

Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory?

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The most selective disorder of central conceptual knowledge arises in semantic dementia, a degenerative condition associated with bilateral atrophy of the inferior and polar regions of the temporal lobes. Likewise, semantic impairment in both herpes simplex virus encephalitis and Alzheimer's disease is typically associated with bilateral, anterior temporal pathology. These findings suggest that conceptual representations are supported via an interconnected, bilateral, anterior temporal network and that it may take damage to both sides to produce an unequivocal deficit of central semantic memory. We tested and supported this hypothesis by investigating a case series of 20 patients with unilateral temporal damage (following vascular accident or resection for tumour or epilepsy), utilizing a test battery that is sensitive to semantic impairment in semantic dementia. Only 1/20 of the cases, with a unilateral left lesion, exhibited even a mild impairment on the receptive semantic measures. On the expressive semantic tests of naming and fluency, average performance was worse in the left- than right-unilateral cases, but even in this domain, only one left-lesion case had scores consistently more than two standard deviations below control means. These results fit with recent parallel explorations of semantic function using repetitive transcranial magnetic stimulation as well as functional imaging in stroke aphasic and neurologically intact participants. The evidence suggests that both left and right anterior temporal lobe regions contribute to the representation of semantic memory and together may form a relatively damage-resistant, robust system for this critical aspect of higher cognition.

Keywords: cognitive neuropsychology; language; semantic memory

Abbreviations: ATL = anterior temporal lobe

Introduction

The evidence to be presented in this article concerns the organization and neural basis of conceptual knowledge or semantic memory. As recently as 25–30 years ago, this issue might scarcely have been considered a legitimate research topic: according to Fodor, for example, a cognitive capacity as central as semantic memory would entail an ‘approximation to universal connectivity’ in the brain and hence have ‘no stable neural architecture’ (Fodor, 1983, p. 119). Since that time, however, research in behavioural neurology/neuropsychology has established that relatively selective disorders of semantic memory can result from consistently located brain lesions, which does suggest a stable neural architecture. This is not to claim that consensus has been reached on precisely what or where that architecture might be, only that it may exist and be worth pursuing.

There are, of course, many facets to this issue and to summarize all of these and the current state of knowledge about them is clearly beyond the scope of any single study. We will therefore side-step many unresolved questions and make the following three assumptions that seem relatively uncontentious: (i) even if semantic memory can be disrupted by focal lesions, it is a cognitive capacity that depends not on one single brain region but rather on a network of regions (Martin, 2007; Patterson *et al.*, 2007; Pobric *et al.*, 2010b); (ii) many of the components of this network are located in the temporal lobe (Binder *et al.*, 2009); and (iii) despite the well-established fact of left-hemisphere language lateralization in the majority of people, the conceptual/semantic network includes both left and right temporal lobes (Tranel *et al.*, 1997; Lambon Ralph *et al.*, 2009; Visser *et al.*, 2010).

The specific question asked by the current study is whether a unilateral lesion to either the left or right anterior temporal lobe (ATL) is sufficient to impair semantic memory, or whether such an impairment requires significant bilateral damage. This question is largely unanswered because the principal aetiologies known to produce semantic disorders, such as Alzheimer’s disease, semantic dementia and herpes simplex virus encephalitis, typically involve bilateral temporal damage. These conditions therefore shed inadequate light on the distribution of the semantic network across the left and right temporal lobes. In Alzheimer’s disease, atrophy and hypometabolism are usually fairly left–right symmetrical (Nestor *et al.*, 2006). In early semantic dementia, degeneration can be highly asymmetrical but, by the time that most cases come to neuropsychological and neuroradiological attention, the temporal lobe atrophy and hypometabolism are clearly bilateral (Studholme *et al.*, 2004; Nestor *et al.*, 2006). Similarly, the temporal damage caused by herpes simplex virus encephalitis—which is usually more medial than lateral—is often asymmetrical but rarely unilateral, at least in patients who present with semantic as well as episodic memory deficits (Lambon Ralph *et al.*, 2007; Noppeney *et al.*, 2007).

A further ‘bounding’ of our question is a restriction to unilateral lesions including the ATL, by which we mean essentially anterior to primary auditory cortex. What is the reason for this specification? In all of the conditions mentioned above, the bilateral temporal lobe damage is more anterior than posterior. What

aetiologies produce unilateral ATL abnormalities? The answer is, first of all, not many and secondly that the ones that do (resection for temporal lobe epilepsy, tumour resection or occasional vascular accident) are imperfect singular sources of evidence for a variety of reasons (see ‘Discussion’ section). Consequently, in this study, we included patients from all of these aetiologies to determine whether the pattern of findings applied across the board.

The design of our study is easily summarized. We identified patients with a unilateral temporal-lobe lesion, either restricted to or at least including the ATL, as a consequence of one of these three aetiologies (resection for epilepsy, resection for tumour or vascular accident). We then administered a battery of semantic tests in regular use for research on semantic dementia, the aetiology associated with the most striking and most selective disorder of semantic memory. The nature of performance on these semantic tests by patients with unilateral temporal lesions will form the basis for our conclusions as to whether it ‘takes both sides’. For the purpose of comparison, we will present these new data alongside previously published results from a set of patients with semantic dementia with a range of severities (Bozeat *et al.*, 2000). No attempt was made to match the patients in these two cohorts, and therefore the patients with semantic dementia do not form a proper component of this new study. The semantic dementia data can, however, offer a ‘yardstick’ picture of how an indubitable semantic disorder affects performance on the same set of tests.

Materials and methods

Participants

Most of the unilateral patients ($n=18$) were recruited from the Cambridge Cognitive Neuroscience Research Panel (a database of volunteers with focal brain lesions). Two additional cases were recruited from the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery (London). Appropriate patients were defined as those who were more than 1 year post-onset and had a unilateral temporal lobe lesion in or extending into the anterior half of the temporal lobe (defined as rostral to Heschel’s gyrus). With this set of criteria, we recruited 11 patients with left and 9 with right temporal lobe damage. Basic demographic and clinical information is summarized in Table 1. We did not select according to aetiology and the recruited patients covered a range of neurological/neurosurgical disorders including resection for tumour, abscess and temporal lobe epilepsy, plus several cases of clipped arteriovenous malformation and haemorrhage. The patients spanned a broad range of ages (23–68 years; mean = 43.8 years) and years post-onset (1–5 years; mean = 2.36 years). There was no difference in the representation of the two sexes (male:female = 9:11).

