doi:10.1093/brain/awl344 *Brain* (2007), **130**, 1138–1147

Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia

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Both herpes simplex virus encephalitis (HSVE) and semantic dementia (SD) typically affect anterior temporal lobe structures. Using voxel-based morphometry (VBM), this study compared the structural damage in four HSVE patients having a semantic deficit particularly affecting knowledge of living things and six SD patients with semantic impairment across all categories tested. Each patient was assessed relative to a group of control subjects. In both patient groups, left anterior temporal damage extended into the amygdala. In patients with HSVE, extensive grey matter loss was observed predominantly in the medial parts of the anterior temporal cortices bilaterally in SD patients the abnormalities extended more laterally and posteriorly in either the left, right or both temporal lobes. Based on a lesion deficit rationale and converging results from several other sources of evidence, we suggest that (i) antero-medial temporal cortex may be important for processing and differentiating between concepts that are 'tightly packed' in semantic space, such as living things, whereas (ii) inferolateral temporal cortex may play a more general role within the semantic system.

Keywords: structural imaging; brain behaviour and relationships; lesion studies; semantic memory; semantic memory disorders

Abbreviations: HSVE = herpes simplex virus encephaltits; SD = semantic dementia; VBM = voxel-based morphometry

Received June 23, 2006. Revised November 6, 2006. Accepted November 13, 2006. Advance Access publication January 24, 2007

Introduction

Semantic dementia (SD) and herpes simplex virus encephalitis (HSVE) are two diseases that affect anterior temporal lobe structures, causing severe impairments of declarative memory functions but with rather differing typical profiles.

SD, also known as the temporal variant of frontotemporal dementia, is characterized by progressive deterioration of conceptual knowledge (Snowden *et al.*, 1989). This deterioration typically applies irrespective of stimulus material (i.e. verbal versus non-verbal), modality of the stimulus (e.g. auditory versus visual) or modality of the required response (e.g. object naming versus object drawing versus object use) (Bozeat *et al.*, 2000; Rogers *et al.*, 2004). The language pattern in SD patients consists of impaired comprehension, profound anomia and speech that is empty of content but fluent, with relatively preserved syntax and prosody. The non-verbal semantic deficits in SD can be more subtle, at least early in the course of the disease; but when the patients are assessed with sensitive test materials, they reveal a consistent pattern of difficulty with recognizing/'understanding' objects and faces (Patterson *et al.*, 2006; Snowden *et al.*, 2004). Although new learning/episodic memory in SD cannot be described as normal, it is relatively preserved at least for certain types of material (Graham *et al.*, 2000; Simons *et al.*, 2001), and the patients most definitely do not have an amnesic syndrome (Warrington, 1975). The pathological basis in the majority of the cases is frontotemporal degeneration with the ubiquitin-positive inclusions that are typically found in motor-neuron disease (Davies *et al.*, 2005). A series of structural imaging studies has identified atrophy that is

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bilateral but often particularly pronounced in the left hemisphere, encompassing the temporal pole, the inferior/middle temporal and fusiform gyri, the amygdaloid complex and sometimes the ventromedial frontal cortex (Levy *et al.*, 2004; Mummery *et al.*, 2000; Rosen *et al.*, 2002). Using fluid registration, longitudinal studies have demonstrated that grey matter atrophy spreads from a left anterior temporal focus both anteriorly and posteriorly with progressive involvement of the right hemisphere (Whitwell *et al.*, 2004). Using volumetric methods, two studies have also reported hippocampal involvement (Chan *et al.*, 2001; Galton *et al.*, 2001). Similarly, functional studies have demonstrated hypometabolism in the anterior temporal lobes spreading posteriorly (Diehl *et al.*, 2004) and extending into the hippocampus (Nestor *et al.*, 2006).

HSVE is the most common viral encephalitis in humans (Kennedy and Chaudhuri, 2002). Pathological and structural imaging studies have demonstrated damage in a widespread temporo–limbic–diencephalic system encompassing the amygdala, hippocampus, peri-/entorhinal, parahippocampal and orbitofrontal cortex, insula and cingulate gyri (Gitelman *et al.*, 2001). The long-term neuropsychology is characterized by dense anterograde amnesia, and sometimes but less commonly by impairments of semantic memory and/or executive functions (Kapur *et al.*, 1994). Importantly, whilst the diagnosis of SD is based on both anterior temporal lobe atrophy and progressive semantic impairments, diagnosis of HSVE is based on positive virology irrespective of the cognitive consequences.

