

Learning related modulation of functional retrieval networks in man

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The medial temporal lobe has been implicated in studies of episodic memory tasks involving spatio-temporal context and object-location conjunctions. We have previously demonstrated that an increased level of practice in a free-recall task parallels a decrease in the functional activity of several brain regions, including the medial temporal lobe, the prefrontal, the anterior cingulate, the anterior insular, and the posterior parietal cortices, that in concert demonstrate a move from elaborate controlled processing towards a higher degree of automaticity. Here we report data from two experiments that extend these initial observations. We used a similar experimental approach but probed for effects of retrieval paradigms and stimulus material. In the first experiment we investigated practice related changes during recognition of object-location conjunctions and in the second during free-recall of pseudo-words. Learning in a neural network is a dynamic consequence of information processing and network plasticity. The present and previous PET results indicate that practice can induce a learning related functional restructuring of information processing. Different adaptive processes likely subservise the functional re-organisation observed. These may in part be related to different demands for attentional and working memory processing. It appears that the role(s) of the prefrontal cortex and the medial temporal lobe in memory retrieval are complex, perhaps reflecting several different interacting processes or cognitive components. We suggest that an integrative interactive perspective on the role of the prefrontal and medial temporal lobe is necessary for an understanding of the processing significance of these regions in learning and memory. It appears necessary to develop elaborated and explicit computational models for prefrontal and medial temporal functions in order to derive detailed empirical predictions, and in combination with an efficient use and development of functional neuroimaging approaches, to further the understanding of the processing significance of these regions in memory.

Key words: Episodic memory, medial temporal lobe, hippocampus, retrieval, recognition, recall, PET, brain activation, functional neuroimaging

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INTRODUCTION

The function of the medial temporal lobe (MTL) has been related to memory for spatio-temporal context and location (Eichenbaum, 1994; Nadel, 1994; Squire, 1992). The MTL has also been associated with memory for conjunctions of objects and location in both man and primates (Gaffan & Parker, 1996; Gaffan & Saunders, 1985; Owen *et al.*, 1996; Parkinson *et al.*, 1988). Experimental studies of declarative memory have used different paradigms to explore retrieval-related effects in functional neuroimaging (e.g., forced choice recognition, sequential yes/no recognition, cued and free-recall). Several previous reports indicate that memory retrieval is subserved by a network of interacting brain regions (Nyberg *et al.*, 1998) and that some may have a dynamic role (Petersson *et al.*, 1997; Petersson *et al.*, 1999a; Raichle *et al.*, 1994). Dynamic is here taken to mean changing as a function of for example practice or repeated encoding. In other words, there seems to be a functional re-organisation or restructuring of the information processing networks during a learning process, indicated by changes in the regional activity, possibly reflecting changes, directly or indirectly, in local or more long-distance connectivity between regions or network modules. We have previously presented data indicating that the activity of the MTL during free-recall of abstract designs is modulated by repeated encoding and recall (Petersson *et*

al., 1997; Petersson *et al.*, 1999a). The data indicated that the activity of the MTL decreases with repeated learning of the abstract designs pointing to an inverse relation between the strength of encoding and the activation of the MTL during retrieval (Mesulam, 1998). Similar MTL results have been reported using an episodic verbal retrieval task (Montaldi *et al.*, 1997). In this study, the left MTL was more active in the less practised memory condition compared to the well-practised (repeated encoding) memory condition. In parallel with the MTL decreases, decreases were also observed in the prefrontal (PFC), the anterior cingulate (ACC), the posterior parietal (PPC), and parts of the inferior temporal (ITC) cortices (Petersson *et al.*, 1999a). These learning related changes have tentatively been related in part to different demands for attentional and working memory resources, reflecting different adaptive processes related to a transition from a non-automatic to a more automatic mode of processing.

In the present paper we extend these investigations of learning related modulation of functional retrieval networks in two different PET studies of episodic recognition of object-location conjunctions as well as free-recall of pseudo-words. The learning related modulation has previously been conceptualised in terms of the interaction between attentional/control processes and learning/memory as well as the development of automaticity or reduced processing

complexity. In the first experiment we used the recognition tasks and adapted the experimental paradigm Owen *et al.* (Owen *et al.*, 1996). This experiment was divided into two sub-experiments, the first being a replication of the study of Owen *et al.* (1996) and the second using a sensory-motor baseline state without explicit demands on encoding or retrieval. In the second experiment we used the paradigm described by Petersson *et al.* (Petersson *et al.*, 1999a; Petersson *et al.*, 1999b). Our primary anatomical focus of interest was the MTL (Desgranges *et al.*, 1998; Fletcher *et al.*, 1997; Tulving & Markowitsch, 1997). Secondly, and in light of our previous results (Petersson *et al.*, 1999a), we also explored the dynamic changes related to practice in the rest of the brain during recognition of object-location conjunctions and free-recall of pseudo-words. We were particularly interested in the dorsolateral prefrontal, middle frontal-frontopolar, anterior cingulate, anterior insula/frontal operculum, posterior parietal, and occipital-occipitotemporal regions (Buckner, 1996; Fletcher *et al.*, 1997; Tulving & Markowitsch, 1997). In the present paper, both PET studies represent multi-trial learning paradigms, the first exploring retrieval of object-location associations while in the second we explore the free-recall of apparently meaningless pseudo-words.

RECOGNITION OF OBJECT-LOCATION CONJUNCTIONS

Material and Methods

Subjects. Sixteen right handed (Edinburgh handedness inventory; (Oldfield, 1971; Raczkowski *et al.*, 1974)) healthy male subjects (25 ± 4 yrs; 2.6 ± 2 yrs of university level education) were included in the recognition experiment. The subjects were pre-screened and none of the subjects used any medication, had a history of drug abuse (including nicotine), head trauma, neurological or psychiatric illness, or a family history of neurological or psychiatric illness. The local Ethics and Radiation Safety committees at the Karolinska Hospital approved the study. All the subjects volunteered and gave informed consent.

The experimental paradigm and procedures. The experimental paradigm was explained to the subjects before they were positioned in the PET camera. In order to get accustomed to the various aspects of the paradigm the subjects practised all aspects of the experimental paradigm with sham injections for approximately 20 min in the PET camera before the PET measurements started.

The stimuli in all experimental conditions were presented in white squares (4.5×4.5 cm) that were presented on a black background, on a computer-screen (31×23 cm). The subject placed the screen at optimal viewing-distance (approximately 60–90 cm). Stimuli were presented for 3 s (1 s inter-stimulus-interval). The experiment consisted of 4 conditions: object-location recognition (OL), practised object-location recognition (POL), location recognition (LR) and a baseline condition (B). Before the OL/POL scans, the subjects successively viewed eight drawings of common objects (Snodgrass & Vanderwart, 1980) in white squares against a black background at various (randomly selected) locations on the screen presented in randomised order for each subject in two cycles (Owen

et al., 1996). The subjects were instructed to encode where on the screen a specific object had been presented (i.e., an object-location conjunction) for a subsequent recognition test. To discourage direct verbal labelling of the spatial location the positions immediately adjacent to the edge of the computer-screen were not used (Owen *et al.*, 1996). Following encoding the subject read a nonsense text presented on the screen for approximately 60 s in order to prevent recency effects and explicit rehearsal (Baddeley, 1995). Then there was an approximately 4 min interval when the subjects were told to relax and the subjects usually engaged in social interaction. After this the recognition part was started, the bolus injection given (the PET scanning started as soon as the bolus reached the brain and continued for the next 60 s). During recognition a list of 24 target-distractor pairs were presented (3 s, 1 s ISI). Each pair consisted of an object presented at two different locations. The subjects indicated which of the two squares containing the object was in the same location (target) as at encoding by pointing with a pointer-device with its tip resting on the screen which was held in the right hand. For each pair, the presented object had occupied one of the locations and the other location had been occupied by one of the other objects in the encoding list. Thus correct recognition could not be based on location alone since both locations had been presented in the list. Instead the decision had to be made on the conjunction of object and location.

A similar procedure was used for the LR scans. A list of 8 empty white squares, randomly localised, was presented in random order 3 times to make subsequent recognition performance similar to that for the OL condition. The subjects were instructed to remember the location of each square. The LR task was identical to OL/POL except that a list of 24 pairs of empty white squares (target and distractor) was presented. Only one of the locations (target) had occurred previously during encoding and the other location was a distractor randomly localised. The subjects pointed to the white square with a location that had occurred in the encoded list. During the B condition, a list of 8 pairs of white squares, one empty and the other containing an X, randomly localised was presented in randomised order three times and the subjects pointed to the square containing the X. In short, the same basic encoding-recognition-cycle was used in OL, LR, and POL (Fig. 1a).

The recognition experiment was divided into two sub-experiments, with eight subjects in each, consisting of 3 identical blocks (Fig. 1b). In the first sub-experiment, the subjects were scanned during OL, LR, and POL. Each block consisted of 3 scans (at least 10 min inter-scan interval) in the order: OL/practice period/LR/practice period/POL. The second sub-experiment was identical with LR substituted with the baseline condition B. Different lists of stimuli were used for each block balanced over subjects.

