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Recollection-based memory in frontotemporal dementia: implications for theories of long-term memory

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Summary

It has been convincingly demonstrated that patients with semantic dementia (the temporal variant of frontotemporal dementia) can show intact recognition memory for pictorial stimuli. As yet, the contribution made by recollective processes to this ability and the status of associated neural regions have not been investigated in the disease. Here, we used both a source monitoring paradigm and an associative memory test to evaluate the ability of patients with semantic dementia to use recollection-based memory processes, and a volumetric MRI technique to assess the extent of atrophy in the hippocampus. Although some patients showed impaired source and associative memory, many performed as well as control participants. Importantly, status of semantic knowledge, as measured by tests of comprehension and production, did not predict recollection-based memory ability. There was no significant positive correlation between recollection and volume of the hippocampus; instead, both source discrimination and associative memory correlated highly with performance on a battery of frontal lobe tests. Consistent with the view that damage to the prefrontal cortex might influence recollection performance, patients with the frontal variant of frontotemporal dementia, with atrophy largely confined to the frontal lobes, all performed at floor level on source discrimination. These results provide further compelling evidence in favour of the multiple input model of long-term memory and highlight the role of frontal lobe systems in recollection-based memory.

Keywords: episodic memory; semantic memory; hippocampus; perirhinal cortex; prefrontal cortex

Abbreviations: fvFTD = frontal variant of frontotemporal dementia; SemDem = group of patients with semantic dementia; SPI = serial-parallel-independent; VOSP = Visual Object and Space Perception test battery

Introduction

The study of patients with semantic dementia (the temporal variant of frontotemporal dementia) has provided a number of insights into the cognitive and neural organization of episodic and semantic memory (Patterson and Hodges, 2000; Hodges and Graham, 2001). One of the more controversial of these has been evidence that patients whose semantic knowledge about previously familiar objects or people has degraded may nevertheless successfully recognize pictures of these items in an episodic memory test (Graham *et al*., 1997, 2000; Simons *et al*., 2001, 2002). This view runs counter to Tulving's prominent serial-parallel-independent (SPI) model of long-term memory (Tulving, 1995; Tulving and Markowitsch, 1998), which holds that the encoding of information into episodic memory is contingent upon successful processing through semantic memory. Recently, Tulving (Tulving, 2001) challenged the results from semantic dementia on two counts: that they may be due to ceiling effects, and that recognition memory may not reflect 'true' episodic memory. The first aim of this article is to examine, in an experiment in which control participants perform below ceiling levels,

Table 1 *Patients and control participants involved in the three experiments*

Experiment	Participants
1	10 patients with semantic dementia (SemDem 1) (W.M., J.P., S.L., J.C., D.S., W.J.H., J.H., V.P., J.W., I.F.) 12 controls for cognitive task analysis (Controls 1) 10 controls for hippocampal volume assessment (Controls 3)
2	8 patients with semantic dementia (SemDem 2) (W.M., A.Tg., S.L., J.C., M.A., J.H., J.G., A.Th.) 8 controls for cognitive task analysis (Controls 2) 10 controls for hippocampal volume assessment (Controls 3)
3	5 patients with frontal variant FTD (J.W.F., T.A., W.L., J.G.U., P.L.) 8 controls for cognitive task analysis (Controls 2)

FTD = frontotemporal dementia.

Table 2 *Summary of the performance of the three patient groups and healthy controls (Hodges and Patterson, 1995) on a range of neuropsychological tests*

	SemDem 1 (n = 10)		SemDem 2 (n = 8)		fvFTD (n = 5)		Controls (n = 20)	
Tests	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Semantic memory								
Picture naming (64)	28.8	22.4	24.9	18.0	63.0	1.0	62.3	1.6
Word–picture matching (64)	43.8	20.6	46.9	15.7	63.6	0.5	63.7	0.5
Category fluency	33.1	26.8	29.6	19.9	80.0	33.9	113.9	12.3
PPT pictures (52)	42.5	6.4	40.3	8.0	50.2	2.5	51.2	1.4
Synonym judgement (50)	27.4	5.5	28.4	8.7	44.0	2.3	47.6	2.1
Episodic memory								
Rey figure recall (36)	16.4	8.5	12.2	7.0	15.0	3.9	15.3	7.4
RMT faces (proportions)	0.8	0.2	0.8	0.1	0.8	0.1	0.9	0.1
RMT words (proportions)	0.9	0.1	0.8	0.1	0.8	0.1	1.0	0.1
Visuoperceptual ability								
Rey figure copy (36)	33.3	3.5	32.2	4.0	35.0	1.0	34.0	2.9
VOSP								
Incomplete letters (20)	19.4	0.7	18.6	2.4	19.4	0.9	19.2	0.8
Object decision (20)	15.2	3.2	16.3	2.7	18.4	0.9	16.9	2.3
Dot counting (10)	9.9	0.3	9.8	0.5	9.8	0.5	9.9	0.3
Cube analysis (10)	9.2	2.2	9.7	0.5	9.6	0.5	9.7	2.5
Working memory								
Digit span forwards	6.1	1.1	6.4	1.2	5.8	1.1	6.8	0.9
Digit span backwards	5.0	0.9	4.6	1.1	3.8	0.8	4.7	1.2

PPT = Pyramid and Palmtrees Test; RMT = recognition memory test (proportion correct); VOSP = Visual Object and Space Perception battery; SemDem 1 = semantic dementia patients from Experiment 1; SemDem 2 = semantic dementia patients from Experiment 2; fvFTD = frontal variant frontotemporal dementia patients from Experiment 3.

whether recollection-based memory in semantic dementia is predicted at an item-specific level by the ability to process information through semantic memory.

In addition, this article seeks to extend our understanding of the neural regions associated with episodic memory impairment. Neuroradiological investigations suggest that atrophy in semantic dementia, although initially most evident in the inferolateral temporal lobe, may progress to affect medial temporal (Chan *et al*., 2001; Galton *et al*., 2001) and frontal (Mummery *et al*., 2000) regions. Recent studies have indicated that if atrophy affects a region including the perirhinal cortex in semantic dementia, recognition memory impairment can result (Simons *et al*., 2001, 2002). These data are consistent with Aggleton and Brown's (Aggleton and Brown, 1999) neural model of long-term memory, which holds that a perirhinal cortex system underlies familiarity-based item recognition, but that a separate system involving the hippocampus supports the recollection of memories with associated context. Other evidence suggests an important role for the prefrontal cortex in recollection, with source memory correlating highly with scores on standard frontal lobe tests (Schacter *et al*., 1984; Craik *et al*., 1990) and recollection difficulties often being observed following frontal damage (Schacter *et al*., 1984; Shimamura *et al*., 1990). In this article, we investigate whether recollection-

based memory in semantic dementia is affected by atrophy progressing into the hippocampus, or whether the functioning of the prefrontal cortex in the disease may have a greater influence on 'true' episodic memory.

