

Noun and verb retrieval by normal subjects

Studies with PET

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Summary

PET activation studies identify significant local changes in regional cerebral blood flow (rCBF) in contrasts of behavioural tasks with control states, and these local changes identify net changes in local synaptic activity. A number of studies on word retrieval have all demonstrated left frontal (dorsolateral and medial) involvement in the task. However, there have been differences in the responses observed in the left temporal lobe, with variously a deactivation (significant decrease in rCBF), no response and an activation (significant increase in rCBF). In the four studies described here, we have examined word (verbs and nouns) retrieval contrasted with a number of different control states. The studies confirmed extensive activation of the left dorsolateral

prefrontal cortex and, medially, the anterior cingulate cortex and the supplementary motor area (SMA). Activations of the left posterior temporal lobe and the inferior parietal lobe were consistently demonstrated when word retrieval was contrasted with a rest state. Contrasts with other single word tasks controlled out the activation in the perisylvian part of the left posterior temporal lobe, suggesting a role for this region in lexical processing. The left inferolateral temporal cortex and the posterior part of the inferior parietal lobe were only activated by word retrieval, particularly verbs. It is proposed that these activated regions reflect access to semantic fields.

Keywords: PET; word retrieval; verbs; nouns

Abbreviations: rCBF = regional cerebral blood flow; SMA = supplementary motor area

Introduction

Tests of verbal fluency are widely used in both clinical and research settings. They all involve the retrieval of words from memory in response to a stimulus (usually a letter prompt, e.g. words that begin with 's', or a superordinate category prompt, e.g. examples of 'animals'). Verbal fluency is usually regarded as a test of a patient's ability to form a simple strategy in response to the task demand, and to be sensitive to lesions of the left dorsolateral prefrontal cortex (Milner, 1964; Benton, 1968; McCarthy and Warrington, 1990). However, impairment in initiating an effective search for words may not be the only cause of impairment in verbal

fluency. Cerebral disease which impairs access to or the integrity of semantic memory (i.e. knowledge of concepts and the meaning of words) will also result in impaired category fluency (Chertkow and Bub, 1990). The anatomical locus of verbal semantic knowledge is uncertain but left temporal or temporoparietal regions are implicated, on the basis of neuropsychological, radiological and emission tomographic data on patients with focal lesions or neurodegenerative conditions (Coughlan and Warrington, 1978; Warrington and Shallice, 1984; Pietrini *et al.*, 1988; Poeck and Luzzatti, 1988; Sartori and Job, 1988; Alexander *et al.*,

1989; Snowden *et al.*, 1989; Graff-Radford *et al.*, 1990; Hart and Gordon, 1990; Kempler *et al.*, 1990; Tyrrell *et al.*, 1990; Hodges *et al.*, 1992).

A number of functional imaging studies of word retrieval have been reported using PET (Petersen *et al.*, 1988, 1989; Wise *et al.*, 1991; Frith *et al.*, 1991a, b; Friston *et al.*, 1993; Raichle *et al.*, 1994). The authors of these activation studies have attempted to define the regions involved in word retrieval, or sub-components of the process, by identifying significant changes in rCBF during the performance of the task. An increase in rCBF is assumed to be associated with a net increase in local synaptic activity. A decrease in rCBF suggests a net reduction in local synaptic activity, although this cannot be due to a local increase in inhibitory synaptic activity, which would increase local energy metabolism and rCBF: the inhibition must be occurring remote to that region and resulting in less activity in projection pathways to that region and/or in local interneuron activity. The resolution of the technique means that the term 'local' refers to a population of many tens of millions of synapses.

The results of the various PET activation studies have differed. This may largely be attributable to variations in their design: the stimuli were read or heard; the rate of presentation of stimuli varied, or there was only one stimulus prior to the onset of scanning; the words retrieved have been nouns in response to a letter prompt, basic level nouns in response to a superordinate prompt or actions (verbs) in response to a basic level noun prompt; the number of responses to each stimulus have varied between one and ~50; words have been retrieved with or without articulation (which clearly has an impact on input processing, as the subjects will have heard their own articulated responses); and the control tasks with which the activation tasks have been compared have varied considerably. The control tasks have usually been chosen to include some of the processes involved in word retrieval, such as listening/seeing the stimuli or articulation, to isolate with the contrast only those regions associated with self-generated retrieval of words from semantic memory. In one study the authors chose a 'rest' state as control, and attempted to avoid the activations associated with perception of words (the voice of another or own voice) by presenting the stimuli at a low rate and by asking the subjects not to articulate the words they had retrieved. The differences in the designs of the studies are summarized in Table I.

Table I also summarizes the main results of these studies. All agree about left frontal activation, lateral and medial, with differences over the exact locations. There is also broad agreement about left temporal lobe involvement, although in some of the contrasts there has been an rCBF increase and in others a decrease. Those studies that have shown temporal lobe decreases in rCBF have demonstrated symmetrical, bilateral deactivations; with increases in rCBF there was lateralization to the left.

In this paper, we report a series of experiments in which we investigated several of the discrepancies in the results

documented above. We aimed to address the following issues: to assess the effect of different control tasks on the regions activated during verbal fluency, with particular reference to posterior regions; more specifically, to investigate which part of the left temporal lobe is involved in word retrieval that is separable from the temporal regions engaged by acoustic, phonological and lexical processing of heard words; and to see whether there are any differences in regional activation between the retrieval of nouns and verbs. The last comparison addresses in part the question about the site of representations of verbs and nouns inferred from lesion data; selective impairment of processing verbs is associated with left anterior lesions, an equally selective impairment of noun processing may be associated with left temporal lesions (Miceli *et al.*, 1984; Damasio and Tranel, 1993).

To investigate the effect of the control states, we have kept one fluency task constant across all experiments (verb retrieval) but introduced a number of different control tasks: silent 'repetition' of pseudowords; a semantic comparison of heard nouns and verbs; and listening to words. The retrieval of nouns and verbs has been directly compared in a further experiment which included both noun and verb generation tasks. The subjects did not articulate their responses to avoid any confounding effects of them hearing their own voice. In each experiment a 'rest' state has been included. This has allowed the effects of both fluency and control task to be compared independently with the rest condition. This improves interpretation of the results, because in the contrast of task with control an apparent local activation in a task could, in fact, be a local deactivation in the control state — the use of two different control states helps differentiate between these two possibilities.

Methods

Experimental design

In all the experiments, volunteers completed a general health questionnaire which included a drug history (none was taking any medication) and questions specifically relating to any previous mental or physical disorders, hypertension, diabetes or previous strokes. A formal neurological examination was not carried out. Handedness was verified by the Edinburgh handedness inventory (Oldfield, 1971) and all the volunteers were right-handed. Three of the experiments were performed at the MRC Cyclotron Unit in London, where the subjects had English as their first language. One of the experiments was carried out in the Department of Nuclear Medicine, Essen, where the subjects had German as their first language. All English subjects gave informed consent to participate in these studies, which were approved by the Administration of Radioactive Substances Advisory Committee (Department of Health) and the research ethics committee at the Hammersmith Hospital. The German subjects similarly gave informed written consent, and their study was approved by the Essen University medical ethics committee.

Table 1 Summary of previous PET word retrieval studies

Study	Activation task	Control task	L. DLPC	L. med. frontal	L. post. temporal	R. post. temporal	L. parietal
Petersen <i>et al.</i> (1988)	Generate verb, with articulation, to heard or seen noun. <i>Speak: 60 w.p.m.</i> <i>Hear: 60 w.p.m.</i> (visual stimuli) or 120 w.p.m. (heard stimuli)	Repeat or read aloud heard or seen noun <i>Speak: 60 w.p.m.</i> <i>Hear: 60 w.p.m.</i> (visual stimuli) or 120 w.p.m. (heard stimuli)	↑	↑	0	0	0
Frith <i>et al.</i> (1991a)	Category fluency (jobs) plus letter fluency ('A'), articulated response, (2 averaged scans). <i>Speak: c. 24 w.p.m.</i> <i>Hear: c. 24 w.p.m.</i>	Count aloud plus lexical decision (articulated response = 'correct'/'incorrect'), (2 averaged scans). <i>Speak: c. 24 w.p.m.</i> <i>Hear: c. 30 w.p.m.</i>	↑	↑	↓	↓	↑
Frith <i>et al.</i> (1991b)	Letter fluency ('F'/'S'), articulated response after hearing 'next'. <i>Speak: 30 w.p.m.</i> <i>Hear: 60 w.p.m.</i> (letter names + 'next')	Repeat heard word <i>Speak: 30 w.p.m.</i> <i>Hear: 60 w.p.m.</i>	↑	↑	↓	↓	0
Wise <i>et al.</i> (1991)	Generate verbs, without articulation, to heard noun, multiple responses in interstimulus interval. <i>Speak: 0 w.p.m.</i> <i>Hear: 15 w.p.m.</i>	Rest <i>Speak: 0 w.p.m.</i> <i>Hear: 0 w.p.m.</i>	↑	↑	↑	0	0
Friston <i>et al.</i> (1993)	Letter fluency, articulated response, to heard letter name. <i>Speak: 30 w.p.m.</i> <i>Hear: 60 w.p.m.</i>	Repeat letter name. <i>Speak: 30 w.p.m.</i> <i>Hear: 60 w.p.m.</i> (letter names)	↑	↑	↓	↓	0
Raichle <i>et al.</i> (1994)	Generate verb, with articulation, to seen noun. <i>Speak: 40 w.p.m.</i> <i>Hear: 40 w.p.m.</i> Unpractised Practised	Read aloud noun <i>Speak: 40 w.p.m.</i> <i>Hear: 40 w.p.m.</i>	↑ 0	↑ 0	↑ 0	Not reported Not reported	Not reported Not reported

Design and results of previous PET activation studies on word retrieval. Information on the activation task and control state includes the number of heard/seen words per minute (if the responses were articulated the subjects heard their own responses). The results are summarized as activations (increases in rCBF) or deactivations (decreases in rCBF) in the left dorsolateral prefrontal cortex (L. DLPC), the anterior cingulate gyrus plus/minus the SMA (L. med. frontal), the left posterior temporal lobe (L. post. temporal), the right posterior temporal lobe (R. post. temporal) and the left inferior parietal lobe (L. parietal).

