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Regional brain activity during working memory tasks

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Abstract

The first aim of our PET study was to replicate previous findings concerning the brain areas activated by a verbal working memory task. The second aim was to specify the neural basis of the central executive, using a task of working memory updating. Our data confirm that the lower left .. supramarginal gyrus and premotor area are the key regions subserving short-term verbal memory processes. They also suggest that the updating memory task is related to mid-dorsolateral prefrontal activation, most probably responsible for the updating function of the central executive. An unexpected, predominantly right activation occurred in the inferior parietal region during the verbal memory updating task, which we related to a visuospatial strategy used to maintain the information in short-term memory. A third purpose was to explore the brain regions activated by a nonverbal, visual memory task, and our results confirm the importance of the superior occipital gyrus in the visual short-term memory.

Keywords: working memory; central executive; PET

Abbreviations: BA = Brodmann area; rCBF = regional cerebral blood flow; SPM = statistical parametric map

1. Introduction

Working memory refers to a limited capacity system that is responsible for the temporary storage and processing of information while cognitive tasks are performed. Baddeley's model represents the most extensively investigated theoretical construct of working memory (Baddeley and Hitch, 1974; Baddeley, 1986, 1992). This model comprises a modality-free controlling central executive that is aided by a number of subsidiary slave systems which ensure temporary maintenance of information. Two such systems have been more deeply explored: the phonological loop and the visuospatial sketchpad. The visuospatial sketchpad system is assumed to be involved in setting up and maintaining visuospatial images. The phonological loop system is specialized for processing verbal material and is composed of two subsystems: a phonological store and an articulatory rehearsal process.

The core of the working memory model is the central executive. The central executive is assumed to be an attentional control system responsible for strategy selection and for control and co-ordination of the various processes involved in short-term storage and more general processing tasks. An important characteristic of this system is that its resources are limited and divided into different processing and storage functions. The theoretical accounts of the central executive are less clearly detailed than those of the slave systems. Baddeley (1986) has suggested that the supervisory attentional system component of the attentional control of action model proposed by Norman and Shallice (1986) might be an adequate approximation of the Central Executive system. According to Norman and Shallice, some action schemata (routine actions) can ran automatically, whereas other actions require deliberate attentional resources. These authors assume the existence of two attentional control processes: the contention scheduling mechanism, which would be involved in making selections between conflicting routine actions, and the supervisory attentional system, which would intervene when the selection of routine actions is not sufficient (for instance, in tasks that require planning or decision making, or when coping with novel or dangerous situations). According to Shallice (1988), dysfunction of the supervisory attentional system could plausibly account for the cognitive deficits following frontal-lobe lesions. Recently, Shailice (1994) has also suggested that the function of the supervisory attentional system could be fractionated into several components.

Convincing evidence for the existence of the different components comprising the working memory model comes from the study of brain-damaged patients with specific short-term memory impairments (for reviews, *see* Gathercole, 1994; Van der Linden, 1994). Some patients have deficits of aαditory short-term memory that can be attributed either to a selective impairment of the phonological store (e.g. Vallar and Baddeley, 1984) or to a disturbance of the articulatory rehearsal process (e.g. Belleville *et al.,* 1992). Other patients have specific impairment of the visuospatial sketchpad (Hartley *et al.,* 1991) or of the central executive (Van der Linden *et al.,* 1992). Other data show that the central executive is particularly sensitive to the effects of Alzheimer's disease (for review, *see* Morris, 1994). More specifically, it appears that patients with Alzheimer's disease manifest a deficit affecting one important component of the central executive, i.e. the capacity to co-ordinate two or more sub-processes (Baddeley *et al..,* 1986, 1991). A similar dual-task deficit has also recently been observed in patients with Parkinson's disease (Dalrymple *et al.,* 1994). Finally, a number of studies have suggested that normal ageing is characterized by a decline in the capacity of the central executive (e.g. Van der Linden *et al,* 1994α, *b).*

Concerning the physiological substrate of working memory, neuroimaging studies of patients with selective deficits of the phonological loop suggest that this component is localized in the left hemisphere. More specifically, in a review of all patients for whom sufficient details were available, Delia SaIa and Logie (1993) *{see* also Shailice and Vallar, 1990) found that the common denominator seemed to be the inferior part of the parietal lobe, close to the junction with the superior, posterior temporal lobe. In the few cases where the lesion was described with more detail, it involved the supra-marginal gyrus of the inferior parietal lobe. A recent PET activation study (Paulesu *et al.,* 1993α) confirmed these findings, localizing the phonological store in the left supramarginal gyrus while the articulatory rehearsal process was localized in Broca's area.

