doi:10.1093/brain/awp083 Brain 2009: 132; 2772–2784 | 2772

BRAIN
A JOURNAL OF NEUROLOGY

Brain regions underlying word finding difficulties in temporal lobe epilepsy

Agnes Trebuchon-Da Fonseca,[1,2] Eric Guedj,[2,3] F-Xavier Alario,[2,4] Virginie Laguitton,[5] Olivier Mundler,[2,3] Patrick Chauvel[1,2,6] and Catherine Liegeois-Chauvel[1,2]

1 INSERM, U751, Marseille, F-13000, France
2 Aix-Marseille Université, Marseille, F-13000, France
3 Assistance Publique – Hôpitaux de Marseille, Hôpital de la Timone, Pôle d'Imagerie Médicale, Marseille, F-13000, France
4 CNRS, Laboratoire de Psychologie Cognitive, Marseille, F-13000, France
5 Hôpital Henri Gastaut, Marseille, F-13000, France
6 Assistance Publique – Hôpitaux de Marseille, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Marseille, F-13000, France

Correspondence to: Agnes Trebuchon-Da Fonseca,
INSERM U751,
laboratoire Epilepsie et Cognition,
Université de la Méditerranée,
faculté de médecine Timone,
27, Bd Jean-Moulin – 13385,
Marseille cedex 05, France
E-mail: agnes.trebuchon@univmed.fr

Word finding difficulties are often reported by epileptic patients with seizures originating from the language dominant cerebral hemisphere, for example, in temporal lobe epilepsy. Evidence regarding the brain regions underlying this deficit comes from studies of peri-operative electro-cortical stimulation, as well as post-surgical performance. This evidence has highlighted a role for the anterior part of the dominant temporal lobe in oral word production. These conclusions contrast with findings from activation studies involving healthy speakers or acute ischaemic stroke patients, where the region most directly related to word retrieval appears to be the posterior part of the left temporal lobe. To clarify the neural basis of word retrieval in temporal lobe epilepsy, we tested forty-three drug-resistant temporal lobe epilepsy patients (28 left, 15 right). Comprehensive neuropsychological and language assessments were performed. Single spoken word production was elicited with picture or definition stimuli. Detailed analysis allowed the distinction of impaired word retrieval from other possible causes of naming failure. Finally, the neural substrate of the deficit was assessed by correlating word retrieval performance and resting-state brain metabolism in 18 fluoro-2-deoxy-D-glucose-Positron Emission Tomography. Naming difficulties often resulted from genuine word retrieval failures (anomic states), both in picture and in definition tasks. Left temporal lobe epilepsy patients showed considerably worse performance than right temporal lobe epilepsy patients. Performance was poorer in the definition than in the picture task. Across patients and the left temporal lobe epilepsy subgroup, frequency of anomic state was negatively correlated with resting-state brain metabolism in left posterior and basal temporal regions (Brodmann's area 20-37-39). These results show the involvement of posterior temporal regions, within a larger antero-posterior-basal temporal network, in the specific process of word retrieval in temporal lobe epilepsy. A tentative explanation for these findings is that epilepsy induces functional deafferentation between anterior temporal structures devoted to semantic processing and neocortical posterior temporal structures devoted to lexical processing.

Keywords: temporal lobe epilepsy; naming; anomia; cerebral metabolism; language

Received November 4, 2008. Revised February 21, 2009. Accepted February 23, 2009. Advance Access publication April 21, 2009

Abbreviations: BA = Brodmann's area; FDG-PET = fluoro-2-deoxy-D-glucose-Positron Emission Tomography; HS = hippocampal sclerosis; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SPM = statistical parametric mapping; TLE = temporal lobe epilepsy

Introduction

Word finding difficulties that interfere with daily life are frequently reported by epileptic patients whose seizures originate in the language dominant cerebral hemisphere (e.g. in temporal lobe epilepsy, or TLE) (Mayeux *et al*., 1980). Impaired word retrieval can be evidenced in clinical practice with the classic test of confrontation naming, a task requiring patients to name aloud pictures of common objects (Kaplan, 1983), or by asking patients to produce a word in response to a simple definition. Despite their apparent simplicity, both the picture and the definition tasks recruit a complex set of mental representations and cognitive processes. These have been described in detail in psycholinguistic models (e.g. La Heij *et al*., 1993; Wheeldon and Monsell, 1994; Caramazza, 1997; Levelt, 1999). Following DeLeon *et al*. (2007), we adopt a simplified version of these models which will only include their major hypothesis. Figure 1 illustrates how, in these tasks, producing a word requires: (i) recognition of the visual stimulus or understanding of the definition as pointing to a familiar concept; (ii) access of the meaning of the object, or the concept, in the semantic system; (iii) retrieval of the lexical representation and access of its phonological word form in the lexical system; and (iv) planning of the motor programmes that drive articulation.

Some of these processes appear to be selectively impaired following brain damage (for review see DeLeon *et al*., 2007). Disruption or degradation of semantic representations, including amodal general and personal knowledge, is seen in patients with semantic dementia (Mummery *et al*., 2000; Woollams *et al*., 2008). Disruption of mechanisms for linking semantic representations with specific word form representations (both during word comprehension and naming), via lexical-semantics, is observed after stroke damaging superior temporal gyrus, inferior parietal cortex or prefrontal cortex (Hillis *et al*., 2001*b*). Pure anomia, defined as a lack of word retrieval despite preserved semantic processing, is observed in patients with lesions in the posterior portion of the middle temporal gyrus (or area 37) and left fusiform gyrus (Raymer *et al*., 1997; Rohrer *et al*., 2008).

Consistent with these observations, healthy speakers producing words during functional imaging show widespread activation of left perisylvian and extrasylvian cortex. During picture naming, distribution of activity in the left anterior, inferior and posterior middle/superior temporal cortex, posterior inferior frontal and inferior parietal cortex has been shown (Hirsch *et al*., 2001; Abrahams *et al*., 2003; Grabowski *et al*., 2003*a*; Indefrey and Levelt, 2004; Price *et al*., 2005; Tomaszewki Farias *et al*., 2005; Kemeny *et al*., 2006; Price *et al*., 2006; Saccuman *et al*., 2006). More specific observations have come from a recent study where naming deficit was correlated to specific areas of tissue dysfunction within 24 h of acute ischaemic stroke (DeLeon *et al*., 2007). Tissue dysfunction was measured with magnetic resonance

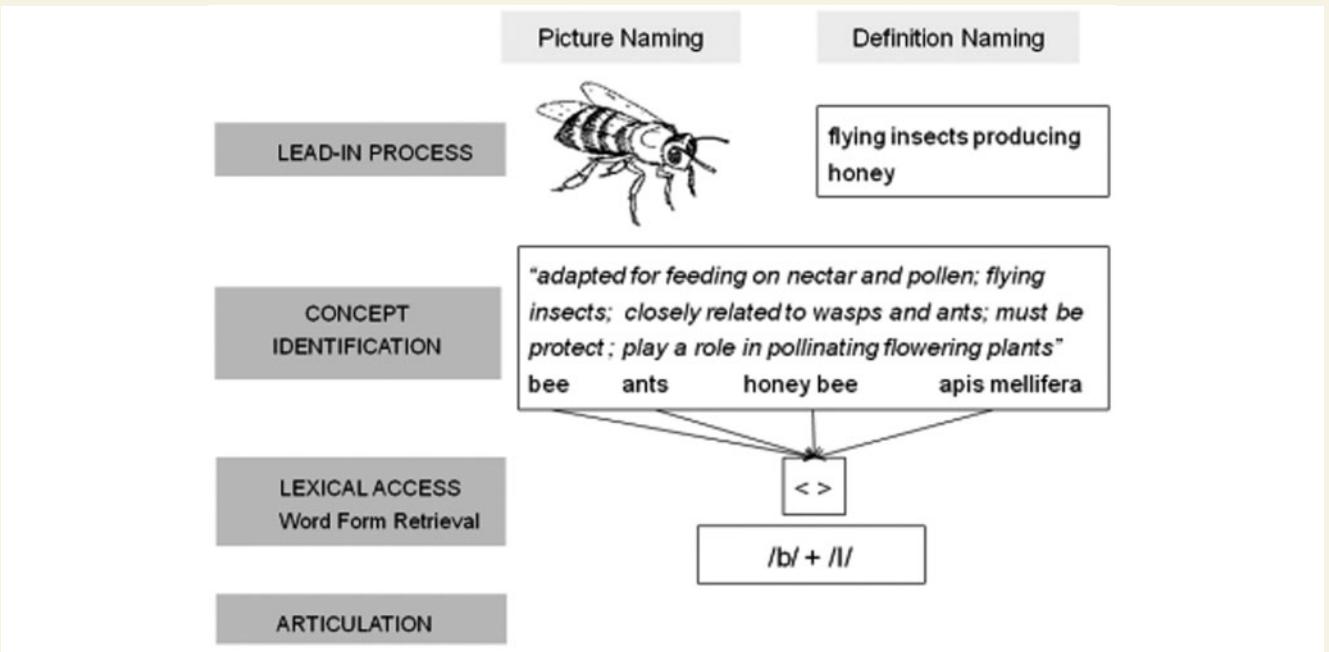


Figure 1 Word production model. LEAD-IN PROCESS = recognition of the visual stimulus or understanding of the definition as pointing to a familiar concept. CONCEPT IDENTIFICATION = access of the meaning of the object, or the concept, in the semantic system. LEXICAL ACCESS = retrieval of the lexical representation and access of its phonological word form in the lexical system. ARTICULATION = planning of the motor programmes that drive articulation.

