# Functional mapping of brain areas implicated in auditory − verbal memory function

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## SUMMARY

Positron emission tomography measurements of regional cerebral blood flow (rCBF)
were performed in normal volunteers during two auditory − verbal memory tasks: a
subspan and supraspan task. The difference in rCBF between tasks was used to identify
brain areas/systems involved in auditory − verbal long-term memory. Increases in rCBF
were observed in the left and right prefrontal cortex, precuneus and the retrosplenial
area of the cingulate gyrus. Decreases in blood flow were centred in the superior temporal
gyrus bilaterally. Separate comparisons were also made between each span task and
a resting state. Brain regions showing increases in rCBF in these comparisons included
the thalamus, left anterior cingulate, right parahippocampal gyrus, cerebellum and the
superior temporal gyrus. The brain areas identified in these comparisons define a number
of the neuroanatomical components of a distributed system for signal processing and
storage relevant to auditory − verbal memory function.

## INTRODUCTION

Auditory − verbal memory has been extensively investigated within the framework of
psychological models of human memory. These have included 'primary' and 'secondary
memory' (James, 1890), 'short and long-term memory' (Atkinson and Shriffin, 1968),
'levels of processing' (Craik and Lockhart, 1972) and more recently 'working memory'
(Baddeley, 1986). The neural substrates that may underlie auditory − verbal memory
and the validity of the models themselves cannot be established on the basis of
neuropsychological experimentation in healthy volunteers alone. Clinical studies of
memory function in brain-damaged patients provide one approach. Among the principle
limitations of this approach are (i) the difficulties in determining the precise location
and extent of neuronal damage, (ii) memory function in the intact brain is not studied
and (iii) localizing memory function to the site of the lesion may be invalid (Damasio
and Geschwind, 1985).

Psychological activation studies in conjunction with positron emission tomography
(PET) provide an alternative approach by measuring regional changes in neuronal activity,

indexed by regional cerebral blood flow (rCBF) or glucose metabolism, in conscious subjects during the performance of specific psychological tasks. Activation paradigms employing PET have successfully mapped brain systems implicated in higher cognitive functions including language, attention and colour vision (Petersen *et al.*, 1988; Posner *et al.*, 1988; Pardo *et al.*, 1990; Zeki *et al.*, 1991).

We report a study that attempts to elucidate the brain regions and/or brain systems that represent the neural substrates of auditory — verbal memory function. Positron emission tomography scans of rCBF in normal volunteers were performed during two auditory — verbal memory tasks: a subspan and supraspan task involving the free recall of auditorily presented word lists. In addition, to identify areas of activation that may have been common to both subspan and supraspan tasks, and therefore not recognized in the supraspan versus subspan comparison, comparison was made with rCBF profiles from a group of subjects studied in a resting non-activated state. In addition, this comparison allowed relative changes in rCBF between supraspan and subspan conditions to be expressed as absolute change from a resting baseline.

## MATERIALS AND METHODS

### Subjects

A total of 18 right-handed male volunteers (age range 25 – 38 years) took part in the study which was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee on the Administration of Radioactive Substances (ARSAC), UK. All subjects gave informed consent which was obtained according to the declaration of Helsinki. Positron emission tomography rCBF data from a pool of 12 normal right-handed subjects (males, age range 22 – 50 years), scanned in a resting state with an identical scanning protocol, were used when making comparisons with subjects who performed the subspan and supraspan tasks.

### Positron emission tomography scanning

Scans of rCBF were obtained for each subject using a CTI model 931-08/12 PET scanner (CTI, Knoxville, TN, USA). The physical characteristics of this scanner system have been described previously (Spinks *et al.*, 1988). Scans were reconstructed using a Hanning filter at a cut-off frequency of 0.5 cycles per pixel giving a transaxial resolution of 8.5 mm full width at half maximum and an axial resolution of 6.75 mm for each of 15 transverse planes with a resulting total field of view of 10.13 cm in this direction.

Subjects inhaled $C^{15}O_2$, mixed with air, at a concentration of 6 MBq/ml and a flow rate of 500 ml/min through a disposable oxygen face mask for a period of 2 min. Two dynamic PET scans were collected over a period of 2.5 min beginning 0.5 min before the inhalation of $C^{15}O_2$ (background scan duration 0.5 min, second scan duration 2 min) (Lammertsma *et al.*, 1990). In this study, the integrated counts per pixel for the 2 min build-up phase of radioactivity in the brain during $C^{15}O_2$ inhalation were used as an index of rCBF (Fox and Mintun, 1989).

### Memory tasks

Two memory studies were undertaken. In the first study each of the 18 subjects undertook a subspan and supraspan auditory — verbal memory task during two PET measurements of rCBF. The subspan task was undertaken during the first scan, the supraspan task during the second scan, 10 min later. In the second study, to control for any order effects, six of the 18 subjects undertook four further measurements of rCBF over the subsequent 50 min with presentations of the subspan task during scans 3 and 5 and the supraspan task during scans 4 and 6.

In the subspan memory task, subjects were required to remember and immediately freely recall a series of five-word lists read aloud by the experimenter during the scan. Nine different five-word lists were presented over the 2 min period of the scan. In the supraspan memory task, subjects were required to remember and immediately freely recall a 15-word list read aloud during PET scanning. Three presentations of the same 15-word list were undertaken during the scan which allowed subjects to learn and store verbal material

from previous presentations of the 15-word list. A total of 45 words were presented per scan for both the subspan and supraspan tasks. The subspan task therefore consisted of 45 novel words, whilst the supraspan tasks consisted of 15 novel words presented three times. Words, in both tasks, were presented at the rate of one every 2 s. The complete listen/recall/repeat sequence lasted for ~ 13 s for each five-word list presented and 39 s for each 15-word list presented. Different five- and 15-word lists were presented in each scan. All words were high frequency, imageable, concrete words taken from the MRC Psycholinguistics Database. Other psychological and physiological components of the two tasks were otherwise considered to be similar, including degree of attention, arousal and auditory stimulation. During scanning, subjects' eyes were closed while performing the memory tasks. Performance on the two memory tasks was assessed as the number and percentage of words correctly recalled during each scan.

*Memory task comparisons*

Three principal comparisons were made. These comprised the differences in the rCBF profile between the subspan and supraspan tasks, the differences between the subspan task and rest and finally the differences between the supraspan task and rest. The latter comparisons were made using a database of 12 normal subjects scanned under a 'rest' condition that comprised eyes closed with no auditory – verbal stimulation or speech output. The subspan task can be considered to involve (i) a short-term auditory – verbal memory system; (ii) auditory perception of spoken words; (iii) speech output processes. The supraspan task can be considered to comprise (i) a short-term auditory – verbal memory system; (ii) a long-term auditory – verbal memory system; (iii) auditory perception of spoken words; (iv) speech output processes. Thus subtraction of the rCBF profile in the subspan task from the supraspan task isolates a rCBF profile that represents the essential difference between tasks which is the engagement of long-term memory processes in the supraspan condition.