There exists less evidence for the neural basis of the visuospatial sketchpad. The only studied case, described as having a specific visuospatial sketchpad deficit, suffered from an extensive lesion in the frontal region of the right hemisphere (Hanley *et al.,* 1991). When group studies are considered, it appears that the most frequent lesion associated with a visuospatial short-term memory deficit involves the posterior parietal lobe near its junction with the occipital lobe *{see* Warrington and James, 1967). However, certain other data also suggest that patients with frontal cortical lesions can present with deficits of spatial working memory (e.g. Pigott and Milner, 1994). PET studies (Jonides *et al.,* 1993; Frackowiak, 1994; Smith and Jonides, 1995) showed that spatial and visual working memory tasks led to different patterns of activation. The spatial working memory task activated the right occipital gyrus (Brodmann area or BA 19; *see* also Dupont *et al.,* 1993), the right posterior parietal gyrus (area 40; *see* also Belger *et al.,* 1995), the right premotor area (BA 6), and the right inferior dorsolateral prefrontal cortex (area 45/47). In another study using functional MRI, however, a spatial working memory task activated the prefrontal area 46 (McCarthy *el al.,* 1994). The visual short-term memory task studied by Smith and Jonides (1995) led to activation of the left inferior temporal cortex at the temporo-occipital junction (area 37; *see* also Belger *et al.,* 1995), the left parietal gyrus (area 40), the left anterior cingulate gyrus (area 32), and the prefrontal gyrus (area 6). In another study, comparing shape judgement task and visual short-term memory task with Korean letters, the working memory task caused a greater activation in right occipitoparietal area 19/40 and in left prefrontal area 47 (Paulesu *et al., 1993b).* Bilateral activation of the prefrontal dorsolateral area was also reported for a shape working memory task, using [^{18}F]fluorodeoxyglucose (Swartz ef al., 1995).

Finally, the localization of the central executive remains to be considered. Some authors have proposed that executive processes involve the frontal lobes (e.g. Shailice, 1988). In recent PET studies, Petrides *et al.* (1993α, *b)* observed bilateral activation of mid-dorsolateral prefrontal cortex (areas 46 and 9) during the performance of verbal and nonverbal random generation tasks, in which subjects were asked to generate random sequences. This task is generally considered to place significant demands on the central executive *{see* Baddeley, 1986: Van der Linden *et al.,* 1994). A similar localization was observed when the subjects performed a task in which they had to monitor random sequences of numbers from 1 to 10 read by the experimenter and to identify the number that had been omitted in the sequence (Petrides *et al.,* 1993α). More recently, in a study using functional MRI, D'Esposito *et al.* (1995) observed a bilateral activation in the dorsolateral prefrontal cortex (areas 46 and 9) as well as in the anterior cingulate during the concurrent performance of two tasks, which is expected to engage the central executive.

However, the frontal localization of certain central executive functions has been questioned *{see* Morris, 1994). Indeed, frontal lobe lesions do not necessarily impair the coordination of dual tasks involving working memory (e.g. Frisk and Milner, 1990). Similarly, we recently described a closed-head injury patient in whom a specific dual-task impairment was interpreted as the consequence of a reduction of central executive resources, with no concomitant signs of frontal dysfunction (Van der Linden *et al.,* 1992). Furthermore, Dalrymple *et al.* (1994) found no association in patients with Parkinson's disease between dual task performance and various indices of frontal performance. These data suggest either that the co-ordination of dual tasks does not implicate the frontal lobes or that there are dissociations within central executive functions. Finally, some researchers consider that executive functioning relies on a network distributed between anterior and posterior areas of the brain (e.g. Fuster, 1993).

A major difficulty in the exploration of the neural basis of the central executive is that a wide range of cognitive functions has been ascribed to this system, i.e. control, processing and even storage activities. In this context, it seems important to explore the neural substrate that underlies different central executive functions (other than dual-task coordination or random generation). Another problem is finding a working memory task in which the role of the central executive can be clearly distinguished from that of the slave systems. In a recent study, Morris and Jones (1990) showed that the running memory paradigm initially used by Pollack *el al.* (1959) meets this requirement. The task requires subjects to watch strings of consonants of unknown length, and then to recall serially a specific number of recent items. The running span task requires considerable flexibility of information processing and a progressive shift of attention, i.e. discarding some items while new ones are registered. Moms and Jones (1990) showed that the running memory task requires two independent mechanisms: the phonological loop (phonological store and articulatory rehearsal process) and the central executive. The updating process requires central executive resources but not the phonological loop. Conversely, the serial recall component of the task requires the phonological loop but not the central executive. Recently, we successfully used a running memory task similar to that employed by Morris and Jones (1990) to show that older subjects have decreased central executive resources (Van der Linden *et al.,* 1994).

The main aim of the present study was to explore the neural basis of what appears to be an important activity of the central executive, i.e. the updating of working memory. We expected mainly dorsolateral prefrontal activation. Another aim was to replicate the findings reported by Paulesu *et al.* (1993a, *b)* concerning the localization of the phonological store and the articulatory rehearsal process, on the one hand, and the functional anatomy of the visual sketchpad, on the other hand.

2. Material and methods

2.1. Subjects

Ten male, European, right-handed volunteers (age range 19— 30 years) gave written informed consent to take part in this study, which was approved by the University of Liège Ethics Committee. None had past medical history nor used any medication.

2.2. PET scanning

Scans of regional cerebral blood flow (rCBF) were obtained for each subject using a CTI model 951/31 R PET scanner (CTI, Knoxville, Tenn., USA) with collimating septa extended. The physical characteristics of the tomograph have been described previously (Degueldre and Quaglia, 1992). Subjects had an individual thermoplastic face mask for head stabilization. A transmission scan was acquired for attenuation correction using three rotating sources of ^{68}Ge. Emission scans were reconstructed using a Hanning filter at a cut-off frequency of 0.5 cycles per pixel giving a transaxial resolution of 8.7 mm full width at half maximum and an axial resolution of 5 mm for each of 31 planes with a total field of view of 10.8 cm in this direction.