During practice the lists of object-location conjunctions were practised using the same randomised sequence used in the first encoding-recognition-cycle, divided into two parts, before and after the B/LR scan (Fig. 1b) in order to keep up the motivation and concentration of the subjects. Each part consisted of alternating encoding and recognition in 9 cycles. The subjects were instructed to try to become as automatic on the recognition task as possible. The stimulus presentation times were shortened somewhat during practice in order to make the practice period shorter. Each of the 3 blocks lasted for approximately 45 min. The subjects were debriefed after the PET scanning in a semi-structured post-experiment interview. Amongst other things, the subjects rated the perceived difficulty or retrieval effort of the different conditions (OL, POL, LR) using a visual analogue scale (VAS; 0 = as easy as the subject could imagine, 10 = as difficult as the subject could imagine).

PET scanning. Each subject underwent 12 measurements of regional cerebral blood flow (rCBF) with a 3D ECAT EXACT

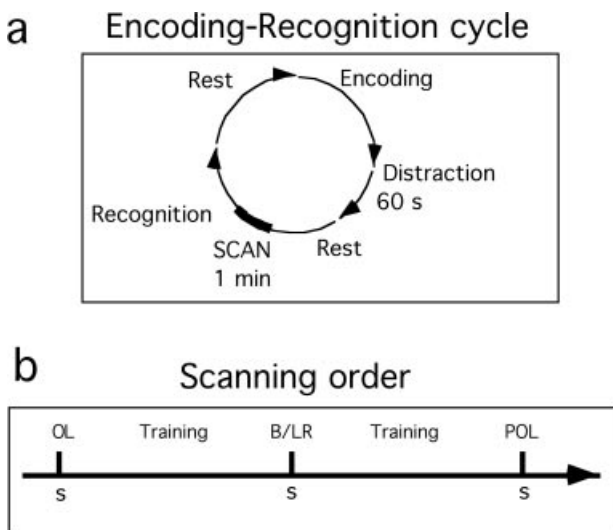


Fig. 1. (a) Encoding-recognition-cycle. During encoding the subjects watched a list of either object-location conjunctions or locations on the computer screen. Then a distractor text was read during 60s. Finally, during recognition a list of target-distractor pairs were presented and the subjects indicated their response. (b) The scanning order of the 3 conditions OL B/LR, and POL during the 9 scans (= 3 identical blocks) of the experiment with the practice periods indicated. S = scanning.

HR PET scanner (Wienhard *et al.*, 1994) and bolus injections of [15-O]butanol (Berridge *et al.*, 1990). The PET scanner was used in 3D-sampling mode producing 60s tracer uptake images. The different tasks were started at the time of tracer injection and the scanning was automatically initiated when the activity level in the brain exceeded a predetermined level above background. Scatter correction was done and a 2D-transmission scan was used for attenuation correction. A second transmission scan was performed if the subject left the scanner.

Data analysis. The PET-images were realigned, spatially normalised and transformed into a common stereotactic space (Talairach & Tournoux, 1988), 3D-Gaussian filtered (14 mm FWHM), proportionally scaled to account for global confounders and analysed with statistical parametric mapping (SPM96) (Frackowiak *et al.*, 1997; Friston *et al.*, 1995; Worsley *et al.*, 1992). Time (= the order of scans) was used as a confounding covariate to account for non-specific time effects (Pettersson *et al.*, 1999b). To test hypotheses about regionally specific condition estimates were compared using linear contrasts. The resulting Z-statistic images SPM[Z] were thresholded at $Z = 3.72$ (omnibus significance $P \leq 0.0001$). The activated regions were characterised in terms of the bivariate spatial extent/local maximum statistic (in the result section) and peak-height (in the tables) of local maxima. All reported P -values are corrected for multiple non-independent comparisons based on the theory of 3D stationary differentiable Gaussian random fields (Adler, 1981; Worsley *et al.*, 1996) except where explicitly indicated. First, since we were specifically interested in the behaviour of the MTL in the different conditions, and to maximise detection sensitivity focusing on the MTL, we accepted activations corresponding to voxels with $Z \geq 2.33$ (or uncorrected $P \leq 0.01$) as significant in this region. In a second step, we were interested in the differential activity between conditions in the rest of the brain. In this exploratory part we were particularly interested in the

dorsolateral prefrontal, middle frontal-frontopolar, anterior cingulate, anterior insula/frontal operculum, posterior parietal, and occipital-occipitotemporal regions since the activity of these regions have been to be modulated by practice or repeated learning opportunities (Pettersson *et al.*, 1999a; Raichle *et al.*, 1994). In these regions we accepted activations as significant if the corrected $P \leq 0.1$. Note that we first characterised the significantly activated regions in terms of the bivariate spatial extent/local maximum statistic (corrected $P \leq 0.1$; in the result section) and within the significant regions we report significant local maxima (corrected $P \leq 0.1$; in the tables). In other words we used the bivariate spatial extent/local maximum and local maximum test statistic in a hierarchical fashion.

Results

Behavioural data. The performance increased significantly from 96% during OLR to 99% correct in practised OLR ($P < 0.001$, Wilcoxon signed rank test) while in LR the subjects performed at 78% correct (significantly worse than in OLR, $P < 0.001$, Wilcoxon signed rank test). The results from the visual analogue rating of perceived difficulty showed that OLR was perceived as more difficult than practised OLR ($P < 0.01$, Wilcoxon signed rank test), and that LR was perceived as more difficult than OLR ($P < 0.05$, Wilcoxon signed rank test).

Regional cerebral blood flow data. In the anatomical description of activated regions below we used the Karolinska Computerised Brain Atlas of Greitz (Greitz *et al.*, 1991) which makes it possible to determine which anatomical structures and Brodmann areas (BA) an activated region covers or partly covers in a comprehensive way. When a region is described to include a Brodmann area, this is not intended in an inclusive sense but only implies that parts of that BA is included in the region.

Medial temporal lobe activations in the object-location experiment. Given the specific regional interest in the behaviour of the MTL and in order to maximise detection sensitivity, we characterised activations corresponding to voxels with $Z \geq 2.33$ (or uncorrected $P \leq 0.01$) in the Karolinska Computerised Brain Atlas of Greitz. In the OL-B and POL-B comparisons there were bilateral occipitotemporal activations only extending into BA 36 of the most posterior parts of the MTL. Clear MTL activations were observed in OL-LR, including robust bilateral occipitotemporal activations ($P < 0.001$) extending all through out the MTL (Fig. 2a). The right MTL activation included parts of BA 28, 34, 35, and 36 (including the local maximum $[x, y, z] = [36, -8, -30]$, $Z = 4.93$), while the left MTL included parts of the BA 28, 34, and 36 ($[x, y, z] = [-28, 2, -24]$, $Z = 4.08$ in the anterior left MTL). The MTL was also activated bilaterally in POL-LR (right: $[x, y, z] = [32, -2, -18]$, $Z = 4.73$; $[x, y, z] = [30, -22, -22]$,

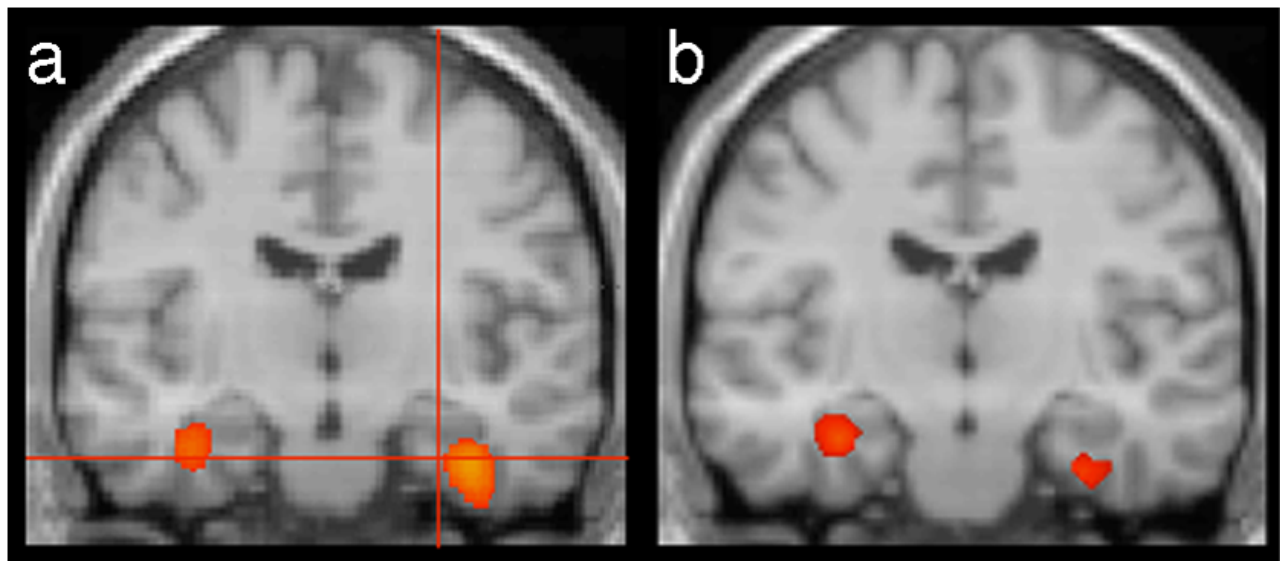


Fig. 2. (a) Medial temporal activation in object-location vs. location recognition, and in (b) in object-location vs. practised object-location. The cross hair indicate the MTL activation of Owen *et al.* (1996), $[x y z] = [28 -13 -29]$.

