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Semantic dementia and the left and right temporal lobes

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ABSTRACT

Semantic dementia, a circumscribed disorder of semantic knowledge, provides a unique model for understanding the neural basis for semantic representation. The study addressed areas of contention: the relative roles of the left and right temporal lobe, the contribution of anterior versus posterior temporal cortex and the status of the anterior temporal lobes as amodal hub. Naming and word comprehension was examined in 41 semantic dementia patients, 31 with left-predominant and 10 right-predominant atrophy. In keeping with expectation, naming and comprehension were significantly poorer in left-predominant patients. Structural magnetic resonance image analysis, using a visual rating scale, showed strong inverse correlations between naming scores and severity of both left anterior and posterior temporal lobe atrophy. By contrast, comprehension performance was more strongly correlated with left posterior temporal atrophy. Analysis of naming errors revealed a correlation between anterior temporal atrophy and associative/functional descriptive responses, implying availability of semantic information. By contrast, 'don't know' responses, indicative of loss of semantic knowledge, were linked to left posterior temporal lobe atrophy. Semantic errors, the hallmark of semantic dementia, were linked to right hemisphere atrophy, especially the right posterior temporal lobe. Matched visual-verbal tasks (famous face and name identification, Pyramids and Palm trees pictures and words, animal knowledge from 3-D models and animal names) administered to nine patients elicited variable correspondence between performance on nonverbal and verbal versions of the task. Marked performance dissociations were demonstrated in some patients: poorer understanding of names/words in left-predominant patients and of faces/pictures/models in right-predominant cases. The findings are compatible with the notion of the anterior temporal lobes as areas of convergence, but are less easily accommodated

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within the framework of amodal conceptual representation. The data, which reconcile some apparent contradictions in the literature, are discussed in the light of the nature and distribution of degenerative change in semantic dementia.
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1. Introduction

Semantic dementia is a disabling neurodegenerative disorder characterised by profound and widespread loss of conceptual knowledge (Snowden, Goulding, & Neary, 1989; Hodges, Patterson, Oxbury, & Funnell, 1992). It is associated with bilateral, albeit often asymmetric, atrophy of the anterior temporal lobes, with particular involvement of inferior and middle temporal gyri (Mummery et al., 2000; Chan et al., 2001; Rohrer et al., 2008). The disorder is underpinned by a unique frontotemporal lobar degeneration pathology, in which the abnormal protein is TDP-43 and the salient histological changes are of dystrophic neurites (Josephs et al., 2011; Snowden et al., 2011).

The cardinal presenting clinical feature is typically a difficulty in naming and in understanding words. In conversation, patients substitute generic terms for precise substantives (Hoffman, Meteyard, & Patterson, 2014) and they may use words over-inclusively. A hallmark of the disorder is the presence of semantic errors (e.g., 'banana' for apple; 'dog' for sheep), which is consistent with the gradual erosion of the capacity for discrimination between related concepts. With progression of disease, naming errors become decreasingly related to the target response (Hodges, Graham, & Patterson, 1995). The semantic disorder is not limited to language and progressively encompasses knowledge in all sensory domains. It affects the ability to recognise the meaning of objects (Snowden, Griffiths, & Neary, 1994; Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000), faces (Snowden, Thompson, & Neary, 2004; Josephs et al., 2008; Luzzi et al., 2017), voices (Luzzi et al., 2017), non-verbal environmental sounds (Bozeat et al., 2000; Goll et al., 2010), smells (Luzzi et al., 2007), tastes (Piwnica-Worms, Omar, Hailstone, & Warren, 2010; Omar, Mahoney, Buckley, & Warren, 2013) and tactile stimuli. By contrast, non-semantic cognitive skills remain well preserved. Patients are able to perceive normally stimuli that they cannot recognise, evidenced by their preserved performance on perceptual discrimination and copying tasks. The findings in semantic dementia exemplify the central distinction between semantic and pre-semantic levels of object processing, eloquently described by Humphreys and colleagues (Humphreys & Forde, 2001; Humphreys & Riddoch, 2006).

The striking, yet circumscribed, semantic loss in semantic dementia raises a number of theoretical questions. Perhaps the most central concerns the neural basis of semantic memory and, in particular, the role of the anterior temporal lobes. There is now widespread acceptance that semantic memory involves distributed neural networks. A prominent, influential view is that object concepts are grounded in action and perception (Martin, 2007; Barsalou, 2008; Kiefer & Pulvermüller, 2012; Meteyard, Rodriguez Cuadrado, Bahrami, & Vigliocco, 2012; Pulvermüller, 2013) as well as in emotion systems (Martin, 2016). By this view, object concepts are not explicitly represented but emerge from weighted activity within property-based brain regions. Hence, object concepts belonging to distinct categories such as animals and tools are represented in overlapping, but partially distinct, sensory- and motor property-based neural networks.

Nevertheless, the semantic loss in semantic dementia exceeds, both in terms of severity and range, that which is found in any other neurological condition. It points compellingly to a pivotal role of the anterior temporal lobes in semantic memory and led to the proposal of an anterior temporal lobe conceptual hub, which binds information from modality-specific systems and stores it in amodal format (Patterson, Nestor, & Rogers, 2007). Proponents of the semantic hub did not dispute the notion of a distributed semantic network, but rather argued that an additional amodal conceptual hub is necessary to serve as a convergence zone to support the interactive activation of representations in all modalities, for all semantic categories.

There are data that appear at odds with the notion of the anterior temporal lobes as an amodal semantic hub. Focal damage to the anterior temporal lobes has been reported to elicit few, if any, signs of semantic impairment (Bi et al., 2011; Busigny, de Boissezon, Puel, Nespoulous, & Barbeau, 2015). Many authors have associated the left anterior temporal region with problems in lexical retrieval (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Mesulam et al., 2013; Miozzo & Hamberger, 2015), particularly for Proper nouns or other unique entities (Grabowski et al., 2001; Tranel, 2006, 2009; Busigny et al., 2015), rather than to frank semantic loss. Even when semantic impairments have been identified, for example following temporal lobe resection or vascular insults (Lambon Ralph, Cipolotti, Manes, & Patterson, 2010; Lambon Ralph, Ehsan, Baker, & Rogers, 2012) such deficits are relatively subtle and typically elicited only for low frequency stimuli. Activation studies too have typically shown little evidence of anterior temporal activation on semantic tasks, with many functional imaging studies reporting posterior rather than anterior temporal activation (Martin & Chao, 2001; Thompson-Schill, 2003). Some authors have argued that the lack of anterior temporal activation may be due to technical limitations and have demonstrated significant activation using transcranial magnetic stimulation

techniques (Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010). Notwithstanding such arguments, evidence for the association of the anterior temporal lobes with semantic memory remains limited.

How then to account for the pervasive semantic loss in semantic dementia? A rational assumption, espoused by a number of authors (Lambon Ralph et al., 2010; Pobric, Jefferies, & Lambon Ralph, 2010; Schapiro, McClelland, Welbourne, Rogers, & Lambon Ralph, 2013), is that it is the bilateral nature of the disease that is responsible, the inference being that both hemispheres contribute to semantic representations and conceptual representations are supported by an interconnected, bilateral anterior temporal network.