During each scanning session the word stimuli were heard via headphones on a previously prepared tape, and throughout the period when a blood flow measurement was taking place the subject's eyes were closed and the lights were dimmed. The subjects were informed of the particular task just before

each scan commenced and an example of a response was given, but no practice was allowed. Each experimental condition was repeated in a balanced order to avoid habituation and order effects (Table 2).

A slow rate of presentation of stimuli during the word

Table 2 Summary of experimental conditions

Experiment, design and conditions	Rate of heard words (w.p.m.)	Estimated retrieval rate (w.p.m.)
Experiment 1 (design: ABCCBA)		
(A) Rest	0	0
(B) Verb/noun comparison	50	0
(C) Verb generation	6	25
Experiment 2 (design: ABCCBAABCCBA)		
(A) Rest	0	0
(B) Listening	4	0
(C) Verb generation	4	20
Experiment 3 (design: ABCCBAABCCBA)		
(A) Rest	0	0
(B) Noun generation	4	29
(C) Verb generation	4	18
Experiment 4 (design: ABCCBA)		
(A) Rest	0	0
(B) Silent 'repetition' of pseudowords	10	0
(C) Verb generation	10	25

Summary of the experimental conditions in the four experiments. The design refers to the ordering of conditions for each experiment. The rate of presentation of each set of stimuli is tabulated. As each subject did not articulate his/her responses during the scans, to avoid activation of the temporal lobes in response to own voice, the rate of word retrieval was estimated after each scan by replaying the stimuli and recording the rate of articulated responses. The mean word retrieval rates for the subjects in each experiment are tabulated.

retrieval experiments was chosen as the result of a previous study (Price *et al.*, 1992), which has shown that the response of the temporal lobes to heard nouns varies in direct proportion to the rate of their presentation. The aim was to reduce the response of the temporal lobes to the stimuli to enhance the chance of revealing temporal lobe signal(s) associated with self-initiated word retrieval from semantic memory. For the same reason subjects were asked not to articulate their responses, which would have resulted in temporal lobe activations related to hearing their own voice. The rate chosen for the presentation of stimuli (one word every 6–15 s) was based on the commonplace experience of testing verbal fluency. Typically, total word retrieval is recorded in 15-s epochs over 1 min. There is almost universally a rush of words in the first epoch, with fewer produced in the subsequent epoch (except for unpredictable late surges) as the hunt for exemplars, without perseveration, becomes more difficult. We wished to capture activations when word retrieval was relatively easy, not when potentially variable individual strategies were being employed in the difficult later stages of the task.

We did not exclude the possibility (indeed probability) that there was subvocal articulatory activity while the subjects thought of words—this would have required recordings of respiration and submental electromyography, a rather cumbersome procedure in the scanning room and this aspect was not under investigation in the present study.

Experiment 1: rest/verb–noun comparison/verb generation

Nine English-speaking volunteers were scanned, five males and four females, with a mean age of 48 years (age range 31–67 years). Each scanning session consisted of six measurements and lasted 1.5 h. There were three experimental conditions, ordered ABCCBA.

(A) *Rest state*. The subject had his/her eyes closed and was asked to 'empty your mind'. The only sound the subject heard was the noise of the scanner's cooling fans. During a 'rest' scan the subjects will variously have had periods when they paid attention to random thoughts and other times when they became aware of the scanning environment. We have assumed randomness of such influences on rCBF across the subjects, which will have added noise to the grouped rest scan data and reduced somewhat the chances of finding activations in the word retrieval tasks. However, the advantage of the rest scan as a control state is that it is 'neutral', in that it incorporates neither language nor focused attention.

(B) *Verb–noun comparison task*. The subject heard verb–noun pairs (at a rate of 25 pairs/min) and was asked to signal when the pair were appropriately matched by opposing his/her left thumb and index finger. Fifty per cent of the pairs were correctly matched [e.g. 'eat (an) orange' but 'knit (the) glasses']. An observer monitored their performance (>95% accuracy in all subjects).

(C) *Verb generation task*. The subject was asked to think,

without vocalization, of as many verbs appropriate to heard concrete nouns (presented at a rate of six nouns/min) as he/she could in the interstimulus interval (e.g. 'apple'→'eat, pick, slice, peel'). He/she signalled by left thumb–index finger opposition (as in B) when he/she had commenced thinking of verbs after each stimulus so that the motor component involved in both tasks was similar. A retrospective estimate of performance was made during the interval between scans (the tape was replayed and the subject was asked to articulate his/her responses, which were recorded), and the average number of verbs generated was 4.2 verbs/noun.

Each language tape was started 30 s before scanning and continued throughout data acquisition.

There was a major difference in the rates of presentation of stimuli in tasks B and C. This was done to match the rates of 'output'; a decision on verb–noun pairs had to be made 25 times/min and verbs were generated at an estimated rate of 25 verbs/min.

There are cognitive differences between the signalling components of tasks B and C. In B the signalling was stimulus-driven, but on 50% of occasions when the verb–noun pair did not match the subjects had to actively inhibit a response; in C the self-initiated retrieval of the first verb to a stimulus was accompanied by a signal, with suppression of signalling for the second and subsequent retrieved verbs. This flaw in design represents a compromise that was made, at the time, to verify that the subjects were paying attention to the tasks. In subsequent experiments we relied on the honesty of subjects self-reporting whether they had complied with task demands.

Experiment 2: rest/listening/verb generation

Four English-speaking volunteers were scanned, three males and one female, with an average age of 48 years (age range 23–71 years). Each scanning session consisted of 12 measurements and lasted 2.5 h. There were three experimental conditions, ordered ABCCBAABCCBA.

(A) *Rest state*. As in Experiment 1.

(B) *Listening task*. Subjects were instructed simply to listen to concrete nouns (at a rate of four nouns/min), to match the rate of hearing noun stimuli in C.

(C) *Verb generation task*. As in Experiment 1, except that the stimuli were presented at a rate of four nouns/min (see above) and the subject was not asked to signal that he/she had commenced thinking of verbs. The retrospective estimate of the average number of verbs generated was five verbs/noun.

Experiment 3: rest/noun generation/verb generation

Nine English-speaking volunteers were scanned, all males, with an average age of 30 years (age range 24–65 years). Each scanning session consisted of 12 measurements and lasted 2.5 h. There were three experimental conditions, ordered ABCCBAABCCBA.

(A) *Rest state*. As in Experiment 1.

(B) *Noun generation task*. The subject was asked to think of, without vocalization, as many basic level nouns appropriate to heard superordinate nouns (presented at a rate of four nouns/min) as he could in the interstimulus interval (e.g. 'furniture'→'table, chair, stool, cabinet'). The retrospective estimate of the average number of basic level nouns generated was 7.2 nouns/superordinate noun.

(C) *Verb generation task*. As in Experiment 2. The retrospective estimate of the average number of verbs generated was 4.6 verbs/noun.

The subjects reported that they found noun generation subjectively 'easier' to perform than verb generation, which accords with the greater number of nouns retrieved/stimulus than verbs.

Experiment 4: rest/silent 'repetition' of pseudowords/verb generation

Six German-speaking volunteers were scanned, all males, with a mean age of 35 years (age range 27–50 years). Each scanning session consisted of six measurements and lasted 1.5 h. There were three experimental conditions, ordered ABCCBA.

(A) *Rest state*. As in Experiment 1.

(B) *'Repetition' task*. The subject heard pseudowords (presented singly at a rate of 10 pseudowords/min) and had to 'repeat' each one silently three times. The pseudowords were derived from the set of noun stimuli (by substituting one phoneme) used in Condition C and were easily pronounceable.

(C) *Verb generation task*. As in Experiments 2 and 3, except that the stimuli were in German and presented at a rate of 10 nouns/min. The retrospective estimate of the average number of verbs generated was 2.5 verbs/noun.

Data acquisition

In Experiments 1 and 4 the measurements were made using inhaled $C^{15}O_2$ as tracer (Lammertsma *et al.*, 1989, 1990). During each 3.5 min scan the subject inhaled $C^{15}O_2$ at a concentration of 6 MBq/ml and a flow rate of 500 ml/min for a period of 2 min. Head counts began 5–10 s after the start of inhalation, and scanning commenced at 30 s. The calculated whole body-effective dosimetry was 10–15 mSv. In Experiments 2 and 3 radiolabelled $H_2^{15}O$ was employed as tracer, administered over 2 min via an intravenous cannula followed by a 30 s flush of saline. Scanning began 30 s after the start of infusion of radiolabelled tracer, coinciding with the arrival of radioactivity in the head. The calculated whole body-effective dosimetry was 5–7 mSv. There were 10–15 min intervals between scans to allow decay of the previously administered tracer. The relative distribution of rCBF in the brain was indexed by the accumulated counts over the scanning period, which reliably reflects flow in

the physiological range (Mazziotta *et al.*, 1985; Fox and Mintun, 1989).