Table 1a. Local activations maxima in object-location recognition (OL) vs. the baseline state (B) in the global search (for MTL results see text). Anatomical designations indicated with ¹ refer to the Karolinska Computerised Brain Atlas of Greitz

Region	Brodmann area	[x, y, z]	Z	P-value
Prefrontal cortex				
Superior/middle frontal gyrus	9/46 dx	46 32 38	5.32	0.001
	9/10 dx	36 50 20	4.77	0.014
Middle frontal gyrus	6 dx	38 -2 54	4.44	0.055
	6/8 dx	30 0 46	4.49	0.046
	10 dx	32 60 6	4.98	0.006
Middle/inferior frontal gyrus	10/11/47 dx	28 48 -18	6.26	<0.001
Anterior cingulate cortex	24/32 dx	8 24 34	5.81	<0.001
Anterior insula/frontal operculum	14/15/49 dx ¹	36 16 -2	4.55	0.036
	14/15/49 sin ¹	-26 22 6	5.36	0.001
Parietal cortex				
Precuneus	7	0 -70 52	6.14	<0.001
	7/19 sin	-20 -66 32	4.86	0.010
Superior/inferior parietal lobule	7/40 dx	32 -64 42	6.79	<0.001
Inferior parietal lobule	39/40 sin	-30 -50 38	4.61	0.028
Occipital cortex				
Inferior occipital gyrus	17/18 sin	-22 -96 -4	6.83	<0.001
Superior/middle occipital gyrus	18/19 dx	30 -82 18	5.08	0.003
Superior occipital gyrus	19 sin	-32 -78 24	4.42	0.060
Occipito-temporal cortex				
Lingual/fusiform gyrus	18/19 dx	18 -92 -10	7.48	<0.001
Inferior occipital/fusiform gyrus	18/19 sin	-34 -86 -12	7.59	<0.001
Fusiform gyrus	19/37 dx	38 -72 -16	7.48	<0.001
	19/37 sin	-40 -74 -20	7.27	<0.001
	19/37 sin	-34 -60 -18	6.50	<0.001
Fusiform/parahippocampal gyrus	36 dx	26 -46 -14	5.54	<0.001
Cerebellum				
		0 -60 -28	6.99	<0.001
	sin	-26 -60 -48	6.50	0.001
	sin	-52 -54 -34	4.43	0.057

Table 1b. Local activation maxima in practised object-location recognition (POL) vs. the baseline state (B)

Region	Brodman area	[x, y, z]	Z	P-value
Occipital cortex				
Inferior occipital gyrus	17/18 sin	20 -92 -8	6.96	<0.001
Occipito-temporal cortex				
Lingual gyrus	18 sin	-18 -92 -10	5.16	0.002
Fusiform gyrus	19/37 dx	32 -62 -12	5.25	0.002
Thalamus	dx	14 -18 16	4.94	0.006
Cerebellum				
	0	-56 -26	6.64	<0.001
	sin	-20 -50 -38	5.40	0.001
	sin	-26 -58 -28	5.05	0.004

$Z = 2.33$; left: $[x, y, z] = [-22, -24, -8]$, $Z = 3.13$) included parts of right BA 28 and 36 as well as parts of left BA 36.

In order to investigate the predicted practice related decreases in the MTL we took advantage of the possibility to define a functional MTL region of interest (ROI) via the OL-LR contrast. Specifically, we used the MTL activation observed in the OL-LR to define a functional MTL-ROI, generating an MTL mask (thresholding at $Z = 2.33$) and used this to mask the OL-POL contrast. Practice related decreases were observed bilaterally in the anterior parts of the occipito-temporal cortex and the MTL, including parts of the right BA 34/36 and the left BA 28, 34, 35, and 36 (Fig. 2b; right: $[x, y, z] = [30, -16, -30]$, $Z = 2.44$; left: $[x, y, z] = [-32, -12, -22]$, $Z = 2.52$).

Exploring the unmasked effects in OL-POL contrast did not yield any additional effects. In other words, the learning related effects observed affected the same MTL regions that were activated in OL-LR (cf. Fig. 2a, b).

Activations in object-location recognition (OL) compared to the reference state (B). In the exploratory part of the comparison we were interested in the differential activity between conditions in the rest of the brain. Here we report the results using the bivariate spatial extent/local maximum statistic as the test-statistic, thresholding at $Z = 3.72$, while the results using only the local maximum as the test-statistic are given in the tables. In the OL-B comparison (Table 1a, Fig. 3a) several regions were significantly activated, includ-

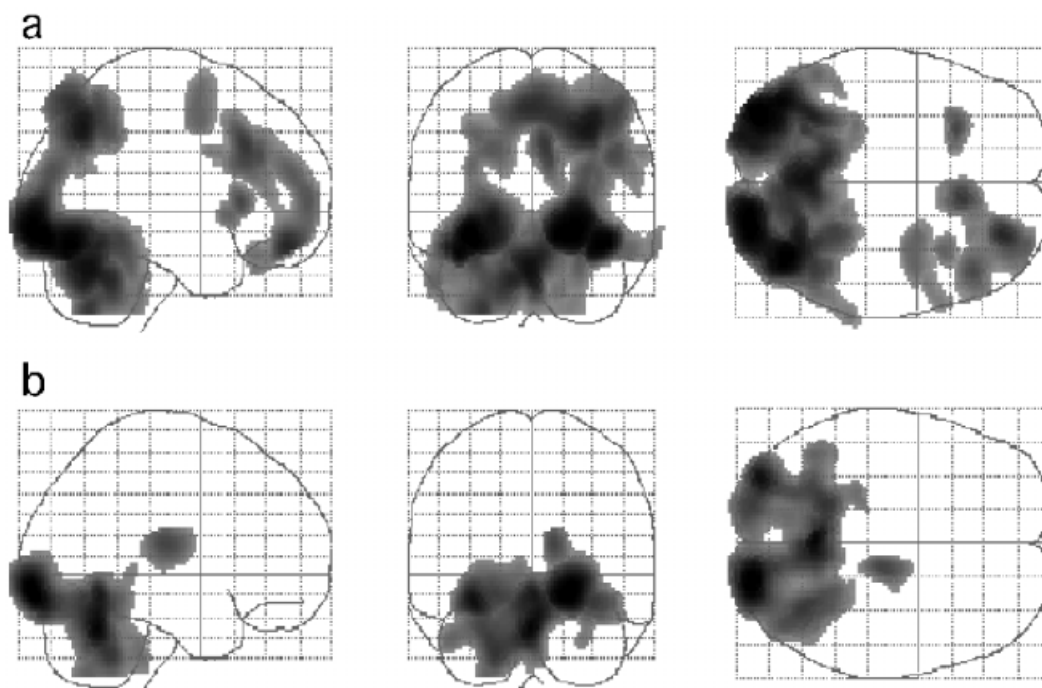


Fig. 3. (a) The pattern of significant activation in object-location recognition and (b) in practised object-location recognition vs. baseline. The images are thresholded at $Z = 3.09$.

ing the right prefrontal (superior-middle BA 10, 46, inferior frontal BA 45 and frontopolar BA 10/11; $P < 0.001$), right frontal eye field (BA 6, 8; $P = 0.001$), anterior cingulate (BA 24, 32; $P < 0.001$), bilateral anterior insular (BA 14, 15; right $P = 0.041$; left $P = 0.002$), and a large cluster ($P < 0.001$) encompassing occipito-parietal (BA 18, 19, 7, 39, 40) and occipito-temporal (BA 18, 19, 37 extending into BA 36) regions as well as medial cerebellum.

Activations in practised object-location recognition (POL) compared to the reference state (B). In the POL-B comparison (Table 1b, Fig. 3b) the activations were mainly localized to the occipital and occipito-temporal regions ($P < 0.001$), including superior occipital gyrus (BA 18, 19), middle occipital gyrus (BA 19), lateral occipital gyrus (BA 19), fusiform and lingual gyrus (BA 19, 37, extending into right BA 36). In addition the medial and left mediolateral parts of the cerebellum were activated as well as the right thalamus ($P = 0.006$).

Activations in object-location recognition (OL) compared to location recognition (LR). In the OL-LR comparison (Table 2a, Fig. 4a) bilateral occipital and occipito-temporal (BA 17, 18, 19, extending into right BA 35, 36 and left BA 28; right $P < 0.001$; left $P < 0.001$) regions were activated. There were also activations in the posterior cingulate region (BA 23/31, $P = 0.034$) and left pre/post-central region ($P = 0.053$).