diffusion and perfusion imaging in a large cohort of patients. The dysfunction was interpreted in a model along the lines of the model described above. A distinction was reported between conceptual identification, associated with dysfunction in anterior temporal brain areas (BA 21-22-38), and word retrieval associated with posterior temporal regions (BA 37-39). These findings provided new evidence that a network of brain regions supports naming, but that separate components of this network were differentially required for distinct cognitive processes (see also Raymer *et al*., 1997; Damasio *et al*., 2004; Price *et al*., 2005).

In temporal lobe epilepsy, word finding difficulties were originally investigated with the picture naming task. Some studies showed worse performance in TLE than in matched controls, while others did not detect significantly poorer performance in left TLE than in right TLE (Hermann and Wyler, 1988; Hermann *et al*., 1991; Saykin *et al*., 1995; Langfitt and Rausch, 1996; Drane *et al*., 2008). Hamberger and colleagues elicited patients' responses with oral definitions instead of pictures. The definition task has proved to be more sensitive than the picture task when it comes to detecting preoperational TLE language deficits (Hamberger and Tamny, 1999; Bell *et al*., 2003; Hamberger and Seidel, 2003).

The neural basis of this deficit, present mostly in left TLE patients, has been investigated using electrico-cortical stimulation mapping. This technique is widely regarded as the gold standard for predicting postoperative functional impairment. For example, stimulation of brain areas during picture naming has been the task of choice for identifying language cortex based on positive naming sites during pre-surgical mapping (Ojemann *et al*., 1989). Within the temporal lobe, Hamberger and colleagues have shown that definition naming sites (i.e. sites at which stimulation impairs auditory but not visual naming) are generally located anterior to visual naming sites or so-called 'dual' sites (i.e. sites at which stimulation disrupts both auditory and visual naming) (Hamberger *et al*., 2003, 2007*a*; Hamberger *et al*., 2005). These results are consistent with the prevalent view in temporal lobe surgery that word finding difficulties follow anterior temporal lobectomy (Bell and Davies, 1998; Davies *et al*., 1998, 2005; Schwarz *et al*., 2005; Drane *et al*., 2008).

The evidence we have reviewed so far indicates an association between word retrieval processes and posterior temporal sites in healthy speakers and ischaemic stroke patients. In contrast, TLE patients' difficulties in word retrieval, most clearly seen in the definition task, are associated with more anterior temporal sites. This apparent discrepancy could be due to fundamental specifics versus reorganization of the language system in pharmaco-resistant epilepsy (Devinsky *et al*., 1993; Hamberger *et al*., 2007*b*). Alternatively, it could point to the need for characterizing naming performance and naming failure in TLE in a much more detailed manner, for example using the processing model briefly described above.

A central aspect of such a model is the distinction between concept identification and word form retrieval. Strong support for this distinction comes from studies of anomic patients and tip-of-the-tongue states in healthy speakers. A characteristic (almost defining) feature of the performance seen in these cases is that speakers have access to the meaning they intend to express but they fail to retrieve the corresponding word (Brown, 1991). This is evident from a preserved ability to provide detailed information about the concept by means of circumlocutions or gestures, while failing to produce the target word. Furthermore, speakers in anomic or tip-of-the-tongue states are usually helped by phonemic cues (e.g. the first letter or sound of the missing word) (Howard *et al*., 1984). In languages with a grammatical gender system (e.g. Italian or French), patients can provide the grammatical gender of the missing word fairly accurately (Badecker *et al*., 1995; Vigliocco, 1997).

The distinction between concept identification and word form retrieval may have been partly overlooked in clinical studies exploring word retrieval performance in epilepsy (e.g. in peri-operative or postoperative settings). This is because the precise origin of defective word retrieval (lack of recognition of the intended concept versus genuine lack of access to lexical representations) has not always been tested precisely on a trial by trial basis. Failure to do so can lead to over-estimations of lexical deficits by confounding them with lack of conceptual retrieval or lack of familiarity with the intended concept. The importance of this distinction was previously noted by Hamberger *et al*. (2003), who distinguished tip-of-the-tongue states from correct naming scores. Drane *et al*. (2008) also distinguished recognition from naming processes in patients with anterior temporal lobectomy. In the latter study, patients with non-dominant TLE exhibited an identification deficit, whereas patients with dominant lobe resection mostly suffered from word retrieval deficits (Drane *et al*., 2008).

In short, the available evidence does not allow strong conclusions to be drawn on the neural substrate that induces word finding difficulties in pre-surgical pharmaco-resistant TLE. We combined detailed neuropsychological assessment of such word finding difficulties with evaluation of resting-state brain metabolism in 18FDG-PET. The main goal of this study was to determine the processing level impaired in naming difficulties in pharmaco-resistant TLE and its possible anatomo-functional substrate.

Materials and Methods

Participants

The study involved 43 adult patients (25 female, 18 male) with drug-resistant epilepsy diagnosed at the department of Hôpital La Timone (Marseille, France) between December 2006 and March 2007.

A standard Oldfield test indicated that 34 patients were right-handed, six left-handed and three ambidextrous (Oldfield, 1971). A total of 18 patients (including all left-handed and ambidextrous patients) underwent fMRI to determine hemispheric language dominance. When doubt regarding language dominance persisted (three patients), a Wada test was performed. Forty-one patients in the study were left-hemisphere dominant, while two patients with atypical language lateralization were excluded. Neurological examinations were normal. The demographic and clinical data are summarized in Table 1. Detailed information is available in the supplementary materials (Supplementary Table 1).

Table 1 Demographics and clinical data

	Left TLE $n = 27$	Right TLE $n = 14$
Age	42 (19–72)	34 (55–18)
Gender	18 (F) 9 (H)	8 (H) 6 (F)
Educational level		
Level 1	14	6
Level 2	7	5
Level 3	6	3
Handedness	18 (1–20)	16 (3–20)
Number anti-epileptic drugs	3 (2–4)	3 (1–4)
Patient treated with Tomiramate	2	4
Duration of epilepsy	22 (1–54) SD = 13	16 (3–41) SD = 13
Age at seisure onset	18 (6–50) SD = 11.1	17 (4–47) SD = 11.6
Current frequency of seizure	24 (1–150) SD = 41.2	29 (1–115) SD = 17.5

Age (min–max); gender (M = male, F = female); educational level (level 1 = not high school graduate, level 2 = high school graduate, level 3 = college undergraduate or more); handedness = right handed score (Oldfield) (min–max); duration of epilepsy in years (min–max, SD); age at seizure onset in years (min–max, SD); current frequency of seizure by month (min–max, SD).

Table 2 Epilepsy features

		Medial	Medio-lateral	Other
Left TLE				
MRI	Normal	5	3	2
	HS	11	1	0
	Lesion	3	2	0
Medial PET	Normal	0	1	2
	Moderate	14	2	0
	Severe	5	3	0
Lateral PET	Normal	12	1	1
	Moderate	7	5	1
	Severe	0	0	0
Right TLE				
MRI	Normal	1	3	2
	HS	4	1	0
	Lesion	2	1	0
Medial PET	Normal	5	3	0
	Moderate	1	1	1
	Severe	1	0	0
Lateral PET	Normal	4	2	0
	Moderate	2	2	1
	Severe	1	0	0

Medial and medio-lateral epilepsy according to Maillard *et al*. (2004). Other = patients had, in addition, an involvement of extra temporal regions (occipital or frontal region). HS = hippocampal sclerosis, lesion = other temporal lesion [dysplasia (6), cavernoma (1), oligodendroglioma (1)]. Medial and lateral PET = ipsilateral 18FDG-PET metabolism visually described for each patient in normal, moderate, or severe.