Volunteers received a 60 s intravenous infusion of $H_2{}^{15}O$ (total activity 35 mCi) through a left forearm cannula. A dynamic PET scan consisting of two frames was collected over a period of 3 min (background frame duration 1 min, second frame duration 2 min). The infusion of ^{15}O-labelled water began 45 s after acquisition start time (Lammertsma *et al.,* 1990). Cognitive activation started upon $H_2{}^{15}O$ infusion, 15 s before the second scan. The integrated counts per pixel recorded during the second scan were used as an index of rCBF (Mazziotta *et al.,* 1985; Fox and Mintun, 1959).

All subjects underwent six consecutive rCBF measurements (two for each experimental and control condition). Fifteen minutes elapsed between scans. The order of memory tasks was randomly distributed between subjects and it was determined by a Latin square design.

2.3. Working memory tasks

The control and the first experimental tasks have previously been described by Paulesu *et al.* (1993a). In the control visual short-term memory task, six Korean letters (which could not be transcoded into a phonological code) were randomly presented on a computer screen at a rate of one per second. Subjects were asked to remember the stimuli using a visual code and to judge if a probe Korean letter displayed 2 s after each sequence was present in this particular sequence. Subjects responded by pressing one of two yes-no response buttons. In the phonological short-term memory (first experimental) task, randomized sequences of six phonologically dissimilar consonants were displayed on the monitor. Subjects were instructed to rehearse the stimuli silently and to remember them serially to detect whether a target consonant presented 2 s after this string was present in the list. The task was otherwise identical to the control one. In the updating working memory (second experimental) task (adapted from Morris and Jones, 1990) *(see* also Van der Linden *et al.,* 1994), lists of eight, nine and 10 phonologically dissimilar consonants were presented at a rate of one per second. Subjects were not informed of the length of each list before presentation. They were asked to rehearse silently and to remember serially only the last six items. They had to judge whether a consonant displayed 2 s after each list was present in the six last consonants for this particular list. Sequences sounding like words and abbreviations were avoided. The various lists were presented in a randomized order, with the restriction that no more than two lists of the same length were presented successively.

Patients were trained 5 or 6 days before the PET session. Five minutes before each acquisition, instructions were rehearsed, followed by a short training period (four sequences). The control and first experimental tasks consisted of nine sequences (six sequences during blood flow measurement). The second experimental task comprised eight sequences (five sequences during blood flow measurement).

2.4. Data analysis

Image analysis was performed on a SPARC workstation (Sun Microsystems Inc., Surrey, UK) using statistical parametric mapping (SPM) software 94 (MRC Cyclotron Unit, London, UK; Frackowiak and Friston, 1994) implemented in MATLAB (Mathworks Inc., Sherborn, Mass., USA). Each reconstructed rCBF scan consisting of 31 primary transverse planes was interpolated to 43 planes to render the voxels isotropic. The six acquisitions from each subject were realigned using the first as reference (Woods *et al.,* 1992). The data were then transformed into a standard stereotactic space (Talairach and Tournoux, 1988). A Gaussian filter (16 mm full width at half maximum) was applied to smooth each image to accommodate inter-subject differences in gyral and functional anatomy and to suppress high frequency noise in the images. Such transformation of the data allows for pixel-by-pixel averaging of data across subjects and for direct cross-reference to the anatomical features in the standard stereotactic atlas. Due to variations of initial head positioning, resultant images obtained in all subjects extended from 28 mm below to 44 mm above the intercommissural plane.

Differences in global activity within and between subjects were removed by analysis of covariance on a pixel-by-pixel basis with global counts as covariate and regional activity across subjects for each task as treatment (Friston *et al.*, 1990).

The across-task comparisons were performed by averaging between paired measurements. For each pixel in stereotactic space, the analysis of covariance generated a condition-specific adjusted mean rCBF value (normalized to 50 ml 100 ml^{-1} min^{-1}) and an associated adjusted error variance. The analysis of covariance allowed comparison of the means across conditions on a pixel-by-pixel basis using the *t* statistic. The resulting sets of *t* values constituted statistical parametric maps [SPM(J)] (Friston *et al.,* 1991). The SPM(O were transformed to the unit normal distribution [SPM(Z)]. The design of our study was (i) a replication of a verbal working memory task (Paulesu *et al.,* 1993α) and (ii) a task involving the central executive, with an *a priori* hypothesis, i.e. midfrontal activation, based on previous reports (Petrides *et al,* 1993; D'Esposito *et al.,* 1995). Since the study was replicative or hypothesis driven, a statistical threshold of 0.01, not corrected for multiple comparisons, was applied to identify significant changes of regional blood flow in previously reported brain regions. Activation foci, not directly predicted by previous studies, were only tentatively reported in a second part of the tables. Moreover, a visual to verbal working memory comparison was planned to obtain information on the visual sketchpad. There, we used an SPM thresholded at $P < 0.001$, and we report activation foci at $P < 0.05$, Bonferroni corrected. We also capitalized on the report of Paulesu *et al.* (1993b) on visual short-term memory task using Korean letters, and we tentatively reported foci of activation obtained with uncorrected $P < 0.01$.