Activations in location recognition (LR) compared to object-location recognition (OL). In the reverse comparison (Table 2b, Fig. 4b) right sided activations included the prefrontal (middle BA 6, 8; inferior BA 44, 45; $P < 0.001$), middle frontal-frontopolar (BA 10, 46; $P = 0.002$) regions. The right superior parietal activation ($P < 0.001$) included the precuneus and the superior parietal lobule (BA 7) extending in to the right inferior parietal lobule (BA 39/40) and superior-middle occipital region (BA 19). There were also separate right inferior temporal (BA 19, 37; $P = 0.001$) and left cerebellar activations ($P < 0.001$).

Table 2a. Local activation's maxima in object-location recognition (OL) vs. location recognition (LR) in the global search (for MTL results see text). Anatomical designations indicated with ¹ refer to the Karolinska Computerized Brain Atlas (CBA)

Region	Brodman area	[x, y, z]	Z	P-value
Posterior cingulate cortex	23/31 sin	-10 -40 36	4.59	0.030
Post-central gyrus/superior parietal lobule	2/5	-16 -38 64	4.37	0.072
Occipito-temporal cortex				
Inferior occipital gyrus	17/18 sin	-22 -98 -8	7.58	<0.001
Inferior occipital/lingual gyrus	17/18 dx	26 -94 -6	7.83	<0.001
	17/18 sin	-30 -94 -8	7.59	<0.001
Fusiform gyrus	19/37 dx	30 -60 -10	5.15	0.003
	36/37 dx	34 -42 -18	5.87	<0.001
Fusiform/inferior temporal gyrus	20/37 sin	-40 -32 -18	6.35	<0.001

Table 2b. Local activation maxima in location recognition (LR) vs. object-location recognition (OL)

Region	Brodman area	[x, y, z]	Z	P-value
Prefrontal cortex				
Middle frontal gyrus	6 dx	44 4 28	5.10	0.003
	6/8 dx	28 8 56	4.49	0.046
	6/8 dx	36 4 46	4.53	0.039
	10 dx	36 48 2	4.91	0.008
Inferior frontal gyrus	9/44 dx	50 12 20	4.77	0.014
Parietal cortex				
Precuneus/superior parietal lobule	7 dx	18 -66 60	4.70	0.019
Superior parietal lobule	7 dx	34 -64 40		0.010
Superior/inferior parietal lobule	7/40 dx	46 -42 46	4.45	0.053
Inferior parietal lobule	40 dx	58 -34 42	5.06	0.004
Occipital cortex				
Superior occipital/parietal gyrus	7/19 dx	18 -78 54	4.50	0.043
Superior/middle occipital gyrus	19 dx	38 -82 28	4.99	0.005
Inferior temporal gyrus	19/37 dx	56 -64 -10	5.38	0.001
Cerebellum	sin	-36 -70 -50	4.78	0.014

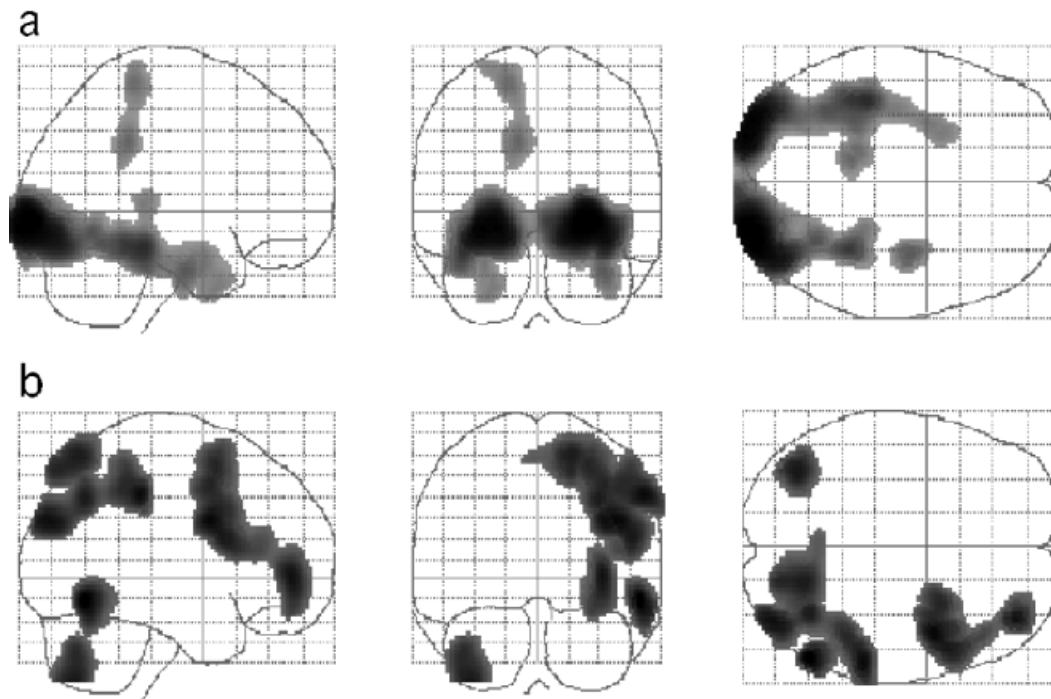


Fig. 4. (a) The pattern of significant activation in object-location vs. location recognition and (b) in location vs. object-location recognition. The images are thresholded at $Z = 3.09$.

Activations in object-location recognition (OL) compared to practised object-location recognition (POL). Practice related decreases were observed (Table 3a, Fig. 5a) in the superior-middle (BA 10, 11; right $P = 0.022$, left $P = 0.016$), left middle-inferior (BA 45; $P = 0.040$), and the superior-orbito

(BA 10, 11, 46; $P = 0.001$) prefrontal, anterior cingulate (BA 24, 32; $P = 0.011$), as well as left anterior insular-frontal opercular (BA 14, 15, 49; $P < 0.001$) regions. Practice related decreases were also observed bilaterally in the occipito-parietal (right $P >$ left; BA 19, 7; right $P < 0.001$, left

Table 3a. Local activation maxima in object-location recognition (OL) vs. practised object-location recognition (POL) in the global search (for MTL results see text). Anatomical designations indicated with ¹ refer to the Karolinska Computerized Brain Atlas (CBA)

Region	Brodmann area	[x, y, z]	Z	P-value
Prefrontal cortex				
Superior/middle frontal gyrus	10 dx	32 62 8	4.71	0.019
	10 sin	-28 50 12	4.76	0.015
Superior/orbito-frontal gyrus	10/11 dx	26 48 -20	5.43	0.001
Middle//inferior frontal gyrus	11/47 dx	22 36 -28	4.40	0.065
	9/44/45 sin	-46 18 34	4.41	0.062
Anterior cingulate cortex	24/32 dx	8 24 36	4.23	0.120
Anterior insula/frontal operculum	14/15/49 sin ¹	-30 24 4	5.67	<0.001
Parietal cortex				
Precuneus	7	-2 -66 52	5.06	0.004
Superior/inferior parietal lobule	7/40 dx	32 -66 50	5.65	<0.001
	7/40 sin	-28 -66 44	4.40	0.065
Inferior parietal lobule/superior occipital gyrus	19/40 dx	30 -78 24	5.25	0.002
Occipital cortex				
Superior/middle occipital gyrus	19 sin	-30 -84 22	5.06	0.004
Occipito-temporal cortex				
Lingual gyrus	18 dx	8 -96 -16	4.44	0.055
Inferior occipital/fusiform gyrus	18/19 sin	-34 -92 -8	4.73	0.017
	19/37 dx	36 -72 -18	6.17	<0.001
	19/37 sin	-40 -72 -22	6.30	<0.001
Cerebellum		-4 -72 -26	4.68	0.021

Table 3b. Local activation maxima in practised object-location recognition (POL) vs. object-location recognition (OL)

Region	Brodmann area	[x, y, z]	Z	P-value
Medial superior frontal cortex	9/10 sin	-8 56 28	4.56	0.034
Paracentral-midcingulate gyrus	6/32	2 -14 50	5.42	0.001
Perisylvian cortex				
Superior temporal gyrus	41 dx	42 -22 8	5.70	<0.001
	41 sin	-44 -24 10	4.85	0.010
	42/22 dx	62 -34 22	5.38	0.001
	42/22 sin	-60 -34 22	5.02	0.005
	22 dx	52 -2 4	5.39	0.001
	22 sin	-48 -10 0	5.97	<0.001
Posterior insula	13/16 ¹ dx	38 -4 6	5.31	0.001
	13/16 ¹ sin	-32 -12 14	4.61	0.029
Anterior inferior parietal lobule	40 dx	62 -40 28	5.23	0.002
Parietal operculum/inferior parietal lobule/ Pre/post-central gyrus	40/43 sin	-38 -20 26	5.68	<0.001
	SE/4 dx	32 -28 52	4.76	0.015
	SE/4 dx	46 -24 52	4.30	0.094
Occipito-temporal cortex				
Inferior temporal gyrus	20/21 sin	-60 -22 -30	5.00	0.005
Thalamus/Pulvinar	sin	-12 -28 8	4.53	0.039