Scans were performed for all patients and interpreted by a neurologist with experience in structural neuroimaging, who was blind to the experimental results (F.M.). Structural scanning for all 20 patients is shown in Fig. 1A and B. Where high-resolution research MRI scans were available, lesions were traced using MRICro (Rorden and Brett, 2000; <http://www.sph.sc.edu/comd/rorden/mricro.html>) and normalized to a standard template using statistical parametric mapping-5 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) with cost-function masking to mask the lesion from the calculation of the normalization parameters

Table 1 Basic demographic and clinical information

Patient	Aetiology	Sex	Age	Education (years)	Years post onset	Handedness
Left temporal lobe damage						
ASM	Tumour resection	Male	57	n/a	2	Right
LH	Resection for TLE	Male	25	13	2	Right
PT	Abscess drain	Female	50	11	3	Right
CP	Haemorrhage	Female	24	15	1	Right
DW	Tumour resection	Female	62	13	3	Right
JL	CVA	Male	51	10	3.5	Right
MJ	Resection for TLE	Male	43	12	3	Right
NC	Tumour resection	Female	66	n/a	3	Right
AL	Tumour resection	Female	68	13	2	Left
SE	Resection for TLE	Female	52	13	4	Right
ASA	Aneurysm	Female	56	11	1.5	Right
Right temporal lobe damage						
SH	AVM	Male	36	n/a	1	Right
AW	Tumour resection	Male	35	10	1.5	Right
FH	Cavernoma	Female	40	16	–	Right
MM	Epilepsy-related lesion	Male	31	13	–	Right
SO	AVM	Female	39	n/a	1	Right
EL	Haemorrhage	Female	23	11	2.5	Right
GB	Resection for TLE	Male	34	11	5	Right
MC	Abscess drained	Female	39	11	2	Right
TD	Resection for TLE	Male	44	11	1.5	Right

AVM = arteriovenous malformation, CVA = cerebrovascular accident, n/a = not available, TLE = temporal lobe epilepsy.

(Brett *et al.*, 2001). If only CT scans were available all lesion locations were determined (by F.M.) and transposed onto templates according to the procedure described by Damasio (1995). The remaining patients had clinical magnetic resonance scans and representative slices are included in Fig. 1. For comparative purposes, similar axial slices from a patient with semantic dementia are shown in Fig. 1C; in contrast to the scans in Fig. 1A and B, these reveal a decidedly bilateral distribution. Another difference between patients with semantic dementia and the unilateral cases is the variation across the latter in selectivity and affinity to the temporopolar region. The damage in semantic dementia (Fig. 1C) has a strong focus in the anterior and polar aspects of the ATL, particularly inferior and lateral. Of the aetiologies included in the patient sample for the current study, the closest to semantic dementia in terms of focus and location of damage (albeit unilateral) is resection for temporal lobe epilepsy. The lesions of some of the tumour and abscess cases also extended into the same anterior, inferolateral aspects of the ATL. The centre of gravity for the remaining, principally vascular, cases tended to be somewhat more superior and caudal, although always (by criterion) with some ATL involvement.

The contrastive semantic dementia data (which, although not directly and formally compared, are provided to give a clear background picture of how this bilateral temporal lobe group typically perform on the same neuropsychological measures) and the normative data were first reported by Bozeat and colleagues (2000). In that study, 10 patients with semantic dementia (age range: 49–78 years; mean = 61.0 years) were recruited according to standard inclusion and exclusion criteria for the disorder. The study also reported the normative data for the range of assessments included in the Cambridge Semantic Battery (described in detail below). These data were collected from 31 neurologically intact control participants [18 females, 13 males; age range 54–82; mean = 68.5 years (standard deviation, SD = 7.1); education mean = 11.6 years (SD = 1.4)]. Performance on other measures was compared with the published normative data with each test.

Neuropsychological assessment

Background assessments

The following subtests of the Wechsler Adult Intelligence Scale (WAIS-R) were administered: (i) non-verbal: picture completion, picture arrangement, block design; and (ii) verbal: digit span, vocabulary, arithmetic and similarities. The Raven's Coloured Progressive Matrices (Raven, 1962) is a well-known forced-choice pattern matching test that provides a measure of non-semantic problem-solving ability. The National Adult Reading Test (Nelson and Willison, 1991) consists of 50 low-frequency printed words with atypical spelling-sound correspondences that are presented to the participant for reading aloud. A person must know these words to pronounce them correctly, otherwise the 'c' in a word like 'cellist' might be pronounced like an 's' (as in 'cell') and the 'c' in 'façade' might be pronounced like a 'k' (as in 'arcade'). The test therefore provides a commonly used estimate of pre-morbid (verbal) IQ.

The Short Recognition Memory Test and the Recognition Memory Test (Warrington, 1984, 1996) were administered. Both tests come in two parts: (i) printed words; and (ii) photographs of the faces of unknown people. The Short Recognition Memory Test, consisting of 25 items, was administered to the majority of cases in this study. Only two patients were given the Recognition Memory Test, consisting of 50 items (see Table 3). In each part, the participant first looks at the sequence of 25 (or 50) items and makes a judgement about whether each word or face seems pleasant or unpleasant. At the end of the 'study' list for each part, a series of 25 (or 50) pairs of words or faces is presented, each pair consisting of one item from the study list and one unrelated and unstudied foil. The participant is asked to choose the previously seen member of each pair.

The Visual Object and Space Perception battery (Warrington and James, 1991) assesses various aspects of visual and spatial processing