Experiment 1 was performed on a CTI-Siemens 931–08/12 PET scanner (Spinks *et al.*, 1988). Measurements in Experiments 2 and 3 were made on a CTI-Siemens 953B dedicated head scanner (Spinks *et al.*, 1992). This scanner was used in three-dimensional mode—the lead collimators were removed and coincidence detection was allowed between, as well as within, the detector rings (Townsend *et al.*, 1991). The increased sensitivity of the scanner used in this mode outweighs the disadvantages associated with increased scatter and random coincidence rates, and the signal-to-noise gain is more than threefold (Bailey *et al.*, 1991). Experiment 4 was performed on a CTI-Siemens 953/15 scanner. As the axial field of view of this scanner is only 5.4 cm, each subject had a prior MRI, and using this as reference the subject was positioned with the lowest PET plane at the level of, but not parallel to, the middle temporal gyrus. At the beginning of each study, a transmission scan with an exposed $^{68}\text{Ge}/^{68}\text{Ga}$ external source was performed to allow correction for attenuation.

A recent report of a multi-centre European PET experiment describes how separate groups of volunteers from nine PET centres performed a verb generation task contrasted with rest, identical in design to the one used in Experiment 3. This showed very good reproducibility of activation patterns across centres despite differences in PET cameras, tracers and languages (Frackowiak, 1995). Hence, despite the methodological variations in this study, it was considered appropriate to compare results across experiments. As it is, and notwithstanding the results from the multi-centre study, our results showed no major discrepancies between experiments; therefore, no speculations were required about differences that might have been the result of varying methodology.

Data analysis

Image analysis was performed on a SPARC STATION 11 (Sun Microsystems Europe Inc., Surrey, UK), using an image display software package (ANALYZE, Biodynamic Research Unit, Mayo Clinic, Rochester, Minn., USA; Robb, 1990). The image matrix manipulations and calculations were performed in PRO MATLAB (Mathworks Inc., Sherborn, Mass., USA) and used statistical parametric mapping (Friston and Frackowiak, 1991; SPM software, MRC Cyclotron Unit, London, UK).

Anatomical normalization

To correct for head movement between scans, all images from each subject were aligned using Automated Image Reconstruction (AIR) software (Woods *et al.*, 1992). Following realignment, images were then stereotactically normalized (Friston *et al.*, 1989, 1991a). Stereotactic normalization of PET images allows comparison of scan data

in identical pixels across different subjects and scans. During normalization a Gaussian filter of $20 \times 20 \times 12$ mm (full width, half maximum in the x , y and z planes, respectively) was used to remove high-frequency noise in the images and to accommodate differences in gyral and functional anatomy between subjects. As a result, each voxel rCBF equivalent value corresponds to a weighted mean rCBF centred in a spherical domain of ~ 20 mm in diameter. The voxel dimensions of each reconstructed scan, after transformation into the standard stereotactic space according to the atlas of Talairach and Tournoux (1988), was $2 \times 2 \times 4$ mm in the x , y and z dimensions, respectively.

Removal of confounding effect of global activity within and between subjects

Following stereotactic normalization, all scans were subject to an analysis of covariance. This procedure removes the confounding effect of differences in global activity across scans and normalizes global activity (radioactive counts) to a notional mean rCBF of 50 ml/dl/min (Friston *et al.*, 1990). This resulted in adjusted mean values of rCBF for each of the experimental conditions with associated error variance required for the comparison of the means.

Statistical analysis and creation of statistical parametric maps

The differences between conditions were assessed by formal comparisons of the condition specific rCBF maps. Adjusted condition means and variances were compared on a pixel by pixel basis by weighting the condition means by an appropriate contrast (Friston *et al.*, 1991a, b). The resulting map of t values constituted the statistical parametric map. With so many voxel by voxel comparisons some t values reach conventional levels of significance by chance. Therefore, the significance threshold was adjusted to $P < 0.005$ to protect from false positives.

In one contrast in Experiment 3, verb generation—rest, we used a jack-knife procedure to compare each subject in turn with the remaining eight in the group (at the $P < 0.05$ significance level) (Miller, 1974). This sample was chosen to check for individual consistency in the activations in response to word retrieval.

Results

Activations

Experiment 1: rest/verb–noun comparison/verb generation

Verb–noun comparison—rest (Table 3; Fig. 1A). There were two main foci of activation, bilaterally in both posterior temporal lobes. These were extensive regions over the lateral surfaces, with both the left and right peaks in the

Table 3 Experiment 1: rest/verb–noun comparison/verb generation—activations

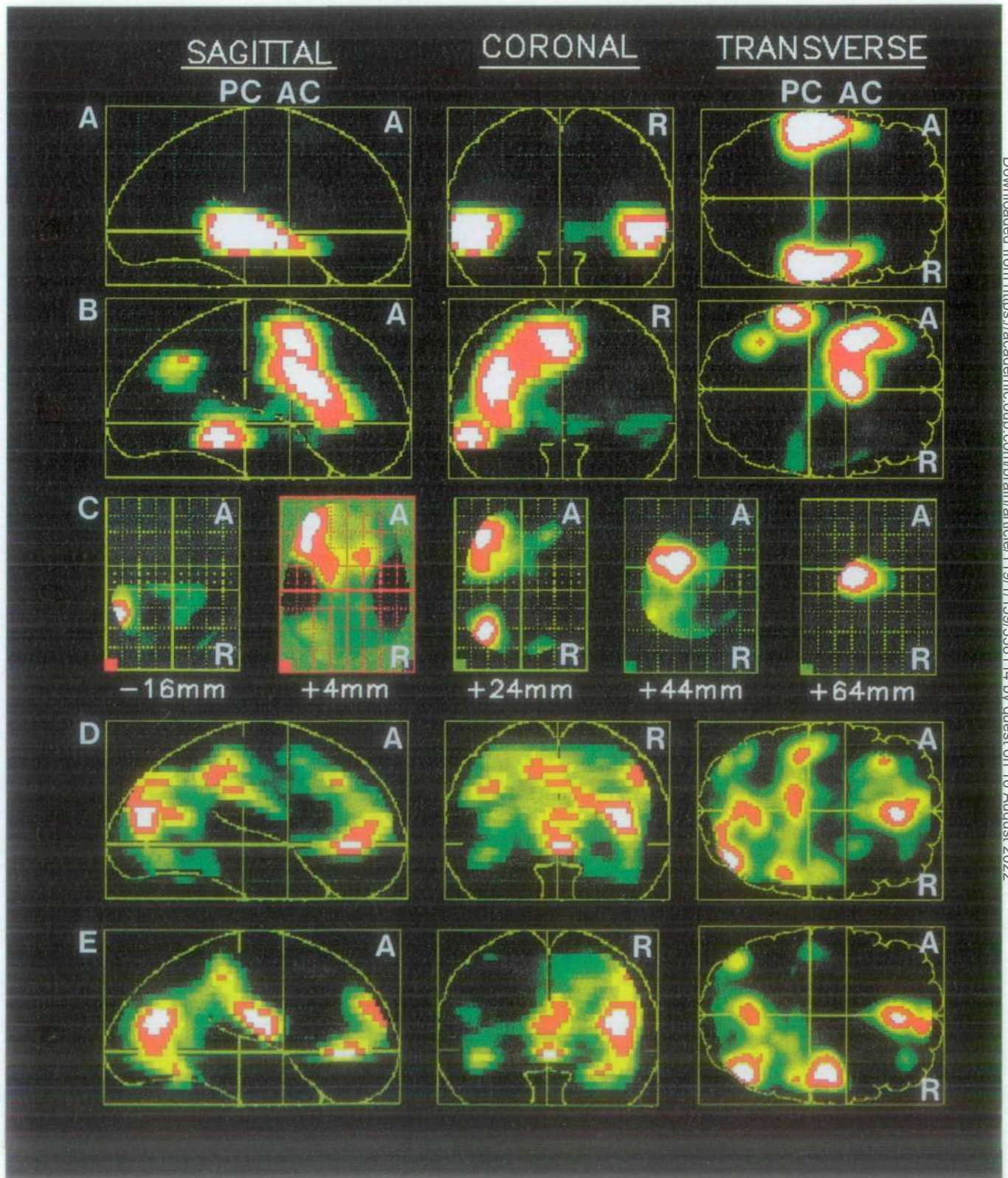
Area	Extent in z-axis (mm)	Peak (x,y,z)	% rCBF increase	Z-score
(A) Verb–noun comparison–rest				
Left hemisphere				
Posterior temporal lobe (peak in superior temporal sulcus, BA 21/22)	–16 to +16	–52,–24, 0	8.3	10.0
Inferior frontal sulcus (BA 6/44)	+16 to +24	–40,+12,+24	1.8	3.2
Right hemisphere				
Posterior temporal lobe (BA 21/22) (peak in superior temporal sulcus, BA 21/22)	–12 to +16	50,–22,0	7.4	10.0
Mid lateral sulcus	Localized region	+48,–8,–4	6.8	8.6
Subcortical				
Thalami		+10,–22, 0	1.6	4.3
(B) Verb generation–rest				
Left hemisphere				
Posterior temporal lobe (peak in middle temporal gyrus, BA 21)	–20 to +16	–50,–38,–4	4.9	8.9
Parieto-occipital junction (BA 19/39)	+20 to +36	–34,–62,+36	2.9	6.5
Lateral premotor/prefrontal:				
Frontal operculum		–42,+22,+4*	3.3	7.0
Inferior frontal gyrus (BA 44)	{ –4 to +60	–40,+10,+28	4.3	7.5
Precentral sulcus (BA 6)		–36,+2,+40*	3.5	7.0
Right hemisphere				
Superior temporal sulcus (BA 21/22)	0 to +4	+48,–34,+4	1.9	3.5
Anterior insula	+4 to +20	+30,+16,+12	1.9	3.6
Superior frontal sulcus (BA 9)	+28 to +32	+34,+34,+32	2.0	3.4
Midline				
Anterior cingulate gyrus and SMA (peak in callosalmarginal sulcus, BA 6/32)	+32 to +64	–6,+4,+48	4.1	7.9
(C) Verb–noun comparison–verb generation				
Left Hemisphere				
Posterior temporal lobe (peak in superior temporal gyrus, BA 22)	–4 to +20	–50,–16,0	5.2	8.3
Right hemisphere				
Posterior temporal lobe (peak in superior temporal gyrus, BA 22)	–8 to +20	+46,–12,0	5.4	9.6
Frontal operculum	Localized region	+40,+28,0	1.7	3.1
(D) Verb generation–verb–noun comparison				
Left hemisphere				
Inferior temporal gyrus (BA 37)	–16 to –8	–50,–50,–12	2.2	5.0
Temporo-parieto-occipital junction (BA 19/39)	+16 to +44	–34,–66,+28	3.4	7.1
Posterior, inferior parietal lobe (BA 40)	+32 to +48	–34,–52,+40	3.4	6.1
Lateral premotor/prefrontal:				
Frontal operculum		–40,+20,+4*	2.3	5.2
Inferior frontal gyrus (BA 46)	{ –8 to +60	–36,+40,+12	4.3	7.1
Precentral sulcus		–32,+10,+40	3.9	7.1
Midline				
Cuneus (BA 18/19)	+24 to +44	+4,–78,+40	2.4	4.0
Anterior cingulate gyrus and SMA (peak in callosalmarginal sulcus, BA 6/32)	+32 to +64	–12,+6,+44	4.8	7.9
Subcortical				
Left lentiform nucleus		–26,+2,+8	1.4	3.5
Right head of caudate nucleus		+16,+8,+8	1.8	3.5