SD has often been described as involving primarily antero-lateral temporal damage and mainly semantic-memory impairment, whereas HSVE has been said to entail primarily antero-medial temporal damage and mainly episodic-memory impairment. This contrast has led at least one group of researchers (Levy *et al.*, 2004) to conclude that medial temporal lobe structures support formation of declarative (particularly episodic) memory while lateral temporal lobe structures underpin representation of semantic knowledge. This conclusion, however, was based on qualitatively descriptive methods rather than standardized quantitative procedures that would enable a direct comparison of the lesion extents. Indeed, this double dissociation between medial and lateral temporal lobe remains disputed in the literature. Thus, other studies have demonstrated a correlation between semantic knowledge and volume of the perirhinal cortex and implicated medial temporal lobe structures in semantic knowledge (Davies *et al.*, 2004). It should be noted that human perirhinal cortex has a complex anatomy: it occupies the banks of the collateral sulcus and medial aspect of the temporal lobe but, because it is cytoarchitectonically continuous with temporopolar cortex, these two areas should probably be considered as part of the same cortical region in terms of connectivity (Hodges *et al.*, 2006; Insausti *et al.*, 1998).

The present study takes a different perspective and compares SD and HSVE patients to gain insight into the organization of semantic memory. Using a lesion-deficit approach, we asked whether different regions of the temporal lobe were associated with distinct types or qualities of semantic information. In particular, as is often the case following HSVE (Gainotti *et al.*, 1995; Capitani *et al.*, 2003; Warrington and Shallice, 1984; Laiacona *et al.*, 2003), the encephalitic patients in this study had a 'category-specific' pattern characterized by a semantic deficit for concepts from the domain of living things, with relative sparing of non-living items or artefacts. In contrast, as is typically the case (Bozeat *et al.*, 2000; Lambon-Ralph *et al.*, 2003; Moss *et al.*, 2005), the SD patients studied here exhibited a non-category-specific semantic impairment affecting both living things and artefacts. Hence, relating the lesions in HSVE and SD patients to their distinct patterns of semantic disorder might provide insight into the neural organization of semantic memory. In order to achieve quantitative characterization of the lesion patterns in SD and HSVE patients, we combined structural imaging with voxel-based morphometry, a whole-brain unbiased objective technique that tests for regional changes in grey (or white) matter volume (Ashburner and Friston, 2000, 2003).

Material and methods

Subjects

Four patients with a history of HSVE, six patients with a diagnosis of SD and 89 control subjects participated in this study. The diagnosis of HSVE was based on standard measures including EEG, neuroimaging and virology. The diagnosis of SD was based on the currently accepted criteria including anomia and semantic impairments. The control subjects were divided into 10 groups with each assigned to one particular patient. This procedure allowed us to match the control group to the patient imaging data with respect to age and gender. Furthermore, it enabled us to make inferences about regionally specific effects that were common to all patients, as each comparison (patients versus control group) was based on independent data. Table 1 presents demographic information and background neuropsychological test scores for the patients individually and for a group of control participants from the participant panel at the MRC Cognition and Brain Sciences Unit.

MRI scanning

Whole brain structural images were acquired from all participants using a 2 T MRI scanner (Magnetom Vision; Siemens, Erlangen, Germany). Two different T_1-weighted scanning sequences (voxel size: $1 \times 1 \times 1.5$–3) were used for HSVE, SD patients and control groups [for further details, *see* Mummery *et al.* (2000) and Gitelman *et al.* (2001)].

Data preprocessing

All image processing and statistical analyses were performed in SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). The images were preprocessed according to the optimized VBM protocol (Good *et al.*, 2001). This involved initial affine registration and segmentation. The structural images were then spatially normalized into standard MNI space using normalization

Table 1

Patient	JBR	JH	RC	YW	DBM	GCB	MJ	DG	JH	MS	Control mean
Disease	HSVE	HSVE	HSVE	HSVE	SD	SD	SD	SD	SD	SD	NA
Age (years)	48	38	43	60	59	59	61	63	59	66	68.5
Sex	M	F	M	F	M	F	F	F	F	F	18 F, 13 M
Test											
MMSE (30)	23	21	24	28	29	25	20	20	24	13	28.8
Digit span forwards	5	NT	NT	6	8	6	6	5	6	6	7
Recognition memory test											
Words	NT	NT	NT	0.50	NT	0.88	NT	0.56	0.60	0.72	0.98
Faces	NT	NT	0.44	0.44	NT	0.80	NT	0.54	0.72	0.72	0.98
Rey complex figure											
Copy	1.00	NT	0.88	0.78	0.94	0.94	0.86	0.71	0.89	0.60	0.95
Delayed recall	0.15	NT	0.00	NT	0.43	0.56	0.19	0.14	0.40	0.23	0.53
VOSP											
Cubes	NT	NT	0.90	NT	NT	1.00	1.00	1.00	1.00	NT	0.93
Position discrimination	NT	NT	1.00	NT	NT	1.00	1.00	0.95	1.00	NT	0.99
Pyramids and palmtrees											
Words	0.81	0.88	0.75	0.89	0.94	0.69	0.75	0.56	0.62	0.75	0.98
Pictures	0.85	0.87	0.73	0.85	0.94	0.85	0.71	0.40	0.71	0.69	0.98
Letter fluency											
F	8	8	9	16	12	4	4	4	7	5	14
S	9	7	11	15	13	4	9	6	5	8	14
Letter total	17	15	20	31	25	8	13	10	12	13	28
Category fluency											
Animals	7	6	3	19	13	2	NT	6	5	4	18
Vehicles	10	6	4	9	6	2	NT	2	5	0	12
Fruit	3	8	3	12	NT	6	5	1	5	2	15
Category total	20	20	10	40		10		9	15	6	45