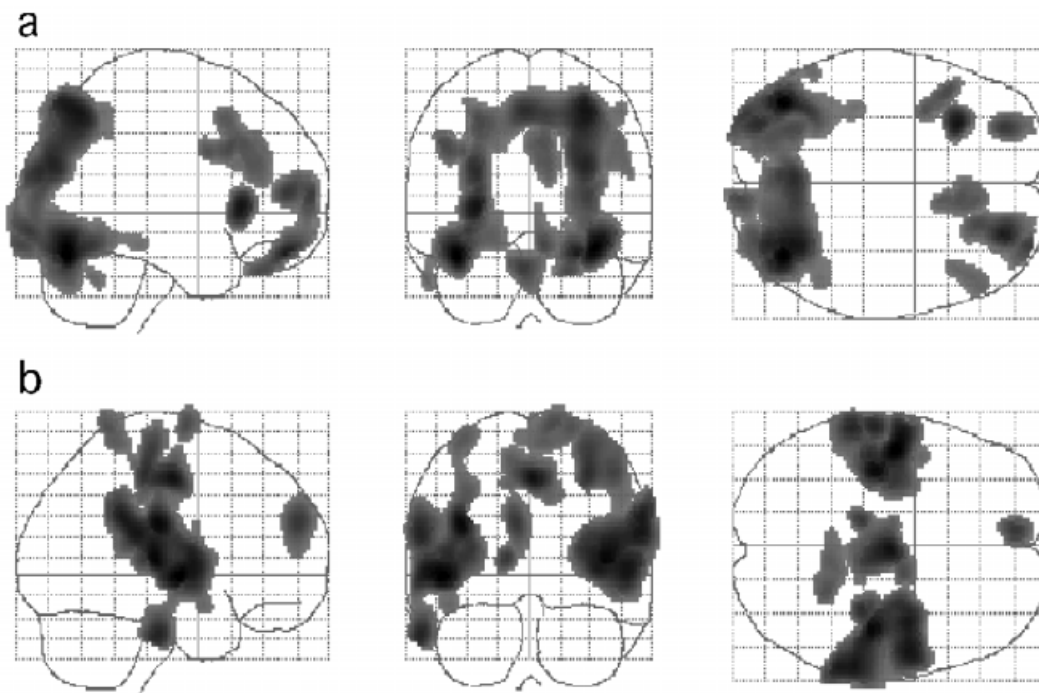


Fig. 5. (a) The pattern of significant activation in object-location vs. practised object-location recognition and (b) in practised object-location vs. object-location recognition. The images are thresholded at $Z = 3.09$.

$P < 0.001$), occipito-temporal (BA 18, 19, 37 extending in to BA 36; right $P = 0.041$, left $P < 0.001$) regions. In addition, there was a medial cerebellar ($P = 0.006$) activation.

Activations in practised object-location (POL) recognition compared to object-location recognition (OL). In contrast, practice related increases were observed (Table 3b, Fig. 5b) in perisylvian parieto-temporal and posterior insular-

opercular (BA 41/42, 43, 50, 52, anterior inferior BA 40; right $P < 0.001$, left $P < 0.001$), paracentral-midcingulate (BA 6 extending into BA 32; $P < 0.001$), and left middle-inferior temporal (BA 21; $P = 0.007$) regions. Practice related increases were also observed in a right pre/post-central (BA SE/4, 6; $P = 0.001$) and left medial superior frontal (BA 10; $P = 0.016$) regions, as well as in the left thalamus/pulvinar ($P = 0.044$).

DISCUSSION

Previous PET data indicate that, during free-recall of abstract designs, the activity of several brain regions may be modulated by repeated encoding and recall. Specifically, decreases in the prefrontal, anterior cingulate, posterior parietal, and medial temporal cortices, and increases in the perisylvian parieto-temporal, posterior opercular-insular, and occipito-temporal regions have been found (Pettersson *et al.*, 1997; Pettersson *et al.*, 1999a). The present PET experiment was designed to investigate if these learning related effects, with specific reference to the MTL, are dependent on the paradigm of retrieval (i.e., recognition and recall). In order to achieve this we used the recognition tasks and adapted the experimental paradigm described by Owen *et al.* (1996). This experiment was divided into two sub-experiments, the first being a replication of the study of Owen *et al.* (1996) and the second using a sensory-motor baseline state without explicit demands on encoding or retrieval.

In the PET study of Owen *et al.* (1996), object-location recognition (OL) was compared to location recognition (LR). The results showed activations in the occipital and occipito-temporal regions bilaterally, and in the (right) MTL, while in the LR-OL comparison, the right mid-dorsolateral prefrontal and right posterior parietal regions were activated. Overall, the results from the first sub-experiment confirm the results of Owen *et al.* (1996) both in OL-LR and LR-OL. In particular, the MTL regions activated in OL-LR is close to the one reported by Owen *et al.* (Fig. 2a). However, in contrast to Owen *et al.* (1996), the MTL was activated bilaterally in the present study. In addition, the MTL was activated bilaterally in POL-LR.

Previously a positive correlation between retrieval success and MTL activity has been reported (Nyberg *et al.*, 1996; Tulving *et al.*, 1999) and the observed increase in MTL activity in OL compared to LR, both in this and the study of Owen *et al.* (1996), is consistent with this finding. This was also paralleled with greater perceived retrieval difficulty in the LR compared to OL. However, the learning related MTL decreases observed in the OL-POL comparison and in Pettersson *et al.* (1997) indicate that there is no simple relation between retrieval performance and MTL activity. Instead it was suggested in Pettersson *et al.* (1997) that there may be a positive correlation between retrieval success and the MTL activity at a given level of encoding strength. This and previous findings (Montaldi *et al.*, 1997) suggest that there may be an inverse relation between the strength of encoding and the activation of the MTL during retrieval (Mesulam, 1998).

An alternative hypothesis concerning the role of the MTL suggests that the hippocampal formation may subserve aspects of recency assessment (Brown, 1990) or novelty detection (Tulving *et al.*, 1996). Both functional neuroimaging (Dolan & Fletcher, 1997; Stern *et al.*, 1996; Tulving

et al., 1994b) and electrophysiological studies (Grunwald *et al.*, 1998; Knight, 1996) of episodic encoding and the MTL have been interpreted in line with this suggestion. Furthermore, it has been suggested that the MTL has other or additional functional significance (e.g., Eichenbaum, 1994; Nadel, 1994; O'Keefe *et al.*, 1998; O'Reilly & McClelland, 1994; Rolls, 1989; Rudy & Sutherland, 1994; Squire, 1992). For example, animal (Eichenbaum, 1994; Squire, 1992) and additional functional neuroimaging data (Henke *et al.*, 1997; Montaldi *et al.*, 1998) suggest that the MTL is related to associative encoding supporting relational representations for flexible use during retrieval in new contexts. In addition, both Henke *et al.* (1997) and Montaldi *et al.* (1999) suggest that the observed MTL effects in their studies were not entirely explainable in terms of novelty detection.

Novelty detection is commonly taken to mean that new information activates the MTL. It appears possible to think of novelty effects in a reverse sense, for example, novelty might be related to attentional effects in combination with retrieval effects during encoding. In other words, new attended information is automatically encoded, engaging the MTL (Morris & Frey, 1997), whereas if the information has already been encoded this may be retrieved, indicating to the learning system that the given information was recently encoded. This in turn may, for several reasons (e.g., avoiding interference effects), signal that the particular information can be less intensively encoded leading to relatively decreased MTL activation. In addition, the effects observed in the MTL may be secondary to the result of novelty processing elsewhere. Alternatively, the observed repetition effects in the MTL may be conceptualised as a form of repetition priming. However, in order to interpret the free-recall results of Pettersson *et al.* (1997) it appears that both the concept of novelty processing and repetition priming acquires a new meaning. Also, the concepts of novelty or recency seem more naturally related to encoding rather than retrieval. If one assumes that encoding takes place in parallel with recognition it appears that the learning related MTL effects observed in the present recognition study might be related to novelty effects. However, Eldridge *et al.* (2000) did not observe any differential activation between unfamiliar and familiar items during recognition, only episodic remembering yielded a differential activation in the hippocampus. This finding is not consistent with the suggestion that the MTL effects observed in the present recognition study are related to novelty processing.

A direct comparison (in a multi-study general linear model) between the practice related decreases disclosed that the decreases were greater in Pettersson *et al.* (1997) compared to the effects in this recognition study (right BA 28, 36, $[xyz] = [30 - 26 - 16]$, $Z = 3.27$, $[xyz] = [18 - 10 - 24]$, $Z = 3.33$; left BA 36, $[xyz] = [-36 - 24 - 28]$, $Z = 2.92$). In addition, the second free-recall experiment of this study encompassed similar novelty aspects as in the present

recognition experiment and that of Petersson *et al.* (1997). However, there were no significant differential MTL effects (cf. below). Together, this indicates that the learning related MTL effects observed in the free-recall task of Petersson *et al.* (1997) is not entirely explainable in terms of novelty processing. Instead several alternative interpretations have been suggested (Petersson *et al.*, 1997). For example, a speculative interpretation suggests that the initial stabilisation of the memory representations is dependent on the MTL-neocortical interaction and the rapid plasticity of the MTL. Presumably, repeated encoding and retrieval would reactivate the neocortical representations and hence strengthen the neocortical interconnections in such a way that the neocortical network eventually can support declarative retrieval less dependent on the interaction with the MTL. Computational considerations concerning parallel distributed processing suggest that rapid learning through synaptic modifications and relational binding in a MTL-module, interaction between a MTL-module and neocortical-modules, and final integrative memory storage in neocortical-modules with slower synaptic dynamics may be a solution to the serial learning problem in certain learning systems (Alvarez & Squire, 1994; Arbib, 1995; Grossberg, 1987; McClelland *et al.*, 1995). Alternatively, repeated encoding and retrieval would transform an initial episodic memory into a more semantic-like memory, the changing role of the MTL then being interpreted as indicating that episodic memory retrieval may be more dependent on the function of the MTL compared to semantic memory retrieval. Slightly differently conceptualised this is consistent with recent findings concerning the role of the MTL (Eldridge *et al.*, 2000). Specifically, initial episodic recognition judgements are mainly based on recollective remembering. With repeated encoding experiences, the stored information will gradually lose its spatio-temporal context, becoming more like a fact. In parallel the recognition judgements are increasingly being based on a familiar knowing.