3. Results

Subjects made only few errors in the different tasks. Errors in the visual short-term memory condition (mean 4.0) were significantly more frequent than errors in the phonological (mean 0.87) and updating (mean 2.25) working memory tasks [ANOVA, $F(2,14) \approx 15.8$, $P = 0.0003$].

When the phonological short-term memory task was compared with the visual task (Table 1, Fig. 1), significant activation foci appeared in left premotor frontal gyrus and adjacent Broca's area (BA 6/44), in the left superior temporal gyrus (BA 22/42) and in left and right insula. There was also activation in the inferior part of the left inferior parietal gyrus (BA 40), near the superior temporal gyrus. Increases of rCBF were observed bilaterally in primary sensorimotor areas of mouth and larynx. Moreover, we tentatively report foci of activation in the anterior cingulate gyrus (BA 24), in the medial part of the frontal pole (BA 10), and in the left parahippocampal region.

When working memory updating was compared with the phonological short-term memory task (Table 2, Fig. 1), foci of increased rCBF were observed in the right middle frontal gyrus (dorsolateral area, BA 9) and to a lesser extent in the left middle frontal gyrus (BA 46) and in the right frontopolar cortex (BA 10). Increased rCBF was found in a broad area of right inferior parietal and angular gyri (BA 40/39), and in the left supramarginal gyrus (BA 40). We also observed not previously hypothesized activation foci in cuneus/precuneus and superior occipital gyri on both sides (BA 18/19), in the right thalamus, in the left BA 10 (middle prefrontal gyrus) and in the cerebellum.

When the visual short-term memory task was compared with the verbal memory task (Table 3, Fig. 1), significant increase of blood flow was seen in both medial occipital gyri (BA 17/18), in the left parieto-occipital sulcus, in the left BA 18, in the right calcarine area, and in the right BA 19. We tentatively report further activation in both fusiformis gyri (BA 37/20), in the left inferior temporal gyrus (BA 20), in the left middle frontal gyrus (BA 46 and BA 10) and in the left frontobasal cortex (BA 11).

***Table** 1: L = left; R = right; sup = superior; inf — inferior; ant = anterior. Stereotactic coordinates refer to the maximal activation indicated by the highest Z score in a particular cerebral structure. Distances refer to the stereotactic space of Talairach and Toumoux (1988). P < 0.01 uncorrected for multiple comparisons.*

Gyms/region	*x* (mm)	*y* (mm)	Z (mm)	Z score
(A) Activation foci associated with a verbal working memory task (replicative study of Paulesu *et al.,*1993)				
L premotor (BA 6/44)	-52	2	8	4.58
L sup temporal (BA 22/42)	-56	-10	0	3.57
	-56	-14	8	3.42
	-60	-38	12	3.00
L insula	-26	-24	12	2.75
R insula	30	-24	4	2.90
L postcentral (BA 1/2)	-54	-14	24	2.89
R postcentral (BA 3/43)	48	-12	20	3.06
	42	-18	28	2.85
	36	-22	24	2.46
L inf parietal (BA 40)	-56	-22	24	3.16
	-58	-26	20	3.09
(B) Brain regions with possible activation (not directly predicted from previous studies)				
L frontal pole (BA 10)	-6	60	8	2.76
R ant cingulate (BA 24)	12	_2	28	3.11
L (para)hippocampal	-24	-46	4	2.74

Table 2: *L = left; R — right; mid = middle; sup = superior; inf = inferior. Stereotactic coordinates refer to the maximal activation indicated by the highest Z score in a particular cerebral structure. Distances refer to the stereotactic space of Talairach and Tournoux (1988). P < 0.01 uncorrected for multiple comparisons.*

Gyrus/region	*x* (mm)	*y* (mm)	*z* (mm)	Z score
(A) Activation foci associated with memory updating (hypothesized from Petrides *et al.)*				
R inf parietal (BA 40)	44	-56	36	3.54
	42	-46	32	3.24
	34	-44	36	3.19
R angular (BA 39)	36	-66	32	3.38
L supramarginal (BA 40)	-50	-52	32	2.54
R mid frontal (BA 9)	40	24	28	3.19
	32	28	36	2.41
L mid frontal (BA 46/10)	*-Al*	46	16	3.46
	-28	52	4	2.58
R frontal pole (BA 10)	20	56	0	3.28
	20	60	8	2.78
(B) Brain regions with possible activation not directly predicted from previous studies)				
from previous studies)				
R thalamus	8	-18	4	3.54
L precuneus (BA 18)	-8	-72	28	4.04
L cuneus (BA 19)	-14	-82	32	2.89
L sup occipital (BA 19)	-24	-84	32	3.06
R cuneus (BA 19)	6	-84	32	4.00
R sup occipital (BA 19)	32	-70	36	3.63
Cerebellum	54	-56	-20	2.83
	-8	-60	-28	2.73
	52	-66	-24	2.66

Table 3: *L = left; R = right; sup = superior; inf = inferior; mid = middle, Stereotactic coordinates refer to the maximal activation indicated by the highest Z score in a particular cerebral structure. Distances refer to the stereotactic space of Talairach and Tournoux (1988).*