Recollection in semantic dementia was investigated in Experiment 1 using a source memory task, with replication sought in Experiment 2 by comparing source memory ability with performance on an associative memory test. Item-specific analyses were conducted in both experiments to examine whether recollection-based memory was affected by degraded semantic knowledge. The effects of hippocampal atrophy and frontal lobe disruption on recollection were assessed by volumetric measurement of MRI scans and analysis of performance on frontally dependent cognitive tests, respectively. Converging evidence on the role of the frontal lobes was sought in Experiment 3, which examined source memory in patients with frontal variant frontotemporal dementia, whose atrophy predominantly affects the prefrontal cortex.

Methods

Participants

Fourteen patients with semantic dementia were involved in the experiments reported here (see Table 1): 10 in Experiment 1 (the 'SemDem 1' group) and eight in Experiment 2 ('SemDem 2'). There were four patients involved in both experiments, which were undertaken a year apart. Five patients with the frontal variant of frontotemporal dementia (fvFTD; also termed dementia of frontal type) took part in Experiment 3, and 30 neurologically intact elderly controls, age-matched to the patients, were additionally involved. Twelve of the controls carried out the cognitive tasks in Experiment 1 ('Controls 1') and eight in Experiment 2 ('Controls 2'); 10 controls underwent MRI scanning and were controls for the assessment of hippocampal atrophy ('Controls 3'). Mean (standard deviation) ages for the groups were: SemDem 1, 59.5 (6.7) years; SemDem 2, 59.8 (6.0) years; fvFTD, 60.6 (5.2) years; Controls 1, 58.6 (4.2) years; Controls 2, 63.8 (5.6) years; Controls 3, 59.0 (5.4) years [$F(5,47) = 1.2$, not significant (n.s.)]. All participants gave informed consent to participation in the study, which was approved by the ethical committee of Addenbrooke's Hospital, Cambridge.

As illustrated in Table 2, the patients with semantic dementia showed marked impairments on tests from the Hodges and Patterson semantic battery (Hodges and Patterson, 1995), such as picture naming, word–picture matching, category fluency and synonym judgement. There were also significant deficits on the pictures version of the Pyramid and Palmtrees test (Howard and Patterson, 1992). The patients showed less of an impairment on standard tests of episodic memory, such as delayed recall of the Rey figure (Osterrieth, 1944) and various versions of Warrington's Recognition Memory Test (Warrington, 1984) (note that because patients completed either the short- or long-form versions of this test, scores have been converted to proportions correct). Consistent with the typical profile of semantic dementia, performance on tests of visuoperceptual ability [such as the Visual Object and Space Perception (VOSP) battery; Warrington and James, 1991] and of working memory (digit span; Wechsler, 1981) was within normal limits.

The patients with fvFTD, whose atrophy is thought to originate in the ventromedial prefrontal cortex (Hodges and Miller, 2001), presented with changes in personality and behaviour. In terms of performance on neuropsychological tests (Table 2), they showed little difficulty with tests of semantic memory, such as picture naming, word–picture matching and the Pyramid and Palmtrees test, although there was some reduction in category fluency. Even stringent tests of semantic memory, such as the synonym judgement task, were performed well, as has been noted in previous reports (Rahman *et al*., 1999; Perry and Hodges, 2000). There was relatively preserved performance on standard tests of episodic memory (such as delayed recall of the Rey figure and Warrington's Recognition Memory Test), visuoperceptual ability (copy of the Rey figure and subtests of the VOSP) and working memory (digit span). Patients were excluded if their MRI scans showed evidence of substantial temporal lobe atrophy, although some pathological involvement of these areas cannot be ruled out.

Cognitive tasks

Source monitoring test

The source monitoring task (Johnson *et al*., 1993) used standard methods involving two study phases and a three-alternative forced-choice test phase. In each of the study phases, participants were shown 30 different line drawings from the Snodgrass and Vanderwart corpus (Snodgrass and Vanderwart, 1980) and asked to name each one. Each of the study sets was then placed upside-down on different sides of the desk. The test phase contained the 60 line drawings seen at study randomly intermixed with 60 novel foil drawings. Participants were shown each item individually and asked to indicate the source of the drawing: whether it had been seen in the first study set, seen in the second study set, or had not been seen before. There were filled delay periods of 10 min each between study phases 1 and 2 and prior to the test phase, during which other tasks, not involving pictures, were carried out. Extensive pilot testing indicated that this protocol produced performance consistently below ceiling levels in healthy elderly participants.

Four sets of 30 items each were selected to be matched for ratings of concept familiarity [$F(3,116) = 0.11$, n.s.], and four different versions of the source monitoring test were constructed. The different versions counterbalanced whether picture sets were studied or used as foils, and the order of presentation of the study sets. The participants in Experiment

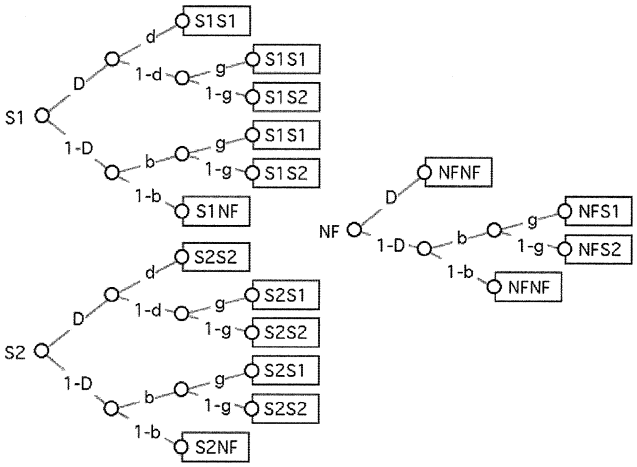

Fig. 1 Tree diagram of the two-high-threshold multinomial model of source memory (see Methods section for details).

1 completed two different versions of the task, each occasion separated by at least 1 month. In Experiments 2 and 3, the version that had the best fit to the multinomial model [$G^2(2) = 0.06$, $P = 0.97$] (see below for details) was administered to participants. Semantic memory for test items was examined in Experiments 1 and 2 primarily by assessing picture-naming ability. For three of the patients with semantic dementia involved in Experiment 2, it was also possible, during a different testing session, to assess comprehension of the items used in the source monitoring test with a picture-pointing task. Patients were shown arrays of line drawings from the Snodgrass and Vanderwart corpus (Snodgrass and Vanderwart, 1980) and were asked to point to the drawing that went with a given name.

The results of the source monitoring task were first analysed using conventional techniques, and then more extensively with a two-high-threshold multinomial model (Fig. 1) (Batchelder and Riefer, 1990; Bayen *et al*., 1996) as implemented using AppleTree software (Rothkegel, 1999). Confirmation of model fits and statistical comparisons between individual data sets were conducted using Dodson and colleagues' spreadsheet-based algorithms (Dodson *et al*., 1998; Dodson and Shimamura, 2000). Multinomial source monitoring models provide parameter estimates of the different underlying factors contributing to task performance: namely, item detection, source discrimination, and various types of response bias (Batchelder and Riefer, 1999). Data were also analysed using the dual-process signal detection model described by Yonelinas and colleagues (Yonelinas *et al*., 1998). The results were very similar to those produced by the multinomial model and are not discussed further.