*Not a separate peak, but tabulated to emphasize the ventral/dorsal extent of the dorsolateral frontal activation.

The activation results for Experiments 1, 2, 3 and 4 are shown in Tables 3, 4, 5 and 6, respectively. The contrasts (activation task—control state) are tabulated in terms of: the activated regions (significant increase in rCBF, $P < 0.001$, $Z\text{-score} \geq 3.1$) and their Brodmann's areas (BA). The ventral–dorsal extent of activation in the z-axis (except in Experiment 4, as the field of view of the camera used for this activation was limited); the x, y, z coordinates, according to the atlas of Talarach and Tournoux (1988), of each peak (defined as the pixel with the highest Z-score within each activated region); the percentage increase in rCBF equivalent counts of each peak; and the value of the Z-score of each peak. Trends of increased rCBF ($P < 0.01$, $Z\text{-score} \geq 2.6$) are shown in italics. The Brodmann's areas are only a guide, as the boundaries of architectonic zones, particularly in association cortices, are not fixed to specific gyri or sulci.

superior temporal sulci. There was also a left prefrontal activation in the inferior frontal gyrus. The signal in the thalami could not be localized precisely because of the

resolution, and there may have been a contribution from the medial geniculate nuclei, relaying acoustic signals from the brainstem to auditory cortex.



Verb generation—rest (Table 3; Fig. 1B). In this comparison, there was predominantly left-sided activation. In the left posterior temporal lobe, the activation extended from the inferior up to the superior temporal gyrus, with the peak posterior to that in the verb–noun comparison task. There was also activation in the posterior part of the inferior parietal lobe, at its junction with the occipital lobe. The most obvious difference in retrieving verbs in contrast to comparing verb–noun pairs was the left dorsolateral frontal lobe (predominantly prefrontal) activation, which extended from the frontal operculum up to the dorsal part of the precentral sulcus, and the activation of the anterior cingulate gyrus and medial premotor cortex (the SMA). There were also a few small posterior and anterior activations in the right hemisphere.

Verb–noun comparison—verb generation (Table 3) and verb generation—verb–noun comparison (Table 3; Fig. 1C). The stimulus nouns in the verb–noun comparison task were delivered at a high rate, so that the rate of hearing words was several times higher than in the subsequent verb generation task. This meant that the rate of making decisions about the word pairs was similar to the estimated rate of retrieving verbs in the verb generation task. In the direct comparisons of the two activation tasks, as might be expected from the results of their comparisons with rest, retrieval of verbs was associated with activation of the left parietal lobe and extensive left dorsolateral and medial frontal regions. As there was a small rCBF decrease in the left inferior parietal lobe during the verb–noun comparison task, the direct contrast of verb generation with verb–noun comparison showed a more extensive activation of this region relative to that observed when the control state was rest (Fig. 1C). Verb–noun comparison was associated with much stronger bilateral posterior temporal lobe activations, which, to a considerable degree, must be related to the much higher rate of hearing words in this task; however, there was a left inferolateral temporal region, peaking in the inferior temporal sulcus, which was more significantly activated by verb generation. A mid-line occipital region, in the cuneus, was also more active during verb generation, but this was a complex interaction—rCBF in the cuneus was the same

during rest and verb generation (Fig. 1C), but was significantly reduced during the verb–noun comparison task.

Experiment 2: rest/listening/verb generation Listening—rest (Table 4). The significant regions of activation were bilateral and posterior in the temporal lobes, peaking in the superior temporal sulci.

Verb generation—rest (Table 4). The results were very similar to those from Experiment 1.

Verb generation—listening (Table 4). This comparison showed significant left cortical activations that were confined to the dorsolateral and medial frontal lobe. However, there was a trend in the left inferior temporal sulcus, although some 25 mm anterior to the ventral left temporal region observed in the contrast of verb generation with verb–noun comparisons in Experiment 1. Using the listening task as control otherwise controlled out the bilateral temporal lobe activations seen in the verb generation–rest comparison in this experiment.

Experiment 3: rest/noun generation/verb generation

Verb generation—rest and noun generation—rest (Table 5). Again, there was consistency with the results from Experiments 1 and 2. These comparisons demonstrate that there is both consistency across groups for the regions activated by verb generation, and that retrieval of nouns from memory is associated with the same distribution of activation as for verbs. In this study, using the same number of subjects as in Experiment 1 but with twice the number of scans per subject and on a more sensitive, higher resolution scanner, two distinct peaks of activation were identified in the left posterior temporal lobe: one inferior and one superior. This gives further support to the results from Experiment 1, that there is a left inferolateral temporal region involved in word retrieval.

Fig. 1 (A–C) Statistical parametric maps: **A**, verb–noun comparisons—rest; **B**, verb generation—rest; **C**, verb generation—verb–noun comparisons; **D**, rest—verb–noun comparisons; **E**, rest—verb generation. All the figures come from Experiment 1. In **A**, **B**, **D** and **E** three whole-brain orthogonal projections (sagittal, coronal and transverse) are displayed. Each voxel with a Z-score > 3.1 ($P < 0.001$) is shown on an arbitrary colour scale from green ($Z = 3.1$) through to yellow and red and white (where white represents the higher Z-scores in that particular contrast). The specific Z-scores for each activated region are given in Tables 3–7. The planes of the anterior commissure (AC) and posterior commissure (PC) are drawn and labelled in **A**, and drawn on all the other sagittal and transverse projections. The horizontal line on the sagittal and coronal projections indicates the transverse plane of the intercommissural line. In **D**, five transaxial slices are shown for this contrast. The grid on each image corresponds to that in the atlas of Talairach and Tournoux (1988). Levels at 16 mm below and 4, 24, 44 and 64 mm above the intercommissural line are displayed. Where appropriate, the anterior (A) and right (R) of an image are indicated. **A** demonstrates the bilateral temporal lobe activations associated with verb–noun comparisons. **B** and **C** show the much more distributed activations (left frontal, medial frontal, left temporal and left parietal) with verb retrieval. The deactivations in response to verb–noun comparisons and verb retrieval are shown in **D** and **E**, respectively. During verb retrieval the strong activations in sulci of the left lateral and medial frontal cortex and in the underlying basal ganglia, after smoothing with a $20 \times 20 \times 12$ mm Gaussian filter, gave the appearance of some white matter activation in the left frontal lobe. However, the peaks of activation documented in the tables show that these activations originate in grey matter.

