported at $t > 3.7$. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

Table 4. Voxel-based morphometry results showing regions of significant grey matter intensity decrease associated with verbal episodic recall performance exclusively in AD and SD, covarying for semantic naming.

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Regions of overlap	No significant clusters					
Exclusive to AD	Temporal pole, parahippocampal gyrus, amygdala, hippocampus, insular cortex, orbitofrontal cortex, inferior/middle frontal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, angular gyrus, superior parietal lobule	L	5,213	-34	2	-24
	Inferior/middle/superior temporal gyrus (posterior)	R	1,388	52	-26	-30
	Parahippocampal gyrus, hippocampus, amygdala	R	885	20	-14	-30
	Temporal pole, inferior frontal gyrus, insular cortex, putamen, frontal operculum cortex	R	857	52	16	-8
	Angular gyrus, lateral occipital cortex	R	829	62	-58	28
	Lateral occipital cortex	L	640	-44	-86	-14

	Lateral occipital cortex, middle temporal gyrus (temporooccipital part)	R	615	62	-62	2
	Superior parietal lobule, angular gyrus, lateral occipital cortex	R	610	36	-48	40
	Precuneus cortex	R	492	14	-58	10
	Occipital pole	R	458	38	-92	-14
	Precuneus cortex	B	362	4	-70	30
	Frontal pole	R	340	22	64	-16
	Posterior cingulate cortex	L	178	-16	-34	40
	Cerebellum	L	169	-18	-74	-40
	Middle temporal gyrus (temporooccipital part), lateral occipital cortex	L	167	-44	-62	10
	Cerebellum	R	166	44	-64	-56
	Heschl's gyrus, parietal operculum cortex	L	160	-52	-24	10
Exclusive to SD	No significant clusters					

MRI scans not available for 1 Control, 2 AD, and 4 SD participants. All clusters reported using voxel-wise contrasts uncorrected at $p < .001$ with a cluster extent threshold of 150 contiguous voxels. Semantic Naming and Age are included as nuisance variables in all contrasts. All clusters reported at $t > 3.7$. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.