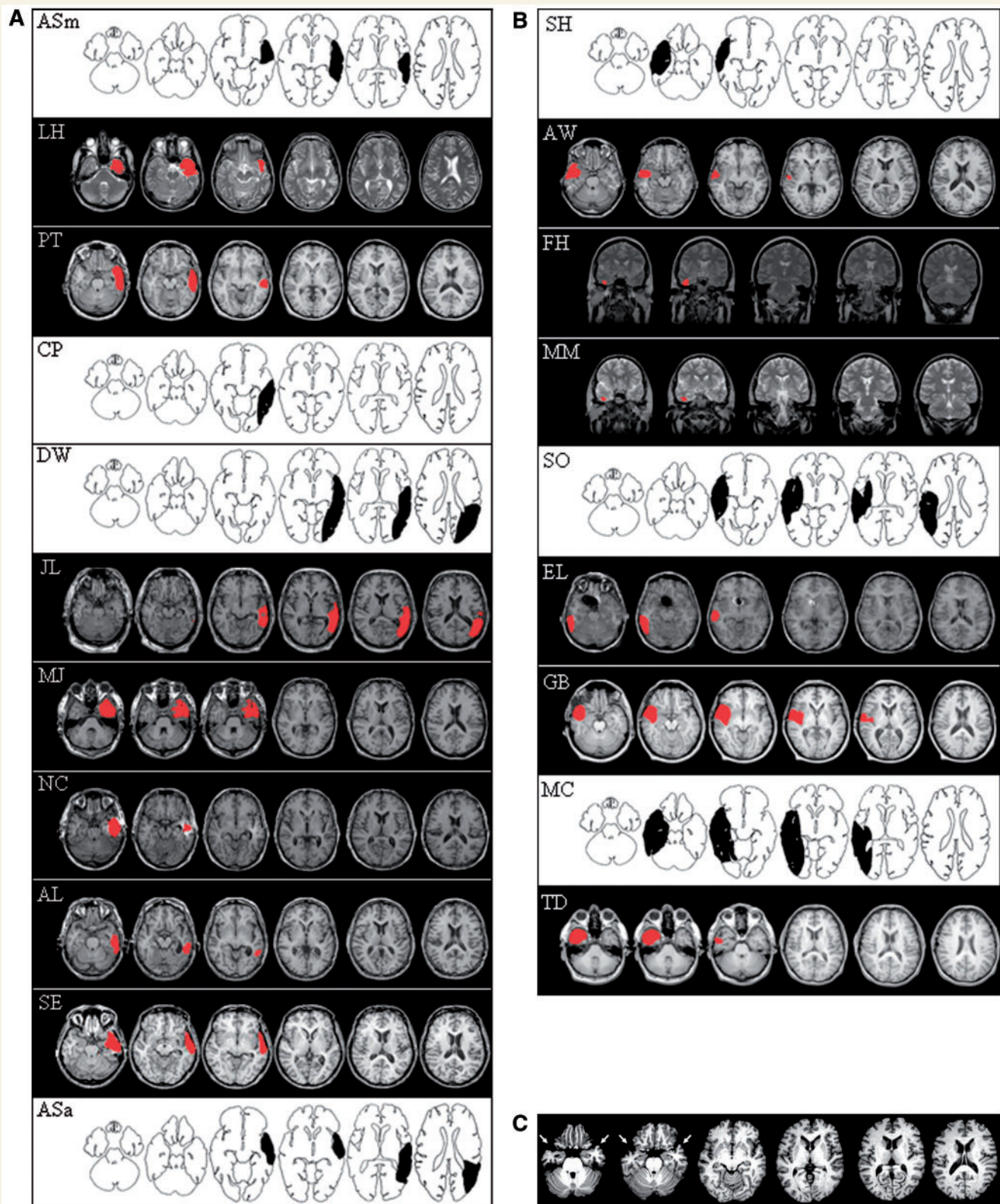


Figure 1 (A) Selected CT/MRI slices for patients with unilateral, left temporal lobe damage. (B) Selected CT/MRI slices for patients with unilateral, right temporal lobe damage. (C) Axial MRI series from a patient with semantic dementia. Standard radiological convention is used (left hemisphere is shown on the right side). Key characteristics of the focus and location of atrophy found in semantic dementia are captured in this axial series. Not only is the atrophy (white arrows) bilateral, but it is focussed in the anterior, inferior aspects of the ATL region. In contrast posterior temporal, parietal and frontal regions are relatively well preserved.

of objects and patterns. Two subtests from the Visual Object and Space Perception battery were administered: (i) cube analysis, which tests the ability to infer how many cubes there must be in a 3D arrangement of cubes from a 2D picture of the arrangement and (ii) object decision, which assesses the participant's ability to recognize the silhouette of a real object presented in the company of three foils that are silhouettes of nonsense objects.

Semantic assessments

The experimental core of the study was a series of eight tests, four expressive (requiring self-generated spoken responses) and four receptive (i.e. requiring only a semantic judgement as indicated by pointing or repeating). We had previously collected data on these same eight tests for a group of 10 patients with semantic dementia as well as a large group of normal controls to provide normative data (see Bozeat *et al.*, 2000). The same battery of tasks has been used successfully in comparative case series investigations in order to reveal the similarities and differences between various semantically impaired patient groups (e.g. Jefferies and Lambon Ralph, 2006; Corbett *et al.*, 2009). This indicates that the battery has sufficient sensitivity not only to grade the degree of semantic impairment in each patient but also to reveal qualitatively different types of semantic impairment.

One expressive test known to be highly sensitive to semantic impairment (Hodges and Patterson, 1995) is category fluency, in which the person is asked to produce as many exemplars of a semantic category as possible in one minute; our version of this test uses six different categories, three natural groups (animals, birds, fruit) and three artefacts (household items, tools, vehicles). We also administered a letter fluency test, which forms a useful contrast to category fluency because it has all of the same executive and monitoring components but minimal semantic demands: letters of the alphabet replace semantic categories as the cue for word retrieval (words starting with F, A or S). The other two expressive tests consisted of two picture naming tasks, one relatively easy (the Cambridge 64-item naming test: Bozeat *et al.*, 2000; Adlam *et al.*, 2006) and one graded and much harder (the 30-item Graded Naming Test: McKenna and Warrington, 1983). In both cases, the participant is shown each item in the test as a line drawing of a familiar (or in the case of the items towards the end of the Graded Naming Test, less familiar but still known) object and asked to supply its name. Performance of the patients was compared to the published norms for this psychometrically graded test.

The first receptive test was an easy one, in which the stimuli are the same 64 items comprising the easier of the two naming tests described above. Each item's name is spoken to the participant as he or she looks at an array of 10 pictures of objects, the target and nine other objects from the same semantic category, and is asked to point to the target. Two harder receptive semantic tests are the picture and word versions of the Camel and Cactus Test (Bozeat *et al.*, 2000; Adlam *et al.*, 2006), a semantic association test in which the participant must select one of four pictures (or written words) that is related to a target picture (or word). In each case, the four response choices belong to a different category from the target and to the same category as each other. For example, the choices for the target 'duck' are all places in the natural world; one has to know that ducks are usually to be found on a 'lake' (the correct choice) rather than on a 'mountain', in a 'desert' or on an 'iceberg' (the three foils). The final receptive semantic test was the graded synonym judgement test (Warrington *et al.*, 1998), consisting of two spoken-word choices for each of 50 spoken-word targets, for example "Does 'marquee' mean the same as 'tent' or 'palace'?" The participant repeats his or her chosen word response. For this latter psychometrically graded test, the patients' performance was compared against the published norms.