Table 4 Experiment 2: rest/listening/verb generation—activations

Area	Extent in z-axis (mm)	Peak (x,y,z)	% rCBF increase	Z-score
(A) Listening—rest				
Left hemisphere				
Superior temporal sulcus (BA 21/22)	0 to +16	-56,-30,+4	3.5	5.8
Inferior frontal sulcus (BA 45/46)		-42,+28,+16	1.6	2.9
Right hemisphere				
Superior temporal sulcus (BA 21/22)	0 to +16	+54,-32,+8	3.3	5.9
Anterior insula		+38,+14,+4	1.6	2.9
(B) Verb generation—rest				
Left hemisphere				
Posterior temporal lobe (peak in middle temporal gyrus, BA 21)	-20 to +12	-56,-34,0	3.6	5.4
Inferior parietal lobe (BA 40)		-48,-50,+40	1.7	2.8
Central sulcus (BA 4)	Localized region	-46,-6,-48	2.7	3.3
Lateral premotor/prefrontal:				
Frontal operculum	0 to +36	-34,+24,+8	4.0	5.9
Inferior frontal sulcus (BA 44/46)		-46,+24,+24	6.3	7.0
Superior frontal sulcus (BA 9) (two peaks)	+28 to +36	{-30,+46,+28 {-36,+36,+32	2.5 3.4	4.1 4.3
Right hemisphere				
Superior temporal sulcus (BA 22/42)	+4 to +12	+54,-34,+8	2.4	4.1
Anterior insula	-4 to +24	+32,+18,+8	2.3	5.0
Midline				
Anterior cingulate gyrus and SMA (peak in dorsal frontal gyrus, BA 6)	+28 to +52	-6,+12,+48	3.3	5.4
Subcortical				
Thalami		-2,-24,0	1.6	3.7
Left thalamus		-16,-10,+12	1.3	3.3
(C) Verb generation—listening				
Left hemisphere				
Inferior temporal sulcus (BA 20/21)		-58,-24,-12	1.6	2.6
Lateral premotor/prefrontal:				
Frontal operculum	+8 to +48	-32,+26,+8	2.8	4.0
Inferior frontal sulcus (BA 44/46)		-46,+24,+24	4.5	5.6
Inferior frontal gyrus (BA 6/44)		-38,+10,+32	2.6	4.2
Precentral sulcus (BA 4/6)		-44,-2,+48	2.8	3.2
Superior frontal gyrus (BA 9)		-26,+46,+32	2.2	3.9
Right hemisphere				
Anterior insula	+8 to +20	+24,+24,+12	2.2	4.0
Midline				
Anterior cingulate gyrus and SMA (BA 32) (Peak in dorsal frontal gyrus, BA 6)	+28 to +52	-12,+14,+48	2.9	4.9
Anterior cingulate gyrus (separate peak)		+4,+16,+20	2.3	4.0
Subcortical				
Thalami		-4,-12,+4	2.1	4.1

For explanation of results see footnotes to Table 3.

To check for consistency of response, the activation during verb generation for each of the nine subjects was compared with the other eight, as described in the section on statistical analysis (see above). The threshold was set at $P < 0.05$. There were no significant differences between any subject and the others within the group, suggesting intersubject consistency of activation during verb generation.

Verb generation—noun generation and noun generation—verb generation (Table 5). When compared directly, verb generation produced greater activation in posterior and anterior regions of the lateral left hemisphere. There was also a trend for greater activity in the SMA. There were only a few regions with greater activation during noun generation. One was in the right

Table 5 Experiment 3: rest/noun generation/verb generation—activations

Area	Extent in z axis (mm)	Peak (x,y,z)	% rCBF increase	Z-score
(A) Verb generation—rest				
Left hemisphere				
Posterior temporal lobe	-16 to +20	-52,-34,0	4.5	4.8
(separate peaks in middle temporal gyrus and superior temporal sulcus, BA 21 and BA 21/22)		-54,-44,+12	5.5	5.5
Posterior, inferior parietal lobe (BA 39)	+32 to +40	-36,-50,+36	4.3	4.4
Lateral premotor/prefrontal:				
Frontal operculum	{ -4 to +60	44,+22,+4	5.2	5.5
Inferior frontal gyrus (BA 44/45)		-52,+18,+12	9.8	6.8
Inferior frontal sulcus (BA 9/44)		-44,+14,+28	7.1	6.6
Precentral sulcus (BA 6)		-38,-6,+44	8.5	7.0
Right hemisphere				
Superior temporal sulcus	+4 to +12	+50,-36,+8	5.1	4.9
Anterior insula	-4 to +12	+42,+14,+8	3.6	4.1
Midline				
Anterior cingulate gyrus and SMA (peak in dorsal frontal gyrus, BA 6)	+36 to +64	-6,+6,+52	7.3	6.4
Subcortical				
Left head of caudate nucleus		-16,+8,+16	3.5	3.8
Right head of caudate nucleus		+14,+16,+16	3.6	3.4
Left thalamus		-8,-16,+4	4.0	4.3
Right thalamus		+8,-16,+12	3.0	3.4
(B) Noun generation—rest				
Left hemisphere				
Posterior temporal lobe	-16 to +16	-54,-38,-12	5.2	4.5
(separate peaks, in inferior temporal sulcus and superior temporal sulcus, BA 21/37 and 21/22)		-52,-40,+12	4.1	4.2
Temporoparietal junction (BA 39)		-32,-54,+28	4.2	2.7
Lateral premotor/prefrontal:				
Frontal operculum	{ 0 to +52	-38,+14,+4	4.2	5.3
Inferior frontal sulcus (BA 44/46)		-42,+24,+24	5.7	5.7
Precentral sulcus		-40,-4,+40*		4.8
Superior frontal sulcus (BA 9)		+24 to +36	-28,+32,+32	3.6
Right hemisphere				
Superior temporal sulcus (BA 21/22)	+4 to +12	+52,-36,+8	4.3	4.0
Lateral premotor/prefrontal:				
Frontal operculum	{ -4 to +40	+44,+14,+4	5.3	4.7
Precentral sulcus (BA 6)		+32,+24,+36	4.3	4.7
Midline				
Anterior cingulate gyrus and SMA (peak in callosalmarginal sulcus, BA 6/32)	+32 to +60	-6,+10,+44	5.4	5.7
Subcortical				
Left head of caudate nucleus		-18,0,+16	4.1	3.7
Left thalamus		-16,-18,+8	4.4	3.9
Right thalamus		+8,-16,+12	3.6	3.7
(C) Verb generation—noun generation				
Left hemisphere				
Inferior temporal sulcus (BA 21/37)	-8 to +20	-56,-52,-4	4.0	4.0
Temporoparietal junction (BA 39)	Localized region	-48,-60,+20	3.6	3.9
Inferior parietal lobe (BA 40)	Localized region	-52,-38,+32	3.3	3.5
Lateral premotor/prefrontal:				
Inferior frontal gyrus (BA 44/45)	+12 to +20	-52,+16,+16	4.0	4.0
Precentral sulcus (BA 6)	Localized region	-40,0,+48	4.9	3.8
Midline				
SMA (BA 6)		-8,+4,+60	3.9	2.7
(D) Noun generation—verb generation				
Right hemisphere				
Superior frontal sulcus (BA 9)	Localized region	+30,+18,+36	2.7	3.2
Midline				
Anterior cingulate gyrus (BA 24)	Localized region	-6,+38,-4	3.9	3.3
Callosalmarginal sulcus (BA 6/32)	Localized region	+18,+10,+48	2.7	3.6
(BA 8/32)		+16,+24,+48	2.5	2.9

*Not a separate peak, but tabulated to emphasize the ventral/dorsal extent of the dorsolateral frontal activation. For explanation of results see footnotes to Table 3.

prefrontal cortex, but at a locus where there was a relative decrease in rCBF during verb generation compared with rest.

Experiment 4: rest/silent 'repetition' of pseudowords/verb generation

Silent 'repetition' of pseudowords—rest; verb generation—rest; silent 'repetition' of pseudowords—verb generation; verb generation—silent 'repetition' of pseudowords (Table 6). The narrower field of view of the camera used in this study limited sampling of the brain from 9 mm below to 16 mm above the AC–PC line. Therefore, the more ventral regions of the temporal lobes were excluded below and the anterior cingulate gyrus and SMA above. Both activation tasks compared with rest activated bilateral posterior temporal regions and left opercular and dorsolateral frontal regions. However, the direct comparisons showed that retrieval of verbs from semantic memory, compared with internally sounding out three times each heard pronounceable nonword, produced a much stronger left dorsolateral prefrontal activation. In contrast, the temporal activations appeared stronger during silent 'repetition'; this despite the rate of hearing the stimuli being identical in the two tasks. There were right insular activations in both tasks, and a ventral primary motor activation on the left during silent 'repetition' suggesting some automatic output to the articulatory muscles despite instructions to the subjects to remain silent.

Deactivations

Experiment 1: rest/verb–noun comparison/verb generation

Rest—verb–noun comparison (Table 7; Fig. 1D) and rest—verb generation (Table 7; Fig. 1E). The deactivations associated with verb–noun comparisons and verb generation were essentially similar, except there were fewer deactivated regions in the left hemisphere associated with verb retrieval. We have only been able to draw limited conclusions from these deactivations, and so the presentation of results is limited to those from Experiment 1; the deactivations for word generation contrasted with rest in Experiments 2 and 3 were very similar.

Both the verb–noun comparisons and verb generation tasks were associated with bilateral deactivations in the more posterior parts of the fusiform gyri and in a number of midline cortical structures (the subcallosal cingulate gyrus, and regions in or close to the precuneus). There were a number of posterior and anterior activations in the lateral right hemisphere.