The epilepsy diagnosis was made during pre-surgical assessment for drug-resistant partial epilepsy on the basis of seizure semiology, ictal and interictal EEG recordings as well as structural and functional neuro-imaging (MRI and 18FDG PET, respectively). Video-electroencephalographic (EEG) recording, performed to analyse usual seizures and interictal EEG, was used to determine the side and extent of the epileptogenic zone. All patients had temporal epilepsy in the broad sense of the term. According to electro-clinical features, temporal epilepsy was classified as medial ($n = 26$) and medio-lateral ($n = 10$) (Maillard *et al*., 2004). In five patients seizures could start in occipital ($n = 3$) or frontal regions ($n = 2$) and spread systematically to temporal lobe structures. Individual hypometabolism was especially analysed in mesial and lateral temporal regions, and described as 'normal', 'moderate' or 'severe'. MRI was normal in 15 patients, and showed hippocampal sclerosis (HS) in 17 patients, and other temporal lobe lesion(s) in 8 patients [dysplasia (6), cavernoma (1), oligodendroglioma (1)]. Epilepsy features in left and right TLE are summarized in Table 2. Further details are available in the supplementary materials (Supplementary Table 2). Patients were not subjected to any invasive procedure, were fully informed about the study and gave their written consent.

Neuropsychological assessment

A standard neuropsychological evaluation was conducted (Wechsler Adult Intelligence Scale and Wechsler Memory Scale III). We then focused on assessing language performance with (i) the word fluency test from MEC (Joanette, 2006); (ii) French versions of the word and sentence repetition tasks from BDAE; (iii) Token Test; and (iv) a syllable deletion task (Giraud *et al*., 2005). Auto-assessment of word finding difficulties was performed by the patients on a scale from 'no word finding difficulties in conversational speech' (scale 0) to 'great difficulties with word finding' (scale 5).

Naming assessment

Two naming tests were administered to all patients: picture naming and auditory definition naming. For picture naming, we selected 80 line drawings representing natural ($n = 32$) or manufactured objects ($n = 48$) taken from the database Lexis (De Partz, 2001). Each item's name was characterized by its lexical frequency and length in syllables.

For auditory definition naming, we adapted the test devised by Hamberger and Seidel (2003) in which patients are required to name items in response to definitions (e.g. 'flying insect producing honey'). We constructed 80 such definitions whose responses were different from those of the picture naming test above, but matched for various relevant variables (same distribution of man-made and natural objects, paired lexical frequency and syllabic length). The terms used in the definitions were expected to be understood by the patients. Normative data obtained from 35 consecutive healthy subjects matched in age and education level to the patients showed very high levels of performance in both tasks (score 95% correct, SD 5).

Procedure

The two naming tests were conducted in two independent blocks. The pictures were printed on paper, one item per sheet. The definitions were spoken aloud by the experimenter to the patient. Participants were asked to name aloud the object depicted, or referred to, using a single word.

Response times were measured with one second accuracy, from the onset of picture presentation in the visual task, and from the end of the definition in the auditory task.

A response was considered to be correct when it coincided with the name of the picture given in Lexis, or to the name of the definition in the pilot study conducted to obtain normative data. Based on previous

studies (Bell *et al*., 2003; Hamberger and Seidel, 2003) correct responses were classified in terms of time to response, with highly delayed responses being excluded (responses were accepted within a delay of 5 s in the picture task and 10 s in the definition task).

Trials in which the patient failed to provide any answer before the time limit were given special attention. Once the time limit was expired, an attempt was made to differentiate recognition failure from word retrieval failure. To do so, the availability of semantic information regarding the target item was tested. Patients were asked to use gestures or circumlocutions to describe the meaning of the word they were searching. The following questions were asked: (i) 'Do you recognize the object?' or 'Do you understand what I mean?'; (ii) 'Can you imagine what the object looks like?' According to the answers, the trial was classified in one of two classes: 'no recognition/unfamiliar' versus 'object identified without name retrieval'. The latter, interpreted as genuine word retrieval failures, were the critical anomic states.

Anomic states were further explored by testing the availability of linguistic information with standard methods previously used in their investigation. The experimenter asked the patient to provide: (i) the grammatical gender (masculine versus feminine) of the target noun; and (ii) the first letter/phoneme of the target word. In case the patient failed to provide the correct responses, the examiner provided a phonemic cue (initial phoneme). A correct response at that point was considered to result from phonemic cueing.

Other erroneous trials included phonetic paraphasias (when the target word was produced but inappropriately articulated) and semantic paraphasias (when a word semantically related to the target was produced, irrespective of how correctly it was articulated).

Brain resting state metabolism

18FDG-PET was performed during pre-surgical assessment for drug-resistant partial epilepsy using an integrated PET/CT scanner Discovery ST (GE health care, Waukesha, USA), which consists of a 4-multislice helical CT scanner and 10 080 BGO crystals arranged in a 24-ring PET tomography. 150 MBq of 18FDG were injected in a quiet environment with eyes closed. Patients rested during the 30-min uptake period. After this, a CT in helicoidal mode was first performed for an attenuation-correction map determination with 80 mA and 140 kV, with 3.75-mm slice thickness spaced by 3.27 mm in a 512_512 matrix. The transaxial spatial resolutions (full width half maximum, average of radial and tangential) of the PET at 1 and 10 cm off axis were 6.2 and 6.7 mm in 3D. The 24 rings of the PET system allow 47 images to be obtained, with a 3.27-mm slice thickness spaced by 3.27 mm in a 256_256 matrix, and covering an axial field of view of 157 mm. Attenuation-corrected images were reconstructed using the ordered subsets expectation maximization algorithm, with 5 iterations and 32 subsets.

Ipsilateral 18FDG-PET metabolism of medial and lateral temporal regions was visually described by the same experienced nuclear medicine physician (EG) for each patient as normal, moderate or severe.

Statistical analysis

Characterization of behavioural performance

Naming performance at the trial level (i.e. occurrence of an anomic state) was analysed with a logistic linear model including fixed effects, as well as crossed random effects for participants and items (Baayen, 2008; Jaeger, 2008; Quené and van den Berg, 2008). We constructed two models. First, we started by estimating the effects of the major predictors: Laterality of epilepsy (left TLE versus right TLE) and Task (picture versus definition), and their interaction. This led us to restrict further analysis to the sub-population of left TLE patients (see details below).

In the second restricted analysis, the model comprised three types of predictors. We tested effects of (i) demographic of the patients; (ii) linguistic properties of the stimuli; and (iii) performance in related non-linguistic neuropsychological tasks.

Clinical and neuroimaging parameters modulating the incidence of anomic states

The possible role of clinical (epilepsy features, see Tables 1 and 2) and neuroimaging factors was assessed in two analyses. Firstly we conducted a logistic linear model similar to those reported above, with epilepsy and neuroimaging features as predictors of the rate of anomic states.

In a second more thorough analysis we estimated the whole brain 18FDG-PET voxel-based correlation, as previously described (Chetelat *et al*., 2003), and estimated the relationship between the occurrence of anomic states and the resting-state brain metabolism. In order to do so, the PET images were converted from the DICOM to the Analyse format using the software MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html), then transferred to the software SPM2 (Welcome Department of Cognitive Neurology, University College, London). The data were standardized onto the Montreal Neurological Institute atlas (MNI) by using a 12-parameter affine transformation, followed by non-linear transformations and a trilinear interpolation. The dimensions of the resulting voxel were $2 \times 2 \times 2$ mm. The images were then smoothed with a Gaussian filtre (12 mm FWHM) to blur individual variations in gyral anatomy and to increase signal-to-noise ratio. Global normalization was performed using proportional scaling. Voxel-based correlations were performed within SPM2 using the 'single subject, covariates only' statistical model. The SPM {T} maps were obtained at an uncorrected height threshold of $P = 0.005$, adjusted for cluster volume ($P < 0.05$). Values of cluster were extracted and MNI coordinates converted into Talairach coordinates using Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html). Spearman's correlation was used to assess the relationship between the occurrence of anomic states and brain PET metabolism of each extracted cluster. In addition, to confirm specific correlation with anomic state, Spearman's correlations between brain PET metabolism of the same extracted cluster and language (word fluency test, token test, syllable deletion task, word and sentence repetition task) or memory (working memory and general memory) tasks were performed.

Results

Neuropsychological assessment

Average performance in neuropsychological assessments is reported in Table 3. There was no difference between left TLE and right TLE. Details are available in supplementary materials (Supplementary Table 2).