Beyond the MTL, regions with decreasing activity as a function of practice included the left middle-inferior prefrontal (BA 9, 45, 46), bilateral and middle frontal-frontopolar (BA 10), right anterior insular-frontal opercular, anterior cingulate, bilateral posterior parietal, occipital, inferotemporal, and cerebellar regions. Regions with increasing activity as a function of practice included bilateral posterior insula-opercular, mid-posterior cingulate-paracentral, and temporal regions. Similar practice related changes were observed in a free-recall task of abstract designs (Petersson *et al.*, 1999a). In Petersson *et al.* (1999a) it was indicated that these practice related changes were not explained by differences in performance. The present results appear consistent with this suggestion since the performance was almost perfect (96% correct) already in the less practiced object-location condition.

In OL-B, the right prefrontal activations included both an anterior frontopolar (centred on BA 10/11/46) and more

posterior dorsolateral regions (BA 6/8 and 9/45/46). This is consistent with the predictions of the HERA model (Tulving *et al.*, 1994a) and its recent re-interpretation in terms of an episodic retrieval mode (Lepage *et al.*, 2000; Nyberg *et al.*, 1995). These findings are also consistent with a retrieval attempt interpretation of the prefrontal activations (Kapur *et al.*, 1995). In LR-OL, additional right prefrontal activations were observed in similar regions, including right middle frontal (BA 6, 8), right middle-frontopolar (BA 10, 46), and right inferior frontal (BA 44, 45) regions. Owen *et al.* (1996) also observed an increased activity in the right prefrontal cortex during LR (vs. OL). They suggested that memory for spatial location in the absence of relevant cues about object identity requires retrieval strategies that preferentially involve this part of the prefrontal cortex, indicating a material specific effect (Wagner *et al.*, 1998b). Patients with frontal lobe lesions are impaired in spatial location short-term memory tasks similar to LR (Owen *et al.*, 1995). The observed additional prefrontal activation in LR-OL (Fig. 4b) was paralleled by greater perceived retrieval difficulty (the VAS-rating of task difficulty was greater) and a lower recognition performance. This is consistent with findings suggesting a role of the right PFC in retrieval monitoring-verification (Shallice *et al.*, 1994). Specifically, retrieval of information characterised by being uncertain or possibly incorrect may induce an increased monitoring-verification of the information retrieved and re-initiation of attempts to retrieve. Furthermore, the results supports a context-dependent view of the retrieval attempt hypothesis (Wagner *et al.*, 1998a). In other words, it is conceivable that the prefrontal cortex supports several aspects of the information processing taking place during retrieval, including selection of retrieval strategies, initiation of retrieval search, evaluation of information retrieved, and repeated initiation of retrieval attempts. The interaction between these different sub-processes may reflect effects of internal and external context. In short, multiple factors appear to affect the retrieval context, including text instructions, on-line monitoring of retrieval success, as well as task design. Thus variable right prefrontal activation may be expected across studies (Wagner *et al.*, 1998a). This suggests a context-dependent view of the retrieval mode hypothesis.

However, the additional prefrontal activation in LR-OL is not explained by a simple interpretation of the retrieval success hypothesis (Rugg *et al.*, 1996), in line with the findings of Wagner *et al.* (1998a). They interpreted their results as inconsistent with the retrieval success hypothesis. In addition, Tulving *et al.* (1999) observed a negative correlation between recognition performance and prefrontal activation, both in anterior frontopolar and more posterior dorsolateral regions. In contrast, the results from a recent event-related recognition fMRI study, were interpreted as indicating a retrieval monitoring role for the dorsolateral prefrontal regions (BA 9/46) and that the activity of the anterior frontopolar (BA 10)

region was consistent with a retrieval success perspective (Henson *et al.*, 2000). Interestingly, in this study, the right prefrontal activations decreased significantly after practice (Fig. 3b). In addition, there were significant learning related left prefrontal decreases (Fig. 5a). Similar effects were observed in the second experiment of this study (cf. below) and when comparing novel with trained free-recall in Petersson *et al.* (1999a). These results are more difficult to reconcile with a strong retrieval mode interpretation (Lepage *et al.*, 2000) but appears to be consistent with a context-dependent view of the retrieval mode hypothesis. This latter suggestion is closely related to process complexity and the proposal that the different prefrontal processing components involved in retrieval are drawn from the same set of underlying prefrontal sub-processes differentially engaged in different specific tasks (Nolde *et al.*, 1998). Both the differential prefrontal effects observed in LR-OL and the practice related prefrontal decreases appear consistent with such an interpretation. However, it should be noted that a recent review concluded that several prefrontal regions are commonly co-activated (Duncan & Owen, 2000) relatively independent of the cognitive demand. Duncan and Owen (2000) also recommended cautious interpretation of prefrontal activations at present, since most of the conceptualisations of prefrontal functions are too general to generate testable predictions.

Finally, in the left medial superior frontal (BA 10) there was a practice related increase (i.e., in POL > OL). This practice related increase was neither observed in the free-recall experiment of the present study or in the free-recall experiment of Petersson *et al.* (1999). Little is known about this region in the context of episodic retrieval and we find no obvious interpretation of this finding.

The posterior parietal cortex has been implicated in memory function and parietal regions have been activated in both verbal and non-verbal memory retrieval indicating a general role in retrieval (Cabeza & Nyberg, 1997; Fletcher *et al.*, 1997). The posterior parietal cortex in co-operation with the prefrontal cortex has been related to visuospatial attention/cognition (Desimone & Duncan, 1995), and it has also been suggested that the precuneus is related to visual imagery processes and the use of visual imagery as a retrieval strategy (Fletcher *et al.*, 1995). Positive correlations between the activity of the precuneus and recognition performance have been reported (Kapur *et al.*, 1995; Tulving *et al.*, 1999). In addition, it has been suggested that working memory resources relating to aspects of the visuospatial sketchpad is localised to the posterior parietal cortex (Baddeley, 1997). In Petersson *et al.* (1999a), the practiced related changes in the posterior parietal cortex encompassed lateral superior parietal (left > right; BA 7) extending into the superior parts of the inferior parietal (left > right; BA 39/40) bilaterally. The corresponding changes in OL-POL were more extensive including the precuneus, and in contrast to Petersson *et al.* (1999a), the posterior parietal decreases were right dominant

(i.e., right > left). These changes were interpreted as indicating a gradual development of automaticity and a decreased reliance on attentional and working memory processing as a consequence of practice (cf. General discussion; Petersson *et al.* (1999)). The significance of the learning related decreases in the precuneus and right dominance of these changes is unclear, but is consistent with a decreasing dependence on visuospatial attention (Nobre *et al.*, 1997). The additional learning related effects are discussed below in relation to the results from the second experiment of this study.

FREE-RECALL OF PSEUDO-WORDS

Methods and materials

Subjects. Ten right-handed (Edinburgh handedness inventory) healthy male subjects (mean age 26 yrs, 20–33 yrs; 1–5 yrs of university level education) were included in the study. The subjects were pre-screened as described above. The local Ethics and Radiation Safety committees at the Karolinska Hospital approved the study. All the subjects volunteered and gave informed consent.

PET scanning, the experimental paradigm, and data analysis. Each subject underwent 12 measurements of rCBF with a 3D ECAT EXACT HR PET scanner as described above. The experimental paradigm is identical with the one described in Petersson *et al.* (1999a) and is only briefly described here. The subjects practised all aspects of the experimental paradigm (with sham injections) for approximately 20 min in the PET scanner before the experiment started. The experimental paradigm consisted of two identical blocks with 10–30 min of rest in between when the subjects were allowed to leave the PET scanner (Fig. 6a). In each block, the subjects were scanned in three different conditions: novel free-recall

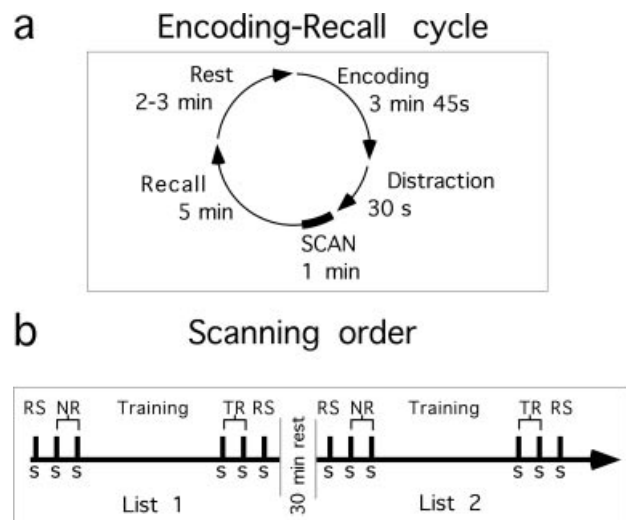


Fig. 6. (a) Encoding-recall-cycle. During encoding, the list of pseudo-words were copied one time. Then a distractor text was read during 30s. Finally, during free-recall the pseudo-words were written with a pen on paper. (b) The scanning order of the 12 scans in the 3 conditions RS, NR, and TR. (S = scanning) and the training period (approximately 30 min) of 6 encoding-recall-cycles in each block.