Response frequencies were recorded for each of nine cells, representing three possible sources—Source One (S1 in Fig. 1), Source Two (S2) and Novel Foil (NF)—multiplied by three possible responses—S1, S2 and NF. By fitting the model to the response frequencies from each participant, parameter estimates and confidence intervals were derived for

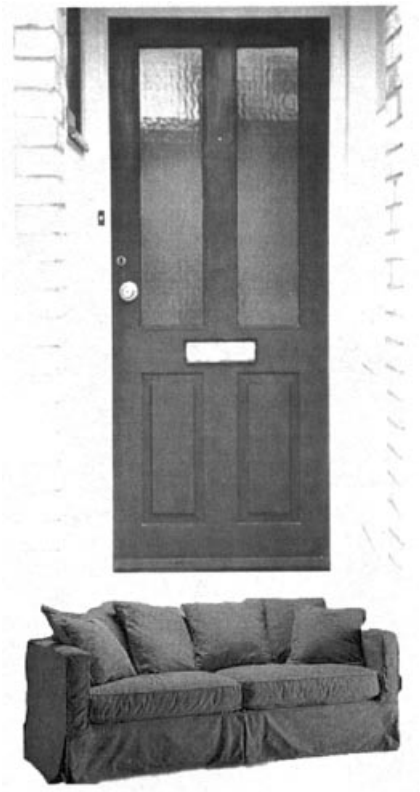

Fig. 2 An example of an item pair from the associative memory test.

correct item detection (parameter D in Fig. 1), correct source discrimination (parameter d), and guesswork (parameters b and g, associated with item detection and source discrimination, respectively). Although the independence of recollection and familiarity is controversial (Yonelinas, 2002), the validity of the assumptions underlying the multinomial model can be tested using the log-likelihood statistic, G^2 (Riefer and Batchelder, 1988), to measure the goodness of fit of the model to the data; a low value of G^2 with two degrees of freedom indicates that the model fits the data well. The same statistic can also be used to compare the performance of an individual patient with that of control subjects. In this situation, a significantly high value of G^2 with one degree of freedom indicates that performance of the two data sets differs significantly on the parameter under test (Dodson *et al*., 1998).

Associative memory test

A visual associative memory test was also administered to the participants in Experiment 2. In this task, participants studied 32 pairs of colour photographs of doors and sofas on sheets of A4 paper, as illustrated in Fig. 2. The photographs were of residential front doors and of sofas taken from furniture company catalogues. Extraneous surrounding details, such as the house number on a door, were edited out using a graphics application. It was explained to participants that they should

Table 3 *Response proportions of the groups of patients with semantic dementia and controls on the source monitoring task used in Experiments 1 and 2*

	Response					
Source	S1	S2	NF	S1	S2	NF
Experiment 1						
	SemDem 1			Controls 1		
Source 1	0.52	0.37	0.11	0.71	0.21	0.08
Source 2	0.27	0.64	0.09	0.24	0.70	0.06
Novel foil	0.05	0.02	0.93	0.01	0.01	0.98
Experiment 2						
	SemDem 2			Controls 2		
Source 1	0.65	0.27	0.08	0.71	0.22	0.07
Source 2	0.26	0.65	0.09	0.27	0.67	0.06
Novel foil	0.04	0.02	0.94	0.01	0.00	0.98

S1 = Source 1; S2 = Source 2; NF = novel foil; SemDem = semantic dementia groups.

try to remember not just the door and the sofa on each page, but that each pair of items had occurred together. Following piloting of the task in healthy elderly individuals, it was decided to allow participants to study the 32 pairs twice to ensure adequate exposure to each pair. A test phase followed immediately, in which participants viewed 48 pairs of doors and sofas: 16 pairs that had been paired together in the study phase; 16 pairs comprising studied items that were re-paired at test; and 16 pairs containing novel items that had not been seen at study. Participants were given a yes/no associative memory test in which they were asked to indicate whether or not pairs of items had occurred together during the study phase.

This test produced three proportion scores reflecting the number of 'yes' responses to items that had been paired at study, items that had been re-paired since study, and items that were novel. The proportion of 'yes' responses to novel items was subtracted from each of the other two scores to control for baseline levels of 'yes' bias. Associative memory score was then calculated using d′ measures of discrimination between paired and re-paired items (Macmillan and Creelman, 1991).

Battery of frontal lobe tests

The participants in Experiment 2 were also given a battery of neuropsychological tests chosen to reflect different aspects of frontal lobe function, such as temporal sequencing, planning, and holding and manipulating information in working memory. Tasks with a heavy language component were not used. Instead, the battery included the modified Wisconsin Card Sorting Test (Nelson, 1976) and the Tower of London task (Shallice, 1982), which were administered according to standard procedures, and computerized versions of a spatial span and a one-back task (Owen *et al*., 1990; Bor *et al*., 1999). In the spatial span task, participants viewed eight red squares on a touchscreen, which blinked blue one by one in a predetermined sequence. After a tone, participants reproduced the sequence by pressing the squares on the touch screen in the same order as had been presented. In the one-back task, the red squares again blinked blue one after another in a sequence, and this time participants had to follow the sequence one move behind, pressing each square on the touch screen. Participants undertook both tasks twice, once using a random array and once with the squares ordered in two rows of four, following evidence that such a manipulation engages the prefrontal cortex more extensively (Owen *et al*., 1990; Bor *et al*., 1999); the presentation order of the two arrays was counterbalanced between subjects. Average span was recorded for the spatial span task, and the percentage of correct squares touched was recorded for the one-back task.

The patients with fvFTD in Experiment 3 also undertook a battery of standard frontal lobe tests. These included the Wisconsin Card Sorting Test (Nelson, 1976), the Tower of London task (Shallice, 1982) and the Test of Everyday Attention (Robertson *et al*., 1996). These tasks were all administered according to standard procedures.

Volumetric assessment of hippocampal damage

Coronally oriented T_1-weighted MRI scans (for the patients, within 12 months of behavioural testing) were used in evaluating the patterns of structural hippocampal damage in the patients with semantic dementia and MRI controls. Volumetric analysis was conducted by a single observer (C.J.G.), who was blind to the participants' details. Volumetric analysis could not be conducted for patients J.G. and A.Th. in Experiment 2. For each remaining patient, the hippocampi were manually traced on 1.5 mm contiguous coronal slices using Analyze software (Mayo Clinic, Rochester, MN, USA) on a Sun Sparcstation 20 and the areas of each of these tracings totalled to produce a volume. The volume of each participant's hippocampi was then corrected for total brain size by dividing by the whole-brain cross-sectional area (producing values measured in mm). Validation of the volumetric measurement technique has demonstrated good intra-rater reliability (>0.9 for the hippocampus) (Galton *et al*., 2001).

