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Semantic dementia and fluent primary progressive aphasia: two sides of the same coin?

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Considerable controversy exists regarding the relationship between semantic dementia (SD) and progressive aphasia. SD patients present with anomia and impaired word comprehension. The widely used consensus criteria also include the need for patients to exhibit associative agnosia and/or prosopagnosia: many authors have used the label SD for patients with non-verbal, as well as verbal, semantic deficits on formal testing even if they recognize the objects and people encountered in everyday life; others interpret the criterion of agnosia to require pervasive recognition impairments affecting daily life. According to this latter view, SD patients have pathology that disrupts both a bilateral ventrotemporal-fusiform network (resulting in agnosia) and the left hemisphere language network (resulting in profound aphasia). These authors suggest that this profile is different to that seen in the fluent form of primary progressive aphasia (fPPA), a neurodegenerative disease primarily affecting language function. We present data on seven patients who met the diagnostic criteria for fPPA. All seven showed deficits relative to matched controls on both verbal and non-verbal measures of semantic memory, and these deficits were modulated by degree of anomia, concept familiarity and item typicality. Voxel-based morphometry revealed reduced grey matter density in the temporal lobes bilaterally (more widespread on the left), with the severity of atrophy in the left inferior temporal lobe being significantly related to performance on both the verbal and non-verbal measures. Together these findings suggest that patients who meet the diagnostic criteria for fPPA, can also meet the diagnostic criteria for early-stage SD provided that the impact of concept familiarity and typicality is taken into account. In addition, these findings support a claim that the patients' deficits on both verbal and non-verbal tasks reflect progressive deterioration of an amodal integrative semantic memory system critically involving the rostral temporal lobes, rather than a combination of atrophy in the left language network and a separate bilateral ventrotemporal-fusiform network.

Keywords: primary progressive aphasia; semantic dementia; semantic memory

Abbreviations: fPPA = fluent form of primary progressive aphasia; SD = semantic dementia

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Introduction

The relationship between the fluent form of primary progressive aphasia (fPPA) and semantic dementia (SD) is a matter of controversy. Both terms have been used to describe a language variant of frontotemporal dementia (FTD). The first cases of this kind, reported by Pick (1892, 1901, 1904), showed a progressive language disturbance associated with atrophy in the left temporal lobe. Scattered cases were reported over subsequent decades (e.g. Thorpe, 1932; Ferrano and Jervis, 1936; Lowenberg *et al.*, 1936, 1939; Neumann, 1949; for review *see* Hodges, 1994) but interest was rekindled by Mesulam's report of 'primary progressive aphasia' in association with focal left perisylvian or temporal lobe atrophy (Mesulam, 1982). This seminal paper was followed by a flood of cases (for review *see* Mesulam and

Weintraub, 1992), and it became clear that PPA can present in both fluent and non-fluent forms. In the former syndrome, speech remains grammatically structured and well articulated but becomes progressively devoid of content words.

In parallel with this focus on PPA, another theme was developing around the same time in research on cognitive disorders associated with neurodegenerative disease: the study of patients described as having a primary progressive deficit in semantic memory (Warrington, 1975; Schwartz *et al.*, 1979). Warrington argued that the progressive anomia observed in these patients was not simply a language deficit but reflected a fundamental loss of semantic memory, affecting object recognition and knowledge as well as word finding and comprehension. The label 'SD' was later introduced following further documentation in these patients of impaired non-verbal conceptual knowledge (semantic memory) as well as anomia (e.g. Snowden *et al.*, 1989, 1996; Hodges *et al.*, 1992, 1994; Neary *et al.*, 1998). The widely quoted 1998 consensus statement (Neary *et al.*, 1998) proposed criteria for SD, which included associative agnosia (difficulty in recognizing/identifying objects) and/or prosopagnosia (difficulty in recognizing/identifying familiar or famous people). As we will argue below, these terms (associative agnosia and prosopagnosia) have created considerable confusion and differences in opinion regarding the status of SD and the relationship between fPPA and SD.

Original descriptions of SD (Warrington, 1975; Snowden *et al.*, 1989; Hodges *et al.*, 1992) concerned patients with advanced disease who had profound deficits in identifying objects. Many recent papers have used the term SD to describe patients with anomia and word comprehension deficits who show deficits on formal tests of non-verbal semantic knowledge but who do not have problems recognizing and using common objects in everyday life (Bozeat *et al.*, 2002*b*; Rogers *et al.*, 2003*a*; Knibb and Hodges, 2005). Mesulam *et al.* (2003) have argued that such patients are better regarded as a subtype of PPA. Whether such cases should be labelled as SD or PPA has implications for both clinical practice and neurocognitive theory. From a practical point of view, consistency of terminology in the literature and consistency of diagnosis in the clinic are of obvious benefit to all concerned. From a theoretical perspective, the two views differ in their assumptions about the neural networks that support language and conceptual knowledge.

The current study was designed to provide further evidence towards understanding whether subtle non-verbal semantic deficits can be found in fPPA and whether such deficits are fundamental to the anomia and reflect, therefore, damage to an amodal semantic system associated with bilateral, though often asymmetric, anterior temporal lobe (ATL) atrophy (for a detailed discussion *see* Patterson and Hodges, 2000; Rogers *et al.*, 2004*a*). We will refer to a positive answer to this question as the single system account of fPPA and SD. In contrast, Mesulam *et al.* (2003) have argued that SD results from a disease process that encompasses two separate neurocognitive networks—a left hemisphere language network and a bilateral fusiform network for face and object recognition—which, though jointly compromised in SD, can also be damaged independently. We will refer to this as the multiple system account of fPPA and SD. By this latter view, patients with fPPA have serious impairments in word finding (and sometimes comprehension as well) without consequential non-verbal deficits, as a consequence of damage to the language network in the left posterior perisylvian area, and/or middle and inferior parts of the left temporal lobe (e.g. Abe *et al.*, 1997; Sonty *et al.*, 2003; Gorno-Tempini *et al.*, 2004). In support of this idea, it is argued that patients with fPPA can typically demonstrate preserved non-verbal recognition of objects and/or people they cannot name (at least within the first two years of illness), through circumlocutions, paraphasias and pantomine. Where other deficits are observed—for instance, on reasoning tasks—these are attributed to the fact that the impaired task normally relies in part on intact language abilities (Mesulam, 2003).

Mesulam *et al.* (2003) stress the critical involvement of the left hemisphere in PPA, and claim that the structural and metabolic state of the right hemisphere may remain in the normal range, especially early in the course of the disease.

At least two factors have probably hindered resolution of this debate. First, patients diagnosed with fPPA versus SD have rarely been tested on the same measures, making it difficult to determine whether apparent differences in patterns of sparing and impairment truly reflect qualitative differences between the two groups, or instead reflect differences in sensitivity across the various measures employed. Second, the precise nature of these non-verbal deficits remains to be clarified. The visual recognition deficits in SD are different from those observed in patients with prosopagnosia and associative agnosia in the context of stroke (e.g. Riddoch and Humphreys, 2003). In particular, on tasks that are either explicitly semantic or are affected by the participant's semantic status, SD performance depends critically upon stimulus characteristics, especially the familiarity, specificity and typicality of the concepts being assessed (e.g. Warrington, 1975; Snowden *et al.*, 1989, 1994, 1996; Bozeat *et al.*, 2002*b*; Rogers *et al.*, 2004*a*; Hodges *et al.*, 2006; Patterson *et al.*, 2006). This is true whether the task is verbal or non-verbal. If assessments include only rather typical and/or familiar objects, concepts or words, SD patients may achieve scores within the normal range (Rogers *et al.*, 2003*a*, 2004*b*). For example, in the non-verbal domain, SD patients typically recognize the faces of their close relatives and other people who are seen frequently, and they can use common everyday objects such as a knife and a fork. These observations suggest that their recognition deficits do not disrupt their daily lives in the manner or magnitude observed in patients with prosopagnosia or object agnosia following posterior hemisphere stroke. In other words, the 'core feature' of agnosia/prosopagnosia in SD applies to less familiar people and objects (e.g. Snowden *et al.*, 1989, 1996; Bozeat *et al.*, 2002*b* and *see* Discussion for more detail).