parameters that were estimated by matching the grey (or white) matter images of each individual to a grey (or white) matter template. Each normalized anatomical scan was segmented (i.e. partitioned into different tissue classes such as grey matter, white matter and CSF) using mixture model cluster analysis techniques. However, warping images to match a template inevitably introduces volumetric differences into the images. For instance, if a subject's brain region has half of the volume of that of the template, then its volume (i.e. voxels labelled as grey matter) will be doubled during spatial normalization. To remove this confound, the ensuing grey (or white) matter images were multiplied by the Jacobian determinants of the deformation fields defined during normalization (Ashburner and Friston, 2003; Attias, 2000). In other words, the spatially normalized grey (or white) matter image intensities were scaled by the amount of contraction and expansion applied during spatial normalization. This adjustment procedure allowed us to compare the absolute amount of grey matter in a particular region rather than its relative concentration. Finally, the images were smoothed using a 12-mm isotropic Gaussian kernel to enable parametric statistics with individual subjects.

Statistical analysis

The segmented grey (or white) matter images were entered into a regression analysis that modelled each patient and control group separately (i.e. 10 patients + 10 control groups) (Friston *et al.*, 1995). In addition, approximate age, gender and global grey (or white) matter values were entered as covariates of no interest. Our statistical analysis tested for the following effects in grey (or white) matter volume:

(i) Decreased for all patients relative to controls. To ensure that the effect was commonly observed for all patients, the main effect (patients < controls) was inclusively masked with 10 contrasts that compared each individual patient to his/her respective control group (single patient < single control group).

(ii) Decreased for all HSVE patients relative to SD patients. To account for the differences in MRI sequence, this analysis involved testing for the interaction (all HSVE patients < HSVE control groups) < (all SD patients < SD control groups). To ensure that the effect was commonly observed for all HSVE patients, the interaction effect was inclusively masked with four contrasts that compared each individual HSVE patient to his/her respective control group (single HSVE patient < single HSVE control group).

(iii) Decreased for SD patients relative to HSVE patients. To account for the differences in MRI sequence this involved testing for the interaction (all SD patients < SD control groups) < (all HSVE patients < HSVE control groups). To ensure that the effect was commonly observed for all SD patients, the interaction effect was inclusively masked with six contrasts that compared each individual SD patient to his/her respective control group (single SD patient < single SD control group). The six SD patients could be classified into two subgroups: five SD patients with left > right atrophy and one SD patient with right > left temporal atrophy. Therefore, we have also separately

masked for these two subgroups. To fully characterize the three different effects described earlier, we also identified:

(iv) Decreased for all HSVE patients relative to controls. To ensure that the effect was commonly observed for all patients, the main effect (HSVE < controls) was inclusively masked with four contrasts that compared each individual patient to his/her respective control group (single HSVE < single control group).

(v) Decreased for all SD patients relative to controls. To ensure that the effect was commonly observed for all patients, the main effect (SD < controls) was inclusively masked with six contrasts that compared each individual patient to his/her respective control group (single SD < single control group).

(vi) The direct comparison of all six SD patients with all four HSVE patients.

Statistical threshold

Unless otherwise stated, we report grey (or white) matter volume changes at $P < 0.05$ corrected for the entire brain using extent thresholds of >0 voxels for grey matter and > 100 voxels for white matter in the tables and the text. To provide a more detailed characterization of the white matter damage, an extent threshold of > 0 voxels was used in all the figures. The inclusive masks were applied at $P < 0.05$ uncorrrected. The inclusive masking option was used to identify grey (or white) matter differences that were commonly observed in all patients within a group. This procedure enabled us to remove non-systematic artefacts that may result from normalizing and segmenting lesioned brains. To assign the anatomic differences to the proper structure and ensure that the observed effects were due to differences in grey (or white) matter rather than registration and misclassification (e.g. displacement) errors, we referenced them to visual inspection of each patient's brain. We only interpret and discuss those effects that qualified as differences in grey (or white) matter *per se* according to visual inspection.

Results

Behavioural results

Table 2 displays scores (in proportion correct) for each individual patient and as averages for each patient group on two different semantic measures: picture naming and word–picture matching. These two tests, from the Cambridge semantic battery (Bozeat *et al.*, 2000), include the same 64 items, and in each case consist of 32 natural kinds or living things (from the subcategories of animals, birds and fruits) and 32 non-living things or artefacts (subcategories: household items, vehicles and tools). For naming, the patient is presented with each line drawing individually and asked to name it; for each item in the word–picture matching test, the patient hears the name of a target picture in conjunction with a visual array of 10 pictures (the target and nine other items from the same category) and is asked to point to the target. Previous studies in Cambridge with these test materials (Bozeat *et al.*, 2000) have established that normal controls in the age range of the SD patients score essentially at ceiling on both naming (mean = 62.3/64, SD = 1.6) and word–picture matching (mean = 63.7/64, SD = 0.5).