*Data analysis*

*Anatomical normalization of scans.* Each reconstructed rCBF scan consisting of 15 primary transverse planes was interpolated to 43 planes to render the voxels approximately cubic. The data were then transformed into a standard stereotactic space (Friston *et al.*, 1989). Such transformation of the data allows for pixel by pixel averaging of data across subjects. In the standard space 1 voxel represents $2 \times 2 \times 4$ mm in the $x$, $y$ and $z$ dimensions, respectively, allowing direct cross-reference to the anatomical features in the standard stereotactic atlas (Talairach and Tournoux, 1988).

*Removal of confounding effect of global activity within and between subjects.* Differences in global activity within and between subjects were removed by analysis of covariance (Wildt and Ahtola, 1978) on a pixel by pixel basis with global counts as covariate and regional activity across subjects for each task as treatment. This was undertaken as inter- and intra-subject differences in global activity may obscure regional alterations in activity following psychological activations (Friston *et al.*, 1990).

*Creation of statistical parametric maps (SPMs).* For each pixel in stereotactic space the analysis of covariance (ANCOVA) generated a condition-specific adjusted mean rCBF value (normalized to 50 ml/100 ml/min) and an associated adjusted error variance. A $1 \times 2$ ANCOVA (blocked) was used for the comparison of subspan versus supraspan tasks, each subject being studied under both conditions. For the comparison with the rest condition a $1 \times 2$ ANCOVA (without blocking) was used as different subjects were studied under each condition (subspan/supraspan versus rest). The ANCOVA allowed comparison of the means across two conditions (subspan and supraspan tasks or subspan/supraspan and rest) using the $t$ statistic. The resulting set of $t$ values constitutes a statistical parametric map [SPM($t$)] (Friston *et al.*, 1991a). The omnibus significance of the SPMs was assessed by comparing the observed and expected distribution of the $t$ statistic under the null hypothesis of no treatment effect.

For the supraspan versus subspan task comparison involving 18 subjects the profile of significant rCBF change was defined as the location of all pixels with a $t$ value corresponding to $P < 0.001$ (*see* Friston *et al.*, 1991a). This threshold has been shown to protect from false positives using phantom stimulations (Bailey *et al.*, 1991).

In the six subjects studied longitudinally the null hypothesis was limited to areas of significant change in rCBF identified from all 18 subjects; the threshold level of significance for $t$ values corresponding to

$P < 0.01$ was therefore used. For the rest versus subspan/supraspan comparisons the lower threshold of $P < 0.01$ was used because of the lesser sensitivity of the unblocked (between subject) ANCOVA design.

In summary the within-subject design of the supraspan versus subspan comparison provides the most robust statistical approach for the detection of memory task-induced changes in rCBF. In contrast, the between-subject design of the subspan/supraspan versus rest comparisons are less statistically robust and primarily aid the interpretation of the direction of relative changes in rCBF in the supraspan versus subspan comparison. In addition the comparisons with rest may identify areas of common activation occurring in both memory conditions.

*Use of filters to increase signal to noise in data set.* A Gaussian filter full width at half maximum (20 mm) was applied at the stage of anatomical normalization to smooth each image to accommodate inter-subject differences in gyral and functional anatomy and to suppress high frequency noise in the images. A further Gaussian filter (8 mm full width at half maximum) was applied at the stage of the computation of the statistical parametric maps to increase signal to noise in the data set. The final resolution of the statistical parametric map was such that values from a weighted sphere of ~20 mm diameter contributed to the values for rCBF at the pixel in the centre of a focus of activation.

Image analysis was performed using SPM software (MRC Cyclotron Unit, London, UK) on a SPARC 1 workstation (Sun Microsystems Inc., Surrey, UK) using an interactive image analysis software package (ANALYZE, Biodynamic Research Unit, Mayo Clinic, USA). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York).

## RESULTS

### Memory performance

All subjects showed a reduced percentage of correctly recalled words during the supraspan memory task compared with the subspan memory task (Table 1). The mean values were

#### TABLE 1. MEMORY PERFORMANCE DATA

| Study | First | Second | Third | Supraspan (%) | Subspan (%) |
|---|---|---|---|---|---|
| First study | 7.0 ± 1.7 | 9.5 ± 1.7 | 10.8 ± 1.4 | 61 | 98 |
| Second study | | | | | |
| Scan 2 | 7.0 ± 2.6 | 9.5 ± 1.5 | 10.7 ± 1.5 | 60 | 97 |
| Scan 4 | 7.5 ± 2.4 | 11.2 ± 2.5 | 12.7 ± 2.7 | 70 | 99 |
| Scan 6 | 8.5 ± 1.8 | 10.8 ± 2.0 | 11.7 ± 1.9 | 69 | 99 |

Memory performance data are shown for the first, second and third presentation of each supraspan word list in studies one and two. Data are expressed as the mean ± SD of words correctly recalled in each presentation of the 15-word list. The percentage of correctly recalled words across three presentations of the supraspan word list is also shown together with the corresponding percentage for the subspan word list.

61% versus 98% correct recall, supraspan versus subspan task for the first study and 66% versus 99% recall, supraspan task versus subspan task for the second study. There was an overall increase in the number of correctly recalled words during three presentations of each supraspan word list (Table 1). In addition, subjects' overall performance in the second study showed a tendency to improvement from the first supraspan scan compared with the second and third supraspan scans (Table 1). All subjects demonstrated primacy and recency effects in the supraspan task (Fig. 1).
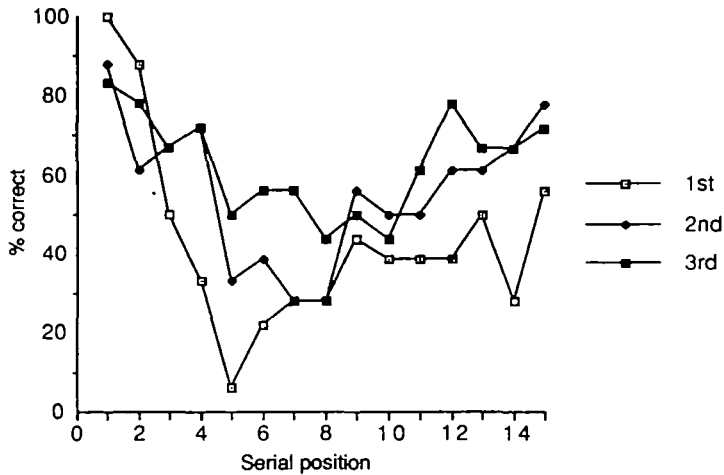
Fig. 1. Serial position curve. The percentage of subjects correctly recalling a word versus its serial position in the supraspan list are shown (data from the first study). Primacy and recency effects are seen. The first, second and third presentations of the supraspan list are plotted separately to illustrate the improvement in performance upon repeated presentation.