Results

Experiment 1

Comparison of control performance on the source monitoring task in the two sessions, separated by 1 month, indicated no significant difference between the two; the data were thus collapsed across testing sessions for further analysis. Table 3 shows the response proportions of the group of patients with semantic dementia (SemDem 1) and the cognitive control group (Controls 1). Mean recognition memory accuracy

(proportion of 'old' items minus proportion of 'new' items ascribed to a source) was 0.90 (SD 0.04) for the control group and 0.83 (0.16) for the patient group; a Mann–Whitney test revealed no significant item recognition difference between the two groups (U = 51.0, n.s.). Mean conditional source accuracy (correct source attributions for all items identified as present at study; Murnane and Bayen, 1998) was 0.76 (SD 0.05) for the control group and 0.64 (0.09) for the patient group; source accuracy of the group of patients with semantic dementia was significantly reduced compared with the control group (U = 16.5, $P < 0.005$).

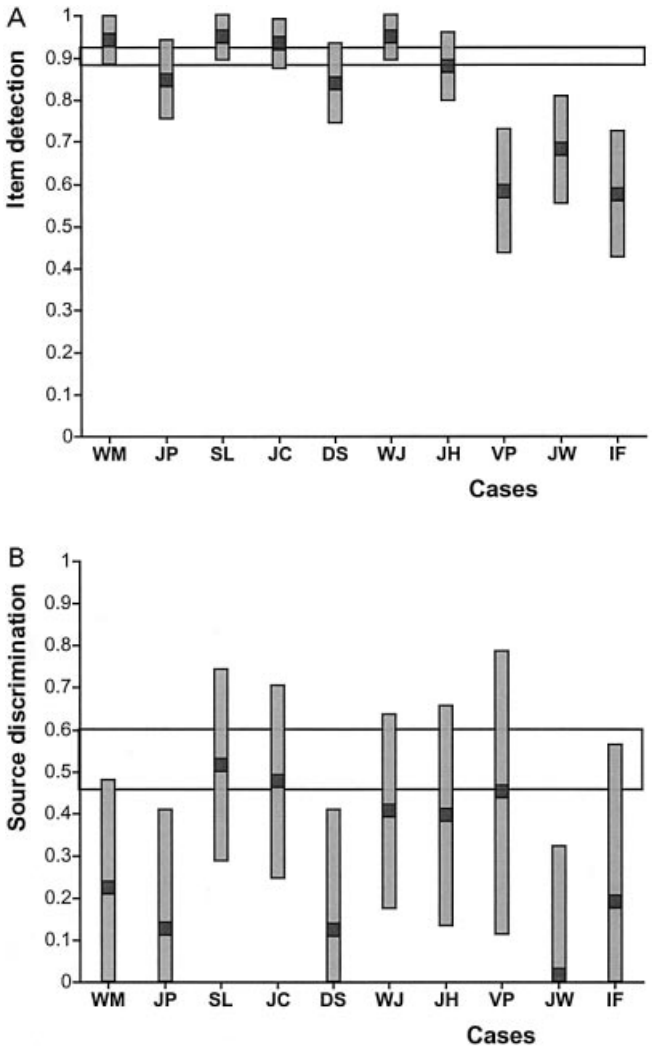

Fig. 3 Performance of the control group (Controls 1) and the patients with semantic dementia (SemDem 1) in Experiment 1 on (**A**) the item detection and (**B**) the source discrimination components of the source monitoring test. Patients are ordered by degree of semantic impairment. The white bar represents the confidence interval of the control group; the black squares indicate the parameter estimate and the grey bars the confidence interval of the patients with semantic dementia. Overlap between confidence intervals of controls and an individual patient indicates no significant difference between the two.

Further analyses of performance on the source monitoring task were conducted using the multinomial model, which provided parameter estimates and confidence intervals for correct item detection and source discrimination. Looking at the performance of the cognitive control group first, the model provided a good fit to the data, as indicated by the low value of the G^2 statistic [$G^2(2) = 3.44$, n.s.] (for details of log-likelihood statistic G^2 see Methods, Source monitoring test). For the control group, the probability of correct item detection was high, but below ceiling ($D = 0.906$, confidence interval 0.88–0.93). Performance of the controls on the correct discrimination of source (d = 0.532, confidence interval 0.46–0.60) was at a level consistent with other studies that have used similar methods (Bayen *et al*., 1996; Dodson and Shimamura, 2000).

The results of each of the 10 patients with semantic dementia were analysed and compared individually with those of the control group, with all contrasts corrected for multiple comparisons (α = 0.005). Figure 3 shows the parameter estimates (black squares) and confidence intervals (grey bars) for each of the patients with semantic dementia. The patients are ranked by performance on the Pyramid and Palmtrees test of semantic association (Howard and Patterson, 1992) as a rough estimate of disease severity. In Fig. 3, the confidence interval of the control group is depicted by the white bar; overlap between the confidence intervals of the control group and an individual patient indicates no significant difference between the two. Looking at item detection first, it can be seen from Fig. 3A that the confidence interval of most of the patients overlapped with that of the control group, indicating no significant difference in performance. Three of the most severely semantically impaired patients (V.P., J.W. and I.F., as measured by performance on the Pyramid and Palmtrees test), however, showed a significant deficit on the item detection parameter [V.P., $G^2(1)$ = 69.4; J.W., $G^2(1)$ = 37.5; I.F., $G^2(1)$ = 71.8; all P values <0.001]. The cross-sectional pattern of performance for item memory is very similar to that previously observed in experiments measuring recognition memory in semantic dementia (Graham *et al*., 2000; Simons *et al*., 2002).

Turning to analysis of the recollection-based source discrimination parameter, Fig. 3B shows that seven of the patients with semantic dementia performed no differently from the control group, but that three of the patients (J.P., D.S. and J.W.) exhibited significant impairment [J.P., $G^2(1)$ = 17.1; D.S., $G^2(1)$ = 16.7; J.W., $G^2(1)$ = 21.7; all P values <0.001]. It should be noted that patient I.F. performed in such a manner that the model did not fit his data set well [$G^2(2)$ = 11.2, $P < 0.005$]; this may explain why the confidence interval of his parameter estimate was so large that his source memory impairment did not quite reach significance [d = 0.192, confidence interval 0.00–0.58, $G^2(1)$ = 6.0, n.s.]. It is apparent from Fig. 3B that source discrimination was not obviously linked to the severity of semantic impairment in these patients. The relationship between semantic knowledge and source discrimination was further assessed on an item-by-

item basis by comparing the naming of an item's picture in the study phase with its subsequent assignment to a source in the test phase. To avoid the possibility of misleading results because of skewing in the data (Poldrack, 1996), a criterion of performance >20% and <80% on both naming and source discrimination was adopted. Four of the patients with semantic dementia, S.L., J.C., W.J. and V.P., met this criterion and their performance was analysed on an item-by-item basis. None showed a significant item-specific correspondence between semantic memory and source discrimination (S.L., $\chi^2 = 0.02$, n.s.; J.C., $\chi^2 = 0.42$, n.s.; W.J., $\chi^2 = 0.06$, n.s.; V.P., $\chi^2 = 0.8$, n.s.). This absence of a significant effect of semantic knowledge on recollection-based memory is shown even more clearly in an analysis of source discrimination performance in the entire patient group split by semantic knowledge status. Source memory was entirely unaffected by the ability of patients with semantic dementia to correctly name pictures of target items ($U = 47.5$, n.s.), with patients averaging 0.58 (SD 0.14) in source accuracy for correctly named items and 0.62 (0.16) for incorrectly named items.