In an assessment of performance accuracy for the patients in the current study, a three-way ANOVA with patient group (HSVE versus SD), semantic category (living versus non-living) and task (naming versus word–picture matching) identified main effects of task and category but no main effect of patient group after Greenhouse–Geisser correction: the patients were more successful at word–picture matching than naming [$F(1,8) = 29.3$; $P < 0.001$]; this effect was consistently observed for both HSVE [$F(1,3) = 17.3$; $P < 0.05$] and SD [$F(1,5) = 21.7$; $P < 0.01$] groups. Furthermore, performance was better on artefacts than living things [$F(1,8) = 37.5$; $P < 0.01$]. Most importantly, a significant interaction between patient group and semantic category [$F(1,8) = 23.2$; $P < 0.01$] was identified, with a much bigger artefact > living advantage for HSVE than SD. Thus, repeated measurement ANOVA performed separately for each subject group revealed an effect of semantic category only for the HSVE group [$F(1,3) = 23.1$; $P < 0.05$].

Voxel-based morphometry results

Grey matter volume

(i) Decreased for all patients relative to controls: the left anterior temporal lobe, extending into the amygdala and insula, and the caudate nucleus showed decreased grey matter volume for all HSVE and SD patients relative to their control groups (*see* Fig. 3 for consistency across subjects).

(ii) Decreased for all HSVE relative to SD: decreased gray matter volume for the HSVE patients relative to both their control group and SD patients was observed predominantly in the medial parts of the anterior temporal cortices bilaterally.

Table 2 Behavioural data for HSVE and SD patients: proportion correct on naming and word–picture matching for a common set of 64 items, half living or natural kinds (e.g. *rabbit*, *strawberry*) and half non-living or artefacts (e.g. *train*, *watering-can*)

Patient	Disease	Naming		Word–picture matching	
		Living	Non-living	Living	Non-living
JBR	HSVE	0.16	0.63	0.31	0.97
JH	HSVE	0.53	0.72	0.63	0.97
RC	HSVE	0.22	0.66	0.38	0.88
YW	HSVE	0.59	0.84	0.66	0.88
Mean		0.38	0.71	0.49	0.92
DBM	SD	0.75	0.66	0.92	1.00
GCB	SD	0.41	0.44	0.69	0.63
MJ	SD	0.16	0.13	0.63	0.81
DG	SD	0.16	0.31	0.34	0.44
JH	SD	0.13	0.16	0.25	0.41
MS	SD	0.06	0.06	0.42	0.42
Mean		0.28	0.29	0.54	0.62

(iii) Decreased for SD patients relative to HSVE: decreased grey matter was observed common to all SD patients in the right lateral inferior temporal lobe. Masking with the five left > right atrophy SD patients relative to their control group revealed decreased grey matter volume in the left inferior temporal gyrus. Likewise, masking with the one right > left atrophy SD case relative to her control group produced decreased grey matter volume in the right inferior temporal gyrus (limited to one single voxel). Therefore, in SD patients relative to HSVE patients, damage spreads more posteriorly and involves lateral inferior temporal areas that can be detected on the left or right depending on the balance of left/right atrophy in the individual patient.

Direct comparisons between HSVE and SD patients yielded equivalent results to the interactions (ii) and (iii), indicating that the statistical differences are due to differences between the patients groups rather than differences between control groups (i.e. scanning sequences). The top row of Fig. 1 shows effects that were (iv) decreased for all HSVE patients relative to controls and (v) decreased for all SD patients relative to controls (Table 3).

White matter volume

(i) Decreased for all patients relative to controls: the left and right anterior temporal lobes showed decreased white matter volume for all HSVE and SD patients relative to their control groups.

(ii) Decreased for all HSVE relative to SD: decreased white matter volume for the HSVE patients relative to both their control group and SD patients was observed predominantly in the anterior parts of the temporal lobes bilaterally.

(iii) Decreased for SD relative to HSVE: no significant effects emerged even when using a liberal extent threshold of > 0 voxel. This was true when (a) all SD patients were included, (b) only the left > right SD patients were included or (c) only the right > left SD patient was included.

Direct comparisons between HSVE and SD patients yielded equivalent results to the interactions reported in (ii) and (iii), indicating that the statistical differences are due to differences between the patient groups rather than differences between control groups (i.e. scanning sequences). See Fig. 1 (bottom row) for (4) decreased for all HSVE patients relative to controls and (5) decreased for all SD patients relative to controls (Table 4).