The question then arises as to the nature of the role of the two hemispheres. In an amodal hub account (Pobric et al., 2010) the assumption is that there is an equivalence of function within the right and left anterior temporal lobes. If concepts are represented in amodal format then damage to the hub should produce a semantic impairment that is independent of the modality of input (verbal, visual, olfactory, gustatory or tactile) or type of material (words, objects, pictures, sounds). Yet, patients with semantic dementia are not identical. Although conceptual impairment cuts across modality and test material there are individual differences. Patients with greater left than right temporal atrophy have shown more severe loss of knowledge of the names of famous people compared to their faces whereas patients with right-predominant atrophy have shown the reverse pattern (Gainotti, Barbier, & Marra, 2003; Snowden, Thompson, & Neary, 2004; Gainotti, 2007; Busigny, Robaye, Dricot, & Rossion, 2009; Gainotti, Ferraccioli, & Marra, 2010; Snowden, Thompson, & Neary, 2012; Luzzi et al., 2017). Similarly, naming deficits have been reported to be more severe in patients with left-predominant temporal atrophy and face familiarity judgements in right-predominant cases (Binney et al., 2016). Recognition of both the faces and the voices of famous people have been specifically linked to right but not left temporal atrophy (Josephs et al., 2008; Gainotti, 2011; Luzzi et al., 2017). Hemispheric differences extend to words and objects (Snowden et al., 2004; Gainotti, 2012, 2015; Luzzi et al., 2017). For example, patients with left predominant temporal lobe atrophy have been reported to perform more poorly on the verbal than the pictorial version of the Pyramids & Palm trees test of semantic association, whereas patients with right predominant atrophy show the opposite pattern (Snowden et al., 2004; Luzzi et al., 2017). Such findings are in keeping with arguments that the left and right anterior temporal lobes support verbal and nonverbal representations respectively (Gainotti, 2012; 2015).

Proponents of the amodal hub hypothesis interpreted such findings in terms of differential connections to modality-specific systems represented more posteriorly (Mion et al., 2010). Hence, left-predominant atrophy is likely to give rise to greater problems in naming than right-predominant atrophy because of the greater connectivity to language areas involved in speech production. In a more recent formulation (Rice, Hoffman, & Lambon Ralph, 2015; Lambon Ralph, Jefferies, Patterson, & Rogers, 2017) it has been proposed that there is graded specialisation within and between the anterior temporal lobes, the graded account providing a compromise between theories that posit no differences between the functions of the left and right anterior temporal lobes and those that argue for complete segregation of function. Whether there remains a role for 'amodal', as opposed to 'multimodal', representation is open to debate.

Theories of semantic representation need to provide an adequate account of findings in patients with semantic impairment. The current study involved patients with semantic dementia and was motivated by the continuing lack of consensus in the literature. It sought, through analysis of naming and word comprehension performance and its relationship to neuroimaging findings and through matched verbal-nonverbal tasks, to increase understanding of the roles of the left and right temporal lobes in semantic memory and of the relationship between functions of the anterior and posterior temporal neocortex.

2. Methods

2.1. *Participants*

The study involved patients who had been assessed in a diagnostic neuroscience unit specialising in early onset and atypical dementias and had a clinical diagnosis of semantic dementia. All patients fulfilled consensus criteria for semantic dementia (Neary et al., 1998). Most also fulfilled criteria for semantic variant primary progressive aphasia (Gorno-Tempini et al., 2011) although in some with more right-sided atrophy the earliest presenting symptom was difficulty in face recognition rather than in the language domain. Patients were included in the study only if a) they had undergone clinical neuropsychological evaluation that included the picture naming and word picture-matching tests described below and b) neuroimaging had been undertaken close to the time of patients' clinical assessment, which supported the clinical diagnosis. In most cases scanning had been undertaken for clinical purposes as part of the patient's work up, although in a minority of cases research scans were available. Patients were excluded if scan images were no longer available, precluding independent verification of the left or right predominance of atrophy specified in the clinical scan report. In addition, in view of the current focus on relative roles of the two hemispheres, patients were excluded if the scan showed no asymmetry in the distribution of temporal lobe atrophy. Patients, or their consultees, had provided written consent for clinical data to be used for research purposes. Ethical approval had been obtained for the clinical research database (NREC reference: 09/h0906/53+5).

The final cohort consisted of 41 patients with semantic dementia (24 men and 17 women). Their mean age at onset of illness was 59 years (s.d.7.3) and duration of symptoms at testing 5 years (s.d. 2.9).

2.2. *Naming and comprehension tasks*

The key data of interest were performance on an undemanding, locally constructed naming test and a word-picture matching test for measuring comprehension. The naming test is a 40-item test that uses pictures drawn from the corpus of

Snodgrass and Vanderwart (1980) and consists of 10 items from each of the following semantic categories: 10 animals, 10 fruits/vegetables, 10 articles of clothing, 10 household objects. The category sets are matched for word frequency and age of acquisition, but clothing and objects are rated as more familiar than the animals and vegetables. The naming test is sufficiently easy to yield ceiling or close to ceiling level performance in healthy controls. Control errors, when they occur, typically represent viable alternative responses (e.g., 'coat' for jacket). The word-picture matching test involves the same 40 items as the naming test, permitting direct, item-by-item comparison of naming and comprehension scores. The participant is required to match a printed word with one of four semantically related pictures. The location of the target picture (top-left, top-right, bottom-left, bottom-right) is balanced across the 40 items. Examples of stimuli for the naming and word-picture matching test are shown in Fig. 1. Performance is measured in terms the number of correct responses, in total and for different semantic categories. In addition, naming responses are classified with respect to the nature of errors.

2.2.1. *Error classification*

Incorrect naming responses were classified into the following broad categories:

Semantic errors (coordinate category) e.g., 'dog' for rabbit.

Associative or functional circumlocutions e.g., 'when it rains' for umbrella.

Omissions/vague generic responses e.g., 'don't know' or 'I like that'.

Unrelated misidentifications e.g., 'hat' for mushroom.

Superordinate category substitutions e.g., 'animal' for rabbit.

Viable alternative responses e.g., 'coat' for jacket.

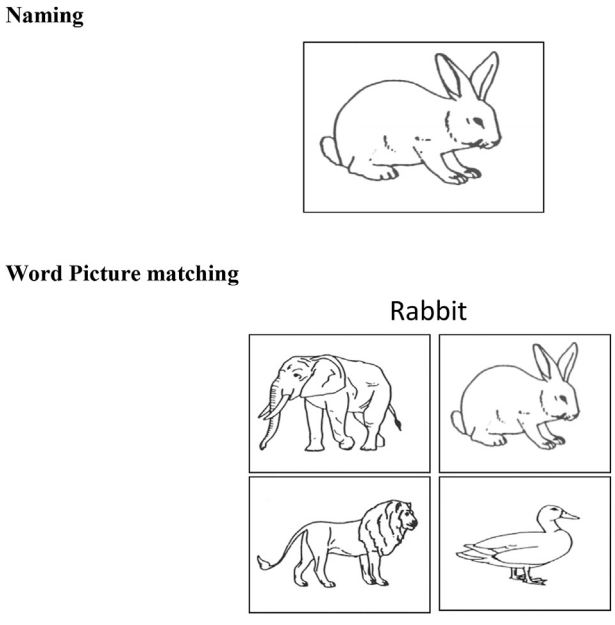

Fig. 1 – Examples of stimuli used in naming and comprehension tasks.