The extent of volume loss in each individual patient's hippocampus was assessed by calculating *Z*-scores for each volume, relative to those of the control group (Controls 3). The *Z*-scores are shown in Table 4, from which it can be seen that the left hippocampal volumes of five patients and the right hippocampal volumes of seven patients were within two standard deviations of those of controls. Relative to the control group, three patients (W.M., J.C. and D.S.) had preserved hippocampal volumes on both sides, just one patient (V.P.) having significantly reduced volumes of both hippocampi. When the volumes of the left and right hippocampi were averaged, the bilateral volumes of seven patients were within two standard deviations of those of controls but those of the other three patients (W.J., V.P. and I.F.) were significantly reduced. The bilateral volumes of two patients (S.L. and J.H.) were borderline (i.e. between 1.95 and two standard deviations of those of controls).

To examine the relationship between source discrimination and the hippocampus, a mean split was conducted on the patient group such that the five patients with bilateral hippocampal volumes higher than the group mean were placed into a 'good HC' group [mean volume *Z*-score = –1.54 (SD = 0.3)] and the other five were placed in a 'poor HC' group [mean volume *Z*-score = –2.18 (0.4)]. Comparing the source discrimination parameters of the two groups, the good HC group [mean $d = 0.192$ (SD = 0.18)] actually did numerically worse at source discrimination than the poor HC group [mean $d = 0.393$ (0.12)], although this difference was not statistically significant ($U = 5.0$). Further evidence comes from Fig. 4, a scatterplot of source discrimination parameter against bilateral hippocampal volume *Z*-score for each patient, which shows that no significant positive correlation existed between the two variables [$r(10) = –0.4$, n.s.]. Examination of left and right hippocampal volumes individually also indicated no significant positive correlations with source discrimination [left, $r(10) = 0.11$, n.s.; right, $r(10) = –0.47$, n.s.].

Table 4 *Z-scores for left and right hippocampal volume in each patient with semantic dementia in Experiment 1 (SemDem 1) relative to the control group (Controls 3)*

	Patients with semantic dementia									
	W.M.	J.P.	S.L.	J.C.	D.S.	W.J.	J.H.	V.P.	J.W.	I.F.
Region										
Left	–1.5	–1.1	–2.2	–1.3	–1.3	–1.2	–2.2	–2.5	–2.9	–2.3
Right	–0.6	–2.1	–1.7	–1.8	–1.3	–2.6	–1.6	–2.9	–0.8	–1.7

Z-score of –2 or less indicates significant volume reduction.

Experiment 2

Table 3 shows the response proportions of the second group of patients with semantic dementia (SemDem 2) and matched controls (Controls 2) on the source monitoring task. Mean recognition memory accuracy was 0.92 (SD 0.04) for the control group and 0.86 (0.09) for the patient group; there was no significant difference between the two ($U = 18.5$). The source memory of the patients with semantic dementia was slightly better than in the first experiment. Mean conditional source accuracy was 0.74 (SD 0.03) for the control group and 0.71 (0.05) for the patient group; the groups were not significantly different ($U = 19.5$). The results of the source monitoring test were analysed using the two-high-threshold multinomial model, which again fitted the control data well [$G^2(2) = 3.81$, $P = 0.15$]. Table 5 shows the item detection and

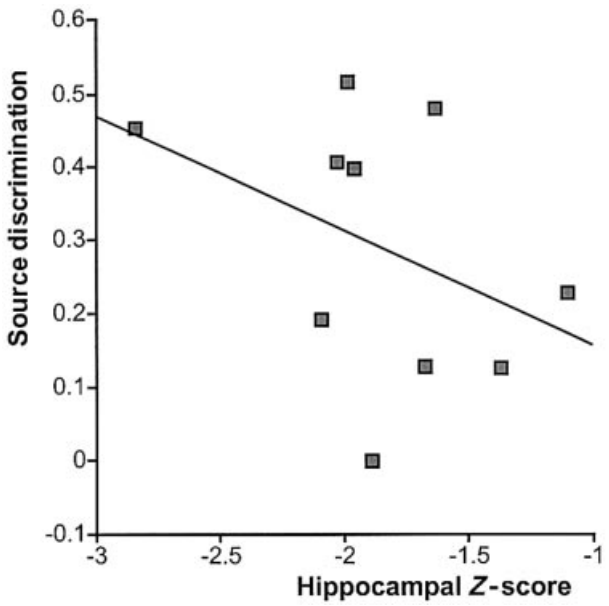

Fig. 4 Scatterplot comparing the source discrimination parameter estimate and bilateral hippocampal volume *Z*-score in the patients with semantic dementia in Experiment 1.

Table 5 *Performance of the patients with semantic dementia (SemDem 2) and controls (Controls 2) on the episodic memory and frontal lobe tests in Experiment 2*

	Patients with semantic dementia								Controls (n = 8)	
Test	W.M.	A.Tg.	S.L.	J.C.	M.A.	J.H.	J.G.	A.Th.	Mean	SD
Episodic memory										
Item detection	0.861	0.754	0.907	0.923	0.833	0.783	0.767	0.767	0.863	0.04
Source discrimination	0.441	0.462	0.587	0.408	0.342	0.353	0.546	0.41	0.467	0.07
Associative memory	1.18	1.83	2.09	0.57	–0.65	T/A	0.21	0.356	1.38	0.4
Frontal lobe function										
WCST categories (6)	6	6	6	3	3	0	6	1	5.88	0.4
Tower of London (16)	14	13	11	10	12	4	11	6	12.5	2.2
Computerized span										
Ordered array	4.3	5.1	4.1	4.7	3.1	3.9	5.1	3.9	5.1	0.6
Random array	4.9	5.3	4.7	4.3	2.4	5.1	4.7	2.9	5.1	0.8
One-back task										
Ordered array (100)	79	94	85	90	60	56	85	61	83.2	13.6
Random array (100)	99	81	79	83	49	43	72	51	78.2	19.4
Composite frontal score	0.02	0.29	–0.41	–1.72	–3.11	–4.4	–0.18	–4.1	0	1

WCST = Wisconsin Card Sorting Test; T/A = test aborted. Composite frontal score is mean Z-score of performance on frontal lobe tests (see text). Figures in parentheses indicate maximum score.