Table 3 Neuropsychological data

	Left TLE		Right TLE		
	M	SD	M	SD	*t*-test
Auto-assesment	2.1	1.3	1.5	1.5	NS
Word Fluency Test (free)	48.4	16.6	46.2	18.9	NS
Word Fluency Test (letter P)	19.3	9.8	21.7	9.1	NS
Word Fluency Test (categorical)	23.6	6	22.3	6.4	NS
Word and sentence repetition	34.5	0.9	34.4	1.4	NS
Syllabe deletion task (errors)	1.2	2.3	1.7	3.2	NS
Syllabe deletion task (time)	152.4	91.1	165.1	102.7	NS
Token Test	19.3	2.1	20.1	1	NS
IQ	84.7	12.2	85.8	12.2	NS
Performance IQ	86.5	13.5	82.5	12.5	NS
Verbal IQ	85.4	12.7	88	10.9	NS
Auditory MQ	95.3	10.3	100.1	14.6	NS
Visual MQ	103.7	15.6	96.6	11.9	NS
Digit Span	8.4	2.6	8.7	2.9	NS
Reverse Digit Span	3.8	0.9	4.3	1	NS
Digit + Letter Span	8.6	2.7	8.1	3.2	NS
Visuo-spatial Span	7.8	2.1	8.4	3.2	NS

No difference was found between left and right TLE patients.
Auto-assessment of word finding difficulties (between scale 0 'no word finding difficulties in conversational speech' to scale 5 'great difficulties with word finding').
Word Fluency test: free = number of word in 2'30; Letter P and categorical = number of word in 2'.
Word and sentence repetition tasks (35 items) = number corrects responses.
Syllable deletion task (20 items): number of errors and time in second.
Token Test (part 5, 22 items): number corrects responses.

Characterization of behavioural performance

The average performance of each patient in each of the two tasks is presented in the supplementary material (Supplementary Table 2). A summary is provided in Fig. 2A. In trials where there was an anomic state, patients were able to provide the correct gender (72.5% accuracy, chance = 50%, Pearson's $\chi^2 = 33.0$, $P < 0.001$), and found the appropriate response when provided with a phonetic cue (68.1% accuracy). This global pattern is typical of anomic states in aphasics and tip-of-the-tongue states in healthy speakers.

The data set comprised the performance of all patients in both naming tasks, yielding a total of 6254 trials (a few definitions could not be tested on all patients). Given our focus on anomic states, we excluded phonetic and semantic paraphasias from the analysis, as well as trials in which participants reported not recognizing or understanding the stimulus or the intended target (302 trials, 4.8% of the data set). This left 5952 trials from 41 patients.

First model: effects of laterality of epilepsy and task

The first analysis showed strong effects of laterality and task (Table 4, model 1). Performance was poorer for left TLE than for right TLE patients, and poorer for the definition than for the picture task in the whole population. We found no evidence for an interaction between the two factors. This suggests that the difference between the definition and the picture tasks was comparable across the two populations of left TLE and right TLE patients. Left TLE patients produced a high and variable number of tip-of-the-tongue states, both in the picture and the definition tasks (Fig. 2B). This rate was considerably lower for right TLE patients, and hence no further attempt was made to understand their origin.

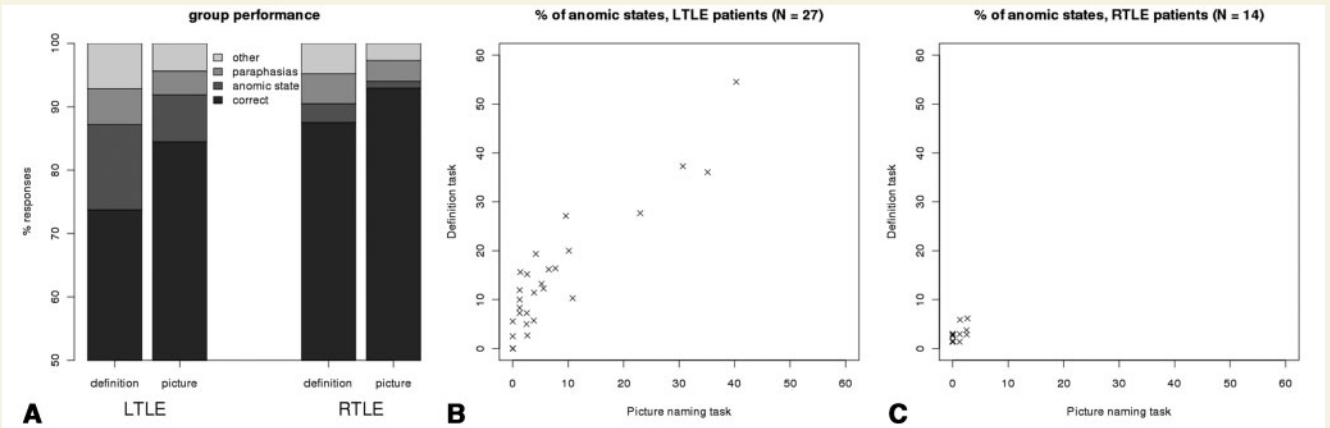


Figure 2 (**A**) Naming performance in the picture and definition tasks. Left TLE (picture task): correct response = 84.5%, anomic state 7.4%, paraphasia (semantic and phonemic paraphasia) 3.8% and other (no recognition of the items or unfamiliar items) = 4.4%. Left TLE (definition task): correct response = 73.7%, anomic state = 13.5%, paraphasia 5.7% and other = 7.1%. Right TLE (picture task): correct response = 92.3%, anomic state = 1.1%, paraphasia 3.3% and other = 2.7%. Right TLE (definition task): correct response = 87.5%, anomic state = 2.96%, paraphasia 4.7% and other = 4.8%. (**B**) and (**C**) Variability of word finding difficulty in both tasks. Left TLE patients (**B**) produced a high and variable number of tip-of-the-tongue (TOT) states, both in the picture and the definition tasks. This rate was considerably lower for right TLE patients (**C**).

Table 4 The significant predictors of anomic states

	Factor	β	St-err	Z-value	*P*
Model 1	Task	0.82	0.12	7.01	<0.001
41 patients	Laterality	1.92	0.50	3.80	<0.001
	interaction	0.33	0.42	<1	0.43
Model 2	Task	0.92	0.20	4.70	<0.001
23 patients[a]	Sex	1.20	0.59	2.03	0.04
	Lexical frequency	0.74	0.07	12.10	<0.001
	IQ	1.17e-3	5.89e-4	2.00	<0.05
Model 3	Lateral hypometabolism	0.90	0.36	2.51	0.01
25 patients	Frequency of seizures	0.27	0.14	1.91	0.06
	Type of epilepsy	0.78	0.41	1.90	0.06

Model 1 showed strong effects of laterality and task. Performance was worse for left TLE than right TLE patients, and it was worst for the definition than for the picture task. We found no evidence for an interaction between the two factors.
Model 2 (left TLE patients) showed an effect of the gender (males tended to produce fewer anomic states than females), an effect of lexical frequency (low lexical frequency word tended to produce fewer anomic states than high lexical frequency) and an effect of IQ.
Model 3 (left TLE patients) showed the effect of hypometabolism in the lateral areas (the rate of anomic states was greater when lateral hypometabolism was more severe), a positive effect of type of epilepsy (anomic states were more common in medio-lateral epilepsy than in medial epilepsy) and an effect of the frequency of the seizures (an increase in frequency lead to an increase in rate of anomic states).
a Similar effects were observed when the model was computed over 27 patients, including those for which IQ measure was not available.

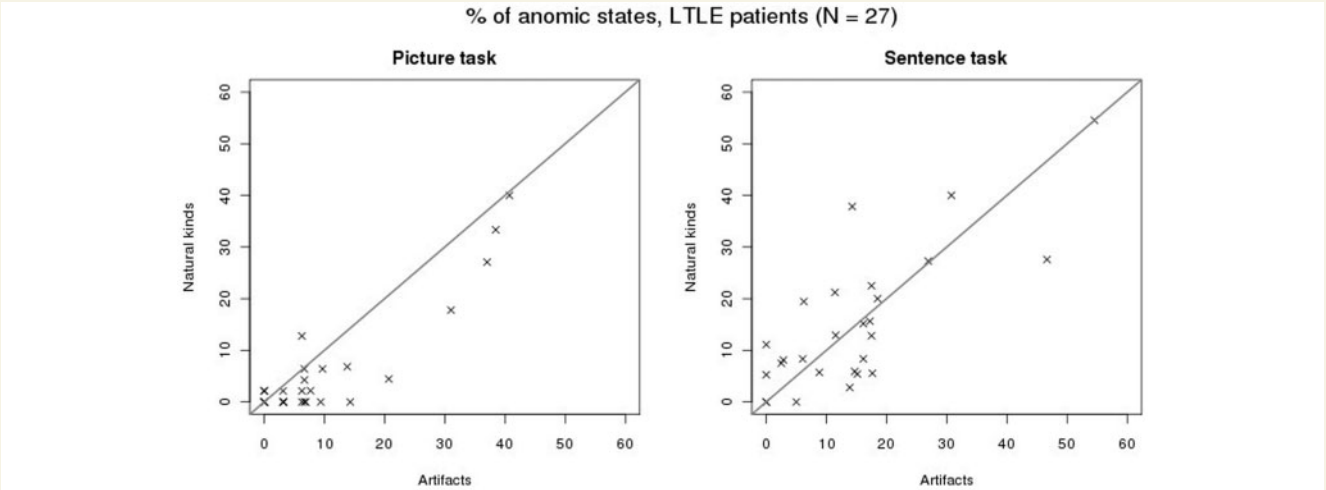


Figure 3 Tip-of-the-tongue states according to semantic classification of the object (natural or man-made/artefact). Tip-of-the-tongue states were evenly distributed across these two categories.