(NR), trained free-recall (TR), and a reference state (RS), in the order: RS/NR/NR/training period/TR/TR/RS (at least 10 min inter-scan-interval). The only difference compared to the experimental paradigm of Petersson *et al.* (1999a) is that pseudo-words were used instead of abstract designs. Briefly, RS, representing a low-level reference state, was identical to the reference state of Petersson *et al.* (1999a) in which the subjects filled in the contours of simple pre-drawn designs (e.g., squares, circles, triangles, and crosses), approximately matching the tasks of interest in visuo-motor coordination. Following the first RS-scan in a block, the subject was engaged in the basic experimental cycle (encoding-recall-cycle) which consisted of an encoding part and a recall part (Fig. 6b).

During encoding a list of 15 pseudo-words were shown 8s each on the computer screen. The subject copied each pseudo-word one time with a pen on paper. Following encoding the subject read a nonsense text aloud for 30s in order to prevent recency effects. After this, the recall part started, the bolus injection given and the subject was instructed to start recalling the pseudo-words. Two different lists of pseudo-words were used, one for each block, balanced over subjects. During each block there was a training period between the

second NR-scan and the first TR-scan. The training period consisted of 6 encoding-recall cycles.

The PET data were pre-processed and analysed as described above in SPM(95). In particular, time (= the order of scans) was used as a confounding covariate to account for non-specific time effects (Petersson *et al.*, 1999b). All reported P-values are corrected for multiple non-independent comparisons except where explicitly indicated. As above, for the regionally specific hypothesis related to the MTL we accepted activations corresponding to voxels with $Z \geq 2.33$ (or uncorrected $P \leq 0.01$) as significant. In a second step, we were interested in the differential activity between conditions in the rest of the brain. In this exploratory part we were particularly interested in the dorsolateral prefrontal, middle frontal-frontopolar, anterior cingulate, anterior insula/frontal operculum, posterior parietal, and occipital-occipitotemporal regions. In addition, we used an interaction approach to characterise learning related effects. This approach assesses learning related effects as an interaction contrast in the general linear model, for a discussion see (Petersson *et al.*, 1999b). The reproduced pseudo-words were scored according to the number of correct letters.

Table 4a. Local activation maxima in novel free-recall (NR) vs. the reference state (RS). ¹ refers to the Karolinska Brain Atlas

Region	Brodmann area	[x, y, z]	Z	P-value
Prefrontal cortex				
Superior frontal gyrus	6/8 dx	16 6 56	4.20	0.027
	10 sin	-30 48 16	8.54	<0.001
Superior/middle frontal gyrus	10 dx	24 46 8	7.66	<0.001
	9/44/46 sin	-38 16 24	7.06	<0.001
Middle/inferior frontal gyrus	11/47 sin	-22 26 -16	5.04	0.001
	44/47 sin	-52 12 0	9.09	<0.001
Inferior frontal gyrus	44/45/46 sin	-52 16 24	7.85	<0.001
	6/44/ sin	-38 -4 32	7.75	<0.001
Inferior frontal/pre-central gyrus	6/44/ sin	-56 -2 20	5.28	0.001
	14/15/49 ¹ dx	30 18 4	9.80	<0.001
Anterior insula/frontal operculum	14/15/49 ¹ dx	-34 16 0	9.22	<0.001
	24/32 sin	-6 18 36	11.95	<0.001
Cingulate gyrus				
Anterior cingulate cortex	24/32 sin	-6 18 36	11.95	<0.001
Mid-posterior cingulate cortex	23 sin	-2 -30 24	4.65	0.005
Parietal cortex				
Inferior parietal cortex	39/40 dx	44 -60 40	5.23	<0.001
	39/40 sin	-32 -58 32	6.51	<0.001
Inferior parietal/superior occipital cortex	dx	34 -60 40	5.23	<0.001
	19/39 dx	34 -76 36	6.51	<0.001
	7/19/39 sin	-32 -78 36	4.96	0.001
Temporal Cortex				
Middle/inferior temporal gyrus	20/21 dx	58 -40 -12	3.98	0.058
	20/21/37 sin	-46 -40 -4	4.62	0.005
Fusiform gyrus	18/19 dx	28 -94 -20	4.70	0.004
	18 sin	-36 -88 -24	4.52	0.008
Lingual gyrus/cerebellum	18 sin	-16 -96 -24	3.95	0.065
Fusiform gyrus/cerebellum	18 dx	32 -88 -28	4.01	0.054
Occipital cortex				
Superior occipital gyrus	19 dx	34 -76 36	5.39	<0.001
Cuneus/precuneus	18/19 sin	-4 -80 28	7.06	<0.001
Lentiform nucleus				
Cerebellum	dx	12 2 12	3.84	0.092
	dx	0 -58 -20	4.57	0.006
	sin	6 -72 -28	4.97	0.001
	sin	-4 -46 -16	4.51	0.008
	dx	32 -66 -28	5.56	<0.001
	sin	-44 -66 -28	6.59	<0.001

Results

Behavioural data. The performance during NR, 42 ± 23 (mean \pm sd; max = 94) was increased to 89 ± 9 during TR. During the approximately 80s from the bolus-injection to the end of scanning, the subjects reproduced $7(\pm 3)$ pseudo-words in NR and $14(\pm 2)$ in TR. During RS the subjects filled in the contours of $17(\pm 6)$ simple designs per scan.

Regional cerebral blood flow data. We used the Karolinska Computerised Brain Atlas of Greitz (Greitz *et al.*, 1991) for the anatomical description. In the exploratory part of the comparison we were interested in the differential activity between conditions in the rest of the brain. Here we report the results using the spatial extent of an activation thresholding at $Z = 3.72$. In addition, the results using the local maximum are reported in the tables. Only regions of spatial extent that were significant $P \leq 0.1$ (corrected) are described. Likewise, only local maxima of significantly activated regions are reported in the tables if the local maxima are significant $P \leq 0.1$ (corrected). When a region is described to

include a Brodmann area, this is not in an inclusive sense but only implies that parts of that BA is included in the region.

Medial temporal lobe activations in the free-recall of pseudo-words experiment. Given the specific regional interest in the behaviour of the MTL and in order to maximise detection sensitivity, we characterised activations corresponding to voxels with $Z \geq 2.33$ in the Karolinska Computerised Brain Atlas of Greitz. There were no MTL activations in NR-RS, TR-RS, NR-TR, or TR-NR.

Activations in novel recall compared to the reference state. In the relatively less practised NR compared to RS (Table 4a, Fig. 7a) several brain regions were activated, including prefrontal, anterior insular and anterior cingulate ($P < 0.001$) regions. More specifically, bilateral posterior parts of superior-middle frontal (left > right; BA 6, 8, 9, 10, 46) extending into left the inferior frontal-frontal operculum (BA 44, 45, 47, 49) regions. The frontal operculum was activated bilaterally extending into the anterior insular cortices (BA 14, 15). The anterior cingulate activation included bilateral BA 24, 32 and 33. Also the

Table 4b. Local activation maxima in practised recall (TR) vs. the reference state (RS). ¹ refers to the Karolinska Brain Atlas