Discussion

This study used voxel-based morphometry to compare the pattern of brain damage in patients with SD and HSVE. We first established different types of semantic memory deficit

Table 3 Differences in grey matter volume for the six SD and four HSVE patients

Regions	Coordinates	*Z*-score
Decreased for HSVE and SD relative to controls (masked inclusively with individual patient < control)		
L. temporal pole	−45 15 −23	> 8
	−44 −8 −44	> 8
	−51 8 −39	7.7
Caudate nucleus[a]	−8 15 0	> 8
Decreased for HSVE relative to SD (masked inclusively with individual HSVE < control)		
R. anterior medial temporal cortex (extending into temporal pole)	27 8 −41	> 8
L. anterior inferior temporal cortex (extending into insula)	−23 −3 −35	6.0
	−33 11 −17	5.6
	−39 −5 −48	4.4
L. post hippocampus/isthmus[a]	−23 −38 0	4.7
R. post hippocampus/isthmus[a]	24 −35 −2	7.0
Orbitofrontal cortex[a]	5 27 −29	6.9
	−2 23 −23	4.3
Subcallosal gyrus/caudate nucleus[a]	9 18 −3	> 8
Thalamus[a]	5 −12 11	5.0
Decreased for SD relative to HSVE (masked inclusively with all individual SD < control)		
R. middle/inferior temporal gyrus	50 −26 −21	4.4
Decreased for SD relative to HSVE (masked inclusively with five 'left > right' SD < control)		
L. middle/inferior temporal gyrus	−51 −24 −18	7.1
R. middle/inferior temporal gyrus	50 −26 −21	4.7
Decreased for SD relative to HSVE (masked inclusively with one 'right > left' individual SD < control)		
R. middle/inferior temporal gyrus	51 −30 −17	5.2
	51 −18 −21	4.4

[a]Anatomical structure is not clearly identifiable on visual inspection.

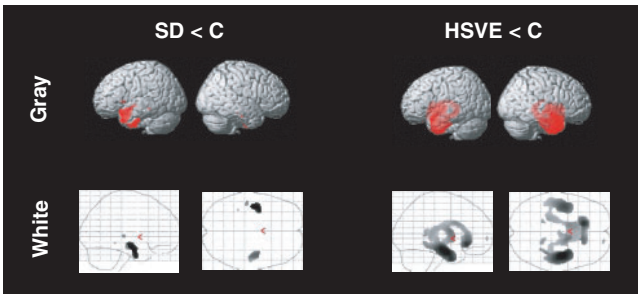

Fig. 1 Grey and white matter volume changes for HSVE and SD patients relative to controls. *Left*: SD patients < controls. Height threshold: $P < 0.05$ corrected, masked with each individual SD patient < control group at $P < 0.05$ uncorrected. *Right*: HSVE patients < controls; height threshold: $P < 0.05$ corrected, masked with each individual HSVE patient < control group at $P < 0.05$ uncorrected. *Top*: grey matter volume differences rendered on a template of the whole brain. *Bottom*: white matter volume differences shown as maximum intensity projections in sagittal and transverse glass brain views. C: controls, SD: semantic dementia, HSVE: herpes encephalitis patients.

Table 4 Differences in white matter volume for the six SD and four HSVE patients

Regions	Coordinates	Z-score
Decreased for HSVE and SD relative to controls (masked inclusively with individual patient < control)		
R. ant. temporal lobe	41 −8 −21	> 8
L. ant. temporal lobe	−41 −3 −30	> 8
Decreased for HSVE relative to SD (masked inclusively with individual HSVE < control)		
L. medial orbitofrontal	−14 27 −11	> 8
R. medial orbitofrontal	14 26 −12	7.6
R. ant. temporal lobe	45 −11 −26	> 8
L. ant. temporal lobe	−47 −11 −32	5.4
R. capsula interna	11 5 0	6.2
Corpus callosum	−8 6 29	5.3
Decreased for SD relative to HSVE (masked inclusively with all, five 'left > right' SD < control, one right > left individual SD < control) None		