Gyrus/region	*x* (mm)	*y* (mm)	*z* (mm)	Z score
(A) Activation foci associated with a visual working memory task *(P* <0.05. Bonferroni corrected)				
L parieto-occipital sulcus	-10	-74	24	5.37
L inid occipital (BA 18/19)	-24	-86	4	4.56
	-30	-82	8	4.31
L cuneus (BA 18)	-18	-92	4	4.71
L lingualis (BA 18)	-2	-84	-8	4.19
R sup occipital (BA 19)	24	-66	32	4.17
R occipital (BA 19)	28	-72	28	4.46
R mid occipital (BA 18/19)	30	-84	4	4.84
R calcarine (BA 17)	6	-94	0	4.45
(B) Brain regions with possible activation (P< 0.01, uncorrected)				
L occipital (BA 18/19)	-24	-70	24	4.07
L lingualis (BA 18)	-10	-82	-12	3.86
	-14	-84	0	3.99
L fusiformis (BA 37)	-34	-48	-8	3.91
	-34	-56	-12	3.80
R fusiformis (BA 20)	30	-44	-20	2.59
L inf temporal (BA 20)	-60	-32	-16	3.24
L medial frontal (BA 11)	-22	22	-12	3.15
L mid frontal (BA 11)	-42	46	16	2.69
L mid frontal (BA 10)	-28	52	8	2.90

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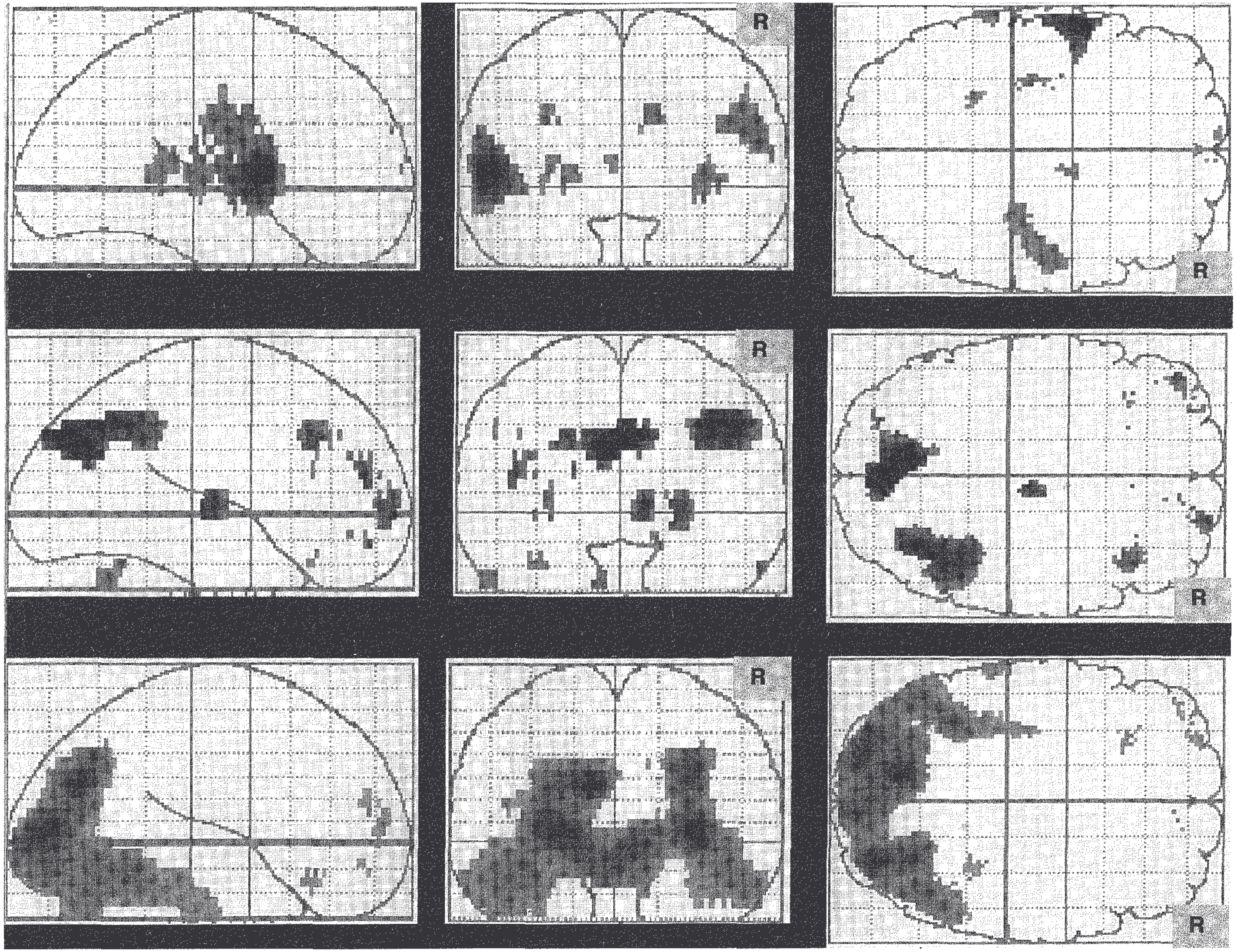

Fig. 1 *Representation in a stereotactic space of the cerebral regions significantly activated during verbal working memory, working memory updating, and visual working memory*