Results

Background neuropsychology

The results of the background assessments are summarized in Tables 2 and 3. In all tables and figures, the patients are ordered by descending scores on the category fluency test. Performance of the patients with left temporal lobe damage (Table 2) was generally normal across the various cognitive domains, including executive skills, visuospatial perception and components of the Wechsler Adult Intelligence Scale. Scores on the recognition memory tests varied somewhat more, with half of the patients exhibiting weak (5–10th percentile) or abnormal (≤ 5 th percentile) performance on one or both subtests (Patients PT, JL, MJ, NC, SE and ASA). The same pattern characterized the patients with right temporal lobe damage (Table 3). Performance on tests other than recognition memory was normal (except for Patient SO's score on the cube analysis subtest of the Visual Object and Space Perception battery). Again, around half of the right-sided patients demonstrated weak or abnormal performance on at least one part of the recognition memory test (Patients SH, FH, TD, MC and SO). There was no apparent material specificity of the kind that one might predict if anticipating an association of the left hemisphere with verbal material and the right with non-verbal stimuli. In summary, at least as reflected by the background tests administered, the most likely consequence of the unilateral temporal lesions in these patients was impaired episodic recognition memory for recently encountered words and/or faces.

Expressive semantic assessment

Figure 2A summarizes the individual and group results across the four measures of expressive semantic skill. Although these patients with unilateral temporal lobe lesions were not (as already explained) matched in any formal way to the previously published group of 10 patients with semantic dementia (Bozeat *et al.*, 2000), the 20 cases in the present study and the 10 in the semantic dementia investigation were all assessed on the same semantic tests. For comparison purposes, therefore, we have plotted the semantic dementia data alongside those from the current cohort, again as both averaged scores and as individual case scores (once again ordered by performance in category fluency). As can be seen, the semantic dementia cases covered the range from mild (Patients JP and WM) to severe (Patients IF and JW), although the difficult Graded Naming Test was sensitive enough to detect abnormality in even the mildest semantic dementia cases.

At the 'group' level, two major aspects of the results are revealed in Fig. 2A. Firstly, average scores for both of the unilateral groups were higher—in three of the four tests, substantially higher—than average scores for the semantic dementia case series. Secondly, on these expressive tasks, the average scores for patients with right temporal lesions were higher than averages for their left-temporal counterparts (category: fluency [$t(18)=2.96$, $P=0.008$]; letter fluency [$t(18)=3.8$, $P=0.001$]; 64-item naming [$t(18)=2.6$, $P=0.02$]; Graded Naming Test [$t(18)=3.3$, $P=0.004$]). This is probably not a reflection of overall

Table 2 Background neuropsychological assessment (patients with left temporal lobe damage)

	ASM	LH	PT	CP	DW	JL	MJ	NC	AL	SE	ASA
NART IQ	121	98	80	108	121	103	101	113	87	116	97
RMT	Faces 22 (25–50%)	25 (90%)	20 (10%)	25 (90%)	25 (90%)	21 (10%)	23 (50%)	24 (75%)	22 (10–25%)	22 (25–50%)	19 (5%)
	Words 21 (10–25%)	23 (50%)	18 (<5%)	24 (25%)	25 (90%)	21 (25%)	23 (5–10%)	21 (10%)	21 (25%)	20 (5–10%)	20 (5–10%)
RCPM	27 (50–75%)	31 (90–95%)	22 (25–50%)	34 (95%)	29 (75–90%)	31 (90–95%)	28 (75–90%)	28 (75–90%)	29 (90%)	33 (95%)	31 (90–95%)
VOSP	Cut-off										
	Object decision	14	19	18	14	19	19	20	18	18	17
	Cube analysis	6	9	9	9	9	10	10	8	10	10
WAIS-R (scaled scores)											
	Picture completion	10	6	5	7	8	10	NT	8	7	9
	Picture arrangement	11	6	12	10	7	13	NT	7	8	5
	Block design	10	14	12	7	6	9	NT	6	9	10
	Digit span	13	12	7	10	7	7	NT	7	5	4
	Vocabulary	7	7	11	12	7	10	NT	11	10	6
	Arithmetic	7	9	4	11	7	11	NT	4	11	6
	Similarities	8	10	6	10	5	12	NT	9	8	5

Table 3 Background neuropsychological assessment (patients with right temporal lobe damage)

	SH	AW	FH	MM	TD	EL	GB	MC	SO
NART IQ	123	107	110	120	97	90	107	82	105
WRMT	Faces 25 (90%)	24 (75%)	38/50^a (5%)	50/50 ^a (75%)	24 (75%)	24 (75%)	25 (90%)	23 (50%)	23 (50%)
	Words 23 (5–10%)	25 (90%)	44/50 ^a (50%)	42/50 ^a (25%)	22 (<5%)	24 (25%)	25 (50–90%)	23 (10%)	21 (10%)
RCPM	34 (95%)	32 (90–95%)	NT	NT	32 (90–95%)	32 (90–95%)	30 (90%)	30 (90%)	32 (90–95%)
VOSP	Cut-off								
	Object decision	14	19	20	16	20	19	20	19
	Cube analysis	6	10	10	10	10	10	10	5
WAIS-R (scaled scores)									
	Picture completion	8	11	11	11	9	10	12	11
	Picture arrangement	7	8	13	7	5	7	7	8
	Block design	14	12	15	12	15	9	8	9
	Digit span	15	7	8	16	8	16	6	13
	Vocabulary	12	9	11	12	8	9	8	10
	Arithmetic	12	8	10	14	10	12	6	8
	Similarities	16	8	12	11	10	10	12	13

^a For these two patients the long-form of the recognition memory test was administered. Abnormal scores are shown in emboldened font.

NART = National Adult Reading Test; NT = not tested; RCPM = Raven's Coloured Progressive Matrices; VOSP = Visual Object and Spatial Perception battery; WAIS-R = Wechsler Adult Intelligence Scale; WRMT = Warrington Recognition Memory Test (short form).