2.3. *Imaging*

Patients' scans were classified as left-predominant or right-predominant temporal lobe atrophy by CK, a specialist neurologist who had training and substantial experience of image analysis. CK had no knowledge of the patients, no access to their cognitive data, and no knowledge of their clinical scan reports, to eliminate potential biases in rating. In most, but not all, instances coronal T1 or FLAIR images were available, permitting rating of severity of atrophy in the left frontal, right frontal, left anterior temporal, right anterior temporal, left posterior temporal and right posterior temporal lobes using the visual rating scale described by Kipps et al. (2007). This visual rating method, based on a 5-point scale of severity ranging from no atrophy (0) to severe atrophy (4), was regarded as optimal for the available data. Voxel-based morphometric analysis was not viable, as scans had been carried out in different clinical centres so data acquisition protocols were not identical for all patients. The visual rating scale has been explicitly designed to be suitable for evaluation of atrophy in patients with forms of frontotemporal dementia. The scale has been demonstrated to show good inter-rater reliability, correlation between atrophy scores and voxel based morphometric analyses and differentiation between frontotemporal lobar degeneration and other forms of degenerative dementia (Kipps et al., 2007; Harper et al., 2016). Ratings were carried out by CK in blinded fashion.

2.4. *Visual-verbal task comparisons*

The Naming and Word-Picture matching tests are largely language-based. Nine patients from the study cohort, seen prospectively, were administered matched visual-verbal tasks to permit direct comparison between performance involving visual (faces, pictures, objects) and verbal (Proper names, common nouns) materials.

2.4.1. *Famous faces versus names*

This locally-constructed task involves a set of 28 famous faces and their corresponding names (e.g., Margaret Thatcher, Princess Diana, Elvis Presley). For each famous face three non-famous faces were drawn from the Internet, matched to the famous face for gender and age band. Similarly, three non-famous names were constructed for each famous name, designed to be similar in style, age association and first-name frequency to the famous name and matched for number of syllables.

In the first part of the test the participant was required to select the famous face from a set of four faces, the position of the target face, amongst the three non-famous distractors being balanced across trials. Having selected a face the participant was asked to provide identifying information. No feedback was given. In the second part of the test, the participant was shown a list of four names and asked to select the famous name, and then to provide identifying information. No feedback was given. In both face and name tasks, allowances were made for patients' nominal difficulties. Hence a response for Margaret Thatcher "She was the one on top, not now" would be regarded as correct.

2.4.2. Pyramids and palm trees test

This published test (Howard & Patterson, 1992), involving 52 trials, requires the participant to select from two alternatives (e.g., a palm tree and a pine tree) that item most closely associated with the target (e.g., a pyramid). The test was presented first in its pictorial form and then its word form.

2.4.3. Animal knowledge

This locally constructed test involved a set of 20 commercially available solid three-dimensional models of animals (dog, cat, horse, pig, cow, sheep, rabbit, squirrel, tortoise, duck, parrot, frog, dolphin, seal, polar bear, penguin, monkey, elephant, giraffe, zebra) and their corresponding names.

In the first part of the test participants were shown each animal model in turn and asked about its usual habitat. To allow for problems in verbal comprehension the instructions were framed in different ways "where would you see it?"/ "where would you find it?"/"where does it live?" until it was clear that the patient had grasped what was required. Responses were recorded verbatim. For vague responses e.g., "it's outside" participants were asked to elaborate. If patients responded "in the zoo" they were prompted with "Anywhere else? Where would they normally live?". The examiner made no mention of the animal's name. No feedback was given. The models were then moved from view and participants were presented (orally and in written form) animal names and asked to indicate the animal's habitat. No reference was made to the animal models.

Responses were scored from 0 to 2 based on the accuracy and specificity of the information provided (0 = no correct information, 1 = correct information but vague or generic, 2 = correct information with some specificity). Allowance was made for limitations in vocabulary so ratings were lenient.

2.5. Statistical analyses

Group comparisons (left-predominant versus right-predominant) were made using parametric and non-parametric analyses, depending on the distribution of the data.

The relationship between naming and word-picture matching performance measures and ratings of severity of atrophy was examined using non-parametric Spearman correlations.

For the visual-verbal comparisons based on item-by-item analysis, measurement of change was examined using McNemar or Wilcoxon test for categorical and ordinal data respectively, and item consistency using contingency coefficients or Spearman correlations.

3. Results

3.1. Demographics and background clinical data in patients with left and right-predominant atrophy

Of the 41 patients with semantic dementia, 31 had left-predominant and 10 right-predominant atrophy. Left-predominant and right-predominant groups did not differ significantly in gender distribution, age at onset of illness, or duration of illness at the time of test.

Background cognitive data are summarised in Table 1. Both left and right-predominant groups performed very poorly (approaching floor level) on the Graded naming test, a standard published test of picture naming (McKenna & Warrington, 1980), and well below normal levels on verbal fluency tasks. There was a small group difference, left-predominant patients having poorer nominal scores than right-predominant. Both groups performed well on the perceptual and spatial tasks of the Visual Object and Space Perception Battery (Warrington & James, 1991) provided that these did not require recognition of identity. Group differences on subtests were not significant.

3.2. Naming and comprehension as a function of left or right predominance of atrophy

3.2.1. Accuracy

In the naming and word-picture matching tests of key interest to the study, left-predominant patients showed both poorer naming ($t = 4.39$, $p < .001$) and poorer matching i.e., comprehension (Mann–Whitney $U = 78.0$, $z = 2.2$, $p = .03$) than right-predominant patients (Fig. 2). The comprehension scores include some ceiling level scores, hence the use of non-parametric analysis. In order to examine directly relative performance between naming and comprehension in the left and right-predominant groups, patients with ceiling level scores were excluded and the data were re-examined using repeated measures analysis of variance. There was a significant main effect of group ($F = 10.3$, $p = .003$), with left predominant patients performing more poorly than right-predominant patients, an effect of task ($F = 57.2$, $p < .001$), naming yielding poorer scores than word-picture matching and a trend towards an interaction effect ($F = 3.6$, $p = .07$), suggesting a disproportionate naming impairment in left-predominant patients.

In both naming and comprehension tests there was a significant main effect of category, with performance being poorer for biological (animals, fruits and vegetables) compared

Table 1 – Background data summary in patients with left and right-predominant atrophy (means and standard deviations).