## Changes in rCBF

The study design allowed for differences in regional brain activity (measured as rCBF) between the two memory tasks or each memory task and the rest condition to be determined. These differences represent relative increases or decreases in rCBF.

*Increases in rCBF in supraspan compared with subspan task.* In both the first and second study, comparing supraspan with subspan conditions, significant increases of rCBF were observed bilaterally in the prefrontal cortex extending across the middle and superior frontal gyri (Brodmann areas 9/10, 46). Increases of rCBF were also observed in the midline posteriorly over an area centred on the precuneus (Brodmann area 31). A more spatially limited focus of increased rCBF was also seen in the retrosplenial area of the cingulate gyrus (Brodmann areas 29/30) (Table 2, Figs 2, 3).

*Decreases in rCBF in supraspan compared with subspan task.* In both the first and second study, comparing supraspan with subspan conditions, significant reductions in rCBF were seen bilaterally in an area that subsumed the middle and superior temporal gyri, the insular and the lower part of the postcentral gyrus (Brodmann areas 21, 22, 41, 42, 43). Areas of maximal decreases in rCBF were located in the posterior part of the superior temporal gyrus and insular bilaterally (Brodmann areas 22/41/42) (Table 2, Figs 4, 5).

*Increases of rCBF in subspan task compared with rest condition.* Increases of rCBF were observed in the left and right superior temporal gyrus (Brodmann areas 41/42/22) and bilaterally in the thalamus. Two areas of increased rCBF were also noted in the region of the right parahippocampal gyrus and the cerebellum. In addition, a focus of increased rCBF was seen in the anterior cingulate lateralized to the left (Brodmann area 32) (Table 3, Fig. 6).

TABLE 2. COORDINATES OF MAXIMAL SIGNIFICANT CHANGE IN rCBF
(SUPRASPAN/SUBSPAN TASK)

| Anatomical location | Coordinates | | | Z value |
|---|---|---|---|---|
| | x | y | z | |
| **Increases in rCBF** | | | | |
| Left prefrontal cortex | | | | |
| First study | −34 | 46 | 0 | 4.52 |
| Second study | −26 | 52 | 4 | 4.26 |
| Right prefrontal cortex | | | | |
| First study | 24 | 52 | 0 | 5.13 |
| Second study | 20 | 56 | −4 | 5.55 |
| Retrosplenial area of cingulate gyrus | | | | |
| First study | 14 | −48 | 16 | 4.55 |
| Second study | −2 | −38 | 12 | 3.07 |
| Precuneus | | | | |
| First study | −14 | −60 | 36 | 5.16 |
| Second study | 16 | −62 | 32 | 6.03 |
| **Decreases in rCBF** | | | | |
| Left superior temporal cortex/insular | | | | |
| First study | −46 | −12 | 0 | 5.48 |
| Second study | −46 | −18 | 8 | 4.51 |
| Right superior temporal cortex/insular | | | | |
| First study | 40 | −8 | 8 | 6.40 |
| Second study | 44 | −14 | 8 | 5.55 |

The stereotactic coordinates of maximal activations and inhibitions for both studies are given in $x$, $y$ and $z$ coordinates in millimetres, from the atlas of Talairach and Tournoux (1988), together with appropriate $Z$ scores. $Z$ scores were calculated by transformation of the $t$ statistic to a Unit Gaussian distribution (*see* Friston *et al.*, 1991*a*). The threshold for significance was set at $P < 0.001$ ($Z = 3.09$) for the first study and $P < 0.01$ ($Z = 2.34$) for the second study.

*Increases of rCBF in supraspan condition compared with rest condition.* Increased rCBF was noted bilaterally in the thalamus and in the left anterior cingulate (Brodmann area 32). In addition, foci of increased rCBF were seen in the region of the cerebellum and right parahippocampal gyrus (Table 3, Fig. 6). Increased rCBF was noted in the left superior temporal gyrus (Brodmann areas 22/42), but was considerably attenuated on the right. In general, the pattern of increased rCBF was similar to that of the subspan−rest comparison apart from the activations in the superior temporal gyrus.

## DISCUSSION

*Regional CBF profiles in supraspan versus subspan and supraspan/subspan versus rest comparisons*

In the supraspan versus subspan comparison, maximal increases of rCBF were located in the prefrontal cortex bilaterally, the precuneus and the retrosplenal area of the cingulate gyrus. In contrast, when comparing the subspan or supraspan task with the rest state, maximal increases of rCBF were located in the thalamus bilaterally, the left anterior cingulate, the superior temporal gyri, the right parahippocampal gyrus and the cerebellum.
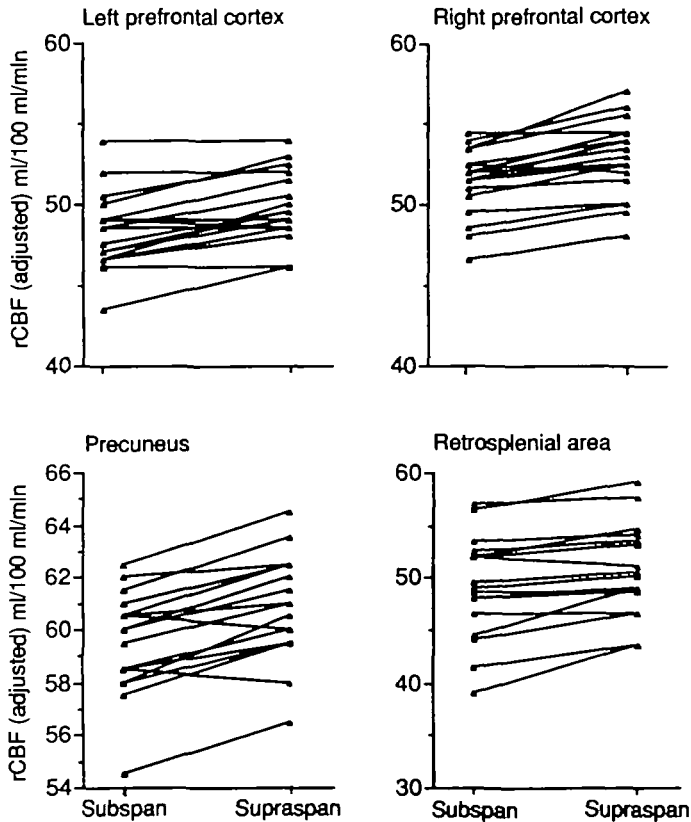
FIG. 2. Regional cerebral blood flow increases when comparing supraspan with subspan task. Values refer to adjusted cerebral blood flow in ml/100 ml/min at the coordinates specified in Table 2 (first study), for each subject, during the subspan and supraspan task.