Table 1 Diagnostic criteria for primary progressive aphasia, adapted from Mesulam (2001)

(1) Insidious onset and gradual progression of word-finding, object–naming, or word comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological testing of language
(2) All limitation of daily living activities can be attributed to the language impairment, for at least 2 years after onset
(3) Intact premorbid language functions (except for developmental dyslexia)
(4) Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits, or sensorimotor dysfunction within the initial 2 years of illness; this criterion can be fulfilled by history, survey of daily living activities, or formal neuropsychological testing
(5) Acalculia and ideomotor apraxia can be present even in the first 2 years. Mild constructional deficits and perseveration (e.g. as assessed by the go no-go task) are also acceptable as long as neither visuospatial deficits nor disinhibition influence daily living activities
(6) Other domains may become affected after the first 2 years, but language remains the most impaired function throughout the course of the illness and deteriorates faster than other affected domains
(7) Absence of 'specific' causes such as stroke or tumour as ascertained by diagnostic neuroimaging

Given these observations, it is difficult to know how to interpret reports of seemingly 'pure' fPPA (e.g. Weintraub *et al.*, 1990; Mesulam and Weintraub, 1992; Weintraub and Mesulam, 1993; Mesulam, 2001, 2003; Mesulam *et al.*, 2003). Do these patients in fact have deficits in non-verbal aspects of semantic memory that do not come to light because the standard tests administered in the clinic are not sensitive to the factors discussed above? Or do such cases truly exemplify degraded language abilities with intact non-verbal recognition and knowledge? Furthermore, what is the distribution of atrophy in such cases, with regard to both left/right and peri-/extra-sylvian regions? To answer these questions, patients meeting the criteria for fPPA must be assessed on verbal and non-verbal tasks known to be sensitive to the impairments observed in SD, and their lesions must be measured with some form of quantitative assessment.

The aim of this study was to determine whether SD and fPPA are best considered the same or separate syndromes, by investigating both behavioural and neuroanatomical profiles in a cohort of patients who met the diagnostic criteria for fPPA. Specifically, we tested three predictions of the multiple-systems account of fPPA and SD: (i) that the deficits of these patients should be primarily in the domain of language, largely sparing non-verbal knowledge; (ii) that these cases should have reduced density of grey matter in the language network, i.e. the left peri-Sylvian temporo-parietal region and adjacent superior temporal gyrus (although the left insula and left inferior frontal region are also part of the language network these are characteristically implicated in non-fPPA rather than fPPA) which in turn should covary with the degree of anomia; and (iii) that, if some of the patients turn out to have a degree of impairment to non-verbal knowledge, this should be linked to bilateral ventro-temporal atrophy.

Material and methods

Participants

Seven newly presenting patients [age mean (range) = 62.8 (57–72) years, education mean (range) = 13 (10–16) years] with progressive anomia were identified by a senior neurologist (J.R.H.) over a 2-year period at the Memory and Cognitive Disorders Clinic at Addenbrooke's Hospital, Cambridge, UK. In addition to a clinical assessment, each patient was given a number of standard psychiatric rating scales to exclude major functional psychiatric disorders such as depression and schizophrenia, as well as MRI scanning and the usual battery of screening blood tests to exclude treatable causes of dementia.

All patients fulfilled previously reported diagnostic criteria for PPA as outlined in Table 1 (Mesulam, 2001). Amongst these criteria, the absence of visual recognition impairments (i.e. non-verbal comprehension impairments) in the first 2 years post-onset is crucial (Mesulam, 2003; Mesulam *et al.*, 2003). Although the precise time of onset is notoriously difficult to ascertain, all testing reported here was performed within 2 years of a patient's first clinic appointment. In addition, all seven patients were reported by family to be recognizing close relatives and using their own everyday objects normally, and generally to be functioning well at home except for anomia and word comprehension deficits. It is important to note that—so long as one is considering common everyday objects and familiar people—these patients did not reach consensus criteria for SD (Neary *et al.*, 1998, p. 1552) as defined by prosopagnosia or associative agnosia '. . . indicated historically by reports of misuse of objects or loss of knowledge of their function . . . demonstrated clinically by patients' reports of a lack of recognition and by their inability to convey the use of an object either verbally or by action pantomime'.

Over the same period we saw eight other newly presenting cases with progressive aphasia who had phonological and/or syntactic deficits and were therefore diagnosed with progressive non-fluent aphasia. Thus the cases included in this study were only those qualifying for a diagnosis of fPPA who presented to our clinic during this 2-year period.

Two groups of normal participants, approximately matched to the patients for age and years of education, were selected from the MRC Cognition and Brain Sciences Unit's volunteer panel. One group (n = 20) was tested on the same general neuropsychological battery reported here [age mean (range) = 71.8 (62–82) years, education mean (range) = 10.8 (9–13) years], and the other group (n = 15) was tested on the experimental measures [age mean (range) = 67.2 (54–80) years, education mean (range) = 11.9 (9–19) years]. MRI scan data from twelve additional controls were included in the voxel-based morphometry analyses [age mean (range) = 65 (55–75) years].

All subjects gave informed consent to participate in the study, according to the Declaration of Helsinki (*BMJ* 1991; 302: 1194), which was approved by the Ethical Committee of Addenbrooke's Hospital, Cambridge.

General neuropsychology

The following battery of neuropsychological tests was administered: the Mini-Mental State Examination (Folstein *et al.*, 1975) as a general measure of cognitive status; the Graded Naming Test (McKenna and Warrington, 1983) as a measure of anomia; the digit span subtest of the Wechsler Memory Scale—Revised (Wechsler, 1987) to assess auditory-verbal short-term memory; verbal fluency for the letters F, A and S as a measure of both executive function and word-finding ability; copy and delayed recall of the Rey–Osterrieth Complex Figure (Rey, 1964) to test visuospatial skills and episodic memory. Various subtests from the Visual Object and Space Perception (VOSP, Warrington and James, 1986) battery were also used to assess visuo-spatial function.

Semantic assessments

The patients and controls were tested on portions of a semantic battery that uses a single set of stimulus items in a variety of tasks in order to assess semantic knowledge across different input and output modalities (Bozeat *et al.*, 2000). The battery consists of 64 items from the corpus of line drawings by Snodgrass and Vanderwart (1980); the items are drawn from three categories of living things (animals, birds and fruit) and three categories of artefacts (household items, tools and vehicles). The following subtests from this semantic battery were administered: category fluency, in which the subject is asked to produce as many exemplars as possible in 1 min for each of the six categories; naming of the 64 line drawings; and word–picture matching in which a single spoken object name is to be matched to its corresponding line drawing from a picture array containing the target plus nine within-category foils.

As additional tests of associative semantic knowledge, the Pyramids and Palm Trees Test (PPT, Howard and Patterson, 1992) and the Camel and Cactus Test (CCT, Bozeat *et al.*, 2000) were administered. In the PPT, triplets of either pictures or words are presented, and the subject is asked to choose one of the two response items that is most closely associated with each target item (e.g. for the target pyramid, the choice is between a palm tree and a pine tree). The CCT was designed on exactly the same principle as the PPT, but (i) the target items are the same as the 64 target pictures/words in our semantic battery, and (ii) the test is slightly harder than the PPT by virtue of having four rather than two response alternatives. For example, in one of the trials the subject was asked to match a camel (either the picture or printed word) to one of four types of vegetation: cactus (the target), tree, sunflower or rose.

In addition to these tests of general semantic memory, the patients were assessed on a series of verbal and non-verbal tasks known to be especially sensitive to the impairments observed in SD, as discussed in the Introduction. These tasks, which were constructed to include a substantial number of items that are somewhat less familiar than the sorts of things encountered in everyday life and/or are atypical in some respect for their category, are as follows.

Levels of specificity and typicality (LOST: Rogers T.T, Patterson K, Lambon Ralph M.A, and Hodges J.R, unpublished data)

Naming

On the basis of extensive pre-testing, we selected a series of 44 coloured pictures of objects that almost all normal individuals can name at a 'specific' level. That is, pictures of boats and of small birds are typically named at the basic level ('boat' and 'bird', respectively); but there are some reasonably well-known types of boats and small birds that most people, if asked, can name more precisely (e.g. yacht or ferry, robin or kingfisher). In the pre-tests, these 44 items had ⩾95% name agreement at this specific level in older controls, and can be divided—on the basis of familiarity ratings from controls—into 22 higher- and 22 lower-familiarity objects (e.g. robin and kingfisher respectively). The pictures were presented for naming to the patients and controls in this study, with the instruction (including a number of examples) to produce the most specific name they could think of for that picture.