	Left-predominant	Right-predominant	Group difference
MMSE/30	20.5 (6.4)	24.3 (4.4)	n/s
Digit span	6.3 (1.4)	7.0 (1.2)	n/s
Graded naming/30	.4 (.9)	1.9 (2.1)	$t = 2.1$, $p = .06$
Animal fluency	4.7 (3.4)	7.8 (4.5)	$t = 2.2$, $p = .04$
Letter fluency FAS	14.0 (11.7)	23.9 (10.6)	$t = 2.2$, $p = .03$
VOSP screening/20	19.6 (.6)	19.0 (1.2)	n/s
VOSP incomplete letters/20	16.0 (6.5)	16.5 (4.2)	n/s
VOSP silhouettes/20	6.3 (6.5)	6.9 (3.8)	n/s
VOSP object decision/20	14.8 (4.2)	13.1 (4.7)	n/s
VOSP dot counting/10	10 (.2)	9.9 (.3)	n/s
VOSP cube analysis/10	9.7 (.6)	9.5 (.7)	n/s

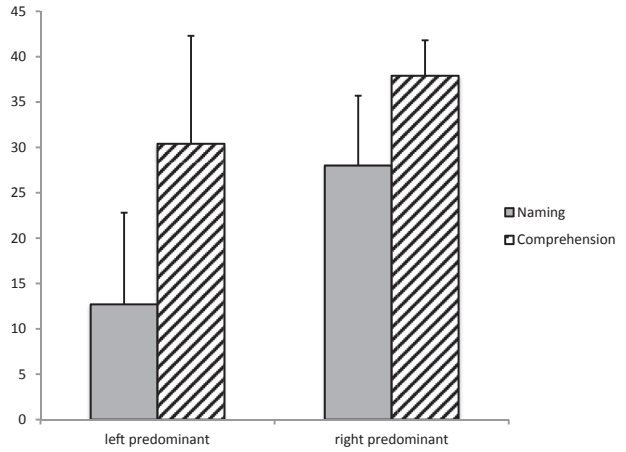

Fig. 2 – Naming and comprehension (word-picture match) performance in left and right-predominant semantic dementia.

to non-biological items (clothing and household objects): naming $F = 40.5$, $p < .001$; comprehension $F = 8.2$, $p = .009$. The interaction between patient group and category was non-significant.

3.2.2. *Naming errors*

The frequency of semantic (coordinate category), associative/functional, omission/generic, misidentification and superordinate category substitution errors was calculated. Viable alternative responses (e.g., 'coat' for jacket) were disregarded in the error analysis. Error breakdown in the left and right predominant groups is shown in Fig. 3. Left-predominant patients made a higher proportion of circumlocutory errors (descriptions of an object's function or a semantic association) than right-predominant patients (Mann Whitney $U = 37.0$, $p < .001$) whereas right-predominant patients made proportionally more semantic errors (Mann Whitney $U = 47.0$, $p = .001$). Comparisons of other error types did not reach statistical significance.

3.3. *Relationship between naming and comprehension and atrophy ratings*

Coronal T1 or FLAIR images were available for visual rating of atrophy in 32 cases, using the Kipps scale (Kipps et al., 2007).

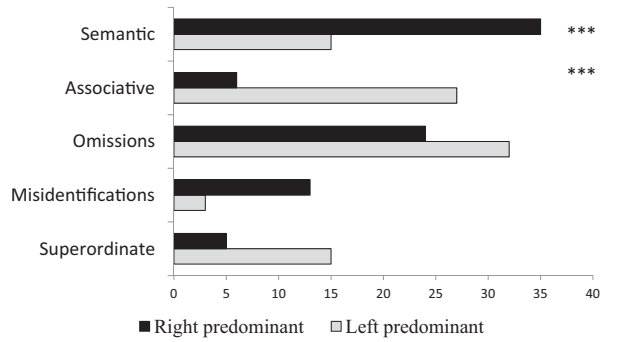

Fig. 3 – Error breakdown in patients with left and right-predominant atrophy. The bar chart shows proportion of total errors.

Twenty-four had greater left than right temporal lobe atrophy and eight had more right-sided atrophy. Examples of images are shown in Fig. 4.

3.3.1. *Performance accuracy and image ratings*

Spearman rank correlations between atrophy ratings and test performance in the 32 patients showed strong inverse correlations between left temporal lobe atrophy ratings and both naming and comprehension (word-picture match) scores (Table 2). That is, poorer test performance was associated with greater left temporal atrophy. There was no association between performance and frontal lobe or right temporal lobe atrophy. Notably, naming performance was strongly associated with both anterior and posterior left temporal atrophy, whereas comprehension, as measured by word-picture matching, was more strongly associated with left posterior temporal atrophy.

When biological (animals and fruit/vegetables) and non-biological (clothing and household objects) were analysed separately the findings were largely similar. Left anterior temporal atrophy correlated inversely with naming scores for both biological ($r_s = -.47$, $p = .008$) and non-biological ($r_s = -.47$, $p = .007$) items, but correlations with comprehension scores were not significant. Left posterior temporal atrophy correlated inversely with naming scores for nonbiological items ($r_s = -.40$, $p = .03$) and particularly biological items ($r_s = -.56$, $p = .001$), and with comprehension scores equally for nonbiological ($r_s = -.57$, $p = .002$) and biological ($r_s = -.57$, $p = .002$) items.

3.3.2. *Naming errors and atrophy ratings*

The frequency of semantic errors, a hallmark of semantic dementia, correlated with right but not left temporal atrophy, the correlation being strongest for the right posterior temporal lobe (Table 3). Associative/functional descriptive responses correlated strongly with the severity of left anterior temporal lobe atrophy, whereas they were negatively correlated with right temporal lobe atrophy. Omissions correlated with left posterior temporal atrophy. Misidentification errors showed a small correlation with right temporal atrophy. Superordinate category substitutions did not yield significant relationships, so are not shown in the table.

The correlations are based on absolute frequency of errors. If semantic errors are measured in terms of the proportion of semantic to total naming errors then a similar pattern of findings emerges, although the left-right distinction is more pronounced. No correlations were found between the proportion of semantic errors and left frontal, left anterior temporal or left posterior temporal atrophy ratings. By contrast, there were significant correlations with right frontal atrophy ($r_s = .41$, $p = .02$), right anterior temporal ($r_s = .45$, $p = .01$) and particularly right posterior temporal ($r_s = .63$, $p < .001$) atrophy ratings.

3.4. *Visual versus verbal task performance and right versus left predominant atrophy*

The naming and word-picture match accuracy data point to a stronger relationship between semantic knowledge and left temporal lobe degeneration compared to right, although error