From these comparisons two broad rCBF profiles can be discerned: (i) rCBF changes representing the essential difference between supraspan and subspan tasks, i.e. auditory – verbal long-term memory function; (ii) rCBF changes common to both the subspan and supraspan tasks. The absence of significant thalamic, parahippocampal, cerebellar or anterior cingulate rCBF increases in the supraspan versus subspan comparisons (despite the use of a statistically sensitive within-subject comparison), suggests that the thalamic, parahippocampal, cerebellar and anterior cingulate activations were equally pronounced in the subspan and supraspan tasks. In contrast, the superior temporal increases in rCBF appear to have been more pronounced in the subspan than the supraspan task. The absence of a significant prefrontal, precuneus or retrosplenial increase in rCBF in either span task compared with rest suggests considerable inter-subject variability in baseline rCBF in these areas (*see* Fig. 2).

The patterns of rCBF change in the first and second memory study were similar. Thus an order effect (the subspan task always preceded the supraspan task in the first study) could not explain such similar results, as the second study contains alternating
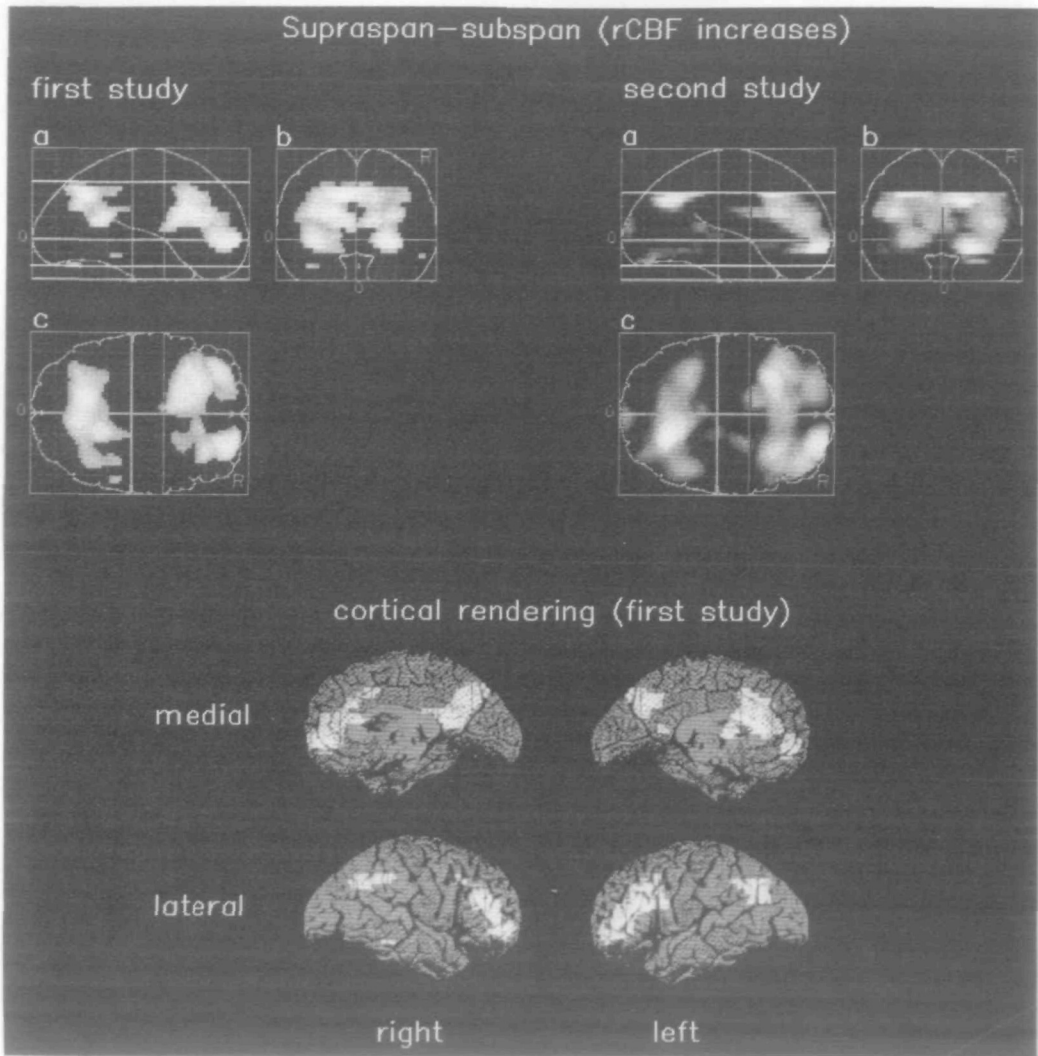
FIG. 3. Location of increase in rCBF (supraspan compared with subspan task). Upper images: the spatial distribution of significant pixels at $P < 0.001$ (first study) and $P < 0.01$ (second study) for increases in rCBF (supraspan−subspan) are shown as integrated projections along sagittal (a), coronal (b) and transverse (c) views of the brain. R = right. The axial extent of the data set is defined by lines in the sagittal view (a). Lower image: to aid interpretation of the above maps significant pixels are rendered onto the medial and lateral cortical surface of each hemisphere. It should be noted that brain areas outside the axial extent of the data set may also have shown changes in rCBF.

subspan and supraspan tasks (the second and third subspan tasks are preceded and followed by a supraspan task).

*Changes in rCBF between tasks: relation to a short-term/long-term model of human memory*

Subspan and supraspan tasks have been extensively used to investigate auditory − verbal memory function (Lezak, 1983), usually within the framework of two component models
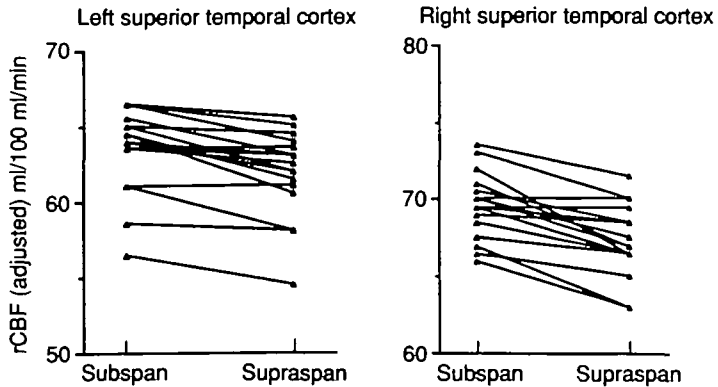
FIG. 4. Regional cerebral blood flow decreases when comparing supraspan with subspan tasks. Values refer to adjusted cerebral blood flow in ml/100 ml/min, at the coordinates specified in Table 1, for each subject, for the subspan and supraspan task.