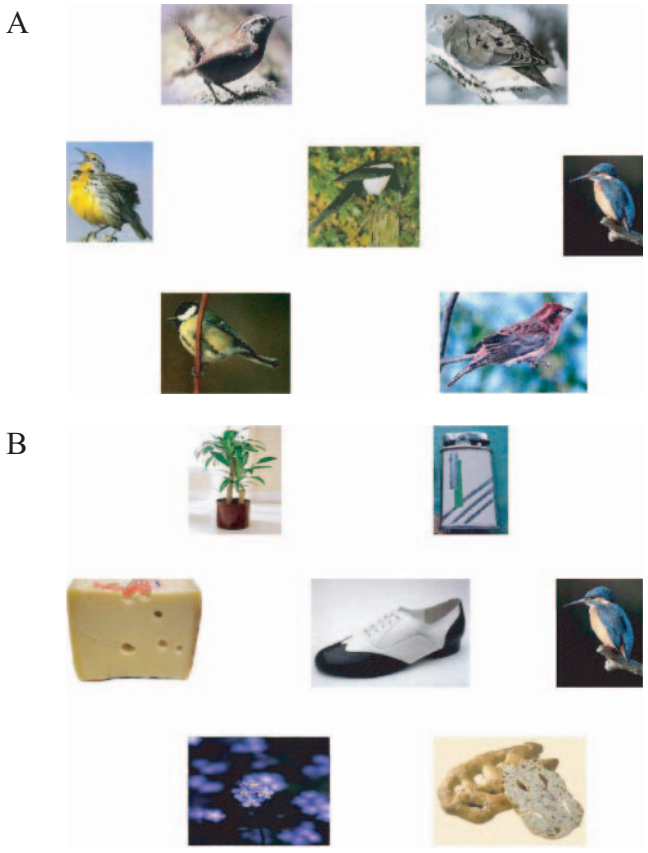

Fig. 1 Example of word–picture matching from the Levels of Specificity and Typicality (LOST) test. In this example, the subject is asked to point to the 'Kingfisher'. (**A**) Close semantic distractors. (**B**) Unrelated distant distractors.

Word–picture matching

Each of the same 44 items from the specific naming test was presented twice (on different occasions) in an array of seven pictures. In one condition (*see* Fig. 1A), the target object was accompanied by six semantically close distractors (e.g. for kingfisher, 6 other small birds); in the other condition (Fig. 1B), it occurred amongst completely unrelated, distant distractors (e.g. for kingfisher, 6 non-living things). The name of the target was spoken by the experimenter and the participant was asked to point to its picture in the array.

Colour knowledge

In one test of colour knowledge, the participants initially attempted to name 10 colour swatches and then, when presented with

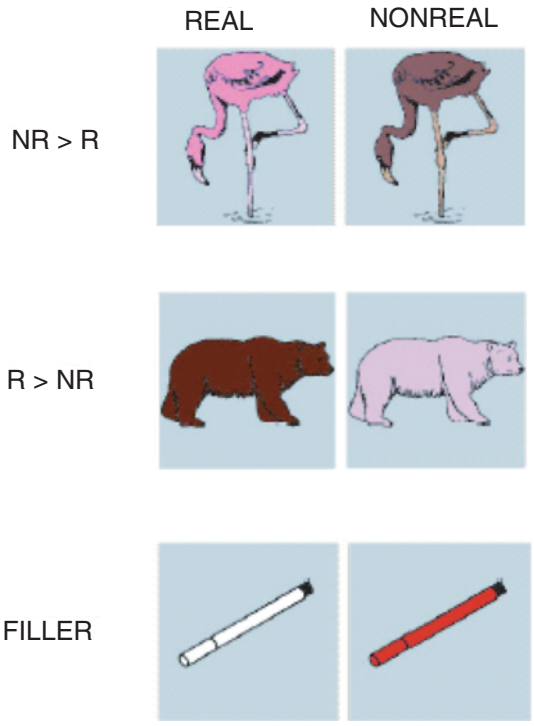

Fig. 2 Example of the object–colour decision task. R = Real, NR = Non-Real.

34 black-and-white line drawings, chose that colour swatch which corresponded to the colour of the object in real life. The critical manipulation in this task is whether the conventionally correct colour of the target object is typical or atypical for its domain. That is, many vegetables are green, so carrots and aubergines are atypical in this regard; many animals and birds are brown, so pink flamingoes are rather unusual in colour. In our colour selection task, 19 of the items had atypical colours while the remaining 15 items were typical of their domains.

In a second task, the object–colour decision test (Rogers *et al.*, 2003*b*), each of the 45 trials consisted of two drawings of the same object. In all critical pairs, this was an object with a specific characteristic colour in the real world, e.g. not a comb which can be in many different colours. The two drawings in each pair were identical except that one instance was presented in the correct colour and the other was incorrect. The critical manipulation for 30 of the pairs involved typicality: for 15 of these pairs, the colour of the foil was more typical of its domain than the correct object [Non-Real > Real (NR > R), e.g. a brown versus a pink flamingo]; for 15 further pairs, typicality favoured the correct choice rather than the foil [Real > Non-Real (R > NR), e.g. a brown versus a pink bear]; finally, there were 15 non-critical filler pairs, where there is not really a domain-typical colour (e.g. a white versus a red cigarette; *see* Fig. 2).

Sound knowledge (Bozeat *et al.*, 2000)

This test consisted of 48 sounds each characteristically associated with an object from one of six categories (domestic animals, foreign animals, people, household items, vehicles and musical instruments). Some less familiar sounds were included in an attempt to create a more sensitive measure of early semantic impairment. There were two conditions, administered on different occasions: matching sounds to pictures and matching sounds to written words. Participants were asked to listen on each trial to a sound and match it to the target stimulus (picture or written word) from an array of 10 within-category items.

Object-use knowledge (Bozeat *et al.*, 2002a)

A multiple component battery was constructed with the purpose of assessing associative information, functional knowledge and use of 36 household objects. These were derived from three categories—tools, kitchen implements and stationery items—and spanned a range of rated familiarity.

Conceptual knowledge for the 36 objects was assessed in a series of matching tasks, which consisted of digital photographs of the target and four possible matches. A picture of the target object was located at the top of the page and the subject was asked to choose one of four response alternatives as the best match according to one of three types of relationship, described below. The order of items was randomized across tasks and each was preceded by four practice trials. Every effort was made to ensure comprehension of the task by the patient.

(i) Matching to function. In this test, subjects were asked to choose one of four objects that could be used for the same purpose as the target item. The foils were chosen to be either visually similar to, or from the same category as, the target (e.g. for the target potato masher, the choice is between a fork, a mallet, an iron and a potato peeler).

(ii) Matching to recipient. Subjects were asked to choose the correct recipient for the target object. The foils were chosen to be visually similar to the correct match or semantically related (e.g. for the target potato masher, the choice is between a potato, a pepper, a flowerbed and a wedge of cheese).

(iii) Matching to action. In this test, subjects were asked to choose one of four objects that is manipulated/moved in the same way as the target. The foils were chosen to be visually similar or semantically related to the target (e.g. for the target potato masher, the choice is between a pizza cutter, a bottle opener, a wallpaper scraper and a plunger).

Naming

The subjects were also shown pictures of each of the 36 objects individually and asked to produce their names.

Familiarity ratings

Each patient's spouse was asked, on behalf of the patient, to rate each individual item from the sound and object knowledge tasks for concept familiarity, using a 5-point scale (1 = very unfamiliar, 5 = highly familiar). The instructions were the same as those used by Barry *et al.* (1997), except that only the names of the items were given.

Statistical analysis of the behavioural data

Group differences were analysed using separate *t*-tests with the appropriate adjustment for inhomogeneity of variance, unless all control participants performed at ceiling, in which case the individual patient data are described. Within-subject regression analyses were conducted to assess the relationship between anomia as a measure of disease severity (independent variable) and performance on each behavioural measure (dependent variable). In

addition, in order to investigate the effect of personal item familiarity on the performance of the patients on the sound and object knowledge tests, separate regression analyses were conducted, with mean patient familiarity rating as an independent variable and task performance as the dependent variables. In order to reduce the probability of Type I error, the statistical analyses were corrected for multiple comparisons within each task domain using a Bonferroni correction, and the adjusted alpha level is indicated.

For all tables the patients are ordered according to disease severity as measured by scores on the 64-item naming test.

MR analysis

All subjects (excluding Case 4, who was unavailable for a research volumetric MRI scan) and 12 age and gender-matched controls were scanned using a 1.5 T GE Signa MRI scanner (GE Medical Systems, Milwaukee, WI, USA). The images were acquired using a T1-weighted 3D sequence in the coronal plane using FSPGR TIW (inversion recovery preparation 650 ms, matrix 256 × 244, NEX 1). The data were analysed using Statistical Parametric Mapping (SPM5) software (Wellcome Department of Cognitive Neurology, University College London, London, UK).