Second model: patients' demographic and neuropsychological performance and stimuli linguistic properties

The following analyses (Table 4, model 2) were restricted to left TLE patients (3882 trials from 27 patients). We observed a significant effect of gender (males tended to produce fewer anomic states than females). We found no evidence for effects of schooling level ($Z<1$), the age of the patient ($Z=1.30$, $P=0.19$). When psycholinguistic variables characterizing the target items were tested, we observed a robust effect of lexical frequency. In contrast, we found no evidence for effects of number of syllables, nor for the semantic classification into natural and man-made objects (both $Z<1$). As shown in Fig. 3, the tip-of-the-tongue states were evenly distributed across these two categories. Finally, we considered the role of IQ and memory performance, in an attempt to capture variability associated with different levels of baseline performance in neuropsychological testing. For this analysis, detailed neuropsychological assessment was only available for 23 of the 27 left TLE patients. We observed a significant effect of IQ (Table 4, model 2). In contrast, no evidence was found in favour of contributions from general memory (QM) or working memory (variables tested: digit+letter, span reverse digit span). The significant predictors and the corresponding statistical tests are presented in Table 4, model 2; a computation of Somers' rank correlation between the data and its estimation indicates a good fit of the model (Dxy = 0.83, compare to 1).

Clinical and neuroimaging parameters modulating the incidence of anomic states

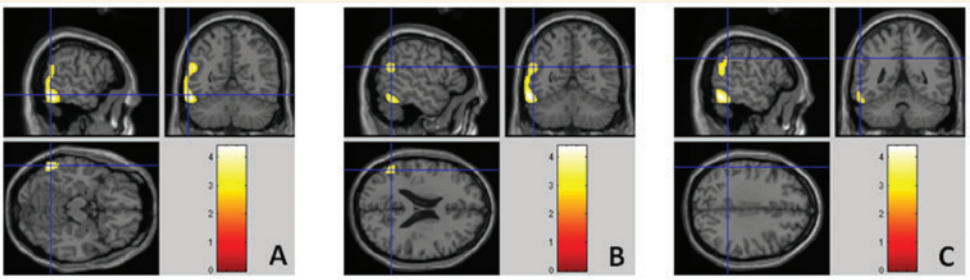
We estimated the relationship between specific epileptic features (Tables 1 and 2), notably neural features of the patients, and the rate of anomic states with a logistic regression model. In light of the findings of the first model reported above, this analysis was restricted to left TLE patients, from which patients diagnosed with occipito-temporal epilepsy were further excluded due to their low numbers ($n=2$). The analysis was conducted on 3602 trials from 25 patients. We found no evidence for effects of the age at the onset of epilepsy ($Z<1$) or its duration ($Z<1$), nor the intake of anti-epileptic drugs (number of anti-epileptic drugs: $Z=1.32$, $P=0.19$; the possible specific effect of topiramate could not be tested due to small group sizes, see Table 1). In addition, we found no evidence for effects of lesion (hippocampal sclerosis; $Z<1.6$, $P>0.1$). Estimates of hypometabolism in the medial areas did not produce a significant effect ($Z<1$). In contrast, estimates of hypometabolism in the lateral areas had a significant contribution (Table 4, model 3); the rate of anomic states was greater when lateral hypometabolism was more severe. We also observed a marginally significant effect of seizure frequency (computed in seizure per month on a logarithmic scale); an increase in frequency lead to an increase in rate of anomic states. Finally, we found a marginally significant positive effect of type of epilepsy; anomic states were more common in medio-lateral epilepsy than in medial epilepsy.

This analysis provides a first indication of an involvement of lateral areas in the occurrence of anomic states. This indication comes from the observation that the rate of anomic states increased in patients with lateral hypometabolism, and in medio-lateral epilepsy patients compared to medial epilepsy. These suggestive effects were observed while the effect of seizure frequency was controlled.

To further ascertain these findings, we conducted the next analysis, in which we sought to identify correlations between brain 18FDG-PET metabolism and the rate of occurrence of anomic states in an unconstrained whole-brain analysis.

The results showed that the rate of occurrence of anomic states was negatively correlated with the metabolism of a left temporo-parietal cluster (Spearman's $\rho=-0.5079$, $P=0.0007$), including left inferior temporal gyrus (BA20-BA37), superior temporal gyrus (BA39) and inferior parietal lobule (BA40) (P-voxel <0.005, P-cluster $=0.05$, Fig. 4 and Table 5). In contrast, the rate of occurrence of other incorrect responses (unfamiliar or no recognized) was not correlated with the metabolism within this cluster (Spearman's $\rho=-0.19$, $P=0.2303$).

This correlation between left posterior metabolism and anomic states persists when patients with lesions other than hippocampal sclerosis were excluded ($n=33$, Spearman's $\rho=-0.5838$, $P=0.0003$), as well as when analysis was separately restricted to patients with normal MRI ($n=16$, Spearman's $\rho=-0.6431$,



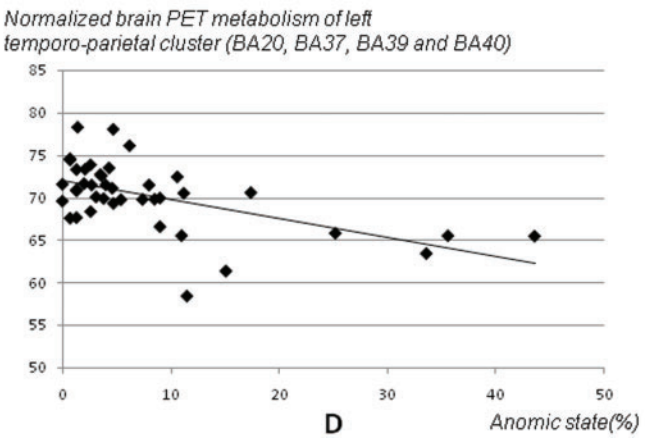


Figure 4 Anatomical localization of peaks of significant correlation between anomic states and brain PET metabolism in patients with temporal lobe epilepsy (**A**–**C**; P-voxel <0.005, and P-cluster $=0.05$, left BA20). (**D**) Rate of Anomic state is correlated with a left temporo-parietal cluster of metabolism ($r=-0.5548$, $P=0.0002$); (**A**) including left inferior temporal gyrus (BA20-BA37); (**B**) superior temporal gyrus (BA39) and; (**C**) inferior parietal lobule (BA40).

Table 5 Correlation between rate of occurrence of anomic states and 18FDG-PET

P-cluster	*k*	*T*-score	*P*-voxel	Talairach coordinates (mm)			Localization
				x	*y*	*z*	
0.042	681	4.39	<0.001	−57	−55	−11	Left Inferior Temporal Gyrus (BA20)
		4.18	<0.001	−58	−57	−9	Left Inferior Temporal Gyrus (BA37)
		3.56	<0.001	−51	−53	23	Left Superior Temporal Gyrus (BA39)
		2.79	0.004	−55	−45	34	Left Supramarginal Gyrus (BA40)

k-value represents the number of significant voxels in the particular cluster. *P*-values are not corrected for multi-comparison for whole-brain analysis.

$P = 0.007$) or patients with hippocampal sclerosis ($n = 17$, Spearman's $\rho = -0.4849$, $P = 0.048$). In addition, no lesion was located within this cluster.

This same cluster was also correlated with anomic states in the subgroup of left TLE patients ($n = 27$, Spearman's $\rho = -0.5049$, $P = 0.0072$), but not in patients with right TLE (Spearman's $\rho = -0.0029$, $P = 0.922$). Within the left TLE subgroup, when analysis was restricted to patients with great word findings difficulties [anomic states > 10 (= median left TLE's anomic states, see Supplementary Table 2), $n = 14$], the same cluster was also correlated with anomic states (Spearman's $\rho = -0.5743$, $P = 0.0384$). Then when analysis was restricted to patient with a unique temporal epileptogenic zone ($n = 25$, medial and medio-lateral), a significant correlation persisted (Spearman's $\rho = -0.4091$, $P = 0.0423$) within this cluster.