of human memory. These models have distinguished a temporary (seconds) limited capacity memory store (or stores) from a long-term (minutes/years) store of almost unlimited capacity (for reviews, see Baddeley, 1976, 1986; Squire, 1987; McCarthy and Warrington, 1990). Within a two component (short-term and long-term memory) model, the subspan five-word list is easily remembered using a phonological (auditory — verbal) short-term memory store whilst the 15-word list exceeds the capacity of this store (Miller, 1956). Other memory systems (i.e. long-term memory), in addition to short-term memory, are considered necessary for successful performance of the supraspan task. Using cognitive subtraction (Fox et al., 1988; Petersen et al., 1988), the difference in the distribution of rCBF between supraspan and subspan tasks was used to identify brain systems activated by long-term auditory — verbal memory function. The memory performance data reported are consistent with this short-term/long-term memory distinction and supports the validity of the subtraction. Thus, the average number of words recalled in the supraspan task (10 words) was considerably greater than the accepted capacity of a short-term store (five to seven words). Also the reduced percentage of words correctly recalled in the supraspan task compared with the subspan task (performance below or up to span was nearly 100%) represents the loading of a shortterm store which is saturated in the supraspan condition. The recency effect, seen in the serial position curves (Fig. 5), represents the operation of a short-term phonological store operating in the supraspan condition (Vallar and Papagno, 1986) whilst the primacy effect may indicate long-term memory function. Furthermore, the overall increase in the number of correctly recalled words during three presentations of each supraspan word list (Table 2) suggests accessing of a stored word list, exceeding the capacity and duration of a short-term store, during the supraspan task.

*Anatomical and functional correlates of observed changes in rCBF*

*Prefrontal cortex.* A site of maximal increase of rCBF in the supraspan versus subspan comparison was centred in the dorsolateral prefrontal cortex bilaterally. Prefrontal rCBF increases were not seen in the comparison of either the subspan or supraspan task with
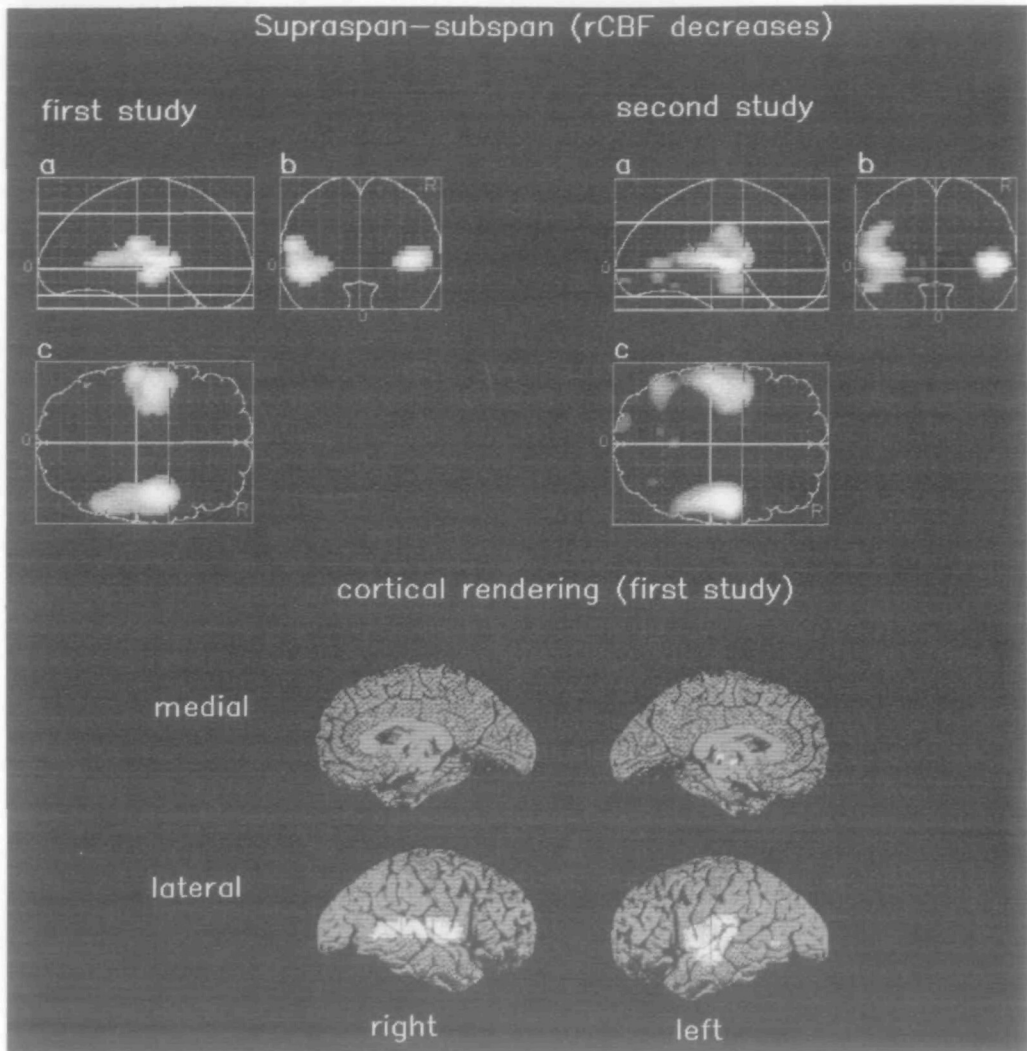
FIG. 5. Location of decreases in rCBF (supraspan compared with subspan task). Upper images: the spatial distribution of significant pixels at $P < 0.001$ (first study) and $P < 0.01$ (second study) for decreases in rCBF (supraspan−subspan) are shown as integrated projections along sagittal (a), coronal (b) and transverse (c) views of the brain. R = right. The axial extent of the data set is defined by lines in the sagittal view (a). Lower image: to aid interpretation of the above maps significant pixels are rendered onto the medial and lateral cortical surface of each hemisphere.

rest (a less sensitive between-subject comparison). This indicates a high degree of inter-subject variability in resting baseline prefrontal rCBF.