Each scan was pre-processed in accordance with the optimized, modulated VBM protocol described by Good *et al.* (2001) with scans normalized to a standardized template (Friston *et al.*, 1995; Ashburner and Friston, 2000). The images were segmented using a Bayesian algorithm (Ashburner and Friston, 1997) and continuous probability maps were produced where values correspond to the posterior probability that the voxel belonged to the grey matter partition. Grey matter images were smoothed with 12 mm isotropic Gaussian kernels. In order to correct for normal variation in premorbid brain size, the total intracranial volume was calculated by summing the grey, white and CSF segments for each participant and this was included as a nuisance covariate in the statistical analyses.

The patient and control groups were first considered in a two-population group comparison to provide an overall indicator of atrophic regions in the patient group. In addition, separate within-patient-group regression analyses were conducted in order to investigate the predicted relationship between areas of atrophy and performance on the behavioural measures. The mean grey matter density values were derived for each patient in each of the six regions of peak atrophy (*see* Table 5) using in-house software (http://www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html). Two composite scores were derived for the verbal and non-verbal behavioural tests. The verbal mean composite score included 64-item naming, high/low familiarity naming (from the LOST), colour naming and naming of items in the object–use task. The non-verbal composite score included colour matching, object–colour decision, object–recipient matching, object–function matching, object–action matching and sound-picture matching.

Results

General neuropsychology

As shown in Table 2, on visual inspection six of the patients were reported to have bilateral but asymmetric atrophy: two patients (Cases 1 and 2) had greater atrophy to the right than left hemisphere; four (Cases 3–6) had more left than right atrophy; one (Case 7) was reported to have bilateral atrophy. In accordance with a diagnosis of fPPA, all of the patients were impaired on the Graded Naming Test. In addition four patients were impaired relative to controls on the MMSE. None showed impairments on the measures of working memory, or visuo-spatial tasks such as the Rey copy or subtests of the VOSP, while four of the patients were impaired on letter fluency, a task dependent on both word finding abilities and executive function. Only the most

Table 2 Individual patient performance on the general neuropsychology and semantic memory battery

Patient	1	2	3	4	5	6	7	Control mean (range)
Asymmetry	R > L	R > L	L > R	L > R	L > R	L > R	R = L	n/a
GNT (30)	10*	4*	0*	0*	0*	0*	0*	24.6 (18–29)
MMSE (30)	29	28	28	26*	25*	23*	23*	28.8 (27–30)
Digit span forwards	8	5	7	8	8	7	7	6.8 (4–8)
Digit span backwards	6	3	7	4	4	5	5	4.8 (3–7)
Fluency (F, A, S)	61	20*	25*	12*	22*	41	6*	44.6 (34–68)
Rey-Copy (36)	34	36	33	31	36	36	36	31.03 (31–36)
Rey-Recall (36)	17.5	13.5	18	22.5	16.5	14.5	4*	18.3 (9–27)
VOSP DC (10)	10	10	9	10	10	10	10	10.0 (9–10)
VOSP CA (10)	9	10	9	10	10	9	10	9.7 (6–10)
Naming (64)	64	52*	48*	34*	13*	10*	8*	62.3 (57–64)
WPM (64)	64	63	62*	53*	48*	57*	22*	63.8 (63–64)
Category fluency	41	16*	12*	17*	15*	6*	4*	48.9 (26–69)
CCT pics (64)	52	45*	54	33*	50*	45*	19*	59.1 (51–62)
CCT words (64)	58	52*	60	41*	4/29*	35*	n/a	60.7 (56–63)
PPT pics (52)	48	51	49	32*	36*	47	33*	51.2 (46–52)
PPT words (52)	47*	46*	n/a	44*	34*	48	n/a	51.2 (48–52)

The patients are ordered by degree of anomia as measured by the 64-item naming battery. *Indicates a score below the control range. R = right, L = left. n/a = not applicable and/or not available. GNT = Graded Naming Test. MMSE = Mini Mental State Examination. VOSP = Visual Object and Space Perception Battery: DC = dot counting; CA = cube analysis. WPM = word–picture matching. CCT = Camel and Cactus Test. PPT = Pyramids and Palm Trees Test.

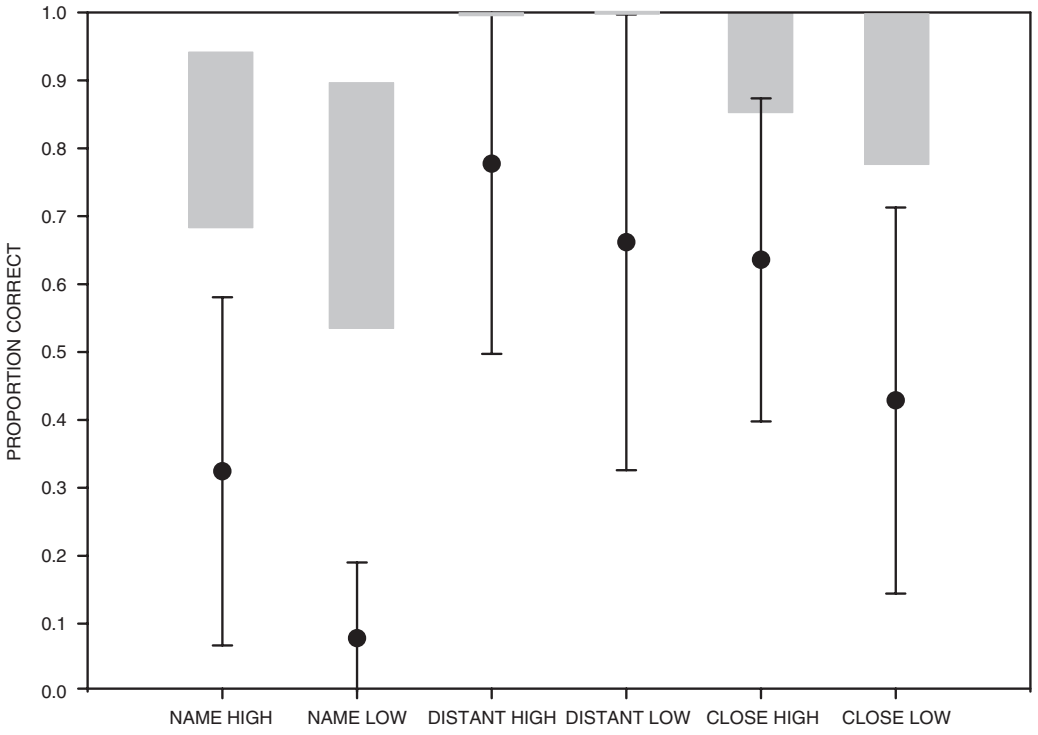

Fig. 3 Performance of the patient group on the three conditions of the LOST: naming, word–picture matching with unrelated distant distractors and word–picture matching with close distractors. Variance bars are 95% confidence intervals. The grey shading indicates the range of control performance in the corresponding condition. HIGH refers to high familiarity items and LOW refers to low familiarity items.

severe case had difficulty recalling the Rey figure. All but one of the patients (Case 1) were impaired on the 64-item naming test and the category fluency test, with five of the patients showing additional impairments on the 64-item word–picture matching comprehension test. Furthermore, five of the patients were impaired on the CCT (words and pictures) with four of the patients showing impairments on at least one version of the easier PPT.

LOST naming and word–picture matching

Statistical analysis (with a corrected alpha of 0.05/6 = 0.008) revealed that the patient group was impaired relative to controls at naming both high- [$t(6.6) = 4.9$, $P < 0.008$] and low-familiarity [$t(17) = 10.68$, $P < 0.008$] items, and matching low familiarity words to target pictures with close distractors [$t(6.4) = 4.04$, $P < 0.008$]. Due to all controls performing at ceiling on the distant distractor subtest, the data were not analysed statistically. However, as shown in Fig. 3, there was some overlap between patient and control performance on both the high and low familiarity conditions of the distant distractor subtest. Patient scores were generally lower for naming and matching low- relative to high-familiarity items, although the same was true of controls in the close-distractor condition. Statistical analysis comparing the difference in performance between the high and low familiarity conditions revealed that the patient group showed a larger familiarity effect (high minus low familiarity) than the control group when the distractor pictures were semantically close to the target [$t(17) = 3.64$; $P < 0.008$]. See Table 3 for individual performance on each word–picture matching condition.