Discussion

Retrieval of verbs or nouns in response to a heard noun, when compared with a rest state, activate widely distributed

brain regions. Very similar results were obtained between different groups of right-handed subjects, and the comparison of individuals against the others within a group study of nine subjects scanned on the most sensitive camera showed no significant difference in the activation patterns between subjects. In right-handed individuals, and particularly for verb retrieval, this task is strongly left lateralized. The regions activated include many of those that Mesulam (1990) has summarized as the brain areas responsible for the comprehension and production of language—lesions in these regions may result in aphasia or a failure to initiate speech.

The experiments using different control states have enabled us to draw a number of conclusions. To perform the verb–noun comparison task in Experiment 1 required acoustic, lexical and semantic analysis of the stimulus pairs. Its execution predominantly engaged posterior temporal lobe regions, with little difference in either rCBF increases or the sites of activation in the two hemispheres. There was only a small region of activation in the left dorsolateral prefrontal cortex. To speculate about the processes that have resulted in the activation of specific regions, acoustic analysis of the stimuli will have engaged primary and association auditory cortex bilaterally, whereas lexical and semantic processing may have been confined to the left temporal lobe or been shared between the two hemispheres. Bilateral posterior temporal activation is, in most regions, linearly related to the frequency of hearing words (Price *et al.*, 1992), but it has yet to be determined what proportion of the rCBF increase can be attributed to early acoustic processing of the stimuli and how much to deeper processing for word recognition and comprehension. The frontal activation, although small, may reflect the load of the task on working memory (Paulesu *et al.*, 1993), with internal phonological rehearsal of the verb–noun pairs while the subjects were deciding whether they were correctly paired.

The internal retrieval of verbs produced both anterior and posterior, lateral and medial activations in the left hemisphere. There was also activation in the right posterior temporal lobe. The differences in the direct comparison between verb retrieval and verb–noun comparisons were activations of the left inferolateral temporal lobe, the posterior part of the left inferior parietal lobe, an extensive activation of the left dorsolateral frontal lobe, predominantly prefrontal, and medially the anterior cingulate gyrus and SMA. The activations of the perisylvian part of the left posterior temporal lobe and of the right posterior temporal lobe were greater in the verb–noun comparison task, although this could have been largely the result of the difference in the rate of hearing words. However, simply listening to real words at the same slow rate (4 w.p.m.) as in the verb generation task in Experiment 2, was also sufficient to cancel out the rCBF increases in the left and right posterior temporal lobes during verb generation, with the exception of a trend in a left inferolateral temporal region. This was also the case when the task was silently 'repeating' pseudowords when the bilateral temporal activations were greater in this task

Table 6 Experiment 4: rest/silent 'repetition' of pseudowords/verb generation—activations

Area	Peak	% rCBF increase	Z-score
(A) Silent 'repetition' of pseudowords—rest			
Left hemisphere			
Posterior temporal lobe:			
Superior temporal sulcus (BA 21/22)	-46,-34,+5	5.7	4.2
Inferior temporal gyrus (BA 37)	-48,-42,-9	5.5	4.1
Ventral primary motor cortex (BA 4)	-48,-4,+5	3.3	3.1
Lateral premotor/prefrontal:			
Anterior insula	-42,+6,-2	3.2	3.4
Frontal operculum	-38,+20,+2	3.2	3.3
Inferior frontal gyrus (BA 44/45)	-48,+14,+16	3.6	3.0
Right hemisphere			
Superior temporal sulcus (BA 21/22)	+56,-32,+2	6.7	5.0
Temporal operculum	+52,-6,0	3.0	3.1
Anterior insula	+34,+4,+12	3.9	2.9
(B) Verb generation—rest			
Left hemisphere			
Superior temporal sulcus (BA 21/22)	-50,-42,+7	4.1	3.3
Inferior temporal gyrus (BA 37)	-48,-50,-7	6.3	3.9
Lateral premotor/prefrontal:			
Frontal operculum	-40,+18,+2	6.6	5.7
Inferior frontal gyrus (BA 44/45)	-48,+14,+16	7.6	5.3
Inferior frontal gyrus (BA 45/46)	-42,+30,+14	5.0	5.1
Right hemisphere			
Superior temporal gyrus (BA 22)	+56,-16,+2	2.9	3.5
Superior temporal sulcus (BA 21/22)	+56,-30,+2	3.5	3.4
Anterior insula	+38,+4,+5	2.9	3.4
Subcortical			
Left lentiform nucleus	-22,-2,+7	3.8	3.3
Right lentiform nucleus	+30,+6,+9	4.3	3.4
Left thalamus	-18,-16,+12	3.7	3.7
(C) Silent 'repetition' of pseudowords—verb generation			
Left hemisphere			
Planum temporale (BA 41/42)	-44,-26,+5	3.3	2.9
Right hemisphere			
Middle temporal gyrus (BA 21)	+54,-42,+2	2.9	2.7
Inferior frontal sulcus (BA 10/44)	+40,+44,+2	3.6	2.5
(D) Verb generation—silent 'repetition' of pseudowords			
Left hemisphere			
Lateral premotor/prefrontal:			
Anterior insula	-38,+14,-2	3.2	3.6
Frontal operculum	-44,+18,+5	4.5	3.8
Inferior frontal gyrus	-34,+30,+12	3.3	4.0
Subcortical			
Left thalamus/lentiform nucleus	-18,-6,+9	3.1	2.7
Thalami	+4,-6,+12	5.9	2.9

For explanation of results see footnotes to Table 3.

compared with verb generation, although the auditory stimuli were presented at the same rate. The more ventral parts of the temporal lobes were not seen in this study (Experiment 4) because of the restricted field of view of the scanner. Therefore, there is abundant and reproducible evidence from these experiments that word retrieval is the product of a very distributed and predominantly left-lateralized network involving the inferolateral temporal lobe, the posterior, inferior parietal lobe, dorsolateral prefrontal/premotor

regions, the anterior cingulate gyrus and the SMA. The question remains as to the contribution of each activated region to the overall task.

Left temporal and parietal activations

Rosen (1980) divides the processes involved in verbal fluency into two components: (i) access to the stored representations in semantic memory; (ii) the formulation and initiation of

Table 7 Experiment 1: rest/verb–noun comparison/verb generation—deactivations

Area	Peak	% rCBF increase	Z-score
(A) Rest—verb–noun comparison			
Left hemisphere			
Posterior temporal lobe:			
Superior temporal sulcus (BA 21/22)	–46,–34,+5	5.7	4.2
Inferior temporal gyrus (BA 37)	–48,–42,–9	5.5	4.1
Ventral primary motor cortex (BA 4)	–48,–4,+5	3.3	3.1
Lateral premotor/prefrontal:			
Anterior insula	–42,+6,–2	3.2	3.4
Frontal operculum	–38,+20,+2	3.2	3.3
Right hemisphere			
Superior temporal sulcus (BA 21/22)	+56,–32,+2	6.7	5.0
Temporal operculum	+52,–6,0	3.0	3.1
<i>Anterior insula</i>	<i>+34,+4,+12</i>	<i>3.9</i>	<i>2.9</i>
(B) Rest—verb generation			
Left hemisphere			
Posterior fusiform gyrus (BA 19/37)	–38,–74,–4	4.7	5.0
Right hemisphere			
Posterior fusiform gyrus (BA 19/37)	+30,–58,–12	5.3	5.2
Temporo–parieto–occipital junction (BA 19/39)	+42,–64,+16	3.3	4.6
Postcentral sulcus (BA 2/40)	+40,–20,+32	3.9	5.8
Medial frontal gyrus (BA 8)	+12,+38,+36	2.5	3.4
Midline			
Precuneus (BA 31)	–2,–66,+20	4.1	5.3
Mid cingulate gyrus/precuneus (BA 7/31) (right callosalmarginal sulcus)	+12,–42,+40	3.5	3.1
Paracentral lobule (BA 7)	–10,–34,+44	3.8	5.8
Subcallosal cingulate gyrus (BA 24/32)	+6,+42,0	5.8	3.6

The contrasts (rest—activation task) are tabulated in terms of: the deactivated regions (significant decrease in rCBF, $P < 0.001$, Z-score ≥ 3.1) and their Brodmann's area (BA); the x , y , z coordinates, according to the atlas of Talairach and Tournoux (1988), of each trough (defined as the pixel with the highest Z-score within each deactivated region); the percentage decrease in rCBF equivalent counts of each trough; and the value of the Z-score of each trough. Trends of decreased rCBF ($P < 0.001$, Z-score ≥ 2.6) are shown in italics.

strategies to search for and retrieve appropriate items within semantic memory. In addition, word retrieval will make significant demands on working memory, and the retrieval of exemplars from a particular category or action words to match an object noun may be assisted by the use of visual imagery.

A number of investigators have suggested that, in patients with neurodegenerative disorders, performance on fluency tasks in response to an initial letter stimulus may dissociate from those based on categories (Martin and Fedio, 1983; Butters *et al.*, 1987; Hodges *et al.*, 1990; Monsch *et al.*, 1994; Rosser and Hodges, 1994). Both require attention, initiation, retrieval and working memory, but it is argued that initial letter fluency is more dependent on the phonologically based word store, whereas category fluency is dependent on access to intact representations in semantic memory. There are a number of publications in which authors address the regional distribution of pathology in Alzheimer's disease (Brun and Gustafson, 1976; Braak and Braak, 1991), and it is suggested that prominent pathology in the left temporal and parietal lobes may account for the impairment of category fluency, relative to letter fluency, seen in Alzheimer's disease. Martin *et al.* (1994) used a dual task study in normal controls

to look for interactions between fluency and either a task designed to activate frontal regions (a motor task) or one to activate posterior regions (an object decision task). The object decision task interfered more with category fluency than initial letter fluency. This suggests that the former is more dependent on temporoparietal regions than the latter. A direct comparison of category and letter fluency tasks with a PET activation study showed activation of the left posterior temporal lobe only (Imamura *et al.*, 1993).