In primates, the prefrontal cortex has a pivotal role in memory function (for example, see Mishkin and Manning, 1978). On the basis of delayed-response tests, Goldman-Rakic (1987) has proposed that the prefrontal cortex is involved in representational memory. In humans, frontal lobe lesions, though not generally recognized as causing deficits

TABLE 3. COORDINATES OF MAXIMAL SIGNIFICANT INCREASE IN rCBF
(SUPRASPAN/SUBSPAN – REST)

| Anatomical location | Coordinates | | | Z value |
| --- | --- | --- | --- | --- |
| | x | y | z | |
| Left thalamus | | | | |
| Subspan – rest | −14 | −20 | 8 | 3.09 |
| Supraspan – rest | −14 | −18 | 12 | 3.70 |
| Right thalamus | | | | |
| Subspan – rest | 12 | −14 | 12 | 3.30 |
| Supraspan – rest | 12 | −16 | 12 | 3.53 |
| Left anterior cingulate gyrus | | | | |
| Subspan – rest | −8 | 22 | 28 | 3.00 |
| Supraspan – rest | −8 | 18 | 32 | 3.57 |
| Right parahippocampal gyrus | | | | |
| Subspan – rest | 16 | −42 | −8 | 2.51 |
| Supraspan – rest | 22 | −36 | −8 | 3.33 |
| Cerebellum | | | | |
| Subspan – rest | 4 | −48 | −4 | 2.60 |
| Supraspan – rest | −4 | −48 | −4 | 2.82 |
| Left superior temporal cortex | | | | |
| Subspan – rest | −52 | −30 | 8 | 2.91 |
| Supraspan – rest | −56 | −30 | 8 | 2.77 |
| Right superior temporal cortex | | | | |
| Subspan – rest | 50 | −28 | 4 | 3.26 |
| Supraspan – rest | − | − | − | − |

The stereotactic coordinates of maximal activations in both span conditions compared with rest. Coordinates are given in $x$, $y$ and $z$ coordinates in millimetres, from the atlas of Talairach and Tournoux (1988), together with appropriate $Z$ scores. $Z$ scores were calculated by transformation of the $t$ statistic to a Unit Gaussian distribution (see Friston et al., 1991a). The threshold for significance was set at $P < 0.01$ ($Z = 2.34$).

on recognition and recall tasks (see Ghent et al., 1962; Stuss et al., 1982; Smith and Milner, 1984; Squire 1987), are reported to impair the free recall of word lists similar to those used in this study (Jetter et al., 1986; Janowsky et al., 1989). Frontal lobe lesions, in addition, impair more subtle aspects of memory function such as judgements of item recency, item frequency, temporal order, the release from proactive interference and the use of mnemonic strategies in memory tasks (see Milner, 1974; Signoret and Lhermitte, 1976; Moscovitch, 1982; Smith and Milner, 1984; Hirst, 1985; Mayes, 1986). Shimamura (1991) has suggested that 'one possibility for the deficit on this sensitive test of free recall (15 word list) [with frontal lobe lesions] is that such tests require extensive use of retrieval strategies and planning'. A neuropsychological explanation for the bilateral rCBF increases in prefrontal cortex in this study may therefore relate to the organization and use of strategies necessary for dealing with large amounts of verbal information such as are present in the 15-word list task.

*Retrosplenial area of posterior cingulate cortex.* The rCBF increases in the retrosplenial area of the cingulate gyrus when comparing the supraspan with subspan task is of considerable interest as this area has anatomical connections with structures implicated
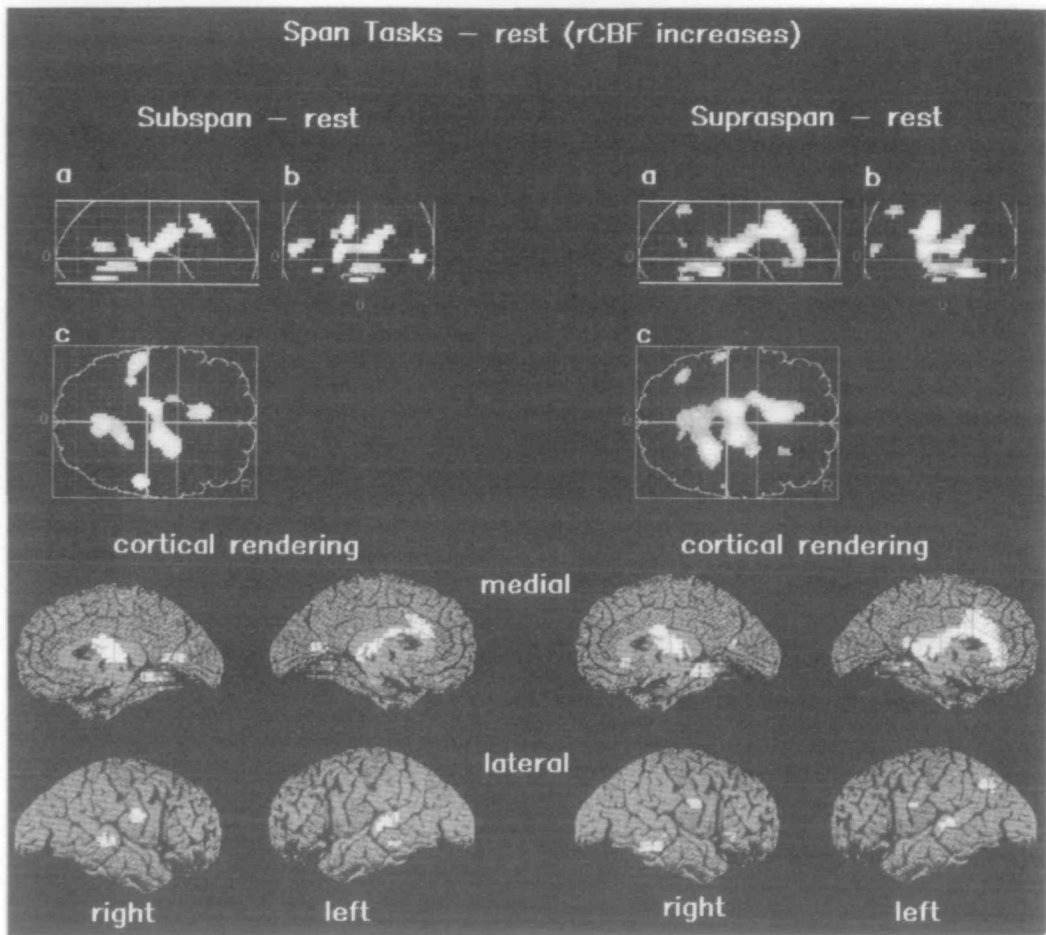
FIG. 6. Location of increases in rCBF (subspan/supraspan tasks compared with rest). Upper images: the spatial distribution of significant pixels at $P < 0.01$ for increases in rCBF (upper left images = subspan−rest; upper right images = supraspan−rest) are shown as integrated projections along sagittal (a), coronal (b) and tranverse (c) views of the brain. R = right. The axial extent of the data set is defined by lines in the sagittal view (a). Lower images: to aid interpretation of the above maps significant pixels are rendered onto the medial and lateral cortical surface of each hemisphere (lower left images = subspan−rest and lower right images = supraspan−rest).