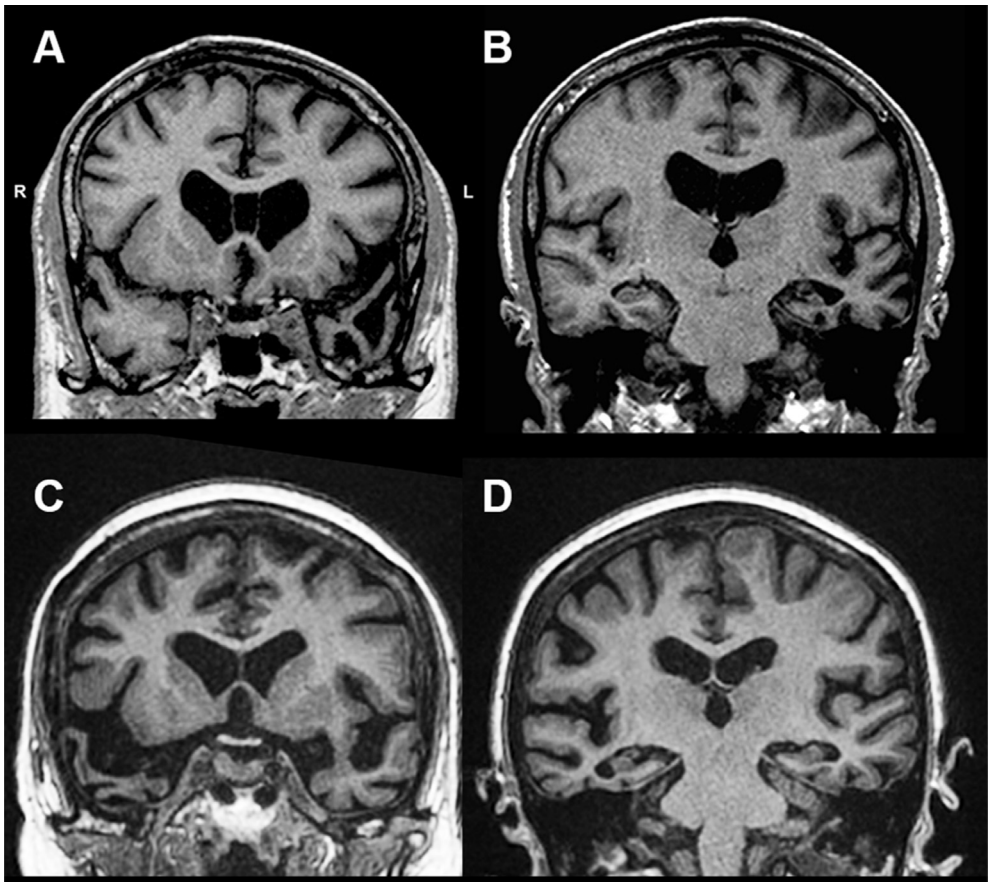

Fig. 4 – T1-weighted coronal MR images in radiological orientation showing temporal lobe atrophy: A) anterior temporal left > right, B) posterior temporal left > right, C) anterior temporal right > left, D) posterior temporal right > left.

Table 2 – Correlations between naming, comprehension and ratings of atrophy.

	Naming		Word comprehension	
	Correlation	Significance	Correlation	Significance
Left frontal	.04	n/s	−.06	n/s
Left anterior temporal	−.50	**p = .003**	−.36	p = .05
Left posterior temporal	−.48	**p = .006**	−.58	**p = .001**
Right frontal	.08	n/s	−.09	n/s
Right anterior temporal	.27	n/s	.12	n/s
Right posterior temporal	.23	n/s	−.02	n/s

Positive correlations at p = .0.1 or greater are shown in bold.

Table 3 – Correlations between naming errors and atrophy ratings. *P* values in parentheses represent inverse correlations.

	Semantic	Associative	Omissions	Misidentify
Left frontal	.29	−.20	.10	.11
	n/s	n/s	n/s	n/s
Left anterior temporal	.14	.47	.21	.18
	n/s	**p = .007**	n/s	n/s
Left posterior temporal	.18	.08	.51	.13
	n/s	n/s	**p = .004**	n/s
Right frontal	.42	−.31	.08	.19
	p = .02	n/s	n/s	n/s
Right anterior temporal	.20	−.44	−.13	.39
	n/s	(*p* = .01)	n/s	*p* = .03
Right posterior temporal	.45	−.49	−.04	.35
	p = .01	(*p* = .006)	n/s	*p* = .05

Positive correlations at p = .0.1 or greater are shown in bold.

analysis highlights the contribution too of the right hemisphere. Both naming and word-picture matching tasks have a strong verbal component. Prospective data on matched nonverbal-verbal tasks were obtained in four patients with left predominant temporal lobe atrophy and five with right-predominant atrophy. Background neuropsychological data for these nine patients are shown in Table 4. They show performance patterns largely similar to those of the larger cohort: impairments on naming and other tasks that make semantic demands and preserved performance on non-semantic tasks.

3.4.1. *Individual patient performance*

Individual patient performance on the matched tasks is shown in Fig. 5. The relationship between performance for the visual and verbal versions of the same task was variable across patients, with some patients showing comparable performance and other showing dissociations (Table 5). Famous face/name 'Identification' is not shown in the table because performance was at or approached floor level performance in most patients.

Even in cases where performance did not differ significantly for the visual/verbal version of a test, item-by-item correspondences were low. Contingency coefficients conducted for Pyramids and Palm trees pictures and words showed no significant correspondence in accuracy of responses elicited for any patient. For famous face and name familiarity judgements significant item-by-item correspondence was found only in patient 1 ($p = .02$).

The greatest disparity in performance on matched tasks was observed in patients 7 and 8. Patient 7's MR scan images were limited to T2 sequences and were therefore not subjected to visual ratings of atrophy. In patient 8, atrophy ratings for the anterior temporal lobes were comparable to those in other patients in the visual-verbal cohort (severity ratings of 2 or 3). By contrast, atrophy ratings for the posterior temporal lobes were more severe: he was the only patient to have right posterior temporal atrophy rated as 4 and left posterior temporal atrophy rated as 3. The clinical presentation of patient 8 is summarised below.

3.4.2. *Case history patient 8*

This man presented to medical attention at 69 years with a two-year year history of progressive difficulty in recognising people and objects. He reported that he no longer recognised the tools in his garden shed or the fruits and vegetables in the supermarket and he encapsulated his problem as "things dropping out of my brain". On examination he spoke fluently and effortlessly, but he used terms over-inclusively (e.g., "container") and he made frank semantic errors. On the Graded naming test he named no items and he reported most pictures to be unfamiliar. He performed at ceiling level on perceptual and spatial tests that do not require recognition of identity. He copied line drawings, including complex abstract figures, quickly and accurately. By contrast, performance was profoundly impaired on all perceptual tasks involving recognition of identity. This included the letter identification test of the Visual Object and Space Perception Battery. He had considerable difficulty grasping the fact that the fragmented letter represented the same thing as solid block letters. On the easy Naming test reported in the current study he named 11/40 items, showing superior naming performance for non-biological compared to biological categories ($\chi^2 = 6.1$, $p = .01$). He made a high number of semantic errors (41% of naming errors) and don't know responses (28%). In the Pyramids and Palm trees test his performance for pictures was at chance level (50% correct), whereas for words it was significantly above chance (75% correct). Similarly, forced-choice familiarity judgement performance for faces was at chance level (29% correct) whereas it was significantly above chance for names (57% correct). In the Animal task he was able to provide more specific identifying information from the animals' name than from the three-dimensional model. Examples of his responses to animal models and their corresponding names are shown in Fig. 6.

His condition deteriorated rapidly over a three-year follow-up period. He used objects inappropriately and attempted to eat inedible objects. He remained able to copy line drawings until the most recent assessment, at which time he no longer recognised a pencil and had no understanding of its function. His comprehension of language also declined and he now has

Table 4 – Naming/comprehension and background data and in individual patients.