4. Discussion

The aim of the present study was, first, to reproduce the brain activation pattern observed by Paulesu *et al.* (1993α) in a verbal working memory task, and then to add further demand on the central executive system by studying a task of verbal working memory updating. When phonological short-term memory was compared with visual short-term memory, the pattern of activation described by Paulesu *et al.* (1993a) was in fact replicated. Activation foci were detected in Broca's area and the adjacent premotor cortex (BA 44/6), in left superior temporal gyrus (BA 22/42), in both insula and in the inferior part of the left supramarginal gyrus (BA 40). Paulesu *et al.* (1993a) suggested that those regions constitute the functional anatomy of the phonological loop, and more specifically, that the left supramarginal gyrus is the primary location of the phonological store and that Broca's area is crucial to the articulatory rehearsal process. Primary sensorimotor areas for mouth and larynx were also activated by our phonological short-term memory task. Those areas could be related to motor aspects of speech planning even though the experiment did not implicate overt speech. Moreover, we observed an unpredicted activation in the left frontal pole (BA 10). It should be noted that according to Baddeley (1986) *(see* also Vallar and Papagno, 1986), a verbal memory span task depends on both the phonological loop system and the central executive. The phonological loop system is able to store only a limited number of items in the correct order but the central executive may increase this number either by increasing the efficiency of the phonological loop (e.g. by grouping items in higher level units), or possibly by using its own storage capacity. In addition, Hulme *et al.* (1991) presented evidence demonstrating a long-term memory contribution to verbal memory span. More specifically, they suggested that the long-term memory of the phonological form of words is important in supporting the retrieval of partially decayed words held in a rehearsal loop. From that perspective, one of the central executive functions is to coordinate the transfer of information between short- and long-term memory. In this theoretical framework, activation of BA 10 could be related to the specific storage function of the central executive, or to its co-ordination function between short- and long-term memory. The left parahippocampal activation that we observed during the task would possibly reflect the contribution of long-term memory. Anterior cingulate cortex (BA 24) was another possible focus of activation. As a matter of fact, the functions of the anterior cingulate cortex appear to be heterogeneous. This region has been implicated in different tasks that require selective attention, significant processing capacity, attention for action, or even preparation and initiation of movement (e.g. Petersen *et ah,* 1988; Pardo *et ah,* 1990; Frith *et ah,* 1991; Paus *et al.,* 1993). The specific contribution of the cingulate gyrus to our phonological short-term memory task remains to be determined.

When working memory updating was compared with phonological short-term memory, we observed activation of a set of frontal and parietal regions. An increase of rCBF occurred in the right mid-dorsolateral prefrontal cortex (BA 9), in left middle frontal regions (BA 46 and possibly BA 10) and in the right frontal pole. Activation of mid-dorsolateral frontal cortex (BA 9/46) was previously observed bilaterally during random generation tasks (Petrides *et al.* 1993a, *b),* and it was associated with activation in the right frontopolar cortex during an externally ordered verbal working memory task (Petrides *et al.*, 1993/3). Since both random generation and updating tasks require considerable flexibility of information processing and a progressive shift of attention, they are considered to place significant demands on the central executive (Baddeley, 1986; Morris and Jones, 1990; Van der Linden *et al.,* 1994). From that perspective, our data confirm that the prefrontal cortex, which was also activated in dual-task condition (D'Esposito *et al.,* 1995), is a key structure for the central executive.

Significant increases of rCBF were also observed in both inferior parietal regions (BA 40/39, predominant on the right side), and possibly in BA 19, when working memory updating was compared with the phonological short-term memory task. Activation of inferior parietal regions has been implicated in visual mental imagery in humans (Kosslyn *et ah,* 1993; Mellet *et ah,* 1995), suggesting that image generation could be an important process in our updating task. A similar bilateral posterior parietal (BA 40/7) activation was also found during verbal and nonverbal random generation tasks, using numbers or abstract figures (Petrides *et al.,* 1993a, *b).* An increase of rCBF was previously reported in left and right posterior parietal cortex during visual and spatial short-term memory tasks, with right activation preferentially related to processing of spatial information (Jonides *et al.,* 1993; Smith and Jonides, 1995). In fact, *post hoc* questioning of our subjects indicated that half of them had used a phonological strategy in the updating memory experiment, while the others had used a visual imagery strategy or a combination of both. The original updating task that requires serial recall of the last six consonants of longer series (Morris and Jones, 1990) was converted, in our experiment, into a recognition task to comply with Paulesu's procedure. We recently obtained preliminary data confirming that the recognition and the recall procedures promote the preferential utilization of visuospatial and phonological strategy, respectively. Now, if visuospatial strategy predominates in our experimental updating condition, parietal activation might be related to generation and short-term storage of visuospatial images. Finally, activation was observed in the right thalamus. Increases in rCBF were also found in both thalami in a subspan task compared with the rest condition (Grasby *et al.,* 1993). On the other hand, the dorsolateral prefrontal cortex and the mediodorsal nucleus of the thalamus were included in Goldman-Rakic's animal model of working memory (1990). In the visual short-term memory task using Korean letters, we observed an activation in the superior occipital gyrus (BA 19) which appears to be crucial for temporary storage of visual information. Effectively, the right BA 19 and the right occipitoparietal junction 19/40 were activated in different studies of visuospatial working memory (Dupont *et al.,* 1993: Jonides *et al.,* 1993; Paulesu *et al.,* 19932/). BA 19 was also possibly activated during our task of working memory updating *(see* above). However, the superior occipital region is not specifically dedicated to short-term memory processes, for it is activated, along with the inferior parietal region, during visual mental imagery (Kosslyn *et al.,* 1993: Mellet *et al.,* 1995). It should be noted that according to Baddeley (1986), the visuospatial sketchpad is also assumed to play a role in holding and manipulating mental images. Significant rCBF increases were observed in the right calcarine area, and bilaterally in BA 18/19. This pattern of activation is probably related to elementary perceptual operations and visual coding taking place within the occipital lobe (Sergent *et al.,* 1992). The possible bilateral activation that we observed in the fusiform gyrus was reported in shape working memory tasks (Corbetta *et al.,* 1991; Belger *et al.* 1995). However, left fusiform and left inferior temporal gyri were also activated during simple object recognition (Sergent *et al.,* 1992). These relative increases in rCBF observed in the 'occipitotemporal pathway' (Mishkin *et al.,* 1983) during the visual short-term memory task compared with the phonological task most probably reflect a higher demand for visual processing of the different attributes of Korean letters than for standard letters. Finally, the left middle frontal gyrus (BA 46 and BA 10) was amongst the brain regions possibly activated by our visual short-term memory task. Paulesu *et al.* (1993) observed an activation in the left BA 47 when comparing the visual short-term memory task with shape judgement on Korean letters. Those activations probably reflect central executive contribution to the visual working memory task.