in memory function. In particular, the retrosplenial cortex connects with anterior thalamic nuclei and the medial temporal structures in a number of species (Rosene and Van Hoesen, 1977; Valenstein *et al.*, 1987). Furthermore, a principal reciprocal connection between the prefrontal cortex (principal sulcus) and the hippocampus and parahippocampal region, in primates, is by way of a relay in the caudomedial lobule (Goldman-Rakic *et al.*, 1984), an area subsumed in the retrosplenial activation seen in our study. It has been suggested that the caudomedial lobule forms an 'important link in the hippocampal outflow to the neocortex that is highly developed in primates' (Goldman-Rakic, 1988). The activation of the retrosplenial area may reflect activation of a prefrontal-hippocampal or thalamic-

hippocampal polysynaptic pathway necessary for auditory–verbal memory function. In keeping with this is the profound anterograde amnesia, particularly for verbal memory function, that has been reported following highly localized damage to the retrosplenial cortex and adjacent splenium (Valenstein *et al.*, 1987).

*Precuneus*. Increased rCBF was noted in the precuneus (Brodmann area 31) when comparing the supraspan with the subspan condition. Although the connectivity of this area is unexplored, von Economo (1929) labelled this area LC1 and assigned it to the cingulate cortex on cytoarchitectonic grounds. Activation of the precuneus and cuneus has been reported when subjects are asked to recall visual information (Roland and Seitz, 1989). All words presented were concrete and therefore imageable. A mnemonic technique frequently used by subjects in supraspan word list learning studies is to relate words to visual images; therefore, we would speculate that the activation of precuneus reported in this study may relate to the use of visual mnemonic strategies.

*Thalamus*. Increased thalamic rCBF was observed when comparing both span tasks with rest. However, no rCBF increases were seen in the comparison of the supraspan to the subspan task. This suggests that thalamic activation was common to both the subspan and supraspan tasks. Thalamic nuclei make widespread and specific projections to the cerebral cortex and receive reciprocal corticothalamic afferents (Saper, 1987). The resolution of the PET technique limits the identification of individual thalamic nuclei activated, although the maximal thalamic activations were, in fact, located in the region of the mediodorsal thalamic nucleus. This nucleus has strong reciprocal connections with the prefrontal cortex (Goldman-Rakic and Porrino, 1985), an area activated in the supraspan–subspan memory comparison. Select thalamic nuclei have been implicated in mnemonic function (*see* Amaral, 1987). In particular, the mediodorsal nucleus of the thalamus has been shown to have a critical role in memory function in both man and primates (Victor *et al.*, 1971; Squire and Moore, 1979; Zola-Morgan and Squire, 1985; Amaral, 1987).

*Anterior cingulate cortex*. Increased rCBF in the left anterior cingulate was observed in both the subspan and supraspan comparison with rest. The cingulate cortex has substantial connections with the frontal, parietal and temporal cortex and limbic structures and receives major inputs from the thalamus and cerebral cortex (Pandya and Kuypers, 1969; Vogt *et al.*, 1979). The anterior cingulate (Brodmann area 32) projects to the lateral prefrontal cortex (Brodmann area 9), mid-orbitofrontal cortex (Brodmann areas 11, 12, 13) and the rostral portion of the superior temporal gyrus (Brodmann area 22) in the rhesus monkey (Pandya *et al.*, 1981); two of these three areas were activated in this study. Anterior cingulate activations have been observed in a number of PET studies involving the internal generation of a 'willed' response (verbal fluency and random finger movement) (Frith *et al.*, 1991*a*), in attentional conflict paradigms (Stroop colour/word task) (Pardo *et al.*, 1990) and in association tasks involving semantic analysis and selection for action (generate uses for heard/seen nouns) (Petersen *et al.*, 1988). These findings suggest an interpretation that the anterior cingulate rCBF increases in both subspan and supraspan conditions results from the attentional demands of response selection in both memory tasks.

*Medial temporal lobe structures.* Considerable evidence from animal brain lesioning experiments, primate 2-deoxyglucose studies and neuropsychological investigations of amnesic patients implicates the hippocampal formation in memory function (Zola-Morgan and Squire, 1986; Friedman and Goldman-Rakic, 1988; Mayes, 1991). In this study we did not obtain evidence for medial temporal lobe (amygdala, parahippocampal gyrus and hippocampal formation) rCBF increases in the comparison of the supraspan with subspan task. However, increased rCBF, maximal in the region of the right para-hippocampal gyrus, occurred when comparing subspan and supraspan conditions with the rest condition. This suggests that medial temporal lobe activation was occurring under both subspan and supraspan tasks. While memory impairments following temporal lobe lesions in man imply that the medial temporal lobe plays an essential role in 'long-term' memory but not 'immediate' or 'short-term' memory (Drachman and Arbit, 1966), the lesion studies do not preclude the possibility that during the subspan task the medial temporal lobe memory system may be automatically engaged, even though it is not essential for performance on a subspan task. This possibility would be consistent with parallel rather than serial processing in memory functioning.

*Superior temporal cortex.* Increased rCBF in the superior temporal cortex was seen in both span comparisons with rest, although it was most apparent when comparing the subspan task to rest (Fig. 6). The relative reduction in this area, when comparing the supraspan with the subspan task, therefore reflects a greater absolute increase in rCBF in the subspan condition over the supraspan condition. The area of increased rCBF in the superior temporal cortex (Brodmann areas 41/42/22) represents primary auditory receptive cortex and auditory association areas. These areas and an adjacent area of the left supramarginal and angular gyrus in the inferior parietal lobule have been implicated in the analysis of auditory information. Auditory stimuli activate the primary auditory areas (Nishizawa *et al.*, 1982; Petersen *et al.*, 1988; Wise *et al.*, 1991), whilst lesions posterior to primary auditory areas (i.e. supramarginal and angular gyri) are reported to give rise to deficits in auditory – verbal short-term memory (Warrington *et al.*, 1971; Shallice and Vallar, 1990). The greater increase in superior temporal gyral rCBF in the subspan task over the supraspan task may reflect a greater stimulation of a putative phonological superior temporal based auditory – verbal short-term memory system. However, other explanations are possible *(see below).* Relative reductions of rCBF in this region have been observed during verbal fluency tasks, which have characteristics in common with the supraspan condition (i.e. recall from memory of a word list). These PET verbal fluency findings can be modelled by a neuronal network for word generation in which the efficient production of intrinsically generated word lists is associated with a reduction of neuronal activity of primary auditory areas (Friston *et al.*, 1991*b*).