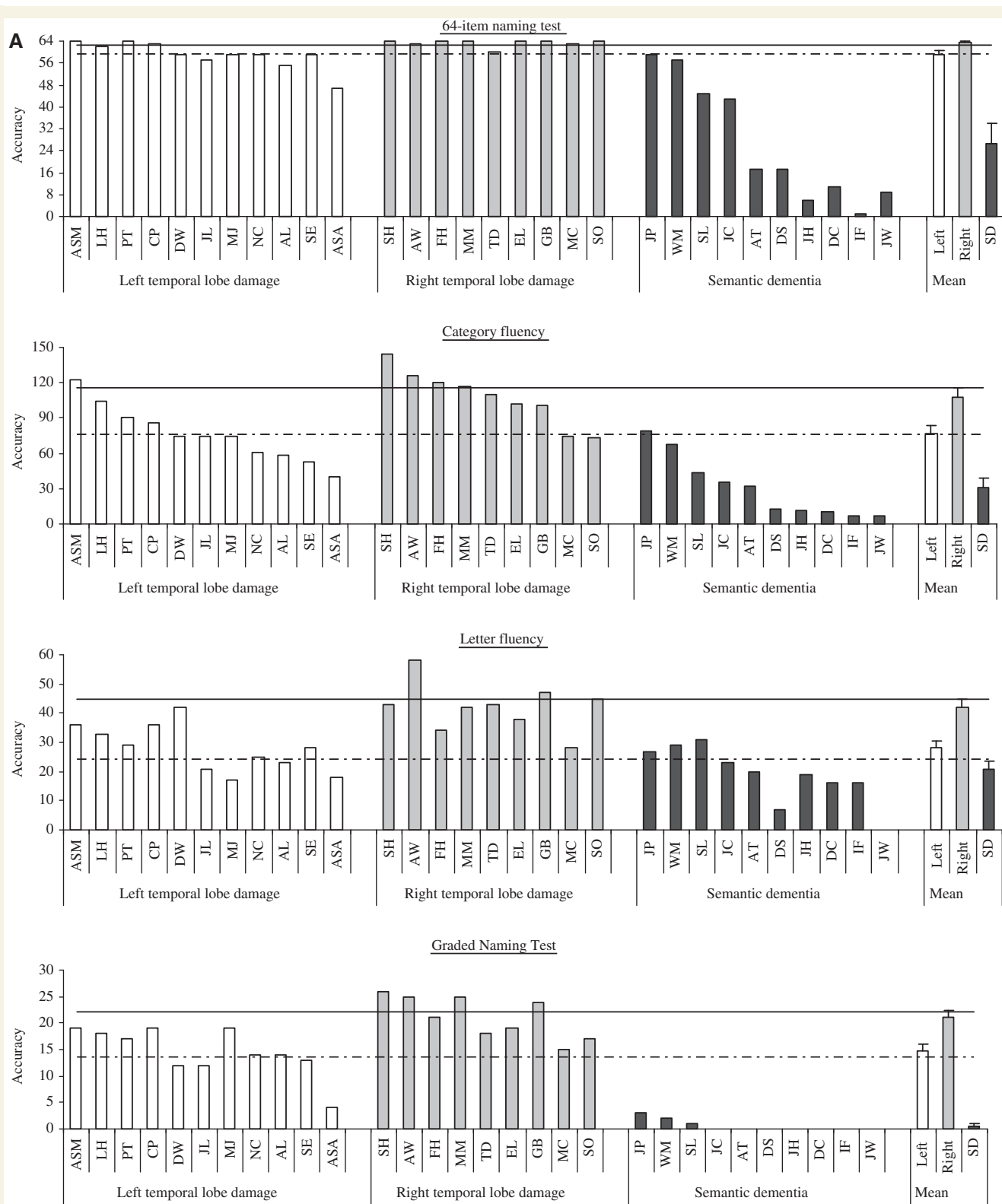


Figure 2 (A) Summary of expressive tasks. **(B)** Summary of receptive semantic tasks. The full horizontal line denotes the control-participant mean performance on each test. The dashed line shows the cut-off score for each assessment (defined as 2 SD below the control mean).