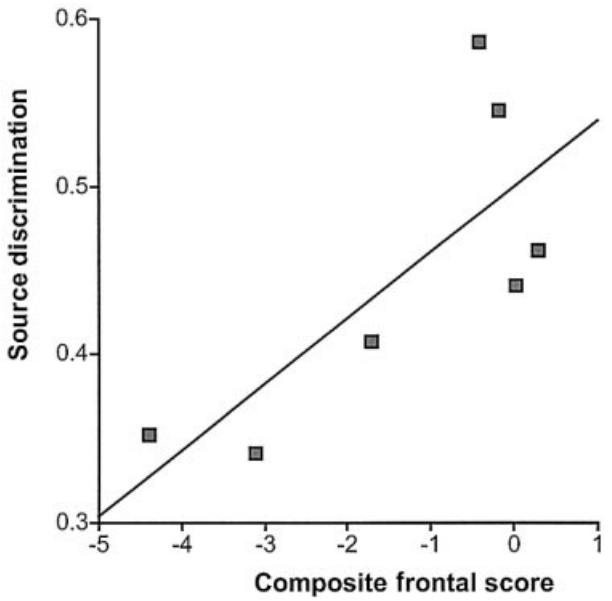

Fig. 5 Scatterplot comparing the source discrimination parameter estimate and composite frontal score in the patients with semantic dementia in Experiment 2.

source discrimination parameter estimates obtained by the patients with semantic dementia and the control group, as well as their performance on the associative memory test. It can be seen that there was a high correspondence between scores on the two tests [$r(8) = 0.68$, $P = 0.063$], suggesting that these different memory tasks were tapping broadly similar recollection-based memory processes (Donaldson *et al*., 1996; Yonelinas, 1997, 1999).

The item-specific relationship between semantic knowledge and recollection-based memory was assessed as in Experiment 1 by comparing the naming of an item with its assignment to the correct source in the test phase. None of the six patients who met the performance criterion (20–80% correct on naming and source) showed a significant item-specific correspondence between semantic memory and source discrimination (W.M., $\chi^2 = 0.43$, n.s.; A.Tg., $\chi^2 = 0.56$, n.s.; S.L., $\chi^2 = 0.05$, n.s.; J.C., $\chi^2 = 1.84$, n.s.; M.A., $\chi^2 = 0.27$, n.s.; A.Th., $\chi^2 = 0.08$, n.s.), consistent with the results of Experiment 1. For three of the patients, comprehension data were also available; combining these data with those from the naming task again revealed no evidence of item-specific correspondence between semantic memory and source (A.Tg., $\chi^2 = 1.42$, n.s.; S.L., $\chi^2 = 0.57$, n.s.; M.A., $\chi^2 = 0.27$, n.s.). Just as in Experiment 1, examination of performance in these three patients indicated no significant difference in source memory between items for which semantic memory was preserved [mean source score = 0.64 (SD 0.2)] and items for which it was degraded [mean source score = 0.69 (0.1)] ($U = 3.0$, n.s.).

The relationship between recollection-based memory and hippocampal volume was assessed by conducting mean splits on the six patients for whom volumetric data were available such that the three patients with hippocampal volumes higher than the group mean were placed in a 'good HC' group and the other three were placed in a 'poor HC' group. The results largely replicated those found in Experiment 1. There were no differences between the good HC and poor HC groups, either in source discrimination [good HC group mean $d = 0.397$ (SD 0.05); poor HC group mean $d = 0.467$ (0.12); $U = 2.0$, n.s.] or in associative memory [good HC group mean = 0.37 (0.93);

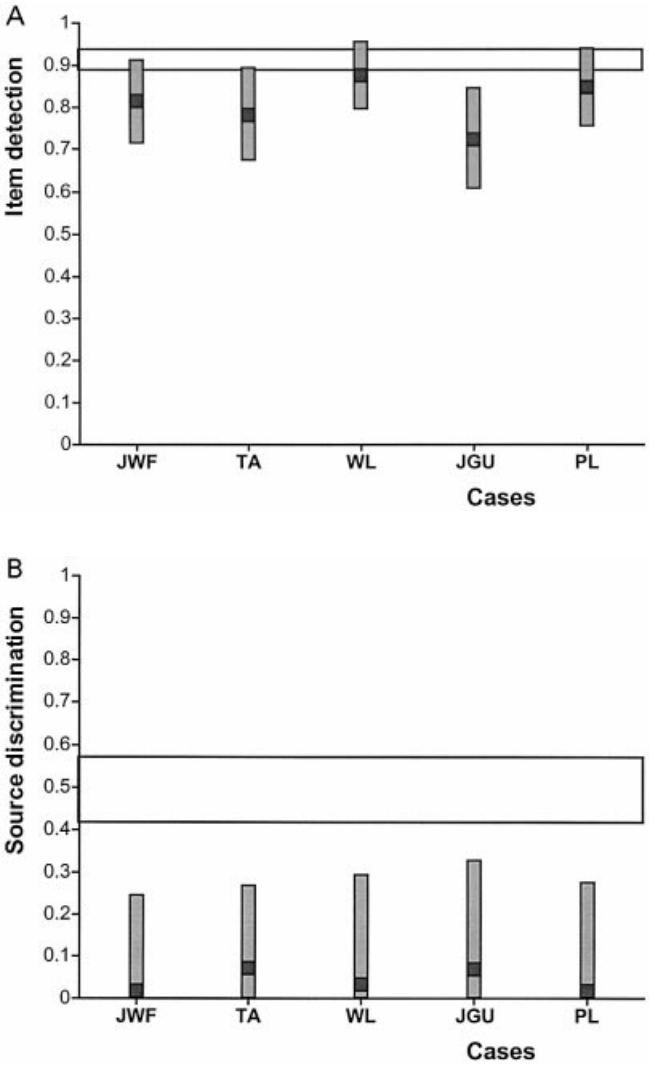

Fig. 6 Performance of the control group (Controls 2) and the patients with fvFTD on (**A**) the item detection and (**B**) the source discrimination components of the source monitoring test in Experiment 3. See legend of Fig. 3 for details.

'poor HC' group mean = 1.31 (1.14); $U = 2.0$, n.s.]. Moreover, non-significant negative correlations were also found in the present experiment between source memory and bilateral [$r(6) = –0.5$, n.s.], left [$r(6) = –0.44$, n.s.], and right [$r(6) = –0.44$, n.s.] hippocampal volumes. To verify whether these negative correlations were non-significant only because of a lack of power, the source and hippocampal volume data from Experiments 1 and 2 were combined (for the four patients involved in both experiments, performance from Experiment 1 only was included in this analysis). When this was done, the correlations were still not significant and, in fact, dropped towards zero [bilateral, $r(12) = –0.28$, n.s.; left, $r(12) = –0.06$, n.s.; right, $r(12) = –0.34$, n.s.]. It seems likely, therefore, that no real relationship exists between hippocampal volume and source memory ability in semantic dementia.