*Cerebellum.* The axial extent of the data set included the more rostral aspects of the cerebellum and increased cerebellar rCBF was noted in both span comparisons with rest. Anatomical connections between the cerebellum and temporal lobes and prefrontal cortex have been established (Heath and Harper, 1974). The cerebellum has a recognized role in motor planning and possibly cognition (Watson, 1978; Decety *et al.*, 1990;

Schmahmann, 1991); thus the cerebellar activation may relate either to speaking or memory function.

*Comments on subtraction paradigms used in this study*

A 'non-memory' linguistic baseline condition was not included in the memory activation studies (studies 1 and 2). The feasibility (using simple cognitive subtraction) of obtaining such a baseline or rest state is questionable as linguistic tasks (such as repeating each word or articulating an arbitrary preselected word) are likely to evoke short-term memory processes which are an integral part of speech comprehension (*see* Shallice, 1988). In this study we attempted to design two task conditions (subspan and supraspan tasks) that differed in the extent to which auditory — verbal long-term memory systems were activated. The memory performance data reported support the validity of the subtraction used. Despite the limitations inherent in the use of 'rest state' comparisons they do provide an indication of the absolute direction of changes in rCBF in the supraspan versus subspan comparison. The rest state comparisons also highlighted a number of brain areas not identified in the supraspan versus subspan comparison. The rest state was a non-linguistic auditory baseline and therefore comparisons of the span tasks with the rest state cannot exclude activations that may relate, in part, to listening to and speaking words. In other reported PET studies, listening to auditorily presented words increases rCBF bilaterally in the superior temporal cortex (Petersen *et al.*, 1988; Wise *et al.*, 1991) whilst speaking words increases rCBF in the inferior premotor cortex (putatively Broca's area or Brodmann areas 44/6): the insular, the sensorimotor cortex representing face and the vocal apparatus (Brodmann area 4) and the supplementary motor area (Brodmann area 6a) (Petersen *et al.*, 1988; Fox and Pardo, 1991). Hearing words or speech output is not reported to increase rCBF in parahippocampal, prefrontal, retrosplenial or precuneus areas; thus it is unlikely that rCBF increases in these areas can be ascribed to differences in auditory input or speech output between tasks. Interestingly a pattern of rCBF change similar to that reported for speech (supplementary motor area, insular and primary sensorimotor representation of vocalization) was identified in our study when comparing rCBF decreases in each span task with rest (data not shown). Speculatively, this apparently paradoxical result may relate to the pattern of auditory stimulation and speech output (intermittent speech output interspersed with periods of auditory stimulation). Additionally or alternatively it may relate to active suppression of these areas due to one or more components of the memory tasks. This finding has some precedence in the literature in that paradoxical decreases in insular rCBF have been noted when subjects are requested to speak a verb in response to hearing a noun. In contrast, when subjects repeat a noun in response to hearing a noun, increased insular rCBF is reported (Raichle *et al.*, 1991).

In the case of rCBF changes in the superior temporal cortex it is possible that differences in speech output or auditory input could account for the observed changes in rCBF. We have recently examined this issue in a series of PET experiments involving the free recall of auditorily presented word lists of between two and 13 words in length. Maximal decreases in rCBF in the superior temporal areas occurred when word list length was increased over the range of two to approximately seven words, when overall speech output, across tasks, as well as auditory input was closely matched (unpublished observations). This suggests that the relative reduction in rCBF in the supraspan task

compared with the subspan task may reflect active suppression rather than a simple performance artefact due to differing speech output or auditory input.

*Distributed systems for memory function*

The brain regions identified are likely to represent sites of signal processing relevant to auditory – verbal memory but in addition may represent storage sites. Accumulating evidence suggests that signal processing and storage may coexist in the same spatial locations. For example, in the monkey, the inferotemporal cortex (area TE) is implicated in both the processing and storage of visual signals (for review, *see* Squire, 1987). For many regions the pattern of activations observed was symmetrical; this is somewhat surprising given the commonly accepted left-sided lateralization of language-related tasks including auditory – verbal memory (Milner, 1974). The failure to observe a distinct left medial temporal lobe activation in any of the comparisons made may indicate that continuous activity in this structure occurs across a variety of cognitive states.

Prefrontal cortex connectivity may be particularly relevant to understanding the overall pattern of activations observed in this study. The principal reciprocal connections of the dorsal prefrontal cortex, in primates, are with the inferior parietal lobule, para-hippocampus, cingulate, retrosplenial and superior temporal gyrus (Jacobson and Trojanowski, 1977; Goldman-Rakic *et al.*, 1984; Goldman-Rakic, 1987; Pandya and Barnes, 1987). Many of these areas were activated in the supraspan to subspan comparison or supraspan/subspan to rest comparisons. In addition to the demonstrated anatomical connections there is accumulating evidence of functional connectivity. In man, rCBF in the left dorsolateral prefrontal cortex correlates negatively with rCBF in the superior temporal cortex during word-finding tasks (Frith *et al.*, 1991*b*). In the primate, single-unit recording from neurons in the frontal eyefields (prefrontal cortex) and the intraparietal sulcus (posterior parietal cortex) of the monkey have a similar pattern of neuronal response when undertaking a delayed eye-movement task (Goldman-Rakic, 1987, 1988). Different patterns of activation between reciprocally connected areas may account for the diverse number of psychological tasks with which the prefrontal cortex is associated (Goldman-Rakic, 1988). In other words, neuropsychological functional specialization within the prefrontal cortex is determined with respect to its diverse extrinsic anatomical and functional connections. Recent PET studies lend support to this postulated anatomical organization of higher cortical functions. For example, verbal fluency tasks increase rCBF in the left dorsolateral prefrontal cortex and parahippocampal regions and decrease rCBF bilaterally in the superior temporal cortices, whilst the internal generation of a motor sequence increases rCBF bilaterally in the dorsolateral prefrontal cortex and decreases rCBF in the primary motor sensory cortex and the posterior parietal lobe (Frith *et al.*, 1991*a*). The pattern of prefrontal, retrosplenial, precuneus and superior temporal gyrus changes observed in this study, when comparing supraspan to subspan tasks, can be interpreted within this framework as part of a specialized functional system for auditory – verbal long-term memory. Similarly the common pattern of thalamic, anterior cingulate, cerebellar and parahippocampal rCBF increases in both span conditions compared with rest, identifies components of a system that may subserve both short- and long-term auditory – verbal memory function.

In summary, this is the first PET study of the functional anatomy of auditory – verbal memory function. The results, obtained from normal volunteers, provide further evidence

that diverse brain regions, identified on the basis of lesion studies in animals and brain-damaged patients, participate in auditory—verbal memory function. The observed pattern of rCBF change identifies a number of the anatomical components of a distributed system necessary for auditory—verbal long- and short-term memory function.

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