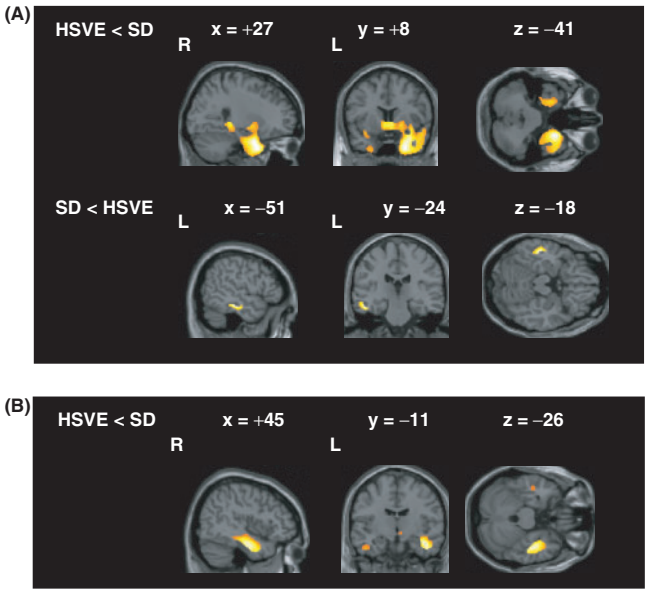

Fig. 2 **(A)** Grey matter volume differences presented on sagittal, coronal and axial sections of a canonical brain. *Top*: HSVE patients < SD patients (interaction); height threshold: $P < 0.05$ corrected, masked with each individual HSVE patient < control group at $P < 0.05$ uncorrected. *Bottom*: SD patients < HSVE patients (interaction). Height threshold: $P < 0.05$ corrected, masked with each individual SD patient < control group at $P < 0.05$ uncorrected. **(B)** White matter volume differences presented on sagittal, coronal and axial sections of a canonical brain. HSVE patients < SD patients (interaction); height threshold: $P < 0.05$ corrected, masked with each individual HSVE patient < control group at $P < 0.05$ uncorrected. C: controls, SD: semantic dementia, HSVE: herpes encephalitis patients

in the two groups: all of the HSVE patients showed a notably category-selective pattern with substantially greater impairment for living things than artefacts in both naming and comprehension; in contrast, all of the SD patients had severe semantic deficits that were of roughly equal magnitude for the two types of concepts, on both production and comprehension tests. We then measured the lesion extents in the HSVE and SD individuals and groups, and related these to the distinct cognitive patterns, in an attempt to gain some insight into the neuroanatomical structure of semantic memory.

Both patient groups, relative to controls, consistently showed reduced grey matter volume in the left anterior temporal lobe extending into the amygdala. Regional volume loss selective or increased for the HSVE patients was observed predominantly in the medial parts of the anterior temporal cortices bilaterally. Regional volume loss selective for the SD patients occurred in the inferior temporal gyri, spreading laterally and posteriorly from the pole, although the extent to which this effect applied to left versus right temporal lobe depended on the patient (Fig. 2).

As usual, lesion extent and location varied considerably across patients, even within the SD and HSVE groups. Nevertheless, assuming a consistent functional neuroanatomy across subjects, it seems reasonable to draw a number of tentative conclusions. We will first discuss the conclusions relating to a category-selective organization of semantic memory and then turn to the neuroanatomy of general semantic functions.

Category-selective organization of semantic memory

The anterior and medial left temporal areas that were highly abnormal in both HSVE and SD patients may be particularly important for semantic knowledge of living items. This is probably not specifically because these concepts have the semantic feature + *living*. Instead, it is more likely to be due to the type of processing required by living items. It has been proposed that living things (or more generally, natural kinds) are characterized by many shared and highly intercorrelated features with relatively few distinctive features (McRae *et al.*, 1997; Randall *et al.*, 2004; Rogers *et al.*, 2004; Tyler *et al.*, 2000). This difference between living things and artefacts is particularly salient at the 'basic' level, which is the conceptual level tested in the behavioural assessments of naming and word–picture matching used in the current study. Basic level refers to names and concepts like *dog* or *car*: at this level, two animal concepts (such as *dog* and *goat*) typically have more features in common than, for example, two vehicle concepts (such as *car* and *aeroplane*). Concepts that are more tightly packed in semantic space, like basic-level living things, place increased demands on identification and differentiation processes at the level of both semantic and perceptual processing during object recognition (Ikeda *et al.*, 2006; Moss *et al.*, 2005; Tyler and Moss, 2001; Tyler *et al.*, 2004).

Alternatively or additionally, it has been suggested that living items are primarily characterized by sensory features that may be supported by the anterior temporal lobe (Farah and McClelland, 1991; Shallice, 1988; Warrington