Table 5 shows the performance of the patients with semantic dementia (SemDem 2) and the control group (Controls 2) on the neuropsychological battery of frontal lobe tests. *Z*-scores for the patients were calculated for each frontal test, relative to the mean performance of the control group. A composite frontal score was then computed for each patient by taking the average of the *Z*-scores for each test. As can be seen from the table, performance on the frontal lobe tests varied somewhat between patients, some performing normally and others showing impairment.

The relationship between recollection-based memory and performance on frontal lobe tests was examined by conducting a mean split on the entire patient group such that the four with composite frontal scores higher than the group mean were placed in a 'good frontal' group [mean frontal score = –0.07 (SD 0.3)] and the remaining four were placed in a 'poor frontal' group [mean frontal score = –3.34 (1.21)]. Comparing the source discrimination parameter estimates of the two groups revealed that the good frontal group [mean d = 0.509 (SD = 0.07)] showed significantly better source memory than the poor frontal group [mean d 0.379 (0.04)] ($U = 0$, $P < 0.05$). A similar result was seen when associative memory of the good frontal group [mean = 1.33 (SD = 0.84)] was compared with that of the poor frontal group [mean = 0.07 (0.53)], although this did not exceed the threshold for significance ($U = 2.0$, $P = 0.1$). As illustrated in the scatterplot in Fig. 5, a significant correlation existed between the source discrimination parameter estimate and composite frontal score [$r(8) = 0.72$, $P < 0.05$], suggesting that performance on tests of frontal lobe function can be a good predictor of recollection-based memory ability in semantic dementia.

Experiment 3

The performance of each of the five patients with fvFTD was analysed and compared individually with the that of control group (Controls 2) in the same way as in the previous experiments. Looking at familiarity-based item detection first, Fig. 6A shows that four of the patients performed normally, as indicated by the overlap between the patients' parameter estimate confidence intervals (light grey bars) and that of the control group (white bar). Patient J.G.U. exhibited an impairment relative to the controls [$G^2(1) = 16.8$, $P < 0.001$]. The striking results of the recollection-based source discrimination component are illustrated in Fig. 6B. It can be seen that every one of the patients with fvFTD was severely impaired in source memory (as indicated by the lack of overlap between the patients' and the control group's confidence intervals), performing indiscriminately from chance [$G^2(1) = 0–0.2$, all P values n.s.].

The performance of the patients with fvFTD on the battery of frontal lobe tasks is shown in Table 6. A composite frontal score was derived in a similar manner as in Experiment 2, which indicated that two of the patients (J.W.F. and P.L.) were significantly impaired on the frontal tasks but three (T.A., W.L. and J.G.U.) performed little differently from

Table 6 *Summary of the performance of the patients with fvFTD on the battery of frontal lobe tests in Experiment 3*

	Patients with fvFTD					Controls	
Test	J.W.F.	T.A.	W.L.	J.G.U.	P.L.	Mean	SD
WCST categories (6)	3	6	5	5	0	5.9	0.4
Tower of London (16)	10	12	10	15	7	12.5	2.2
Test of Everyday Attention							
Elevator counting (10)	7	7	7	7	–	6.6	1.2
Counting with distraction (10)	4	2	7	9	–	8.2	2.8
Map search (80)	27	33	48	44	28	61.8	11.7
Composite frontal score	–2.47	–0.84	–0.98	–0.45	–7.33	0	1

WCST = Wisconsin Card Sorting Test; Composite frontal score is mean *Z*-score of performance on frontal lobe tests. See text for test references. Figures in parentheses indicate maximum score.

controls. On the source monitoring task, however, all of the patients performed at least five standard deviations below the control mean. Bearing this in mind, there was still a high (but non-significant because of the small *n*) correlation between source discrimination and composite frontal score [$r(5) = 0.75$], indicating that disruption to frontal lobe regions supporting performance on these executive tasks is an important factor in explaining recollection-based memory impairment.

Discussion

The three experiments described in this article investigated recollection-based memory in patients with semantic dementia and those with fvFTD. Using tests of both source and associative memory, many patients with semantic dementia showed intact recollection, although some were impaired. Critically, the state of semantic knowledge about target items, assessed using tests of comprehension and production, had no bearing upon a patient's recollection of these items. Using volumetric MRI measurements of the hippocampus, there was no evidence that hippocampal atrophy predicted source or associative memory. Instead, evidence suggested that disruption to frontal lobe function in semantic dementia might influence recollection ability: scores on both recollection memory tasks correlated highly with performance on a battery of frontal lobe tests; similarly, patients with fvFTD all performed at chance on source discrimination.

Semantic dementia and cognitive models of memory

The results of these experiments directly address the issues raised by Tulving (Tulving, 2001). They provide important confirmation that, in a paradigm in which control participants performed below ceiling, normal levels of 'true' recollection-based episodic memory can be seen regardless of the state of semantic knowledge. As such, the results provide compelling evidence against the serial encoding assumption of Tulving's SPI model (Tulving, 1995; Tulving and Markowitsch, 1998). Building upon previous studies of recognition memory in semantic dementia, the results described here confirm that it is possible for patients to exhibit preserved episodic memory (in every sense of the term) for non-verbal stimuli that they cannot comprehend (Graham *et al*., 1997, 2000; Simons *et al*., 2001, 2002). Although the present data cannot be wholly explained by the SPI model, they are consistent with a modification to the model in which episodic memory typically relies upon multiple inputs from perceptual and semantic systems, and, in the absence of meaningful semantic input, perceptual information alone can be sufficient to support successful remembering (Graham *et al*., 2000; Hodges and Graham, 2001; Simons *et al*., 2001).

Both views can explain many aspects of the data in the literature, such as the large body of evidence from healthy volunteers that the depth of semantic processing used at encoding can affect episodic memory accuracy (Craik and Tulving, 1975). Similarly, both can account for the evidence from patients with amnesia that semantic knowledge can be acquired even in the apparent absence of functioning episodic memory (Vargha-Khadem *et al*., 1997; Kitchener *et al*., 1998; Verfaellie *et al*., 2000). Where the two views differ is in the inability of the SPI model to explain why patients with semantic dementia are able to show accurate memory for previously studied line drawings (Graham *et al*., 1997; Simons *et al*., 2002), colour pictures (Graham *et al*., 2000) and photographs (Simons *et al*., 2001) of stimuli that they can no longer comprehend. According to the multiple input account, this preserved episodic memory is due to the use of perceptual information, inherent in the studied stimuli, during the episodic task. While healthy subjects may utilize both semantic and perceptual information to make a decision about prior occurrence, therefore, the evidence suggests that when semantic knowledge has become degraded successful episodic memory can be achieved when stimuli are pictorial, and therefore perceptually distinctive.