Colour knowledge

As a group (corrected alpha of 0.05/7 = 0.007) the patients were significantly impaired relative to controls on atypical colour–object matching [$t(6.2) = 5.19$, $P < 0.007$], and object–colour decision when the foil was a more domain-typical colour than the target [NR > R: $t(6.7) = 5.1$, $P < 0.007$]. The performance on colour naming was not statistically analysed due to all of the controls performing at ceiling. However, as shown in Fig. 4A, there was some overlap between patient and control performance on both colour naming and colour–object matching when the colour of the item was typical of its domain. In addition, Fig. 4B shows that the patients' performance was lower than that of the control group on the two-alternative forced choice colour decision task when the foil was a more domain-typical colour than the target (NR > R), but neither when the target was typical (R > NR) nor for the filler items.

Individual patient scores are shown in Table 3. All seven patients showed better performance (in some cases, substantially better) when choosing the correct colour swatch for domain-typical than domain-atypical coloured exemplars, and the difference in performance between the two

Table 3 Performance of the individual patients on the non-verbal experimental measures

Patient	1	2	3	4	5	6	7	Normal range
Word–item matching								
LOST distant word–picture matching								
High familiarity	1	**0.95**	1	**0.95**	**0.32**	**0.86**	**0.36**	1.00–1.00
Low familiarity	**0.86**	**0.86**	1	**0.64**	**0.09**	**0.95**	**0.23**	1.00–1.00
LOST close word–picture matching								
High familiarity	0.91	0.86	**0.82**	**0.59**	**0.32**	**0.68**	**0.27**	0.86–1.00
Low familiarity	0.77	**0.64**	0.77	**0.14**	**0.05**	**0.45**	**0.18**	0.77–1.00
Environmental sound–word matching	**0.69**	**0.69**	**0.58**	**0.48**	**0.23**	**0.46**	**0.15**	0.77–0.98
Non-verbal subtests								
Object colour matching								
Atypical targets	**0.79**	**0.47**	**0.79**	**0.53**	**0.21**	**0.58**	**0.26**	0.84–1.00
Typical targets	1	0.87	0.87	**0.67**	**0.67**	**0.73**	**0.53**	0.80–1.00
Object–colour decision								
Non-real > real	**0.8**	**0.8**	**0.67**	**0.47**	**0.6**	**0.8**	**0.47**	0.87–1.00
Real > non-real	0.93	0.87	0.87	0.87	**0.67**	**0.8**	**0.33**	0.87–1.00
Filler	0.87	0.93	**0.8**	**0.6**	**0.6**	0.87	**0.4**	0.87–1.00
Object–matching								
Recipient	0.94	0.89	0.86	**0.61**	**0.64**	**0.64**	**0.44**	0.86–1.00
Function	0.86	**0.75**	**0.61**	**0.44**	**0.5**	**0.25**	**0.19**	0.78–1.00
Action	0.67	0.86	**0.56**	**0.42**	**0.47**	**0.28**	**0.28**	0.61–0.97
Environmental sound-picture matching	**0.77**	**0.65**	**0.63**	**0.46**	**0.21**	**0.52**	**0.08**	0.79–0.96

Data in boldface indicate performance outside the control range.

conditions was greater in the patient group compared with the control group [$t(21) = 5.61$; $P < 0.007$]. The impact of target typicality in the two-alternative forced choice colour decision task was not so impressive, and the difference in performance between the two conditions did not significantly differ between the patient and control groups. Nevertheless, a few cases (e.g. Cases 1, 3 and 4) did reveal the predicted advantage for R > NR compared with NR > R, and the one patient (Case 7) who showed the opposite pattern did not exceed chance performance in either condition.

Sound knowledge

As shown in Fig. 5A, as a group, the patients' sound knowledge was impaired relative to controls (corrected alpha of 0.05/4 = 0.0125) on both conditions of the environmental sounds test [pictures: $t(6.3) = 4.3$, $P < 0.0125$; words: $t(6.3) = 4.5$, $P < 0.0125$]. Regression analyses revealed that item familiarity was significantly associated with performance on both the word [$F(1,47) = 16.6$; $P < 0.0125$] and picture [$F(1,47) = 14.8$; $P < 0.0125$] versions of the task, accounting for 26.5 and 24.3% of the variance respectively. Figures 5B and C show that performance was better on the more familiar items.

Object use knowledge

The patients were impaired relative to controls (corrected alpha of 0.05/8 = 0.006) on naming [$t(6.1) = 6.1$, $P < 0.006$]; matching to function [$t(6.3) = 4.3$, $P < 0.006$]; and matching to action [$t(7.2) = 4.3$, $P < 0.006$], but not matching to recipient. Figure 6A shows that there was no overlap in performance between the patient group and control group on either object naming or the matching-to-function subtest, but there was some overlap between the groups on matching to recipient and matching to action. As shown in Table 3, all but the mildest single case were impaired in at least one of the three subtests; and all but three of the patients (Cases 1–3 with the mildest degree of anomia) were impaired on all of the matching subtests.

Regression analyses revealed that item familiarity was significantly associated with performance only on the naming measure [$F(1,35) = 34.7$; $P < 0.006$], accounting for 50.5% of the variance. Figure 6B shows that more items with a high- than a low-familiarity rating were named correctly.

Relationship with disease severity

As shown in Table 4, disease severity (as measured by performance on 64-item naming) was associated significantly (corrected for multiple comparisons $P < 0.003$) or marginally ($P < 0.1$) with 15 of the 18 measures, the only exceptions being matching to low familiarity items when distractors were unrelated (LOST distant) and two of the object–colour decision conditions. In all of these exceptions, the relationship is probably 'disrupted' by the good performance of Case 6 (one of the most anomic patients) on these three matching or decision tasks.

Summary of individual cases

A summary of each patient's performance relative to the control group on the experimental tests is shown in Table 3. All patients were selected to have impairments in naming and in some cases had verbal comprehension deficits at presentation as well; so the impairments to verbal semantic

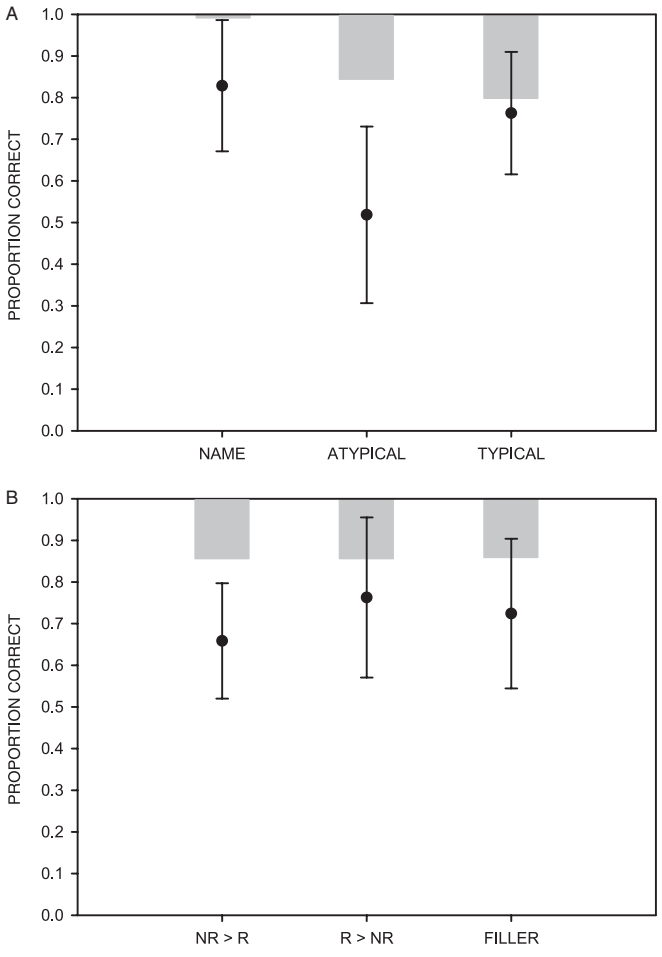

Fig. 4 Performance of the patient group on the three tests of colour knowledge: (**A**) colour naming and colour object matching; (**B**) colour–object decision. Variance bars are 95% confidence intervals. The grey shading indicates the range of control performance in the corresponding condition.

tasks indicated in the table are not surprising. More interesting is performance on the non-verbal tasks: every individual patient was below the control range in the critical conditions of the two colour tests and the sound-picture matching test; and all but the mildest single patient had scores outside the control range on at least one of the action knowledge tests. Thus, there is no evidence for preserved non-verbal knowledge, either in any individual case or in the group as a whole.