Other investigators, using other language activation tasks in PET studies, have activated temporoparietal regions. The results of Demonet *et al.* (1992, 1994) and Zatorre *et al.* (1992) have implicated the left posterior temporal lobe in phonetic processing, but with concurrent activation of the left inferior frontal gyrus. Rhyming tasks on real words have been shown to activate a left temporoparietal region (Petersen *et al.*, 1989). Howard *et al.* (1992) have localized auditory lexical processing to the left middle temporal gyrus. The neural correlates of verbal working memory have been identified as the left supramarginal gyrus, the inferior frontal gyrus and the SMA (Paulesu *et al.*, 1993). None of these observations offer an explanation for the activations in the left inferolateral temporal lobe and the posterior part of the

inferior parietal lobe specific to word retrieval in this study. However, a semantic task included in the study of Demonet *et al.* (1992), when the subjects heard the names of animals associated with an adjective and had to make a categorical decision about both the size of the animal and the nature of the attribute, showed additional activation of a ventral left temporal region and the posterior part of the inferior parietal lobe (the coordinates were similar to the ones obtained in this study). Therefore, one candidate to account for the left posterior activations is the semantic system. To develop this hypothesis requires converging evidence from studies using different methodologies.

Word semantic priming studies, in which the effect of prior exposure to semantically related and unrelated words on reaction times to target words are measured, have demonstrated that activation of semantic representations can be automatic, especially when the experiments are designed to restrict the subject's ability to make conscious use of the prime (e.g. Fischler, 1977; Neely, 1977; Marcel and Patterson, 1978). Studies on Wernicke's aphasics and other patients with poor comprehension, most of whom presumably had posterior perisylvian lesions (although lesion data was not reported), showed that the patients were impaired when performing explicit semantic judgements on seen or heard words (Zurif *et al.*, 1974; Goodglass and Baker, 1976). Similarly, Whitehouse *et al.* (1978) presented evidence that a group of anomic subjects with posterior lesions had difficulties categorizing a percept (cup or bowl, when the shape was varied along a continuum between the two prototypical shapes), which was interpreted as evidence that these patients had a disorganization of semantic representations rather than poor access to an intact system. However, Wernicke's aphasics may show intact semantic priming effects, suggesting that these patients have intact semantic fields that can be automatically accessed, despite impairments when it comes to consciously retrieving words from memory (Milberg and Blumstein, 1981; Blumstein *et al.*, 1982). Shallice (1988) has developed the discussion about the degraded store/impaired access dichotomy. He points out that the evidence from the group data of Blumstein *et al.* (1982) was relative rather than absolute, and not conclusive proof of solely an access disorder. He then cites evidence from single case studies, and lists the neuropsychological criteria that may differentiate disorders of representations from disorders of access to those representations. Nevertheless, the evidence is equivocal and, as Shallice (1988) points out, the data from the few single case studies presented in the literature as access disorders are also explicable in terms of mixed disorders.

However, it is worth developing this theme a little further, in relation to neurology, cortical stimulation studies, cortical and intracerebral recordings of event-related potentials, the distribution of the posterior activations in this study and the suggestion about the organization of semantic representations made by Warrington and McCarthy (1987).

To a neurologist, the first thing that is noteworthy about

the inferior temporal and posterior, inferior parietal activations is that both regions lie at the junction ('the watershed') between middle and posterior cerebral artery territories. If posterior perisylvian infarcts, which lie in middle cerebral artery territory, do not often result in a loss of semantic fields as suggested by Blumstein *et al.* (1982) then the anatomical explanation would have to be that these fields were, by and large, not included in the various lesions of their group of Wernicke's aphasics. Middle and posterior cerebral artery watershed regions in temporal and parietal lobes are obvious candidates as sites less vulnerable to ischaemia following middle cerebral artery occlusion. Access to these relatively intact fields would be impaired by the perisylvian infarct that damaged and separated acoustic, phonological and lexical processing from the semantic fields. This argument is a speculative starting point, as the precise site of cerebral infarction is usually not discussed in neuropsychological studies.

In relation to the basal temporal region, there is increasing evidence for its role in language function, and in particular verbal semantics. In semantic dementia, which is associated with progressive loss of verbal semantic knowledge, the atrophy seen on MRI may be maximal in the inferolateral temporal cortex (Hodges *et al.*, 1992; J. R. Hodges, personal communication). Furthermore, there is evidence going back a decade that cortical stimulation of the basal temporal region (including inferior temporal and fusiform gyri) prior to surgery for epilepsy can produce transient language dysfunction, both comprehension and production, spoken and written (Luders *et al.*, 1986, 1991; Burnstine *et al.*, 1990). More recently, direct recordings of field potentials from the left fusiform gyrus have shown an anterior region which is preferentially sensitive to the semantic content and context of the presented material (Nobre *et al.*, 1994; Nobre and McCarthy, 1995). The neural source for this event-related potential recorded ~400 ms (N400) after the stimulus onset would appear to have Talairach and Tournoux atlas coordinates of $x = -25$ mm; $y = 0$ mm; $z = -20$ mm. This region is anterior to the left infero-lateral signal recorded in this study, but the anterior extent of the PET activation signal may have been underestimated—the lowest plane at which data was available for all subjects in Experiments 1, 2 and 3 was -16 to -20 mm (determined by the field-of-view of the camera and the wish to include the anterior cingulate gyrus and SMA); adequate examination of the anterior fusiform gyrus would have required scanning down as far as $z = -32$ mm. However, other than reservations about the exact extent of the region, this study and others, using different techniques and methodologies, have shown that the basal temporal region is involved in language processing, and may have a key role linking meaning with words. Yet further evidence comes from lesion data. De Renzi *et al.* (1987) studied the neuropsychological correlates of left posterior cerebral artery territory infarcts with occipital and inferior temporal ischaemic damage. As well as alexia and impairment in naming objects and photographs presented

visually, the subjects were impaired on naming to tactile presentation of objects and to verbal descriptions. The authors concluded that 'the search for a name is likely to require a continuous exchange of information between the language centre and the associative cortices storing different memories of the stimulus and to be markedly hampered if the visual image of the object cannot concur to trigger its naming'. Other relevant lesion data comes from studies on transcortical sensory aphasia. These patients are fluent with intact repetition but have a severe deficit in comprehension. Alexander *et al.* (1989) discuss the distribution of lesions associated with this classical aphasic syndrome, and the left inferior temporal lobe (Brodmann's area 37; *see* also Nielsen, 1946), the posterior, inferior parietal lobe (the junction of Brodmann's areas 39 and 19) and the white matter connecting these regions and the left thalamus are considered as a distributed system subserving semantic representations.

Discussion about the relationship between naming and sensory input modalities was developed by Warrington and McCarthy (1987) when they set out to explain dissociations between categories of verbal knowledge. These authors suggest that 'different weighting values from multiple sensory channels will be important in the acquisition of different categories of knowledge and that such differential weightings could be the basis of the categorical organization of systems in the brain subserving semantic knowledge'. If we extend this argument to the posterior activations reported in this study, the inferior temporal region lies in or close to the ventral visual stream while the posterior parietal region is related anatomically to the dorsal visual stream (Ungerleider and Mishkin, 1982). The ventral stream has been associated predominantly with identifying what an object is. It has been suggested that the dorsal stream is important in identifying where an object is in space, but there is evidence that it is also involved in guiding exploratory movements of the hands to reach and grasp objects (Goodale and Milner, 1992). If we extend Warrington and McCarthy's (1987) arguments, it would be a reasonable hypothesis that knowledge about the appearance of an object (its colour, shape, etc.) is located in or close to the ventral visual stream, while for manipulable objects knowledge about how they are held and used would be related to the dorsal visual stream. Thus, when asked to generate action words for, say, 'banana', its characteristic shape and colour will be retrieved along with memories that it can be peeled and sliced, and these semantic associations will activate mental images of appearance and manipulability, which may be accounted for by the inferior temporal and posterior parietal activations. Clearly other recollections about bananas involving other senses might be recalled during the task, such as its smell and the texture of its skin, which might generate activations in association cortex related to these sensory modalities; however, appearance and manipulability are likely to be the dominant associations used when generating appropriate actions to match the object noun. This hypothesis is potentially testable: a future verb generation study could contrast nouns that generate actions

not associated with grasping/manipulation with nouns strongly associated with such actions. One problem is that it is very much easier to think of nouns in the latter category than the former; even a large animate object such as a horse is associated with actions that require use of the hands ('saddling, grooming, riding'). Furthermore, there is already one demonstration that the left posterior, inferior parietal lobe is activated by associations other than object manipulability; as previously mentioned, Demonet *et al.* (1992) used adjective/animal noun phrases as stimuli, and the subjects had to make a decision about the positive/negative emotional associations of the adjective and a judgement about the size of the animal. This task is not going to demand access to representations about object use/manipulability, and yet the left inferior temporal and inferior parietal activations seem indistinguishable from those observed in this study. Finding anatomical dissociations within regions activated by different types of semantic task may not prove easy, or even possible, but future studies that directly address this subject, enquiring about the modularity of the semantic system, would seem worthwhile.