When visually presented words are used as stimuli, recognition memory impairment is often seen in semantic dementia (Warrington, 1975), especially for items about which semantic knowledge has become degraded (Graham *et al*., 2002*b*). These data can be accounted for by assuming

that perceptual information is much less useful in discriminating between words than it is between pictures. As a result, episodic memory for words is likely to be far more reliant upon semantic knowledge than episodic memory for other kinds of stimuli, such as pictures. Importantly, none of these data require a serial encoding assumption by which information can only be encoded into episodic memory after successful processing in semantic memory (Tulving, 1995; Tulving and Markowitsch, 1998), and can be fully explained by a model in which perceptual and semantic systems contribute jointly to episodic memory.

Given the evidence that patients with semantic dementia typically exhibit normal recognition memory for pictorial stimuli (Graham *et al*., 2000; Simons *et al*., 2001, 2002), it is possible that performance on the recollective tasks employed in the present experiments could be supported by the familiarity-based processes principally underlying recognition memory. While there is controversy about the relationship between recollection and familiarity (for a recent review see Yonelinas, 2002), the present data would appear inconsistent with such a proposal. Inspection of Fig. 3A and B suggests markedly different profiles of performance on item detection (based primarily on familiarity) and source discrimination (based predominantly on recollection) in semantic dementia. Moreover, consideration of individual patients provides indications of double dissociations between the two parameters. For example, J.P. and D.S. performed normally on item detection but were significantly impaired at source discrimination; V.P. and, to a lesser extent, I.F. exhibited impaired item detection, but were not significantly different from controls in terms of source memory.

It should also be noted that some theorists (e.g. Conway and Pleydell-Pearce, 2000) distinguish between episodic recollection (e.g. source and associative memory) and the remembering of autobiographical information, which may, in some circumstances, be more affect-laden in nature. The present study addresses the predictions of Tulving's SPI model (Tulving, 1995) which, as currently formulated, concentrates on the first type of recollection. However, other data suggest that patients with semantic dementia are capable of recollecting autobiographical memories, at least from the recent past (Snowden *et al*., 1996; Graham and Hodges, 1997; Graham *et al*., 2002*a*). Direct comparison of semantic knowledge and autobiographical memory, and the implications for Tulving's model of any relationship between the two, awaits further investigation.

Semantic dementia and neural models of memory

The performance of patients with semantic dementia on tests of familiarity- and recollection-based memory has significance for theories about the neural regions underlying long-term memory processes. While some researchers argue that the hippocampal formation supports both recollection and familiarity (Squire, 1992; Zola *et al*., 2000), others have proposed that two anatomically separate systems involving the hippocampus and perirhinal cortex contribute to recollection and familiarity (Aggleton and Brown, 1999). There is certainly evidence to support the separation of recollection- and familiarity-based memory on cognitive grounds (Mandler, 1980; Gardiner and Java, 1990; Jacoby, 1991). The hypothesis that the two memory processes are also separable neurally stems primarily from lesion studies of animals. For example, many studies involving rats and non-human primates have found little effect of selective hippocampal or fornix damage on recognition memory (Gaffan *et al*., 1984; Shaw and Aggleton, 1993; Murray and Mishkin, 1998; Zola *et al*., 2000), while experimentally induced lesions of the perirhinal cortex typically lead to severe recognition memory deficits (Meunier *et al*., 1993; Ennaceur *et al*., 1996; Buckley *et al*., 1997).

There is also evidence of functionally separate familiarity- and recollection-based memory systems from clinical studies in humans. Two patients, with extensive bilateral perirhinal cortex damage, showed impaired recognition memory when the study–test delay was >2 s (Buffalo *et al*., 1998; Holdstock *et al*., 2000), as did another patient, whose lesion affected the dorsomedial thalamus (Isaac *et al*., 1998). Semantic dementia is potentially informative to this debate because there is radiological evidence that atrophy may significantly affect the temporopolar region, which includes the rostral part of the perirhinal cortex, as well as the anterior parahippocampal gyrus, from which it can be deduced that the perirhinal cortex is almost certainly involved (Chan *et al*., 2001; Galton *et al*., 2001). Accordingly, recent studies have demonstrated that pictorial recognition memory in semantic dementia is disrupted to a significantly greater extent by atrophy affecting a 'parahippocampal' region that includes the perirhinal cortex than by atrophy of the hippocampus (Simons *et al*., 2001, 2002).

Turning to the effects on episodic memory of selective Papez circuit damage, several studies observed that amnesic patients with selective damage to the hippocampus or fornix performed normally at recognition memory but were severely impaired on tests of free recall (Aggleton and Shaw, 1996; Vargha-Khadem *et al*., 1997; Aggleton *et al*., 2000; Holdstock *et al*., 2000). Other researchers, however, have reported patients with apparently selective hippocampal damage but impaired recognition memory (Reed and Squire, 1997; but see also Bachevalier and Meunier, 1996). In terms of recollection-based memory, Aggleton and Brown's model argues that 'recollection of [a] stimulus … is hippocampally dependent' (Aggleton and Brown, 1999, p.426) and that significant disruption to the hippocampus should result in recollection-based memory impairment. The evidence from the present study that hippocampal volume (whether assessed bilaterally or restricted to the left or right hippocampus individually) did not correlate with source or associative memory suggests that, in semantic dementia at least, the volume of the hippocampus may not be the only

factor playing a role in recollection-based memory ability. It should be noted that, in many studies of amnesia, both human and animal, hippocampal damage is often bilateral and largely complete. In the present experiment, it is possible that the patients with semantic dementia who had significantly reduced hippocampal volumes might have retained sufficient neuronal populations to support successful recollection.

While many neural models have concentrated on the involvement of medial temporal lobe structures in long-term memory, other evidence suggests an important role for regions of the prefrontal cortex. Several studies have found that a large amount of the variance in source memory performance can be explained by scores on neuropsychological tests of frontal lobe function (Schacter *et al*., 1984; Craik *et al*., 1990; Glisky *et al*., 1995). Problems in recollection-based memory, especially for contextual information such as the source or temporal order of events, have been noted as prominent features of frontal lobe damage (Schacter *et al*., 1984; Janowsky *et al*., 1989; Shimamura *et al*., 1990). Similarly, functional imaging studies have highlighted the involvement of prefrontal cortex regions in source memory (for a recent review see Fletcher and Henson, 2001). The results of the present experiments are consistent with this view, indicating that disruption of frontal lobe function has a major impact on the recollection-based memory of patients with semantic dementia. Performance on both source and associative memory was shown to correlate highly with performance on frontal lobe tests. Furthermore, patients with fvFTD, who have atrophy predominantly affecting the frontal lobes, were at chance on source memory. It is worth noting that this was despite some of the patients with fvFTD performing relatively well on tests of executive function. Further research is required to elucidate exactly which aspects of frontal lobe functioning are critical for recollection.

To conclude, the present experiments have confirmed that, contrary to Tulving's SPI model (Tulving, 1995), it is possible for patients to exhibit normal levels of 'true' recollection-based episodic memory for stimuli they are no longer able to comprehend. Furthermore, the evidence suggests that the source or associative memory impairment exhibited by some patients with semantic dementia is not predicted by hippocampal atrophy, but that functioning of the prefrontal cortex is critical for successful recollection.

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