Atrophy	Left-predominant				Right-predominant				
Patient	1	2	3	4	5	6	7	8	9
Naming/40	9	3	18	0	32	22	16	11	11
Word-picture match/40	34	36	40	25	40	38	32	27	26
MMSE/30	25	22	28	27	29	24	29	21	27
Digit span	5	7	8	7	8	8	8	5	8
Graded naming/30	0	1	0	1	5	6	3	0	0
Animal fluency	6	3	9	5	18	9	10	4	8
Letter fluency FAS	21	12	32	12	34	37	34	8	28
VOSP screening/20	20	20	18	19	20	18	20	20	19
VOSP incomplete letters/20	20	19	20	18	19	18	19	8	20
VOSP silhouettes/30	–	5	7	4	11	10	10	0	5
VOSP object decision/20	–	14	18	–	–	15	–	12	17
VOSP dot counting/10	10	10	10	10	10	10	10	10	10
VOSP cube analysis/10	10	10	10	10	9	10	9	10	10

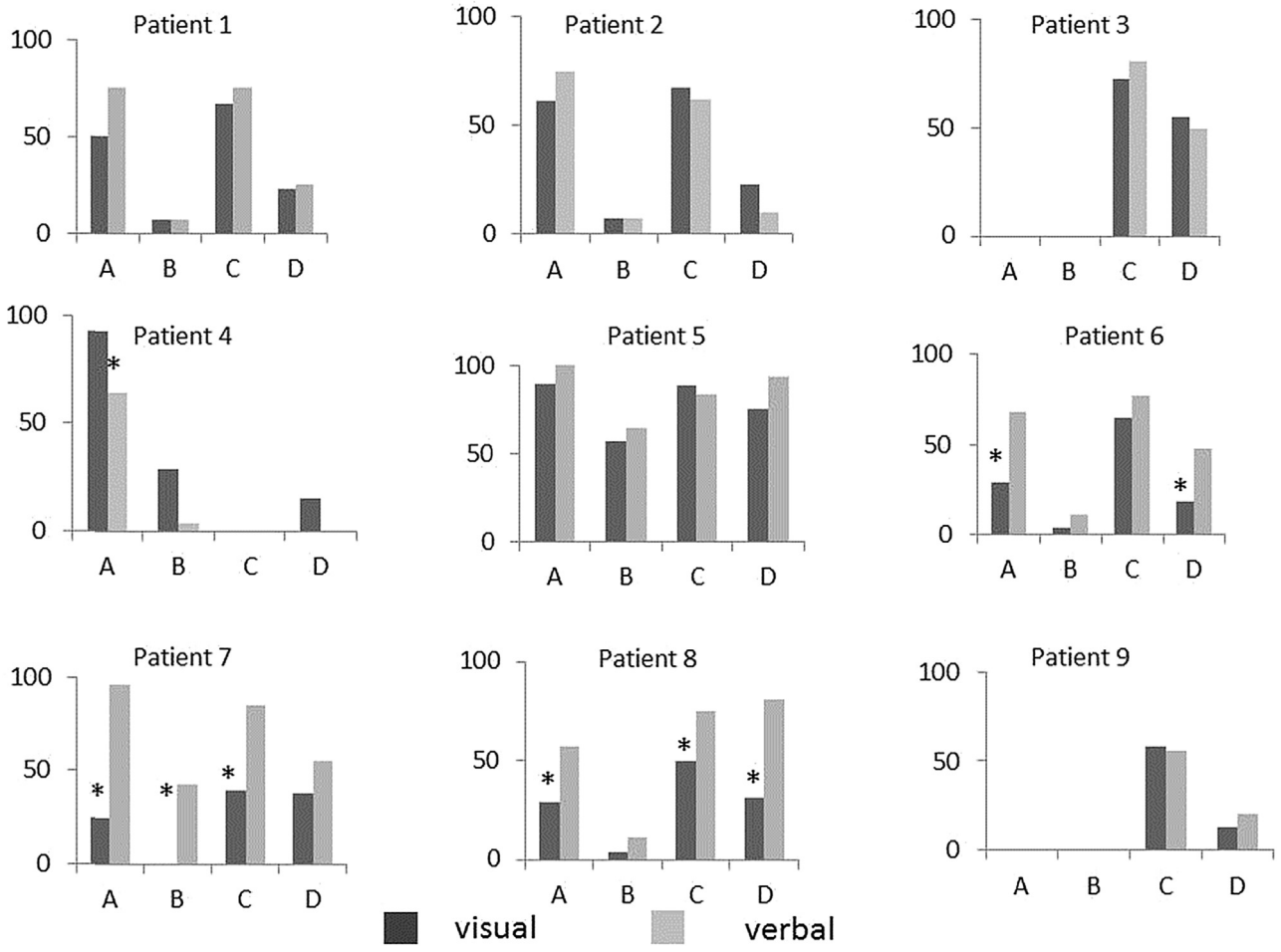

Fig. 5 – Matched visual-verbal task performance in individual semantic dementia patients. Patients 1–4 have left predominant and patients 5–9 right predominant atrophy. A = famous face/name familiarity judgement (chance = 25%), B = famous face/name identification, C = Pyramids and Palm Trees test pictures and words (chance = 50%), D = Animal habitat identification from models and names. Data for measures A and B are missing in patient 3 and 9, and for task C in patient 4. Patients 4 and 7 had floor level performance respectively for animal names and for face identification.
*** = significant difference between visual-verbal task performance.**

Table 5 – Performance differences for verbal and non-verbal tasks (item-by-item analysis).

Patient	Atrophy dominance	Famous faces and names (familiarity)	Pyramids & Palm Trees	Animal habitat 3-D models versus names
		McNemar	McNemar	Wilcoxon
1	Left	n/s	n/s	n/s
2	Left	n/s	n/s	n/s
3	Left	–	n/s	n/s
4	Left	$p = .02$ Faces superior	n/s	$p = .06$ (trend) Models superior
5	Right	n/s	n/s	$p = .06$ (trend) Names superior
6	Right	$p = .01$ Names superior	n/s	$p = .03$ Names superior
7	Right	$p < .001$ Names superior	$p < .001$ Words superior	$p = .08$ (trend) Names superior
8	Right	$p = .02$ Names superior	$p = .004$ Words superior	$p = .008$ Names superior
9	Right	n/s	n/s	n/s

Stimulus	Response	Stimulus	Response
	I don't know	FROG	In water
	In the house. It's a dog	COW	On a farm
	Outside the house. There are lots of them. They fly about.	DUCK	On ponds. I see them on the river when I go walking.
	In water. It's got a bushy tail so it's good at swimming.	SQUIRREL	In the woods, in the country. They are wild.
	In the house. It's somebody's son.	MONKEY	In trees, in Africa.

Fig. 6 – Examples of patient 8's responses in Animal habitat task. The patient is asked: Where would you find this?

no understanding of spoken or written language. He remains physically well.

4. Discussion

Semantic dementia is an important natural model for understanding the neural underpinnings of semantic knowledge. Yet, it has also been a source of perplexity. Its association with anterior temporal lobe atrophy appears at odds with a) the traditional link between language comprehension and posterior temporal function and b) the limited evidence of semantic disturbance arising from anterior temporal lobe lesions from non-degenerative causes. The findings from the current study have the potential to reconcile such disparities.

A core finding was that naming and word picture matching performance was more closely associated with left temporal atrophy than with right. This finding is consistent with expectation. There is strong evidence of a link between naming and the left temporal lobe (Damasio et al., 2004; Baldo, Arevalo, Patterson, & Dronkers, 2013; Mesulam et al., 2013; Migliaccio et al., 2016). Moreover, in semantic dementia naming and word comprehension has been found to be more impaired in patients with more severe left-sided atrophy than right (Thompson, Patterson, & Hodges, 2003). Indeed, semantic dementia has traditionally been associated with left temporal lobe atrophy (Mummery et al., 2000). In the current study, naming in patients with left-predominant atrophy was disproportionately affected relative to comprehension, albeit to a modest degree. This finding mirrors a previous report (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001), which interpreted the greater naming deficit in terms of the greater connectivity of left anterior temporal lobe to left-lateralised speech production systems.