MR analysis

Figure 7 displays areas of significant grey matter atrophy in the patients relative to controls. The figure has a threshold at $P < 0.05$ (FDR corrected), to demonstrate the extent of damage, which encompassed the right inferior temporal lobe and more widespread areas in the left temporal lobe. Table 5 shows the Montreal Neurological Institute coordinates and significance level of the peak areas that survived whole brain correction.

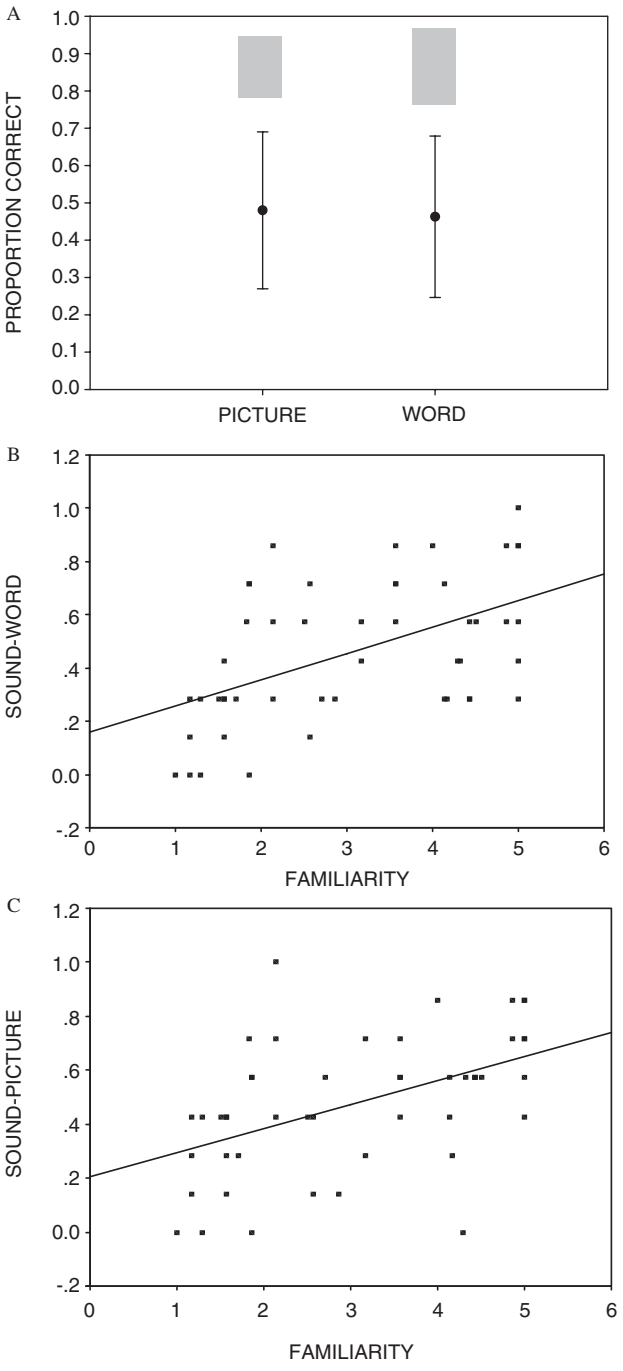

Fig. 5 (**A**) Performance of the patient group on the sound–picture and sound–word matching tests. Variance bars are 95% confidence intervals. The grey shading indicates the range of control performance in the corresponding condition. (**B**) The significant relationship between mean familiarity rating per item and the mean patient score on the sound–word matching test. (**C**) The significant relationship between familiarity rating and sound–picture matching performance in the patient group.

Relationship with degree of atrophy

Separate regression analyses (corrected alpha $P = 0.05/2$) revealed that only grey-matter density in the left ventral temporal region was significantly associated with semantic

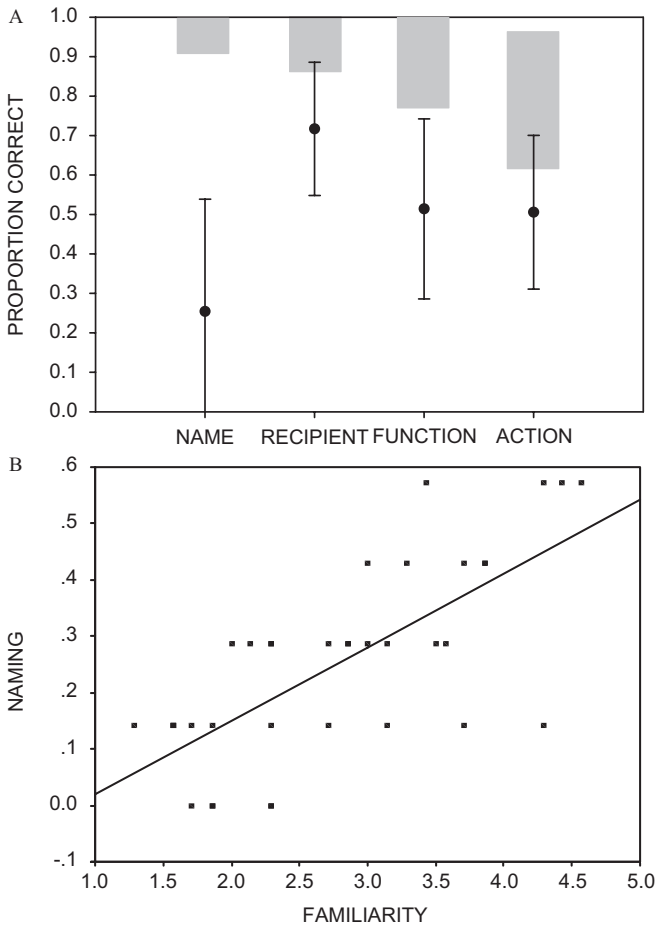

Fig. 6 (**A**) Performance of the patient group on the object naming condition and the object matching subtests. Variance bars are 95% confidence intervals. The grey shading indicates the range of control performance in the corresponding condition (**B**) The significant relationship between mean familiarity rating per item and the mean patient score on the object naming subtest.

Table 4 Relationship between disease severity (64-item naming) and performance on the experimental measures within the patient group using regression analyses

	R^2	Significance
Naming		
LOST naming		
High familiarity	0.87	$P < 0.003$
Low familiarity	0.74	$P = 0.01$
Colour naming	0.47	$P = 0.09$
Object–matching naming	0.89	$P < 0.003$
Word–picture matching		
LOST distant word–picture matching		
High familiarity	0.57	$P = 0.05$
Low familiarity	0.38	$P = 0.14$
LOST close word–picture matching		
High familiarity	0.73	$P = 0.01$
Low familiarity	0.60	$P = 0.04$
Environmental sound–word matching	0.68	$P = 0.02$
Non-verbal subtests		
Object–colour matching		
Atypical targets	0.54	$P = 0.06$
Typical targets	0.79	$P = 0.008$
Object–colour decision		
Non-real > real	0.22	$P = 0.29$
Real > non-real	0.54	$P = 0.06$
Filler	0.40	$P = 0.13$
Object–matching		
Recipient	0.82	$P = 0.005$
Function	0.85	$P = 0.003$
Action	0.69	$P = 0.02$
Environmental sound–picture matching	0.83	$P = 0.004$

performance, on both the verbal (t = 12.3; β = 409.9; $P < 0.025$) and non-verbal composite measures (t = 5.0; β = 311.4; $P < 0.025$; *see* Fig. 8). It is important to note that a lack of significant association between performance and the other regions of peak grey matter reduction does not rule out a relationship; it only indicates that the association did not reach conventional levels of significance (P = 0.2–0.6).

Discussion

In seven patients selected to meet the diagnostic criteria of fPPA, we found no evidence that the deficits were restricted to language. Relative to matched controls, the patients as a group had significantly impaired knowledge of objects and their associated function, colours and sounds, with the degree of this impairment further modulated by the familiarity and typicality of the objects/object features tested. Of the nine experimental tests involving neither verbal stimulus nor response, four of the seven patients (Cases 4–7) had scores below—usually far below—the control range on either all or all-but-one of these nine assessments (see the lower section of Table 3). Only the very mildest patient, Case 1, could be described as having a near-normal profile on these measures of non-verbal conceptual knowledge, and even his scores were mostly at or slightly below the bottom of the control range. Note also that the same could be said of the verbal performance of Case 1: he only qualified for fPPA status on the basis of his score on the rather challenging Graded Naming Test (which, for his pre-morbid profession as a head teacher, was clearly abnormal).