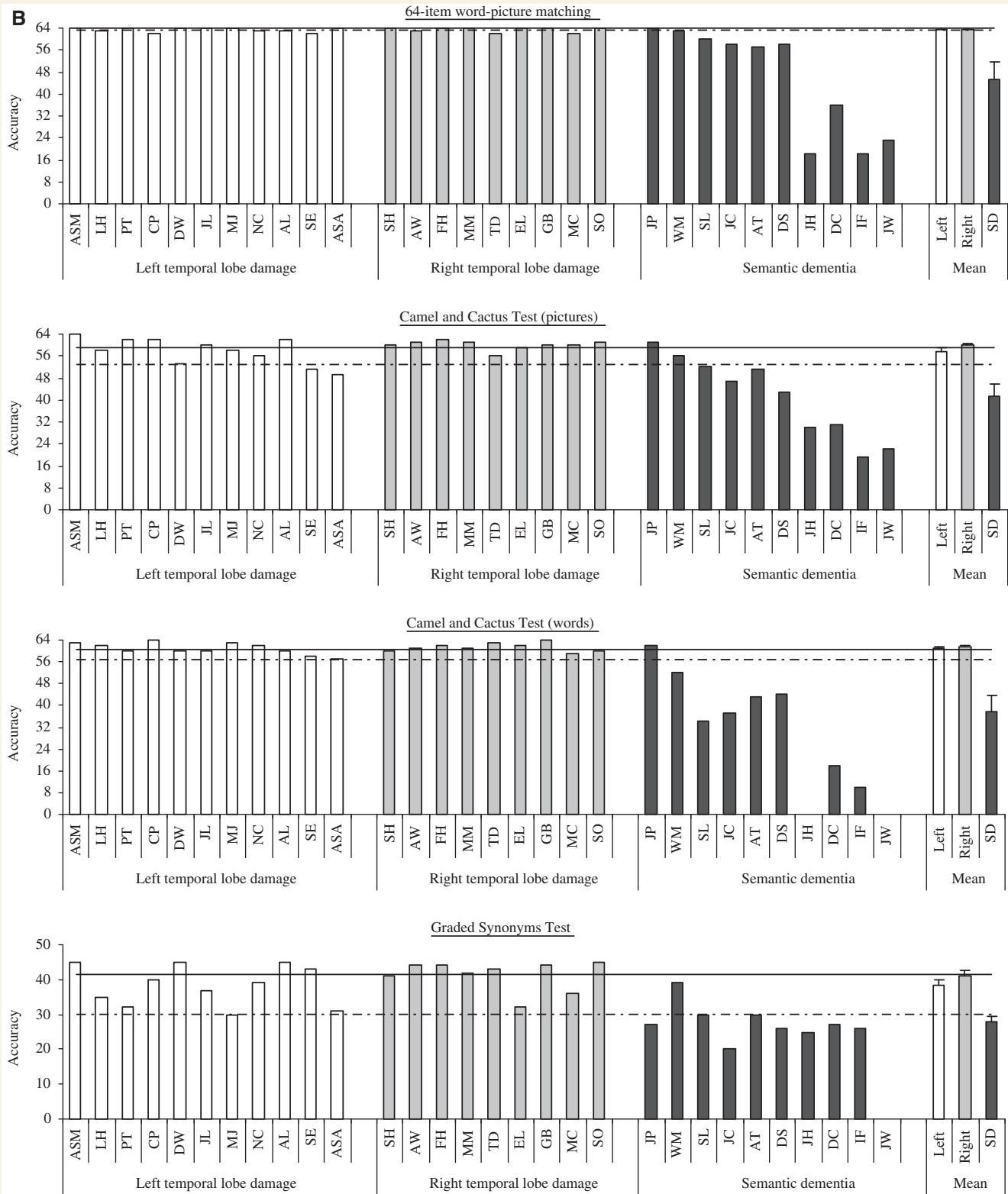


Figure 2 Continued.

Table 4 Distribution of error types on the Cambridge 64-item naming test

Left temporal patients	ASM	LH	PT	CP	DW	JL	MJ	NC	AL	SE	ASA
Correct	64	62	64	63	59	57	59	59	55	59	47
Error type											
Semantic	0	2	0	1	5	4	3	3	4	2	6
Omission/descriptions	0	0	0	0	0	3	1	2	5	3	10
Visual	0	0	0	0	0	0	0	0	0	0	0
Phonological	0	0	0	0	0	0	1	0	0	0	1
Other	0	0	0	0	0	0	0	0	0	0	0
Right temporal patients	SH	AW	FH	MM	TD	EL	GB	MC	SO		
Correct	64	63	64	64	60	64	64	63	64		
Error type											
Semantic	0	1	0	0	2	0	0	0	0		
Omission/descriptions	0	0	0	0	2	0	0	1	0		
Visual	0	0	0	0	0	0	0	0	0		
Phonological	0	0	0	0	0	0	0	0	0		
Other	0	0	0	0	0	0	0	0	0		

severity given that performance on the receptive semantic tasks, which are admittedly easier tasks, turned out to be well matched for the two unilateral groups. Instead, this result probably reflects a phenomenon that we have reported before: for patients with semantic dementia with relatively asymmetric left > right versus right > left distributions of bilateral temporal lobe atrophy, comparable degrees of comprehension impairment in the two groups are associated with more severe expressive (naming) deficits for the left > right subset (Lambon Ralph *et al.*, 2001). The relationship between that finding and the present study is considered in more detail in the 'Discussion' section. We also compared each patient group against the participants who provided the normative data during the original formulation of the semantic battery (Bozeat *et al.*, 2000). As would be expected from viewing Fig. 2A, the right unilateral cases were, on average, as good as these control participants on the 64-item naming and letter fluency tasks, whilst the small difference on the category fluency test was non-significant [$t(38) < 1$]. Although the degree of anomia in the left unilateral group was not in the same league as that observed in semantic dementia, the naming accuracy for this group was significantly lower than the control participants [all measures: $t(40) > 2.23$, all $P < 0.05$].

The 'individual' scores from the unilateral cases for the expressive semantic assessments followed a similar left versus right pattern. On the category fluency task (which is especially demanding of the semantic system as well as several other cognitive domains), three of the unilateral left cases had scores at the normal cut-off (Patients DW, JL, MJ) and four below it (Patients NC, AL, SE, ASA). In comparison, for the right-sided cases, only Patient MC fell at the cut-off point and Patient SO just below it. On the letter fluency tasks one left-sided case scored at the cut-off (Patient NC) and four below (Patients JL, MJ, AL, ASA) whereas all of the right-sided cases performed within 2 SD of the normal mean. The same was true for naming on the 64-item and Graded Naming tests: all right-sided cases were in the normal range but about half of the left-sided cases performed at or below the cut-off score.

The distribution of naming errors for each patient on the Cambridge 64-item test is summarized in Table 4. The distribution of errors was very similar across the patient case series, for left and right temporal subgroups, and across different aetiologies. By far the most common error types were semantically related responses (e.g. pineapple → 'apricot') or some form of omission (either no response or a partial description of the item without offering a specific name). There were only two phonologically related errors across the entire case series and no visually related errors.

Receptive semantic assessment

Performance on the receptive semantic assessments is summarized in Fig. 2B, again plotted alongside scores on the same tests from the earlier semantic dementia case series. This comparison is striking and easy to summarize. In terms of 'group' means, the left and right unilateral groups performed firmly within the normal range across all four tests, whereas the average scores of patients with semantic dementia dropped considerably below the normal cut-off. In contrast to the expressive semantic abilities, there was no difference between the left versus right unilateral cases on any of these receptive measures [all $t(18) < 1.2$, $P > 0.24$], even though the tests ranged from the easy word–picture matching assessment through to the challenging graded synonyms task. This pattern was mirrored in the individual data: the great majority of individual patients scored within 2 SD of the normal mean on these receptive tasks. To search for more subtle group-level trends, we compared each unilateral group to the controls who provided normative data for the semantic battery (Bozeat *et al.*, 2000). For all receptive assessments, there were no significant differences between either unilateral group and the control participants (all $t < 1.61$, all $P > 0.13$).

Discussion

The core observation from this study is that unilateral temporal lesions do not cause significant disruption to semantic memory,

at least in terms of accuracy on a range of semantic tests that demonstrate clear impairment in three different neurological diseases associated with bilateral, ATL damage (semantic dementia, Alzheimer's disease, herpes simplex virus encephalitis). There are, as always in research, caveats and complications to this unembellished conclusion, but before we come to these, an overview of the data is as follows. First, treating the patients as two groups—those with left or right unilateral temporal lesions—the 'average' performance of both groups was within 2 SD of the control means on all four expressive tests and on all four receptive tests. Secondly, again dealing with averages, both unilateral groups had substantially higher mean performance on all eight tests than a group of patients with semantic dementia assessed on the same measures: average scores for the semantic dementia cases fell below the normal range on every test. Thirdly, the unilateral-left group performed more poorly than the unilateral-right group on the expressive but not the receptive tests. On all three genuinely semantic expressive tests (category fluency and the two object naming tests), the average scores of the unilateral-left cases were significantly below the control mean.