Whereas IQ was a significant factor to explain the occurrence of anomic state (see above), IQ was not correlated with the metabolism of the left temporo-parietal cluster ($n = 36$, Spearman's $\rho = 0.1168$, $P = 0.49$), even when we restricted the analysis to left TLE patients ($n = 25$, Spearman's $\rho = 0.0904$, $P = 0.66$).

In addition, the metabolism of the left temporo-parietal cluster was not correlated with scores in other language tasks such as sentence and repetition tasks, word fluency test or syllable deletion task, even when the analysis was restricted to left TLE patients. Equally, the metabolism of this same cluster was not correlated with score in general memory tasks or in working memory tasks, even when the analysis was restricted to left TLE patients (details available in Supplementary Table 3).

Discussion

The present study provides evidence that many cases of word finding difficulty in TLE can be considered as anomic states. This deficit is related to the lateralization of epilepsy, as anomic states are considerably more frequent in left than in right TLE. Furthermore, this impairment is strongly correlated with resting-state metabolism of the postero-infero-temporo-basal region (BA 20-37), of the posterior part of GTS (BA39) and inferior parietal lobule (BA 40). We discuss the behavioural and neural aspects of these findings in turn.

Lexical access difficulty in TLE

Using similar protocols, previous studies have shown naming difficulties in TLE patients (Hamberger and Tamny, 1999; Bell *et al*., 2003). However, clearly distinguishing between different types of deficit (in particular, word retrieval failure versus impaired concept retrieval) is difficult, as a global naming score (e.g. rate of correct responses) does not separate these functions. In light of the difference between picture and definition naming scores, Hamberger and Seidel (2003) suggested an impairment at the level of the semantic system. Bell and colleagues (2001) tried to specify the level of the deficit: they compared picture object naming ability and depth of semantic knowledge and found that patients with TLE had difficulties in both lexical and concept retrieval (Bell *et al*., 2001). In the current study, we identified trials in which word finding difficulties could be unambiguously established, based on the model of anomic or tip-of-the-tongue states. We selected trials in which participants (i) provided evidence of having understood the concept that the picture or definition referred to; and (ii) were not able to produce the corresponding name. In addition, during many of these trials, patients were able to provide reliable lexical information (in terms of the grammatical gender of the missing word) and benefited from phonological cues. This analysis indicated that a sizeable proportion of trials eliciting naming difficulties indeed corresponded to anomic states/lack of word retrieval. Our findings strongly suggest that this naming impairment corresponds to a deficit in lexical retrieval (Rapp and Caramazza, 1997; Raymer *et al*., 1997).

We showed that rate of anomic states was sensitive to the laterality of epilepsy and the task. Left TLE patients presented more lexical access difficulty than right TLE patients in both modalities, with worse performance in the definition than in the picture task without interaction between these two factors. This result is in contrast with a previous report which only showed difference in the score of the definition task, but not in the picture task between left and right TLE (Hamberger and Tamny, 1999; Hamberger and Seidel, 2003). This discrepancy could be explained by our analysis at the single trial level, which evidenced a difference between left and right TLE patients in the picture task that was not observed in previous studies. Furthermore, the presence of patients with severe deficit that showed very poor performance in picture naming (see Supplementary Table 2) contributes to an important difference between left and right TLE in this task. This being said, as shown by Hamberger and colleagues and the present data, the definition task is indeed more sensitive than the picture task.

Anomic states are considerably more frequent in left than in right TLE. Furthermore, no difference in performance in other language tasks such as comprehension tasks, token test, repetition tasks and syllable deletion task was observed. This suggests that

the left TLE deficit is relatively circumscribed to the ability to retrieve words from memory, not a general language deficit.

In addition, the anomic state was further characterized by considering possible contributions of psycholinguistic and neuropsychological factors. Psycholinguistic analysis showed that patients have more lexical access difficulty with low frequency words, as previously observed in naming studies (Raymer *et al*., 1997). This is a standard observation in healthy and impaired language performance (Nickels and Howard, 1994). In contrast, the analysis provides no evidence for an effect of object properties (man-made or not). As shown in Fig. 3, the tip-of-the-tongue states were evenly distributed across these two categories. Although category specific deficits have previously been reported (Drane *et al*., 2008), they do not seem to be present in this population. This provides a further argument in favour of deficit at the lexical rather than semantic level of processing. Among neuropsychological factors, no significant effect was observed for variables measuring immediate memory and working memory, yet a significant effect of IQ was observed. This result is probably the sum of several facts: (i) assessment of mental ability depends upon multiple cognitive processes and one explanation could be that poor lexical access promotes lower IQ; and (ii) severe pharmaco-resistant epilepsy could impair lexical acquisition and other general learning leading to poor IQ and greater rate of anomic states. A recent review of longitudinal studies has suggested the existence of a relationship between seizure frequency and changes in IQ or memory function (Dodrill, 2004). A marginal effect of lexical access difficulty with increased seizure frequency was observed in our study; it might be hypothesized that higher seizure frequency could induce a larger functional language deficit due to post-ictal disturbance. However there was no evidence for effects of other epileptic variables (age of seizure onset, duration of epilepsy, anti-epileptic drugs), hence this proposal will have to be re-examined in future studies

Anatomo-functional substrate of lexical access difficulty

We found no evidence for effects of hippocampal sclerosis or medial hypometabolism in anomic states. Some previous studies showed a significant relationship between correct responses in picture naming and hippocampal pathology (Davies *et al*., 1998; Martin *et al*., 1999; Sawrie *et al*., 2000*b*) whereas others have not (Sass *et al*., 1992; Baxendale *et al*., 1998). Sawrie, using quantitative magnetic resonance spectroscopy, found that speech dominant hippocampus was a significant component of the overall neuroanatomical network of visual naming (Sawrie *et al*., 2000*a*). However, this study looked only at medial temporal structures and did not consider the possible role of other temporal regions. Overall, the question of the role of mesial temporal region in naming thus remains open.

In our study, the rate of anomic states increased in patients with lateral hypometabolism as measured using PET, or in those patients defined as having medio-lateral epilepsy as opposed to purely medial epilepsy. This result indicates an involvement of lateral areas in the occurrence of anomic states.

To further ascertain these findings, the anatomo-functional substrate of lexical access difficulty was investigated on the basis of unconstrained whole-brain metabolism evaluated with 18FDG-PET. The rate of tip-of-the-tongue states showed a correlation with brain metabolism mainly in inferior and posterior temporal regions (BA 20-37-39) and to a much lesser degree in the parietal region (BA 40). This finding was confirmed both within the subgroup of left TLE and within the subgroup of patients with severe anomia. To our knowledge this provides the first evidence of a correlation between verbal processing dysfunction in TLE and brain metabolism.

Our observations of a negative correlation between temporal lobe metabolism and the rate of occurrence of anomic state are consistent with a growing body of literature demonstrating a relationship between lexical access and the left infero-posterior temporal region. Impaired naming of both visual and tactile stimuli in the presence of intact word comprehension (a pattern indicative of disruption at the level of modality-independent lexical access) is associated with tissue dysfunction in the left part of the posterior middle/inferior temporal and fusiform gyri (BA 37) (Hillis *et al*., 2002; Raymer *et al*., 1997). Furthermore, restored blood flow leading to restored neural function in left BA 37 is associated with improvement in naming but not comprehension (Hillis *et al*., 2001*a*; Hillis *et al*., 2006). Additional evidence that this area is important for naming comes from functional imaging studies of normal subjects that show activation of left middle temporal gyrus (Howard *et al*., 1992) and fusiform gyrus (Grabowski *et al*., 2003*b*; Price *et al*., 2005; Kemeny *et al*., 2006; Saccuman *et al*., 2006) during naming tasks. Other data have also suggested that BA 37 and 20 are important in word selection and are believed to be multimodal (Buchel *et al*., 1998).