In the patient group as a whole, verbal impairments were more marked than non-verbal deficits, not only on our tests but in the sense that only language difficulties permeated all aspects of daily life. This fact, of course, is a major aspect of the claim that these patients meet the criteria for fPPA. More importantly from the perspective of the motivation for this study, however, the non-verbal > verbal pattern is to be expected on the basis of the way in which objects versus words relate to meaning (Lambon Ralph and Howard, 2000; Patterson and Hodges, 2000; Benedet *et al.*, 2006). The mapping between the visual appearance of an object (either the whole form or parts of it) and its meaning is always more coherent than is the case for words, whose surface forms have an arbitrary relationship to their meanings. Furthermore, word comprehension is easier than naming

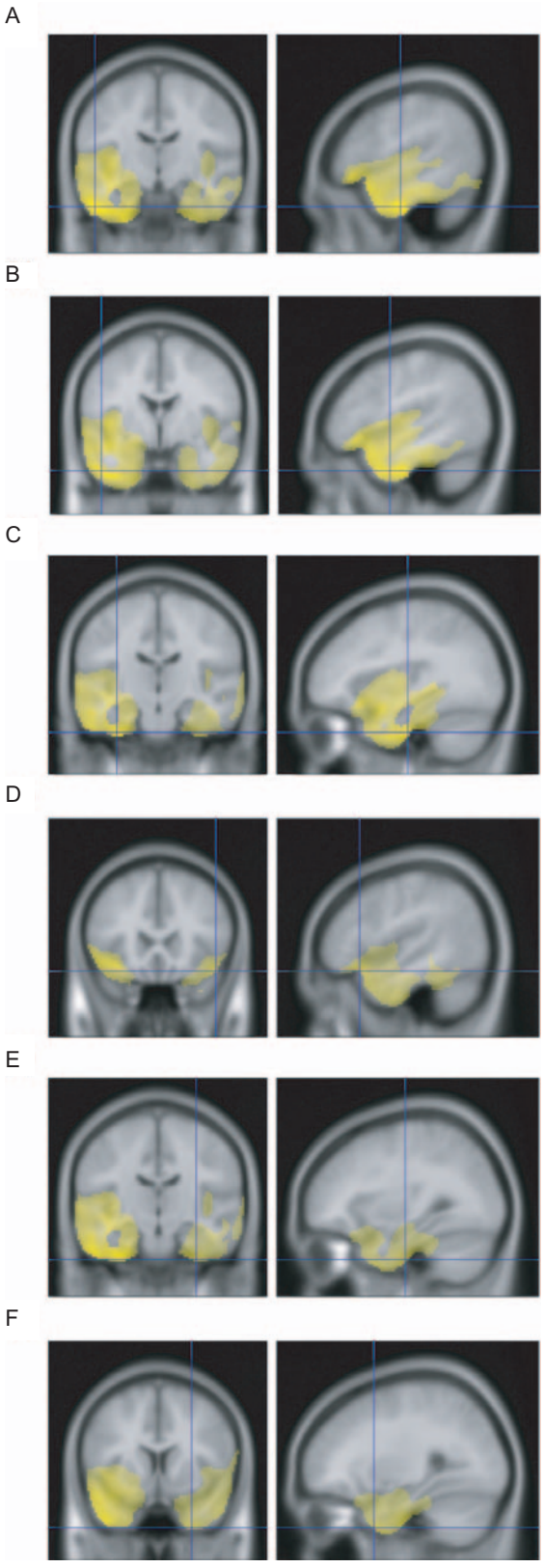

Fig. 7 Results from the whole brain corrected (FDR 0.05) VBM analysis of grey matter reduction in patients relative to controls (yellow). The cross hairs on the figure indicate the peak areas of atrophy: (**A**) −52, −12, −34; (**B**) −48, −2, −36; (**C**) −34, −18, −38; (**D**) 48, 22, −18; (**E**) 32, −16, −42; (**F**) 28, 10, −46.

because it is better contextualized and/or, in the case of tests like word–picture matching, more similar to recognition than recall. By this analysis, even if the disease affects a general amodal semantic system from the very outset, one would expect the same pattern of object knowledge > word comprehension > word finding/naming in the initial phases, and as such this does not indicate that verbal and non-verbal abilities constitute separate neural/functional systems.

As outlined in the Introduction, this study was designed to test three predictions from the 'multiple-systems' account of SD regarding patients who meet the diagnostic criteria for fPPA: (i) that the deficits of these patients should be primarily in the domain of language, largely sparing non-verbal knowledge; (ii) that these cases should have reduced density of grey matter in the language network, i.e. the left peri-Sylvian temporo-parietal region and adjacent superior temporal gyrus, which in turn should covary with the degree of anomia; and (iii) that, if some of the patients turn out to have a degree of impairment to non-verbal knowledge, this should be linked to bilateral ventro-temporal atrophy. The detailed pattern of our results will now be discussed with reference to each of these issues.

Non-verbal impairments and concept familiarity/typicality

According to the reports of Mesulam (2001, 2003) and Sonty *et al.* (2003), patients with fluent speech but difficulties with word finding and word comprehension can be classified as a subtype of PPA, provided that face and object recognition are relatively preserved (at least within the first 2 years of illness). Such patients are often reported as being able to demonstrate the use of objects correctly despite being unable to name them (e.g. Mesulam, 2001). In partial confirmation of this conclusion, the current study demonstrated that, when the items were judged to be of high familiarity and did not include many atypical or unusual features, the patients performed relatively well on non-verbal tests. For example, most patients could accurately demonstrate the use of a pair of scissors, select the appropriate recipient, action and function for it, and in some cases even name it. These same patients, however, were impaired when required to demonstrate knowledge of less familiar objects, such as a corkscrew, and furthermore showed significant impairments on other simple non-verbal tasks such as knowing what colour a beetroot should be or matching the sound of a xylophone to its picture. These findings accord with our own and others' clinical observations that object familiarity has a profound impact in SD (e.g. Snowden *et al.*, 1989, 1996; Bozeat *et al.*, 2002*b*).

In the tasks where familiarity was measured or manipulated, the influence of this factor was consistent: the patients were more impaired at naming low familiarity items, identifying their sounds, and demonstrating

Table 5 Areas of significant decreases in grey matter density in the patient group relative to controls

Location	Montreal Neurological Institute coordinates (*x*, *y*, *z*)	*Z*-score	*P*-value (FDR)
Left ventral temporal lobe	−52, −12, −34	5.84	<0.0005
Left rostro-ventral temporal lobe	−48, −2, −36	5.45	<0.0005
Left ventral temporal lobe	−34, −18, −38	5.43	<0.0005
Right temporal pole	48, 22, −18	4.31	0.001
Right ventral temporal lobe	32, −16, −42	4.28	0.001
Right rostro-ventral temporal lobe	28, 10, −46	4.18	0.001

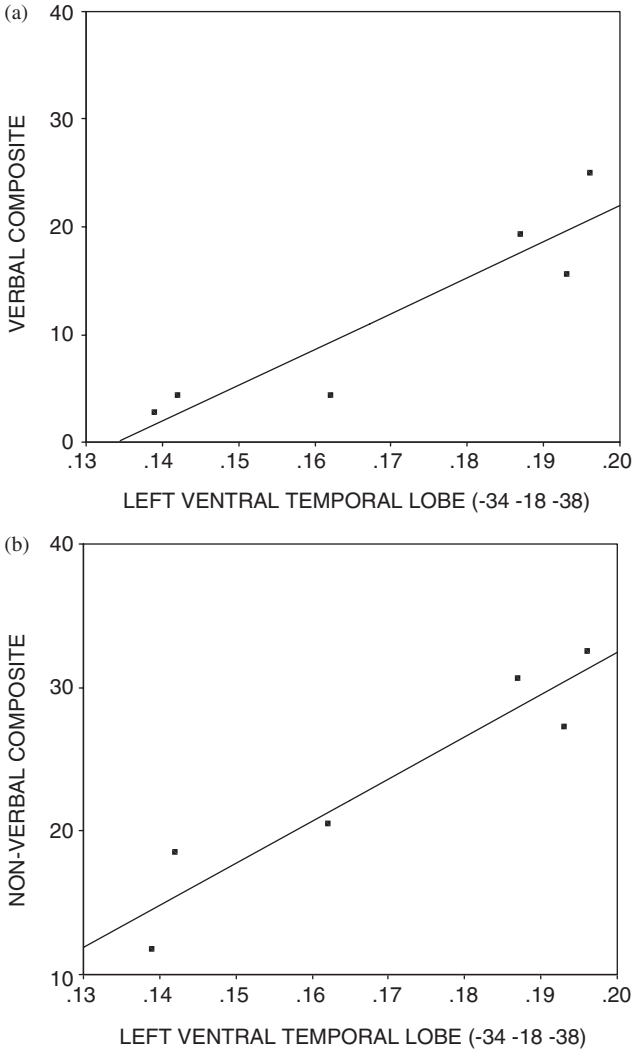

Fig. 8 The significant correlation between mean grey matter density values in the left ventral temporal lobe in the patient group and: (**A**) performance on the naming tests [composite score including 64-item naming, high/low familiarity naming (from the LOST), colour naming and naming of items in the object–use task]; and (**B**) the non-verbal tests (composite score including colour matching, object–colour decision, object–recipient matching, object–function matching, object–action matching and sound–picture matching).