Turning to individual performance, for unilateral-right patients: all nine were comfortably within the normal range on six of the eight tests. One of the two test exceptions was category fluency, on which two patients (MC and SO) were just at or barely below the cut-off score. Category fluency is not only a demanding semantic assessment but also requires many other cognitive skills; nevertheless, since these executive and non-semantic memory abilities are also required for success in letter fluency, on which patients MC and SO had normal scores, the data suggest a mild semantic abnormality for these two cases. The second minor exception was the easy word–picture matching task, on which two unilateral-right cases (patients TD and MC) made a few errors. This is a sensitive test only because controls perform at ceiling, but again, these two patients' performance indicates a possible, albeit slight, semantic abnormality.

For the unilateral-left patients, all 11 were within the normal range on only two of the eight tests, both receptive: Camel and Cactus Test words and the Graded Synonym Test (though note that the 2 SD below the 'normal' mean on the Graded Synonym Test is barely above chance). On the remaining receptive tests, there were very minor abnormalities for two cases on word–picture matching (but see the comments above about ceiling effects in normal performance) and two not so trivial, but still only moderate abnormalities on Camel and Cactus Test-pictures. Expressive tests for unilateral-left cases tell a somewhat different story. The four mildest cases (as determined by category fluency—the test that we used to rank the cases) had completely normal scores on all of the expressive tests, but the remaining seven patients were all below the cut-off score on at least one of the expressive tests, and one patient (ASA) had abnormal scores on all four expressive tests. In fact, patient ASA's test scores—both expressive and receptive—resemble those of patients with mild semantic dementia (Adlam *et al.*, 2006). We do not intend to gloss over this impairment, which constitutes an important qualification to the bald conclusion that it requires bilateral damage to yield semantic impairment (see below). We do note, however, that this pattern emphasizes the importance of case series studies as opposed to

single-case research: only patient ASA, of 11 patients with unilateral-left temporal lesions and 20 patients with unilateral temporal lesions, was consistently below control cut-off scores on our expressive semantic tests, and even her degree of abnormality on most tests equated to mild rather than moderate or severe semantic dementia. Our summary thus remains that it 'typically' requires bilateral temporal lobe damage to generate 'significant, clinically notable' disruption to conceptual knowledge. Why should this be so?

Our hypothesis is the following. The widespread semantic network in the brain consists of many different regions, some of them specific to certain modalities of information and some of them biased towards one or other hemisphere; but the ATL component of this network, which supports the most central, amodal 'hub' of conceptual knowledge (Patterson *et al.*, 2007; Lambon Ralph *et al.*, 2010; Pobric *et al.*, 2010b), may be distributed across left and right ATLs in a largely undifferentiated fashion. This would have at least two consequences. Firstly, a bonus of distributed representations is 'graceful degradation' (Farah and McClelland, 1991), where low levels of damage produce little behavioural decline and clear impairment only follows considerable damage. Note that, if 'considerable' means >50%, then, by definition, it would take damage to both temporal lobes to generate notable semantic impairment. Secondly, forming amodal semantic representations across two partially but not fully interconnected neural substrates may result in at least some duplication of the representation in each hemisphere. Like back-up storage for any computer or mirror website, such duplication will make the bilateral ATL semantic system more robust to the effects of unilateral damage. To the extent that one can draw parallels between human and non-human primates, this proposal is supported by the fact that object recognition in the macaque monkey is severely affected by experimentally induced bilateral temporal lesions but scarcely impacted by unilateral lesions in this region (Buckley and Gaffan, 2006). Likewise, other aspects of temporal lobe function, including paired-associate learning and auditory recognition, seem to become chronically impaired only after bilateral ablation (Hefner and Heffner, 1986; Li *et al.*, 1999). Supporting this idea, in recent formal meta-analyses of the functional neuroimaging literature, bilateral (albeit often left > right) activations are observed when normal participants complete semantic tasks (Binder *et al.*, 2009; Visser *et al.*, 2010). Likewise, a recent functional neuroimaging study of stroke aphasic patients reported that comprehension ability was better predicted by the status of the functional connectivity between the left and right ATL than by the level of regional cerebral blood flow in the left ATL (Warren *et al.*, 2009); in line with our working hypothesis, patients with compromised inter-ATL functional connectivity had impaired comprehension, even if both neural areas were structurally intact.

The proposal of absent specialization in the ATL semantic system might seem counter to reports of differences in the impairment profile of semantic dementia patients with left > right versus right > left ATL atrophy. For example, Snowden and colleagues (2004) assessed identification of and familiarity with famous people, and reported that 10 patients with semantic dementia with more left > right abnormality achieved higher scores when knowledge was probed by the famous people's faces rather than

their names, whereas three semantic dementia cases with right>left atrophy had the reverse pattern of success: names better than faces. A parallel finding was observed on a more general test of semantic knowledge (Pyramids and Palm Trees): patients with left>right demonstrated worse performance on the verbal than picture version, whilst the opposite pattern (pictures<words) was found in the right>left cases. Snowden *et al.* (2004) interpreted these results as indicating specialization of the left ATL for names and of the right ATL for faces. Although we did not test semantic performance on faces, people's names or other specific-level concepts, the results from the present unilateral cases exhibit little evidence for word versus picture differences in receptive semantic tasks, such as Pyramids and Palm Trees and the more taxing Camel and Cactus Test. As can be seen in Fig. 2B, neither unilateral left nor unilateral right temporal lesions were associated with impaired average performance on either the word or picture version of the Camel and Cactus Test, and in fact, out of 40 available scores (20 patients \times 2 modalities of stimulus), the only two mildly impaired scores were for left-unilateral cases on the picture version (Patients SE and ASA).

By contrast, it seems fairly clear that patients with left-temporal lesions are more likely than their right-temporal counterparts to have a mild degree of naming impairment and that, within patients with semantic dementia (all of whom are anomia), those with left>right temporal atrophy have more severe naming impairments than their right>left counterparts even with matched degrees of comprehension deficit. How is this set of findings to be reconciled with our hypothesis of a relatively undifferentiated semantic network in the ATL? The answer, we propose, lies in the connectivity of the ATL with other more modality-specific brain regions. Two well-known facts are crucial here: (i) speech production is strongly left-lateralized in the majority of people; and (ii) apart from some cross-hemisphere connections between homologous brain regions, the vast majority of brain connections are within rather than across the two hemispheres. The result of these facts is that left-hemisphere speech regions almost certainly have much stronger connections with the left than the right side of the ATL system. And the implication of this arrangement is that, even if the ATL component of the semantic network turned out to be completely distributed and undifferentiated across the two hemispheres, left>right asymmetry of damage to this system would have more deleterious consequences for speaking and naming than right>left damage. The impact of differential white-matter connectivity has been shown in the tractography and functional imaging literature. In particular, the uncinata fasciculus—in both the macaque monkey and human—connects the ATLs to the ventrolateral prefrontal cortex (especially to Brodmann areas 47/12; Petrides and Pandya, 1988). Increased activity in the latter areas is observed during active retrieval for verbal information in the left hemisphere and for visual or visuospatial information in the right hemisphere (Cadoret *et al.*, 2001; Petrides, 2005).