Evidence regarding language processing in TLE has also come from post-surgical data and intracranial stimulation. Postoperative naming deficits have been observed after anterior temporal lobectomy. Such a result has prompted the conclusion that the anterior part of the temporal lobe plays a critical role in the occurrence of word finding difficulties. Numerous intra-cranial stimulation data have demonstrated a widespread temporal area associated with speech arrest and naming failure. Recent studies of intra-cranial stimulation have sought to specify these conclusions by investigating sites that compromise word production in the picture task, the definition task, or both. Anterior temporal lobe sites were associated with disruption of performance only in the definition task, whereas more posterior temporal lobe regions were associated with disruption of both definition and picture naming task (the so-called 'dual sites') (Hamberger *et al*., 2001, 2005). Because the definition task was shown to be more sensitive than the picture task, the role of the anterior temporal lobe was particularly highlighted in these studies. However our results make it clear that posterior areas play an essential role in the word retrieval process. Furthermore, given that posterior areas were 'dual' sites in the brain stimulation studies cited previously (Hamberger *et al*., 2001, 2005), an overarching conclusion could be that word retrieval processes *per se* (common to both tasks) are indeed associated with posterior sites, whereas anterior sites play a more critical role in the semantic processes of understanding the definition.

In recent years evidence has emerged regarding the role of the so-called Basal Temporal Language Area (BTLA), located 2–9 cm from the tip of the temporal lobe. Among this evidence is the demonstration that speech arrest and naming deficits can be induced during stimulation of this region (Luders *et al*., 1986, 1991; Burnstine *et al*., 1990; Schaffler *et al*., 1994). Interestingly, in the present study, the correlation between rate of tip-of-the-tongue states and PET brain metabolism was also observed in the inferior-basal temporal region. In addition, resection of infero-temporal language sites may be associated with a decrease in confrontation naming, where postoperative naming deficit was more closely correlated with removal of BTLA than with overall size of temporal lobe resection (Krauss *et al*., 1996). Despite the fact that these studies did not characterize naming difficulties in detail, the conclusions reached provide additional support for the role of posterior temporal structures in lexical retrieval.

We propose, therefore, that lexical retrieval in TLE is associated with a temporal lobe network, within which the left posterior and basal areas play a crucial role. More anterior bilateral temporal areas might be associated with semantic processing (Sharp *et al*., 2004). The distinction between semantic and lexical processes is of course somewhat artificial as they are so closely connected in the course of error free speech production. Yet the study of certain pathological states (e.g. anomia or tip-of-the-tongue) provides a means for dissociating these two entities. This proposal is in contrast to those of previous studies, which insisted on the involvement of anterior sites in TLE in producing word finding difficulty while our results evidence the importance of posterior sites. This observation might be tentatively explained by a functional deafferentation between anterior and neocortical posterior temporal structures due to epileptic disorganization. Similarly, the naming failures that follow from anterior lobe resection could be due to a disconnection of the network linking semantic and lexical processing. Finally, the current data provide no indication that the word retrieval system in TLE should basically differ from that observed in studies of normal subjects or patients with ischemic stroke.

Conclusion

The present study reports an investigation of word finding difficulties present in left TLE patients irrespective of input modality (picture or definition tasks). The results support the idea that this deficit, similar to anomic or tip-of-the tongue states, concerns the stage of lexical access. A significant correlation between the rate of occurrence of anomic states and resting brain metabolism was observed in inferior and posterior temporal regions (BA 20-37-39). Such correlation highlights the importance of posterior regions in the specific process of word retrieval in TLE, as part of a large antero-posterior-basal temporal network.

Acknowledgements

The authors thank Dr Fabrice Bartolomei, Dr Martine Gavaret and Dr Maxime Guye for clinical and electrophysiological assessment of studied patients, Kristell Blaise and Albane Dejax for the language assessment of studied patients, Dr Aileen McGonigal and anonymous reviewers for discussions and helpful comments.

Funding

Ligue Française Contre Epilepsie research fellowship (to A.T.-D.F.). Agence Nationale de la Recherche (France) (ANR-07-JCJC-0074-01 to F.-X.A.).

Supplementary material

Supplementary material is available at *Brain* online.

References

Abrahams S, Goldstein LH, Simmons A, Brammer MJ, Williams SC, Giampietro VP, et al. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum Brain Mapp 2003; 20: 29–40.

Baayen AR, Davidson DJ, Bates DM. Mixed-effects modeling with crossed random effects for subjects and items. J Mem Lang 2008; 59: 390–412.

Badecker W, Miozzo M, Zanuttini R. The two-stage model of lexical retrieval: evidence from a case of anomia with selective preservation of grammatical gender. Cognition 1995; 57: 193–216.

Baxendale SA, Van Paesschen W, Thompson PJ, Duncan JS, Harkness WF, Shorvon SD. Hippocampal cell loss and gliosis: relationship to preoperative and postoperative memory function. Neuropsychiatr Neuropsychol Behav Neurol 1998; 11: 12–21.

Bell BD, Davies KG. Anterior temporal lobectomy, hippocampal sclerosis, and memory: recent neuropsychological findings. Neuropsychol Rev 1998; 8: 25–41.

Bell BD, Hermann BP, Woodard AR, Jones JE, Rutecki PA, Sheth R, et al. Object naming and semantic knowledge in temporal lobe epilepsy. Neuropsychology 2001; 15: 434–43.

Bell BD, Seidenberg M, Hermann BP, Douville K. Visual and auditory naming in patients with left or bilateral temporal lobe epilepsy. Epilepsy Res 2003; 55: 29–37.

Brown AS. A review of the tip-of-the-tongue experience. Psychol Bull 1991; 109: 204–23.

Buchel C, Price C, Friston K. A multimodal language region in the ventral visual pathway. Nature 1998; 394: 274–7.

Burnstine TH, Lesser RP, Hart J Jr, Uematsu S, Zinreich SJ, Krauss GL, et al. Characterization of the basal temporal language area in patients with left temporal lobe epilepsy. Neurology 1990; 40: 966–70.

Caramazza A. How many levels of processing are there in lexical access? Cognitive Neuropsychol 1997; 14: 177–208.

Chetelat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Landeau B, et al. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. Brain 2003; 126: 1955–67.

Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A. Neural systems behind word and concept retrieval. Cognition 2004; 92: 179–229.

Davies KG, Bell BD, Bush AJ, Hermann BP, Dohan FC Jr, Jaap AS. Naming decline after left anterior temporal lobectomy correlates with pathological status of resected hippocampus. Epilepsia 1998; 39: 407–19.

Davies KG, Risse GL, Gates JR. Naming ability after tailored left temporal resection with extraoperative language mapping: increased risk of decline with later epilepsy onset age. Epilepsy Behav 2005; 7: 273–8.

De Partz MP, Bilocq V, De Wilde V, Seron X, Pillon A. LEXIS, tests pour le diagnostic des troubles lexicaux chez le patient aphasique. Marseille 2001; 3: 1–80.

DeLeon J, Gottesman RF, Kleinman JT, Newhart M, Davis C, Heidler-Gary J, et al. Neural regions essential for distinct cognitive processes underlying picture naming. Brain 2007; 130: 1408–22.

Devinsky O, Perrine K, Llinas R, Luciano DJ, Dogali M. Anterior temporal language areas in patients with early onset of temporal lobe epilepsy. Ann Neurol 1993; 34: 727–32.

Dodrill CB. Neuropsychological effects of seizures. Epilepsy Behav 2004; 5 (Suppl 1): S21–4.

Drane DL, Ojemann GA, Aylward E, Ojemann JG, Johnson LC, Silbergeld DL, et al. Category-specific naming and recognition deficits in temporal lobe epilepsy surgical patients. Neuropsychologia 2008; 46: 1242–55.

Giraud K, Demonet JF, Habib M, Marquis P, Chauvel P, Liegeois-Chauvel C. Auditory evoked potential patterns to voiced and voiceless speech sounds in adult developmental dyslexics with persistent deficits. Cereb Cortex 2005; 15: 1524–34.

Grabowski TJ, Damasio H, Eichhorn GR, Tranel D. Effects of gender on blood flow correlates of naming concrete entities. Neuroimage 2003a; 20: 940–54.

Grabowski TJ, Damasio H, Tranel D, Cooper GE, Ponto LL, Watkins GL, et al. Residual naming after damage to the left temporal pole: a PET activation study. Neuroimage 2003b; 19: 846–60.

Hamberger MJ, Goodman RR, Perrine K, Tamny T. Anatomic dissociation of auditory and visual naming in the lateral temporal cortex. Neurology 2001; 56: 56–61.

Hamberger MJ, McClelland S 3rd, McKhann GM 2nd, Williams AC, Goodman RR. Distribution of auditory and visual naming sites in nonlesional temporal lobe epilepsy patients and patients with space-occupying temporal lobe lesions. Epilepsia 2007a; 48: 531–8.

Hamberger MJ, Seidel WT. Auditory and visual naming tests: normative and patient data for accuracy, response time, and tip-of-the-tongue. J Int Neuropsychol Soc 2003; 9: 479–89.