The findings are also in keeping with those reported by Woollams and Patterson (2017) in this Special Issue.

A theoretically more challenging finding is the strength of the association respectively with anterior and posterior temporal atrophy. Whilst naming was strongly associated with both anterior and posterior temporal lobe atrophy, comprehension was more closely associated with posterior temporal atrophy. The implication is that the left anterior temporal lobe is crucial for naming, but that the involvement of posterior temporal lobes is critical for the loss of understanding of those words that the patient cannot name. The findings are consistent with the established association in aphasic patients between comprehension impairment and posterior temporal lobe lesions (Hart & Gordon, 1990), with functional imaging studies that have reported posterior rather than anterior temporal activation on semantic tasks (Chao, Haxby,

& Martin, 1999; Martin & Chao, 2001; Thompson-Schill, 2003) and with arguments that damage to left anterior temporal lobe gives rise to naming impairment but not loss of conceptual knowledge (Bi et al., 2011; Mesulam et al., 2013; Busigny et al., 2015).

Naming errors provide complementary findings. Left anterior temporal lobe atrophy was strongly associated with circumlocutory responses entailing a description of the object's function or provision of a semantic association. Such errors imply that the patient has some conceptual knowledge about the object that they cannot name. By contrast, posterior temporal lobe atrophy was strongly associated with 'don't know' responses and vague generic responses that convey minimal information. The inference from such errors is that the patient has impaired conceptual knowledge about the object.

What of the role of the right temporal lobe? At first sight it may seem to have little role. Ratings of atrophy showed no significant relationship between right temporal atrophy and performance on either naming or comprehension tasks. An examination of naming errors, however, suggests that this is an oversimplification. Semantic errors, the hallmark of semantic dementia, showed an association, not with left but rather with right temporal lobe atrophy, and in particular with atrophy in the posterior rather than anterior temporal lobe. By contrast, there was a strong inverse correlation between right temporal lobe atrophy and associative/function description error responses. A logical interpretation of semantic errors in semantic dementia is that the patient no longer has available knowledge of the visual featural characteristics that distinguish semantically related items (e.g., rabbit and dog; apple and banana). Such errors underscore the important contribution of sensory information to object knowledge, and point to the importance of visual perceptual processing systems of the right hemisphere. The findings complement those from a positron emission tomography study in healthy controls (Kellenbach, Hovius, & Patterson, 2005): decisions about an object's structure activated the right posterior middle/inferior temporal gyrus, whereas associative decisions task activated the left anterior middle/superior temporal gyrus and temporal pole. The findings reinforce arguments that both hemispheres are crucial for semantic knowledge (Gefen et al., 2013) and that the bilateral nature of the disease is an important factor in giving rise to the uniquely severe loss of conceptual knowledge in semantic dementia (Lambon Ralph et al., 2010; Pobric et al., 2010; Schapiro et al., 2013). The findings also argue for differential contributions of the two hemispheres to semantic memory.

The semantic dementia patients in this study showed poorer naming and comprehension performance for biological compared to non-biological items. This finding is in keeping with those of Libon et al. (2013), but at odds with reports that such category differences are not a feature of semantic dementia (Lambon Ralph, Lowe, & Rogers, 2007; Lambon Ralph et al., 2017). The stimuli in this study were matched for word frequency and age of acquisition, but living things (e.g., sheep, rabbit, lion) were associated, according to Snodgrass & Vanderwart data, with lower familiarity ratings than non-living things (e.g., trousers, scissors, toothbrush). There is good evidence that familiarity and in particular personal familiarity (what the patient encounters in their daily lives) is a significant factor in determining what patients with semantic dementia know (Snowden et al., 1994) and this factor is likely to contribute to the category differences in performance. It is noteworthy, however, that whereas left anterior temporal lobe atrophy correlated similarly with naming of biological and non-biological items left posterior temporal atrophy correlated more strongly with naming of biological items. This finding would be in keeping with the traditional argument that category differences reflect differential weightings of sensory and functional attributes in a concept's representation (Warrington & Shallice, 1984), and with the notion that living things such as animals place particular demands on visual information for their differentiation (Humphreys & Riddoch, 2003) and are disproportionately dependent upon visual processing regions of the posterior hemispheres.

Evidence for differential contributions of the two cerebral hemispheres is reinforced by the visual-verbal data. An argument hitherto advanced in favour of the anterior temporal lobes as an amodal hub is the fact that semantic loss in semantic dementia cuts across modalities, types of concepts and conceptual domains and there is typically a correlation between performance in different modalities (Patterson et al., 2007; Lambon Ralph & Patterson, 2008). Nevertheless, is not uncommon for patients with semantic dementia to recognise the meaning of an object whilst not recognising the object's name. A traditional explanation for such a disparity is that objects provide clues to meaning that are absent from a verbal label, which is essentially arbitrary. Pictorial features such as the presence of ears, eyes and legs might reasonably suggest, for example, that a rabbit is an animal rather than an article of clothing or a means of transport, whereas the characteristics of the word 'rabbit' provide no such clues. Thus, if a concept is partially degraded, the picture or object may provide sufficient information to permit a correct response whereas the word does not. By this account, discrepant findings for word and object recognition could be readily assimilated within the framework of an amodal account of semantic memory representation.

Such an explanation cannot, however, explain the converse finding of significantly better knowledge from the word compared to the object. The direct comparison of verbal and nonverbal task performance in this study yielded, in some patients, better understanding of names/words than faces/objects. Thus, patient 8 failed to distinguish a 3-dimensional model of a duck from common garden birds, yet from the word, he had relatively precise information. From the model, he showed no recognition of a squirrel and made an educated guess based on perceptual characteristics, yet from the word he showed good knowledge. Most strikingly, he identified a model of a monkey as a human child, yet from the word he could give entirely appropriate information. At the time of the study, and up until such time as he no longer recognised the significance of a pencil, patient 8 could copy line drawings accurately suggesting preserved elementary perceptual skills. Indeed, he was able to describe perceptual characteristics (e.g., "It's got a bushy tail") of the animals that he did not recognise. Thus, the dissociation in his performance for words and objects could not be ascribed to the presence of super-

added deficits in elementary perception. In patient 8, the severity of atrophy in the anterior temporal lobes was equivalent to that seen in other semantic dementia patients in this study. By contrast, atrophy in the posterior temporal lobes, especially the right, was rated as more severe. It would be reasonable to infer therefore that his disproportionately impaired object knowledge is linked to right posterior temporal atrophy. This inference is in keeping with findings by Tranel, Damasio, and Damasio (1997), which indicated that retrieval of animal knowledge was linked to ventral temporal and occipital regions of the right hemisphere. The observed dissociations in performance for famous faces and names too are in keeping with evidence that has linked knowledge of famous faces and names respectively to the right and left temporal lobe (Tranel et al., 1997; Snowden et al., 2004, 2012; Josephs et al., 2008; Drane et al., 2013; Luzzi et al., 2017).