their uses. Only the two colour knowledge tasks directly contrasted knowledge for category-typical versus category-atypical properties, but here again performance matched past assessments of SD (Rogers *et al.*, 2003*a*, *b*; 2004*b*; Patterson *et al.*, 2006): patients were more impaired when responding to items that have domain-atypical colours, such as a pink flamingo or a purple aubergine. These findings suggest that, if tested on low familiarity items, or domain-atypical items, fPPA patients with seemingly selective language impairments will also show non-verbal semantic memory deficits.

Proponents of the multiple-systems view might argue that 'apparent' deficits on non-verbal tasks in PPA may arise because such patients are unable to employ verbal reasoning strategies that are available to healthy controls. Although this seems a possible contribution to impaired performance in the sound-matching task (in which participants may first name the sound and then search for the matching word or picture) and—though less plausibly—perhaps even to impaired knowledge of object use, it seems an unlikely explanation for performance in the two colour tasks. That is, it seems implausible that associations between the shape of an object and its colour, two manifestly visual properties, are mediated by a verbal code. Yet performance on the colour tests was consistently degraded in this patient cohort, suggesting that the deficits observed were truly non-verbal (Rogers *et al.*, 2003*b*).

In summary of this issue: how are we to classify patients like the ones studied here, who present with a prominent fluent, anomic aphasia and a less prominent but still significant agnosia that is modulated by concept familiarity/typicality? These patients qualify for a diagnosis of fPPA on the basis of their preserved everyday function and the predominance of their aphasia; but (i) when tested with appropriate materials, they have clear non-verbal impairments, even at this early stage, and (ii) in our (by now fairly extensive) experience, they invariably progress to a pattern that every FTD researcher would call SD. It seems more logical and more useful to label them as having mild or early-stage SD.

Atrophy of the left hemisphere language network (LHLN)?

Authors of previous research on patients with fPPA have argued that their language impairments result from atrophy in the left hemisphere language network including the temporo-parietal region (e.g. Mesulam and Weintraub, 1992; Abe *et al.*, 1997; Sonty *et al.*, 2003; Gorno-Tempini *et al.*, 2004). In our study, however, the VBM analysis of a cohort of patients who met criteria for fPPA identified focal

bilateral temporal lobe atrophy with particular emphasis on the ventral rostral surface. This pattern is essentially identical to that reported in previous imaging studies of patients with SD (Mummery *et al.*, 2000; Rosen *et al.*, 2002; Diehl *et al.*, 2004; Nestor *et al.*, 2006). Importantly, only the degree of atrophy in the left inferior temporal lobe was significantly associated with performance on both verbal and non-verbal measures. The absence of statistically reliable abnormality in the temporo-parietal region of the LHLN may reflect the relatively low power of the analysis due to the small sample size, and so does not prove normality in this region. Nevertheless, we suggest that our findings may differ from previous evidence on this question because studies like Sonty *et al.* (2003) included non-fluent as well as fPPA in their imaging analysis: there is clear evidence that cases of progressive non-fluent aphasia typically have significant atrophy or hypometabolism in the LHLN (Nestor *et al.*, 2003; Gorno-Tempini *et al.*, 2004). There was no evidence from the current findings that joint impairments to verbal and non-verbal semantic memory result from damage to two independent neural networks.

We would like to emphasize that, by the account of SD to which we subscribe, there is nothing puzzling about the fact that in patients with an apparent aphasia, the areas of most marked abnormality are not in traditional peri-Sylvian language regions. By this account, the language disorder in SD, though prominent, is not primary: it is the inevitable but indirect consequence of a deteriorating central, amodal semantic system. As explained above, language function—especially expressive language—should always be more vulnerable to semantic degradation than non-verbal measures of conceptual knowledge because of the differential nature of the mappings. Hence SD patients are profoundly anomic and, lagging slightly behind but always in concert, have impaired verbal comprehension. Unlike aphasia from stroke, however, these language impairments do not arise from disruption of language regions *per se*: they, along with the non-verbal deficits that lag still further behind but are always also present, result from the semantic deterioration caused by anterior, inferior temporal-lobe atrophy.

Bilateral temporal lobe atrophy?

The VBM analysis confirmed bilateral temporal lobe atrophy in the patient group as a whole. On visual inspection of MRI scans, however, five of the seven patients had either more prominent atrophy in the left than right ATL or (in one case) relatively symmetrical ATL damage, and only two cases (1 and 2) had an apparent pattern of right > left atrophy. It is perhaps not surprising, therefore, that the regression analysis did not identify a significant relationship between right temporal lobe atrophy and cognitive performance for the (small) group as a whole. It is however important to note that, apart from the fact that cases 1 and 2 were somewhat more mildly impaired than the remaining cases on both verbal and non-verbal assessments, these two cases were characterized by largely the same profile of performance as the others. This suggests that significant bilateral damage to the temporal lobes, independent of its degree or side of asymmetry, typically disrupts both verbal and non-verbal semantic memory.

Conclusion and current criteria for semantic dementia

Our findings support the view that patients who meet the diagnostic criteria for fPPA can and typically do show non-verbal as well as verbal deficits in conceptual knowledge and other tasks that depend upon such knowledge, provided that the measures employed allow for the vital impact of concept/feature familiarity and typicality. Furthermore, the findings suggest that this profile of combined verbal and non-verbal deficits is most likely the result of temporal lobe atrophy, rather than of damage to two separate neurocognitive networks. Whether one places more emphasis on the prominent language disorder and, hence, classifies such cases as fPPA, or more emphasis on the multi-modal pattern of deficits and hence calls them SD, can be viewed as a matter of preference. Our preference for the second option is based partly on the already-mentioned fact that progression in such cases appears invariably to yield an SD profile (e.g. Patterson and Hodges, 2000; Papagno and Capitani, 2001), and that it therefore seems both theoretically and clinically more coherent to 'begin as one means to go on' in the patients' diagnosis. A second important basis for our choice is the strikingly similar pattern of the patients' verbal and non-verbal deficits, in which three factors—disease severity, item familiarity and concept/feature typicality—together provide an almost complete basis for predicting performance on any cognitive test, and errors essentially always demonstrate that what is retained is knowledge of the typical structure in the relevant stimulus domain (Hodges *et al.*, 2006; Patterson *et al.*, 2006). We argue that this represents the signature of a single, degrading semantic network with an impact on verbal and non-verbal abilities that may be (for principled reasons) unequal in degree but is entirely parallel in nature.

The difference between our application of the term SD (e.g. Hodges *et al.*, 1992, 1994, 1995; Patterson and Hodges, 2000; Patterson *et al.*, 2006) and a literal interpretation of the consensus criteria (e.g. Neary *et al.*, 1998; Mesulam *et al.*, 2003) has been a source of confusion. The associative agnosia and/or prosopagnosia displayed by patients even with an advanced stage of SD (e.g. Snowden *et al.*, 1989) is not of the magnitude to impact on all aspects of everyday life in the way that patients with bilateral occipito-temporal stroke can be affected. Even severely affected SD patients often remain capable of recognizing family members and using highly familiar objects yet show gross impairment when asked to identify famous people (e.g. Snowden *et al.*, 2004) or less familiar objects (e.g. Snowden *et al.*, 1996; Bozeat *et al.*, 2002*a*). We suggest, therefore, that the widely quoted consensus criteria (Neary *et al.*, 1998) be modified to reflect this difference in usage of the term agnosia and be

replaced with 'impairment on tests of non-verbal associative knowledge'.

Acknowledgements

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