Hamberger MJ, Seidel WT, Goodman RR, Perrine K, McKhann GM. Temporal lobe stimulation reveals anatomic distinction between auditory naming processes. Neurology 2003; 60: 1478–83.

Hamberger MJ, Seidel WT, Goodman RR, Williams A, Perrine K, Devinsky O, et al. Evidence for cortical reorganization of language in patients with hippocampal sclerosis. Brain 2007b; 130: 2942–50.

Hamberger MJ, Seidel WT, McKhann GM 2nd, Perrine K, Goodman RR. Brain stimulation reveals critical auditory naming cortex. Brain 2005; 128: 2742–9.

Hamberger MJ, Tamny TR. Auditory naming and temporal lobe epilepsy. Epilepsy Res 1999; 35: 229–43.

Hermann BP, Wyler AR. Effects of anterior temporal lobectomy on language function: a controlled study. Ann Neurol 1988; 23: 585–8.

Hermann BP, Wyler AR, Somes G. Language function following anterior temporal lobectomy. J Neurosurg 1991; 74: 560–6.

Hillis AE, Kane A, Tuffiash E, Ulatowski JA, Barker PB, Beauchamp NJ, et al. Reperfusion of specific brain regions by raising blood pressure restores selective language functions in subacute stroke. Brain Lang 2001a; 79: 495–510.

Hillis AE, Kleinman JT, Newhart M, Heidler-Gary J, Gottesman R, Barker PB, et al. Restoring cerebral blood flow reveals neural regions critical for naming. J Neurosci 2006; 26: 8069–73.

Hillis AE, Tuffiash E, Caramazza A. Modality-specific deterioration in naming verbs in nonfluent primary progressive aphasia. J Cogn Neurosci 2002; 14: 1099–108.

Hillis AE, Wityk RJ, Tuffiash E, Beauchamp NJ, Jacobs MA, Barker PB, et al. Hypoperfusion of Wernicke's area predicts severity of semantic deficit in acute stroke. Ann Neurol 2001b; 50: 561–6.

Hirsch J, Moreno DR, Kim KH. Interconnected large-scale systems for three fundamental cognitive tasks revealed by functional MRI. J Cogn Neurosci 2001; 13: 389–405.

Howard D, Patterson K, Franklin S, Morton J, Orchard-Lisle V. Variability and consistency in picture naming by aphasic patients. Adv Neurol 1984; 42: 263–76.

Howard D, Patterson K, Wise R, Brown WD, Friston K, Weiller C, et al. The cortical localization of the lexicons. Positron emission tomography evidence. Brain 1992; 115 (Pt 6): 1769–82.

Indefrey P, Levelt WJ. The spatial and temporal signatures of word production components. Cognition 2004; 92: 101–44.

Jaeger TF. Categorical data analysis: away from ANOVAs (transformation or not) and towards logit mixed models. J Mem Lang 2008; 59: 434–46.

Joanette Y, Ska B, Côté H. Protocole MEC: Montréal d'Evaluation de la Communication, 2006.

Kaplan E, Goodglass H, Weintraub S. The boston naming test. Philadelphia: Lea & Febiger; 1983.

Kemeny S, Xu J, Park GH, Hosey LA, Wettig CM, Braun AR. Temporal dissociation of early lexical access and articulation using a delayed naming task–an FMRI study. Cereb Cortex 2006; 16: 587–95.

Krauss GL, Fisher R, Plate C, Hart J, Uematsu S, Gordon B, et al. Cognitive effects of resecting basal temporal language areas. Epilepsia 1996; 37: 476–83.

La Heij W, Starreveld PA, Steehouwer LC. Semantic interference and orthographic facilitation in definition naming. J Exp Psychol Learn Mem Cogn 1993; 19: 352–68.

Langfitt JT, Rausch R. Word-finding deficits persist after left anterotemporal lobectomy. Arch Neurol 1996; 53: 72–6.

Levelt WJ. Models of word production. Trends Cogn Sci 1999; 3: 223–32.

Luders H, Lesser RP, Hahn J, Dinner DS, Morris H, Resor S, et al. Basal temporal language area demonstrated by electrical stimulation. Neurology 1986; 36: 505–10.

Luders H, Lesser RP, Hahn J, Dinner DS, Morris HH, Wyllie E, et al. Basal temporal language area. Brain 1991; 114 (Pt 2): 743–54.

Maillard L, Vignal JP, Gavaret M, Guye M, Biraben A, McGonigal A, et al. Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes. Epilepsia 2004; 45: 1590–9.

Martin RC, Sawrie S, Hugg J, Gilliam F, Faught E, Kuzniecky R. Cognitive correlates of 1H MRSI-detected hippocampal abnormalities in temporal lobe epilepsy. Neurology 1999; 53: 2052–8.

Mayeux R, Brandt J, Rosen J, Benson DF. Interictal memory and language impairment in temporal lobe epilepsy. Neurology 1980; 30: 120–5.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neurol 2000; 47: 36–45.

Nickels L, Howard D. A frequent occurrence? Factors affecting the production of semantic errors in aphasic naming. Cogn Neuropsychol 1994; 11: 289–320.

Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989; 71: 316–26.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.

Price CJ, Devlin JT, Moore CJ, Morton C, Laird AR. Meta-analyses of object naming: effect of baseline. Hum Brain Mapp 2005; 25: 70–82.

Price CJ, McCrory E, Noppeney U, Mechelli A, Moore CJ, Biggio N, et al. How reading differs from object naming at the neuronal level. Neuroimage 2006; 29: 643–8.

Quene H, van den Bergh H. Examples of mixed-effects modeling with crossed random effects and with binomial data. J Mem Lang 2008; 59: 413–25.

Rapp B, Caramazza A. The modality-specific organization of grammatical categories: evidence from impaired spoken and written sentence production. Brain Lang 1997; 56: 248–86.

Raymer AM, Foundas AL, Maher LM, Greenwald ML, Morris M, Rothi LJ, et al. Cognitive neuropsychological analysis and

neuroanatomic correlates in a case of acute anomia. Brain Lang 1997; 58: 137–56.

Rohrer JD, Knight WD, Warren JE, Fox NC, Rossor MN, Warren JD. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain 2008; 131: 8–38.

Saccuman MC, Cappa SF, Bates EA, Arevalo A, Della Rosa P, Danna M, et al. The impact of semantic reference on word class: an fMRI study of action and object naming. Neuroimage 2006; 32: 1865–78.

Sass KJ, Sass A, Westerveld M, Lencz T, Novelly RA, Kim JH, et al. Specificity in the correlation of verbal memory and hippocampal neuron loss: dissociation of memory, language, and verbal intellectual ability. J Clin Exp Neuropsychol 1992; 14: 662–72.

Sawrie SM, Martin RC, Faught RE, Maton B, Hugg JW, Kuzniecky RI. Nonlinear trends in hippocampal metabolic function and verbal memory: evidence of cognitive reserve in temporal lobe epilepsy? Epilepsy Behav 2000a; 1: 106–11.

Sawrie SM, Martin RC, Gilliam FG, Faught RE, Maton B, Hugg JW, et al. Visual confrontation naming and hippocampal function: a neural network study using quantitative (1)H magnetic resonance spectroscopy. Brain 2000b; 123 (Pt 4): 770–80.

Saykin AJ, Stafiniak P, Robinson LJ, Flannery KA, Gur RC, O'Connor MJ, et al. Language before and after temporal lobectomy: specificity of acute changes and relation to early risk factors. Epilepsia 1995; 36: 1071–7.

Schaffler L, Luders HO, Morris HH 3rd, Wyllie E. Anatomic distribution of cortical language sites in the basal temporal language area in patients with left temporal lobe epilepsy. Epilepsia 1994; 35: 525–8.

Schwarz M, Pauli E, Stefan H. Model based prognosis of post-operative object naming in left temporal lobe epilepsy. Seizure 2005; 14: 562–8.

Sharp DJ, Scott SK, Wise RJ. Retrieving meaning after temporal lobe infarction: the role of the basal language area. Ann Neurol 2004; 56: 836–46.

Tomaszewki Farias S, Harrington G, Broomand C, Seyal M. Differences in functional MR imaging activation patterns associated with confrontation naming and responsive naming. AJNR Am J Neuroradiol 2005; 26: 2492–9.

Vigliocco G, Antonini T, Garrett MF. Grammatical gender is on the tip of Italian tongues. Psychol Sci 1997; 8: 314–7.

Wheeldon LR, Monsell S. Inhibition of spoken word production by priming a semantic competitor. J Mem Lang 1994; 33: 332–56.

Woollams AM, Cooper-Pye E, Hodges JR, Patterson K. Anomia: a doubly typical signature of semantic dementia. Neuropsychologia 2008; 46: 2503–14.