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References

Baddeley AD. Working memory. Oxford: Clarendon Press, 1986.

Baddeley A. Is working memory working? The fifteenth Bartlett Lecture. Q J Exp Psychol [A] 1992; 44: 1-31.

Baddeley AD, Hitch G. Working memory. In: Bower GH, editor. The psychology of learning and motivation, Vol. VIII. New York: Academic Press, 1974: 47-90.

Baddeley A, Logie RH, Bressi S, Delia SaIa S, Spinnler H. Dementia and working memory. Q J Exp Psychol [Al 1986; 38: 603-18.

Baddeley AD, Bressi S, Delia SaIa S, Logie R, Spinnler H. The decline of working memory in Alzheimer's disease. A longitudinal study. Brain 1991; 114: 2521-42.

Belger A, McCarthy G, Gore J, Goldman-Rakic P, Krystal J. Dissociation of parietal and temporal lobe activation during working memory tasks: a functional MRI study [abstract]. Hum Brain Map 1995;Suppl 1: 416.

Belleville S, Peretz I, Arguin H. Contribution of articulatory rehearsal to short-term memory: evidence from a case of selective disruption. Brain Lang 1992; 43: 713-46.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 1991; 11: 2383-402.

Dalrymple-Alford JC, Kalders AS, Jones RD, Watson RW. A central executive deficit in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 360-7.

Degueldre C, Quaglia L. Performance evaluation of a new whole body positron tomograph: the ECAT 951/31 R. Proceedings of the 14th Annual International Conference of the IEEE. EMBS 1992: 1831-3.

Delia SaIa S, Logie RH. When working memory does not work: the role of working memory in neuropsychology. In: Boiler F, Grafman J, editors. Handbook of neuropsychology, Vol. 8. Amsterdam: Elsevier, 1993: 1-62.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995; 378: 279-81.

Dupont P, Orban GA, Vogels R, Bormans G, Nuyts J, Schiepers C, et al. Different perceptual tasks performed with the same visual stimulus attribute activate different regions of the human brain: a positron emission tomography study [see comments], Proc Natl Acad Sci USA 1993; 90: 10927-31. Comment in: Proc Natl Acad Sci USA 1993; 90: 10901-3.

Fox PT, Mintun MA. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2{}^{15}O$ tissue activity. J Nucl Med 1989; 30: 141-9.

Frackowiak RSJ. Functional mapping of verbal memory and language. [Review]. Trends Neurosci 1994; 17: 109-15.

Frackowiak RSJ, Friston KJ. Functional neuroanatomy of the human brain: positron emission tomography—a new neuroanatomical technique. [Review]. J Anat 1994; 184: 211-25.

Frisk V, Milner B. The relationship of working memory to the immediate recall of stories following unilateral temporal or frontal lobectomy. Neuropsychologia 1990; 28: 121-35.

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RSJ. The relationship between global and local changes in PET scans. J Cereb Blood Flow Metab 1990; 10: 458-66.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 1991; 11: 690-9.

Frith CD, Friston K, Liddle PF, Frackowiak RSJ. Willed action and the prefrontal cortex in man: a study with PET. Proc R Soc Lond B Biol Sci 1991; 244: 241-6.

Fuster JM. Frontal lobes. [Review]. Curr Opin Neurobiol 1993; 3: 160-5.

Gathercole SE. Neuropsychology and working memory. Neuropsychology 1994; 8: 494-505.

Goldroan-Rakic PS. Cellular and circuit basis of working memory in prefrontal cortex of nonhutnan primates. LReview]. Progr Brain Res 1990; 85: 325-36.

Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ. Functional mapping of brain areas implicated in auditory-verbal memory function. Brain 1993; 116: 1-20.

Hanley JR, Young AW, Pearson NA. Impairment of the visuo-spatial sketch pad. Q J Exp Psychol [A] 1991; 43: 101-25.