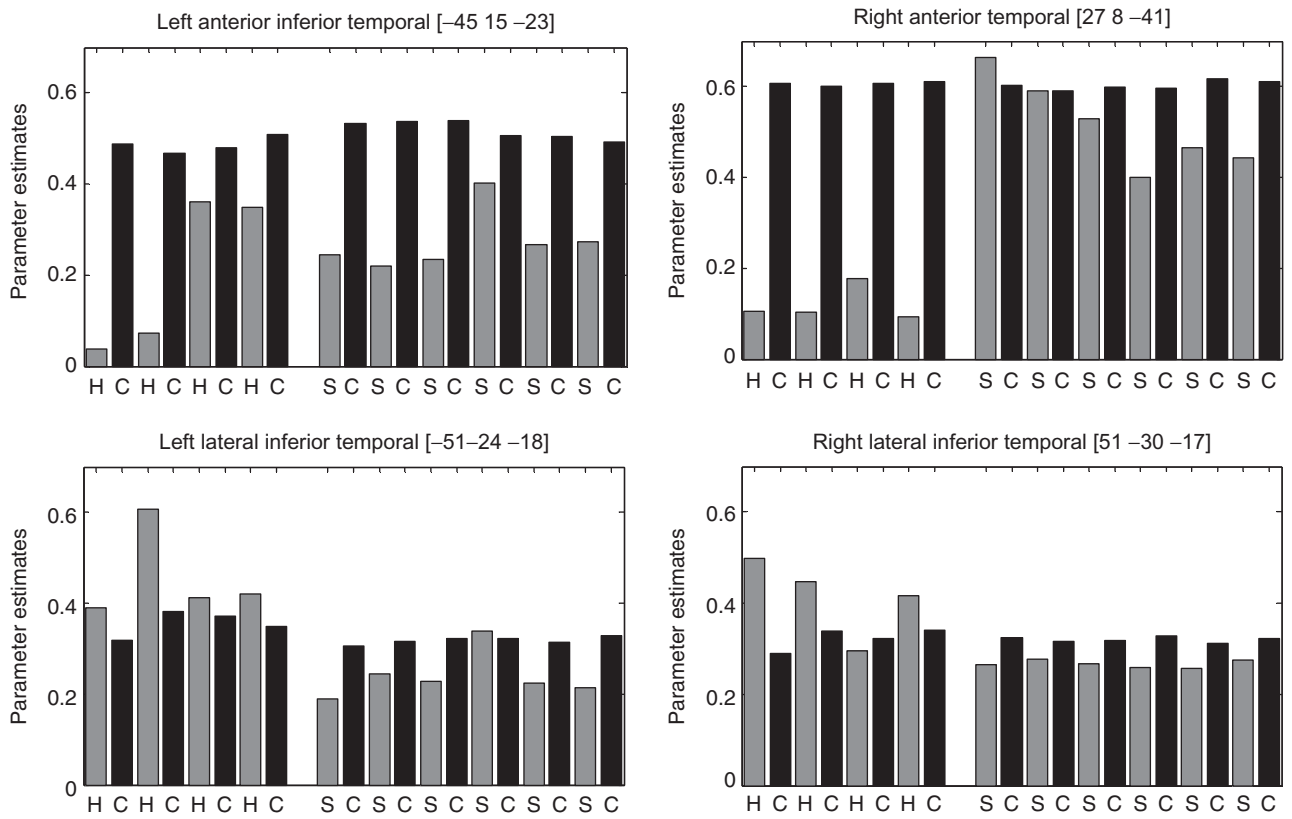

Fig. 3 Parameter estimates for grey matter values of HSVE (H, grey) or SD (S, grey) patients and control (C, black). The bar graphs represent the size of the effect in non-dimensional units (corresponding to % whole brain mean).

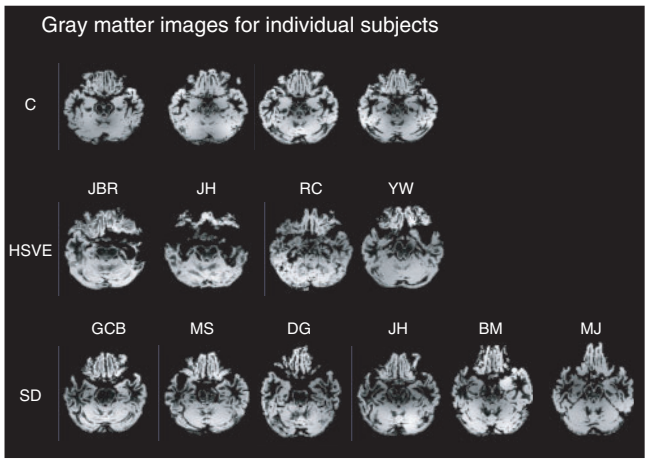

Fig. 4 Axial sections of grey matter images for individual subjects. C: controls, HSVE: herpes encephalitis, SD: semantic dementia.

and Shallice, 1984). Selective deficits for living items, however, have only rarely been associated with semantic impairments on sensory properties (De Renzi and Luchelli, 1994; Gainotti and Silveri, 1996; Forde *et al.*, 1997; Hart and Gordon, 1992). Similarly, functional imaging studies have only inconsistently shown anterior temporal activations selectively for semantic retrieval of sensory properties (e.g. colour, form) (Chao and Martin, 1999; Martin *et al.*, 1995; Mummery *et al.*, 1998; Noppeney and Price, 2002*b*, 2003; Pulvermuller and Hauk, 2006; Wiggs *et al.*, 1999; Thompson-Schill *et al.*, 1999; Noppeney and Price, 2003).