The study of Demonet *et al.* (1992) showed that, in addition to the two postero-lateral activations, a medial signal in the precuneus was present; and the task demand ('is the named animal larger or smaller than a chicken?') is likely to have engaged mental imagery. Other studies have related this region to visual imagery (Grasby *et al.*, 1993; Fletcher *et al.*, 1995), although in relation to retrieval from episodic rather than semantic memory. The absence of an activation in the precuneus in this study suggests that visual imagery plays little role in semantic fluency.

Activation of the right superior temporal lobe in all tasks associated with auditory stimuli, contrasted with rest, is consistent with other PET studies using language tasks in response to heard stimuli (e.g. Petersen *et al.*, 1988, 1989; Wise *et al.*, 1991; Price *et al.*, 1992), the peaks being in similar positions across the experiments. It is not possible to decide from these studies whether the involvement of this region is solely at an early level of acoustic processing or whether it also contributes to lexico-semantic processing. However, Howard *et al.* (1992) used listening to reversed words as control to a task of repeating heard words and showed no right temporal activation. Hearing words played backwards gives minimal phonetic, lexical or semantic information, but contains all the complex frequencies of speech; as listening to these stimuli controls for the rCBF increase associated with listening to words, parsimony requires that the right temporal activation reported here should only be interpreted as evidence of early acoustic analysis of heard words. This is not conclusive evidence that deeper processing is not carried out by the right temporal lobe, but different activation techniques will be required to address this question.

The reason that Petersen *et al.* (1988) and Frith *et al.* (1991a, b) did not see activation of the left inferior temporal region in their studies of word generation may be rather

prosaic—their subjects were not scanned low enough to include this region in the field of view of the scanner. In fact, fig. 1 in Frith *et al.* (1991*b*) does suggest a left inferior temporal activation at the lowermost edge of the field of view. Of greater interest is why one group showed bilateral deactivations in the superior temporal lobes in response to both category and letter fluency in three studies (Frith *et al.*, 1991*a, b*; Friston *et al.*, 1993). As our results were obtained in the same laboratory, using the same statistical parametric mapping software for data analysis, the answer must relate to experimental design, particularly in relation to the control state with which the fluency tasks were contrasted. It would appear that word retrieval contrasted with repetition produces the temporal deactivations. The results of Experiment 4 support this conclusion. Petersen *et al.* (1988, 1989) only reported significant increases in rCBF, but their ‘reverse’ contrasts (repeating heard words—verb generation) may show the same bitemporal deactivations. It is not clear why repetition should be associated with significantly greater superior temporal lobe rCBF than word retrieval, when the rate of hearing stimuli or own articulated responses is matched between the two tasks.

Finally, there is the question as to why the semantic demands of the verb–noun comparisons task were not associated with inferior temporal and parietal activations. One possibility is that a simple judgement about the appropriateness of the pairing of a verb and noun requires only a basic level of semantic processing, and that this is a property of Wernicke’s area. Alternatively, there is the possibility of local inhibition during word retrieval that is not present during verb–noun comparisons; Blaxton and Neely (1983) demonstrated retrieval inhibition when normal subjects generated target words given category labels and initial letter cues: ‘subjects were slower to produce these items under conditions in which they had already generated several items in a row from the target category (e.g. generating ‘baseball’, ‘tennis’ and ‘hockey’ before ‘football’) than when they had been retrieving words from an unrelated category prior to the target trial (e.g. generating ‘banana’, ‘pear’ and ‘watermelon’ before ‘football’). The task design is somewhat different from the word generation tasks used in this study, and the physiological correlates of an increase in reaction time are uncertain, but it could be that retrieval of multiple examples per stimulus produces a local increase in inhibitory synaptic activity in semantic fields, and therefore an increase in rCBF (see Introduction), thereby fortuitously enhancing the signal from semantic retrieval in this study. This hypothesis is open to test, by varying the number of responses expected per stimulus. We already have preliminary data from such an experiment using category fluency (R. J. S. Wise, personal communication), and it appears that generating many exemplars per stimulus compared with one does not, in fact, produce greater posterior (or anterior) activations.

Frontal activations

The frontal activations reported here for word retrieval are similar to those reported previously. The lateral activation of

the left frontal lobe was very extensive, from the frontal operculum, through the inferior frontal gyrus, the posterior part of the middle frontal gyrus and into the dorsal part of the precentral sulcus. Brodmann’s areas 44, 45, 46 and 47 are difficult to separate on grouped data following anatomical normalization with smoothing of the images—if these closely adjacent regions are not all activated by word retrieval, this could only be revealed by single subject studies co-registered with MRI. More dorsally, the activation lies at the junction of premotor and prefrontal cortex. Medially, both the anterior cingulate gyrus and the SMA are activated. The functions that may be attributed to these activated regions include the formulation and initiation of a strategy to identify the appropriate words from memory, attention to the task, components of short-term verbal working memory, and preparation for articulation of the responses even though the tasks were performed silently. The number of different psychological processes and the widespread left lateral and medial activation preclude precise functional–anatomical associations. This is reflected in the way different authors have come to different conclusions about the structure–function relations in the left dorsolateral prefrontal cortex during verbal fluency. For example, Frith *et al.* (1991*a, b*) attribute involvement of the this region to the exercise of will to perform a volitional act—in support of this claim they have shown that a similar region is activated when subjects perform another, non-verbal, willed act (Frith *et al.* 1991*b*). Tulving *et al.* (1994) attributes the activation to the encoding of novel verbal information (the items retrieved from semantic memory to match the stimulus) into episodic memory, and a study that separated encoding of episodic memory from retrieval has demonstrated activation of the left prefrontal cortex (Fletcher *et al.*, 1995). Tulving *et al.* (1994) further argue that once word retrieval—stimulus matching becomes familiar through practice, episodic memory encoding should cease and the left dorsolateral frontal activation should no longer be observed, as has been reported by Raichle *et al.* (1994). Paulesu *et al.* (1993) have shown that the left inferior frontal gyrus and SMA are components of verbal working memory, and both regions are activated by word retrieval. To perform verbal fluency efficiently requires considerable attention to the task to achieve the desired goal, which may be a functional property of the anterior cingulate cortex (Duncan, 1995). Therefore, the lateral and medial frontal activations seen with word retrieval must reflect the parallel involvement of a number of different psychological processes, and word fluency studies do not lend themselves to defining precise structure–function relationships in the frontal lobes. The same can be said for the thalamic nuclei, where activations were observed for both verb–noun comparisons and word retrieval. The resolution of the technique does not permit thalamic activations to be related to particular thalamic nuclei, and different parts of the thalamus are connected to different and widely distributed anterior and posterior cortical regions.

Word class effect in verb and noun retrieval

In terms of the whole left lateral hemisphere network associated with word retrieval, there is clearly a word class effect; in temporal, parietal and premotor/prefrontal regions, verb retrieval produces significantly stronger activations than noun retrieval. We were not able to demonstrate a simple anterior/posterior dissociation between verb and noun retrieval as has been suggested by the lesion data (Miceli *et al.*, 1984; Damasio and Tranel, 1993); in other words, we did not reveal a clear difference in regional activation for verbs and nouns that might have implied different anatomical sites for their representations. In the left hemisphere, all the processes associated with word retrieval for verbs and nouns produced very similar distributions of activations, but verbs produced a significantly greater rCBF increase in all three lobes. A more sensitive way to investigate word class effects with PET activation studies will require measurements of relative rCBF responses to word input/retrieval across a greater range of word classes (perhaps analogous to the event-related potential study of Nobre *et al.*, 1995). The significantly greater right dorsolateral prefrontal activation with noun compared with verb retrieval was complex, with rCBF in this region being greater during the rest state than during verb retrieval.

Deactivations

The deactivations with verb–noun comparisons and verb retrieval were broadly similar, except that there were fewer deactivations in the left hemisphere during verb retrieval. Both comparisons showed bilateral posterior fusiform gyral deactivations. We have shown these regions to be activated by letter strings and letter-like strings during reading tasks (Price *et al.*, 1996), as have Nobre *et al.* (1994), and the deactivations in this study may be the consequence of attention to auditory based language tasks. We have no explanation for the other deactivations, particularly as they may reflect common processing strategies during ‘rest’ to which we have no insight. The rest state was useful as a common reference control state across experiments because it was ‘neutral’ as regards directed attention and language processing, but the subjects’ minds were active and there may have been some ‘rest’ activations common to the group.

Conclusions

Word retrieval has become one of the more widely-used activation tasks in PET activation studies of human cognition. It produces robust signals in response to the task demand, and there are many psychological processes involved in the execution of the task. As it activates many regions known to be involved in the comprehension, initiation and production of language, it may prove to be a useful explicit activation task with which to study the recovery of language functions after focal cerebral injury.

The discussion of the studies reported here have concentrated particularly on the activations in the left inferior temporal and posterior, inferior parietal regions. The demonstration of a widely distributed network precludes the precise attribution of function to structure, but converging evidence from other studies using lesion data and neurophysiological techniques would support the hypothesis that the left posterior activated regions reflect access to representations in semantic memory. This suggests a role for the use of word generation activation studies in the investigation of the breakdown of semantic knowledge that accompanies a number of neurodegenerative disorders, including Alzheimer’s disease (Hodges and Patterson, 1995).

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