Hulme C, Maughan S, Brown GDA. Memory for familiar and unfamiliar words: evidence for a long-term memory contribution to short-term memory span. J Mem Lang 1991; 30: 685-701.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET Lsee comments]. Nature 1993; 363: 623-5. Comment in: Nature 1993; 363: 583-4.

Kosslyn SM, Alpert NM, Thompson WL, Maljkovic V, Weise SB, Chabris CF, et al. Visual mental imagery activates topographically organized cortex: PET investigations. J Cogn Neurosci 1993; 5: 263-87.

Lammertsma AA, Cunningham VJ, Deiber MP, Heather JD, Bloomfield PM, Nutt J, et al. Combination of dynamic and integral methods for generating reproducible functional CBF images. J Cereb Blood Flow Metab 1990; 10: 675-86.

Mazziotta JC, Huang SC, Phelps ME, Carson RE, MacDonald NS, Mahoney K. A noninvasive positron computed tomography technique using oxygen-15 labeled water for the evaluation of neurobehavioral task batteries. J Cereb Blood Flow Metab 1985; 5: 70-8.

McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder R ct al. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. Proc Natl Acad Sci USA 1994; 91: 8690-4.

Mellet E, Crivello F, Tzourio N, Joliot M, Petit L, Laurier L, et al. Construction of mental images based on verbal description: functional neuroanatomy with PET [abstract]. Hum Brain Map 1995; Suppl 1: 273.

Mishkin M, Ungerleider LG, Macko KA. Object vision and spatial vision: two cortical pathways. Trends Neurosci 1983; 6: 414-17.

Morris RG. Working memory in Alzheimer-type dementia. Neuropsychology 1994; 8: 544-54.

Morris N, Jones DM. Memory updating in working memory: the role of the central executive. Br J Psychol 1990; 81: 111-21.

Norman DA, Shallice T. Attention to action: willed and automatic control of behavior. In: Davidson RJ, Schwarts GE, Shapiro D, editors. Consciousness and self-regulation. Advances in research and theory, Vol. 4. New York: Plenum Press, 1986: 1-18.

Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci USA 1990; 87: 256-9.

Paulesu E, Frith CD, Frackowiak RSJ. The neural correlates of the verbal component of working memory [see comments]. Nature 1993a; 362: 342-5. Comment in: Nature 1993; 363: 583-4.

Paulesu E, Frith CD, Bench CJ, Bottini G, Grasby PG, Frackowiak RSJ. Functional anatomy of working memory: the visuospatial 'sketch pad' [abstract]. J Cereb Blood Flow Metab 1993b; 13 Suppl 1: S552.

Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. J Neurophysiol 1993; 70: 453-69.

Petersen SE, Fox PT, Posner ML Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 1988; 331: 585-9.

Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 1993a: 90: 873-7.

Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 1993b; 90: 878-82.

Pigott S, Milner B. Capacity of visual short-term memory after unilateral frontal or anterior temporal-lobe resection. Neuropsychologia 1994; 32: 969-81.

Pollack I, Johnson LB, Knaff PR. Running memory span. J Exp Psychol 1959: 57: 137-46.

Sergent J, Ohta S, MacDonald B. Functional neuroanatomy of face and object processing. A positron emission tomography study. Brain 1992, 115: 15-36.

Shallice T. From neuropsychology to mental structure. Cambridge: Cambridge University Press, 1988.

Shallice T. Multiple levels of control processes. In: Umiltâ C, Moscovitch M, editors. Attention and performance XV. Conscious and nonconscious information processing. Cambridge (MA): MIT Press, 1994: 395-420.

Shallice T, Vallar G. The impairment of auditory-verbal short-term storage. In: Vallar G, Shallice T, editors. Neuropsychological impairments of short-term memory. Cambridge: Cambridge University Press, 1990: 11-53.

Smith EE, Jonides J. Working memory in humans: neuropsychological evidence. In: Gazzaniga MS, editors. The cognitive neurosciences. Cambridge (MA): MIT Press, 1995: 1009-20.

Swartz BE, Halgren E, Fuster JM, Simpkins E, Gee M, Mandelkern M. Cortical metabolic activation in humans during a visual memory task. Cereb Cortex 1995; 5: 205-14.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart: Thieme, 1988.

Vallar G, Baddeley AD. Fractionation of working memory: neuropsychological evidence for a phonological short-term store. J Verb Learn Verb Behav 1984; 23: 151-61.

Vallar G, Papagano C. Phonological short-term store and the nature of the recency effect: evidence from neuropsychology. Brain Cogn 1986; 5: 428-42.

Van der Linden M. Neuropsychologic de Ia mémoire. In: Seron X, Jeannerod M, editors. Traité de neuropsychologic humaine. Bruxelles: Mardaga, 1994: 282-316.

Van der Linden M, Coyette F, Seron X. Selective impairment of the 'central executive' component of working memory: a single case study. Cogn Neuropsychol 1992; 9: 301-26.

Van der Linden M, Beerten A, Pescnti M. Age-related differences in random generation [poster]. International Conference on Working Memory. Cambridge, 1994a.

Van der Linden M, Brédart S, Beerlen A. Age-related differences in updating working memory. Br J Psychol 1994b; 85: 145-52.

Warrington EK, James M. Disorders of visual perception in patients with localised cerebral lesions. Neuropsychologia 1967; 5: 253-66.

Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and rcslicing PET images. J Comput Assist Tomogr 1992; 16: 620-33.