Performance dissociations for nonverbal and verbal materials are not elicited in all patients with semantic dementia. Nevertheless, the fact that they can occur at all challenges the notion of amodal representation of concepts. As cogently argued by Gainotti (2017), evidence for performance dissociations has led to gradual shifts in the conceptualisation of the hub-and-spoke model of semantic representation of Patterson et al. (2007), with heightened emphasis on the 'spoke' contribution and revision of the notion of amodal representation.

In 2012, Hoffman, Jones, and Lambon Ralph (2012) argued that the semantic deficits in semantic dementia are best explained by a combination of a) degradation of modality-independent conceptual representations, present throughout the disorder and a consequence of atrophy focused on the ventrolateral anterior temporal lobes (i.e., the hub) and b) a later additional deficit for concepts that depend on visual colour/form information, caused by spread of atrophy to posterior ventral temporal regions specialised in representing that visual information. The implication of that argument is that modality-independent conceptual loss is primary and therefore should be present early in the disease whereas material/modality effects are super-added deficits that should occur later. Such an account is at odds with the fact that modality/material effects in semantic dementia, if they occur, are present early rather than late in the course of the disease. Patient 8 is a case in point. He presented to medical attention complaining of problems in face and object recognition. Dissociations between his knowledge of faces/objects and their corresponding names were apparent early in the disease but later they became subsumed by generalised loss of comprehension that cut across all material types and input modalities.

In their most recent formulation of the anterior temporal hub Lambon Ralph and colleagues (Rice et al., 2015; Lambon Ralph et al., 2017) have moved away from the notion of a strictly 'amodal' hub, with equivalence of function between the two hemispheres (Pobric et al., 2010). They refer rather to a 'transmodal' hub in which there is pan-category semantic representation, supported jointly by left and right anterior temporal lobes, but also subtle functional gradations between and within the anterior temporal lobes, which emerge as a consequence of differential connectivity with primary sensory, motor and limbic regions.

The present data suggest that functional differences between the two hemispheres may be substantial rather than subtle. More importantly, if the anterior temporal lobes are so crucial, why in the current study was comprehension of words associated with posterior rather than anterior temporal lobe atrophy?

Some clues may be found from imaging studies of semantic dementia. Structural imaging studies have invariably highlighted prominent atrophy of the anterior temporal lobes, which in most cases in most marked on the left side (Mummery et al., 2000; Rosen et al., 2002; Desgranges et al., 2007; Guo et al., 2013; Collins et al., 2017). Functional imaging studies have commonly shown more extensive abnormalities. An early positron emission tomography (PET) study of semantic dementia (Mummery et al., 1999) showed functional changes in posterior temporal cortex, whereas structural changes were confined to the anterior temporal lobe. Similarly, a more recent study (Guo et al., 2013) showed that patients with focal anterior temporal degeneration also had physiological deficits outside the anterior temporal lobe, which correlated with scores on semantic tasks. Studies of white matter connectivity in semantic dementia, using diffusion tensor imaging-based tractography (Whitwell et al., 2010; Acosta-Cabronero et al., 2011; Agosta et al., 2010, 2013; Collins et al., 2017), have provided evidence of extensive loss of white matter connectivity from ventrorostral temporal lobes, affecting uncinate and inferior longitudinal fasciculus and including pathways to the supramarginal gyrus and the posterior superior temporal gyrus, classical language areas. The imaging findings have been interpreted (Acosta-Cabronero et al., 2011) in terms of degeneration of axons whose cell bodies arise in the anterior temporal lobe and project to posterior cortical regions including classical language areas. Interestingly, Acosta-Cabronero et al. found that inferior longitudinal fasciculus involvement, viewed as a conduit for visual object information, was restricted to rostral temporal regions and did not extend caudally into the occipital lobes. They interpreted the findings as evidence of preservation of feed-forward inferior longitudinal fasciculus fibres (and hence visual information), compatible with the notion of a failure, in semantic dementia, of integration of elements into a semantic concept and consistent with a putative semantic hub. Agosta et al. (2010) showed more extensive involvement of the inferior longitudinal fasciculus, perhaps reflecting more severe semantic impairment in their patients. The studies are, however, difficult to compare because of differences in image analysis methodology.

Collins et al. (2017) showed the left temporal pole to be the site of maximal atrophy, the magnitude of atrophy in other brain regions being predicted by the strength of functional connectivity of those regions to the temporopolar seed region, as determined by connectivity data from healthy adults. The findings of Collins et al. provided support for the view that degenerative change in semantic dementia follows connectional pathways within a large-scale network that converges on the temporal pole.

Pathological studies of semantic dementia provide findings complementary to the imaging data. Semantic dementia is associated with a distinct and unique form of pathology

(Josephs et al., 2011; Snowden et al., 2011). As in many cases of behavioural variant frontotemporal dementia (bvFTD) the pathological protein is TDP-43. Yet, in contrast to bvFTD, where the predominant pathological changes occur within the cell body, in semantic dementia the predominant changes are in the connections between neurones. The pathology, referred to as TDP-43 type C in contemporary pathological nomenclature (Mackenzie et al., 2011), is characterised by numerous elongated dystrophic neurites, which traverse the entire depth of the cerebral cortical ribbon. The pathological profile is consistent with damage to cortical connections that originate in the anterior temporal lobes (Mann & Snowden, 2017).

From a clinical perspective, a striking feature of semantic dementia patients is that they come to medical attention relatively late in the course of their disease. Most patients, at the time of their initial referral, score at or close to floor level performance on the Graded Naming test. Most already show striking anterior temporal lobe atrophy. These factors suggest that the degenerative process is likely to have begun some time, possibly a number of years, prior to the time of patients' clinical presentation. Thus, whilst the anterior temporal lobes are indisputably the primary site of pathology it does not necessarily follow that damage to those regions is sufficient to account for patients' semantic impairment. Arguably, it is only when the pathology has evolved sufficiently to result in widespread secondary disruption of function of ventral pathways that the profound semantic loss characteristic of semantic dementia becomes apparent. Such an argument would be consistent with findings reported by others of the critical role of white matter tracts in semantic processing (Duffau et al., 2005; Han et al., 2013). The study by Han et al. (2013), involving patients with various forms of brain pathology, showed significant correlations between semantic impairments and lesion volume and fractional anisotropy value of the left inferior fronto-occipital fasciculus, left anterior thalamic radiation and left uncinate fasciculus.

A central argument originally advanced for an amodal hub (Patterson et al., 2007) was the need to abstract away from surface features and generalise across concepts. Gainotti (2017) has highlighted the possibility that this capacity to generalise might be due more to language functions and language derived encyclopaedic information than the format of representations in the semantic hub.

Hitherto, a challenging question has been why the semantic impairment in semantic dementia is so profound and pervasive whilst non-degenerative lesions of the anterior temporal lobes give rise to subtle semantic deficits at most. The bilateral nature of semantic dementia is likely to be important. However, it can also be argued that the magnitude of conceptual loss is tied to the fact that semantic dementia uniquely damages connectional pathways that link anterior temporal lobes to other parts of the brain. The anterior temporal lobes may be important in so far as they are a site of rich connectivity, or areas of convergence, from which the pathological changes of semantic dementia can spread, but, damage to the anterior temporal lobes, in isolation, may be insufficient to cause widespread semantic loss. The data highlight both the importance of posterior temporal regions in conceptual understanding and the differential roles of the two hemispheres in semantic processing.

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