A previous study documenting the more severe anomia in patients with semantic dementia with left>right atrophy was accompanied by a computational model that implemented differentially strong connectivity from the two sides of a bilateral semantic system to a unilateral speech production system (Lambon Ralph *et al.*, 2001). After training and 'lesioning' of the model,

irrespective of degree of overall damage to the undifferentiated semantic units, the model's naming performance was more impaired if the simulated damage had an asymmetric left>right distribution. As far as we are aware, no similar modelling effort has been devoted to names versus faces as probes to person knowledge, but precisely the same logic would apply (indeed a related idea has been encapsulated in other computational models of semantic memory; Plaut, 2002). Processing of faces is probably not unilateral but has a strong affinity with the fusiform face area in the right temporal lobe. Connections between this region and the ATL will therefore be stronger on the right. What might seem to be ATL differences in semantic knowledge derived from faces could in fact be explained by hemispheric processing differences further back in the temporal lobe combined with differential connection strength.

Two other issues require brief consideration. The first is lesion volume, given that bilateral lesions will almost invariably lead to greater total volume loss than unilateral damage. An attempt to equate lesion extent in forms of brain injury/disease as different as temporal lobe resection versus semantic dementia is probably impossible, but if one could do this, perhaps a very large unilateral lesion would produce as much semantic disruption as smaller bilateral lesions. Indeed, our working hypothesis is that both ATL centres contribute to a single modality-invariant semantic system. These might work together in a super-additive manner, maximizing redundancy and graceful degradation as described above; but unless this duplication of information and connectivity is complete (i.e. each is a full 'back-up' of the other), then it seems very likely that large unilateral lesions should produce at least mild levels of semantic disruption: Patient ASA may be the closest example in the present study. Large-scale studies of patients with temporal lobe epilepsy (Bell *et al.*, 2001; Giovagnoli *et al.*, 2005) have demonstrated that, as a group, the semantic performance of these patients falls a small but significant degree below control levels (a drop in accuracy that is typically too small to measure reliably at the individual level but is consistent across participants). Recent results from right-sided transcranial magnetic stimulation in neurologically intact participants also fit this pattern. Following stimulation of the left or right lateral ATL, normal participants demonstrate a selective slowing, although no drop in accuracy, on semantic tasks (Lambon Ralph *et al.*, 2009). This holds for both verbal and picture-based semantic tasks (Pyramids and Palm Trees Test and Camel and Cactus Test) irrespective of whether the left or right ATL is stimulated (Pobric *et al.*, 2010a). Whilst these documented impairments from right-sided transcranial magnetic stimulation and in patients like patient ASA are important, it should be remembered that they are not in the same league as the impairments observed in patients with semantic dementia with bilateral ATL damage. Instead, they fit with the notion of graceful degradation where systems are relatively robust to moderate levels of damage.

The second issue concerns caveats with regard to the interpretation of data from temporal lobe resection for epilepsy or tumour, or damage after vascular accident, because of the possibility of re-learning or reorganization/recovery of semantic function. A long-standing seizure history complicates attempts to generalize findings from patients with resection for temporal lobe epilepsy

to people with normal brains or even people with brains damaged by other aetiologies. This point is supported by at least three findings: (i) post-operative deficits of cognition/language tend to be more severe in association with a later age of seizure onset (Hermann *et al.*, 1999); (ii) there is a significant change in the pattern of language-related white-matter pathways in patients with long-standing epilepsy (Powell *et al.*, 2007); and (iii) there is significant alteration in neurotransmitter function (Hammers *et al.*, 2003). In the face of these neuroanatomical changes, semantic function may be shifted away from this region, such that subsequent resection will have less dramatic consequences than an acute neurological event. Some of the same concerns about reorganized function apply to slow-growing tumours. There is now clear evidence that the prolonged time-course of low-grade glioma growth can enable plasticity-related shifts in language function (Thiel *et al.*, 2001, 2005; Duffau *et al.*, 2003) and the same may apply to ATL semantic systems. Pre-damage reorganization of function does not, of course, apply to vascular accidents, but spontaneous recovery occurs to at least some extent in most patients (Enderby and Philipp, 1986). Unfortunately, there are insufficient numbers of each aetiology in this study to make formal comparisons between the three clinical groups, but this would be an interesting avenue for future investigation.

By contrast, an insidiously progressive condition like semantic dementia, which often does not even come to medical attention until it is moderately advanced, probably offers limited scope for relearning. Furthermore, the few studies of attempted semantic rehabilitation with patients with semantic dementia suggest that the kind of learning/re-learning of which they are capable is rigid, rote and context-bound (e.g. Graham *et al.*, 2001; Snowden and Neary, 2002). One might argue that, in contrast, the very essence of conceptual knowledge is its flexibility and generalizability to different situations (Lambon Ralph and Patterson, 2008; Lambon Ralph *et al.*, 2010). Thus, even if semantic dementia patients manage to learn and remember 'some' things (and hence, for example, produce delayed recall of the complex, meaningless Rey figure that is within the normal range: Adlam *et al.*, 2009), generalizable semantic information is not one of them.

In conclusion, the results from this study support a neurological model in which yoked ATL regions within both left and right hemispheres function together to support a redundant and thus robust system for semantic representation (Lambon Ralph *et al.*, 2001). As a result, unilateral damage generates either no receptive semantic impairment (as observed here) or small deficits that can only be measured in large group studies or via reaction times in right-sided transcranial magnetic stimulation investigations of the left or right ATL. The redundancy of the bilateral temporal system is such that the only way to observe substantial semantic impairment is if the damage is itself bilateral (as is the case in semantic dementia, herpes simplex virus encephalitis, etc.) or if the functional connectivity between the two hemispheres is disrupted (Warren *et al.*, 2009).

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