The results presented here converge with at least four other lines of evidence to suggest that the left temporal pole plus anteromedial temporal regions on the left are particularly implicated in detailed semantic identification and differentiation: (i) lesions to perirhinal cortex in non-human primates disrupt object recognition, especially in tasks requiring discrimination between highly similar exemplars (Buckley and Gaffan, 2006; Buckley *et al.*, 2001; Murray and Richmond, 2001; Murray and Bussey, 1999). (ii) Several functional imaging studies of semantic memory in normal human participants have demonstrated activation in the left anteromedial temporal lobe or temporal pole, again particularly when the concepts to be processed/differentiated have considerable semantic overlap (Moss *et al.*, 2005; Rogers *et al.*, 2006; Tyler *et al.*, 2004). (iii) Studies of semantic memory in SD patients with relatively selective atrophy to these regions consistently demonstrate that, amidst difficulty in all semantic tasks, the patients are most impaired when the task requires the kind of specific semantic knowledge necessary to differentiate similar objects (Hodges *et al.*, 1995; Warrington, 1975). (iv)

Identification of people from their faces is probably a supreme example of the kind of semantic task requiring such fine differentiation; this ability (a) is typically devastated in both HSVE and SD (Snowden *et al.*, 2004; Tranel *et al.*, 1997), and (b) results in anterior temporal activation in functional imaging studies of normal participants (Damasio *et al.*, 1996; Gorno-Tempini *et al.*, 1998; Grabowski *et al.*, 2001; Rotshtein *et al.*, 2005).

The association of the anteromedial temporal lobes with the recognition of living things more than artefacts is consistent with functional neuroimaging evidence (Devlin *et al.*, 2002; Moss *et al.*, 2005). It is perhaps surprising that the semantic advantage for artefacts > natural kinds has not been observed more frequently in SD. The literature contains two reports of SD patients who did demonstrate this pattern (Barbarotto *et al.*, 1995; Lambon-Ralph *et al.*, 2003), and it is possibly worth noting that both of these cases had right > left temporal atrophy, like DG (Table 2) who probably came the closest of any SD patient in the current study to a degree (though non-significant) of this category differential (Fig. 4). The anteromedial focus of damage observed in HSVE in association with a living-things deficit might predict the observation of this behavioural phenomenon in early-stage SD if atrophy were limited to the medial temporal lobes (Brambati *et al.*, 2006). If atrophy starts more laterally before spreading to the medial temporal lobe structures, however, then we would predict a parallel degradation of conceptual knowledge even in the early stages, as is typical in SD.

The neural basis of semantic retrieval

The more widespread lateral inferior temporal lobe abnormalities in SD compared to HSVE may indicate the importance of this larger temporal region in semantic processing more generally. Inferior temporal together with frontal activation is frequently reported during semantic retrieval or naming tasks in functional imaging studies (Vandenberghe *et al.*, 1996; Roskies *et al.*, 2001; Noppeney and Price, 2002*a*; Sabsevitz *et al.*, 2005; Tranel *et al.*, 2005; Gold *et al.*, 2006). These semantic activations can be observed irrespective of stimulus material (e.g. pictures or words (Vandenberghe, *et al.*, 1996), modality (e.g. sounds or pictures (Buckner *et al.*, 2000; Tranel *et al.*, 2005) or semantic content (Noppeney *et al.*, 2003). Thus, lesion and functional imaging results suggest a more general role for the lateral inferior temporal cortex in semantic processing that may depend on interactions with frontal cortex (Wagner *et al.*, 2001; Gold and Buckner 2002; Noppeney *et al.*, 2004).

Finally, five out of the six SD patients studied here had bilateral anterior temporal damage, consistent with previous claims that semantic memory is underpinned by a bilateral network of regions (Damasio, 1989; Damasio *et al.*, 1996; Hodges *et al.*, 2006). Although unilateral lesions can disrupt some aspects of semantic processing or manipulation (Jefferies and Lambon-Ralph, 2006), damage to one side of the brain—even the left—rarely if ever results in genuinely degraded conceptual knowledge.

Despite their plausibility and support from other lines of evidence, these proposed lesion-deficit or structure–function relationships can only—at this stage of our knowledge—be hypotheses. One important issue challenging the direct comparison of SD and HSVE patients is that their gray-matter losses result from very different pathological processes: neurodegenerative in the former case, viral/inflammatory in the latter. Identical volume loss in SD and HSVE may therefore not be functionally equivalent. Furthermore, the gross temporal lobe distortions in HSVE and SD may lead to some degree of ambiguity when interpreting the statistical comparison between the two patient populations (Gitelman *et al.*, 2001). Thus, decreased regional grey matter volume in the patients may not only be caused by regional grey matter loss *per se*, but also by misclassification errors due to changes in grey matter intensity values or registration difficulties. Nevertheless, the medial temporal and inferior temporal abnormalities identified by our VBM analysis could be referenced consistently to the appropriate anatomical structures in each patient's brain. The consistency of our results with the known histopathology provides further face validity.

It is so rare to find groups of these different patient types tested on the same, or even comparable, assessment measures that we offer our current observations in the hope that this study will be followed by more and better research of a similar kind.

Acknowledgements

This work was funded by the Wellcome Trust. U.N. is supported by the DFG, L.K.T. by the MRC and Newton Trust. We are grateful to Professor John R. Hodges for permission to publish details of these six SD cases, Dr Sharon Davies for help with data for the SD patients and controls and Professor Andrew Mayes for referring the HSVE patients to us.

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