Region	Brodmann area	[x,	y,	z]	Z	P-value
Prefrontal cortex						
Superior/middle frontal gyrus	9/10 dx	22	48	4	5.40	<0.001
Middle frontal gyrus	10/46 sin	-32	44	20	6.25	<0.001
	9 sin	-38	24	28	4.15	0.033
	9/45/46 sin	-50	24	24	4.14	0.034
	10/11 sin	-28	50	-4	3.81	0.102
Middle frontal/precentral gyrus	6 sin	-42	-8	36	6.91	<0.001
Inferior frontal gyrus	44/47 sin	-52	10	0	7.34	<0.001
Precentral gyrus	4/6 sin	-58	-4	16	5.78	<0.001
Pre/postcentral gyrus	SE/4 sin	-38	-26	48	3.98	0.058
Anterior insula/frontal operculum	14/15/49 ¹ dx	28	18	4	7.70	<0.001
	14/15/49 ¹ sin	-32	16	4	6.30	<0.001
Cingulate gyrus						
Anterior cingulate cortex	32 sin	-6	8	44	9.11	<0.001
Mid-posterior cingulate gyrus	23 sin	-2	-30	24	4.44	0.011
Parietal cortex						
Inferior parietal lobule/superior occipital gyrus	19/39 dx	32	-72	36	4.94	0.001
Inferior parietal lobule	39/40 sin	-28	-56	28	4.94	0.001
Occipito-temporal cortex						
Lingual gyrus/calcarine sulcus	17/18 dx	18	-64	12	4.95	0.001
Fusiform gyrus	18 dx	24	-98	-16	5.71	<0.001
Occipital cortex						
Cuneus/precuneus	18/19 sin	-4	-78	28	6.19	<0.001
Lingual gyrus/cerebellum	18 sin	-20	-96	-24	5.00	0.001
Fusiform gyrus/cerebellum	18 dx	-28	-94	-24	5.07	0.001
Thalamus						
	dx	0	-28	12	4.29	0.019
	sin	4	-22	16	4.02	0.052
	sin	-8	22	16	4.04	0.048
Lentiform nucleus						
	sin	-24	-10	8	4.44	0.011
	sin	-18	-2	4	4.43	0.011
Cerebellum						
	dx	2	-58	-16	7.92	<0.001
Cerebellum	dx	28	-60	-28	5.73	<0.001
Cerebellum	sin	-44	-64	-28	4.61	0.005

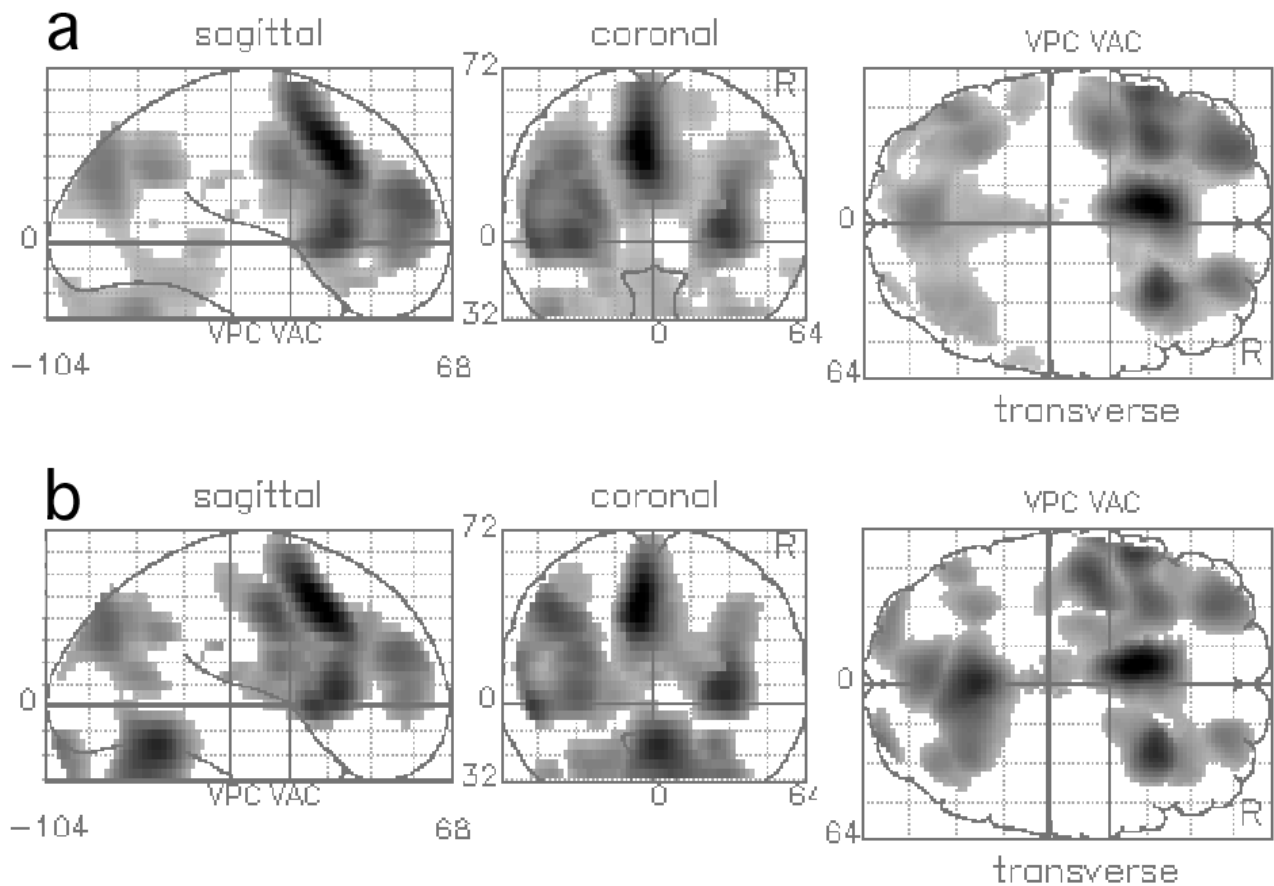


Fig. 7. (a) The pattern of significant activation in novel recall and (b) in trained recall vs. the reference condition. The images are thresholded at $Z = 3.09$.

mid-posterior cingulate cortex was activated bilaterally ($P = 0.079$, BA 23 extending into BA 26/29/30). Other areas that were activated included parieto-temporo-occipital ($P < 0.001$), infero-temporal (right $P < 0.093$; left $P < 0.028$) and cerebellar ($P < 0.001$) regions, encompassing the precuneus and superior parietal lobule (BA 7)

bilaterally, extending into the superior parts of inferior parietal, supramarginal (BA 40), right angular (BA 39), and superior-middle occipital (BA 19) regions. The activated region also included the bilateral inferior occipital gyrus (BA 19), and the posterior parts of left inferior temporal gyrus (BA 37).

Table 5a. Local activation maxima in novel recall (NR) vs. practised recall (TR)

Region	Brodmann area	[x, y, z]	Z	P-value
Prefrontal cortex				
Medial superior frontal gyrus	6 sin	-8 6 64	4.76	0.003
Superior frontal gyrus	6 sin	-22 8 56	4.10	0.038
Middle frontal gyrus	10/46 sin	-26 52 8	4.57	0.006
Middle/inferior frontal gyrus	11/47 sin	-26 24 -16	3.95	0.065
	10/11/47 dx	26 42 -8	4.21	0.026
Inferior frontal gyrus	9/44 sin	-50 16 28	5.35	<0.001
	44/45 sin	-54 18 12	4.53	0.008
	45/47 sin	-38 24 0	4.95	0.001
Anterior cingulate cortex	32 sin	-6 18 44	5.37	<0.001
Cingulate gyrus	32 sin	-4 22 36	5.34	<0.001
Inferior parietal lobule	39/40 dx	50 -50 40	4.09	0.040
Temporal cortex				
Middle/inferior temporal gyrus	21/37 sin	-46 -44 -4	3.98	0.060
Inferior temporal/fusiform gyrus	20/37 sin	-56 -42 -16	4.06	0.044

Activations in trained recall compared to the reference state. Similar activations were observed in the relatively more well practised TR compared to RS (Table 4b, Fig. 7b) including prefrontal, anterior insular and anterior cingulate ($P < 0.001$; right PFC $P = 0.003$; right anterior insular $P < 0.001$). The prefrontal activations included the middle frontal-frontopolar (BA 10, 46), the posterior parts of middle frontal (BA 45) extending bilaterally into the inferior frontal-frontal operculum (BA 44, 45, 46, and 49) and the anterior insular (BA 14, 15) cortices. In addition to the anterior cingulate (BA 24, 32) there was a mid-posterior cingulate cortex was activated (BA 23; $P = 0.085$). Other areas that were activated included parieto-temporo-occipital ($P = 0.008$), occipital ($P < 0.001$), right occipito-temporal

($P = 0.028$), and cerebellar ($P < 0.001$) regions. These activations included the precuneus extending into parietal (BA 7) and posterior cingulate (BA 23, 31) areas. There were also bilateral activations (right > left) in inferior parts of the superior parietal lobule (BA 7) extending on the right into the superior parts of superior-middle occipital gyri (BA 19). The occipital and occipito-temporal activations encompassed posterior parts of the superior occipital gyrus (BA 18) bilaterally and a small activation in the left lingual-fusiform (BA 19, 37).

Differential activations in novel recall compared to trained recall. Practice related decreases were observed (Table 5a, Fig. 8a) in the left anterior cingulate (BA 24, 32; $P < 0.001$)

Table 5b. Local activation maxima in practised recall (TR) vs. novel recall (NR)

Region	Brodmann area	[x, y, z]	Z	P-value
Pre/postcentral gyrus	SE/4 sin	-30 -32 52	4.14	0.034
Superior parietal lobule	5/7 dx	10 -56 52	4.01	0.052
Superior temporal gyrus	22/38 dx	48 -2 4	4.42	0.012
Mid-cingulate cortex	31 dx	6 -14 44	5.62	0.000
Thalamus	sin	-28 -14 8	4.89	0.002
Cerebellum	dx	4 -58 -16	4.29	0.019
	dx	20 -46 -20	4.35	0.015
	dx	14 -58 -20	4.06	0.045

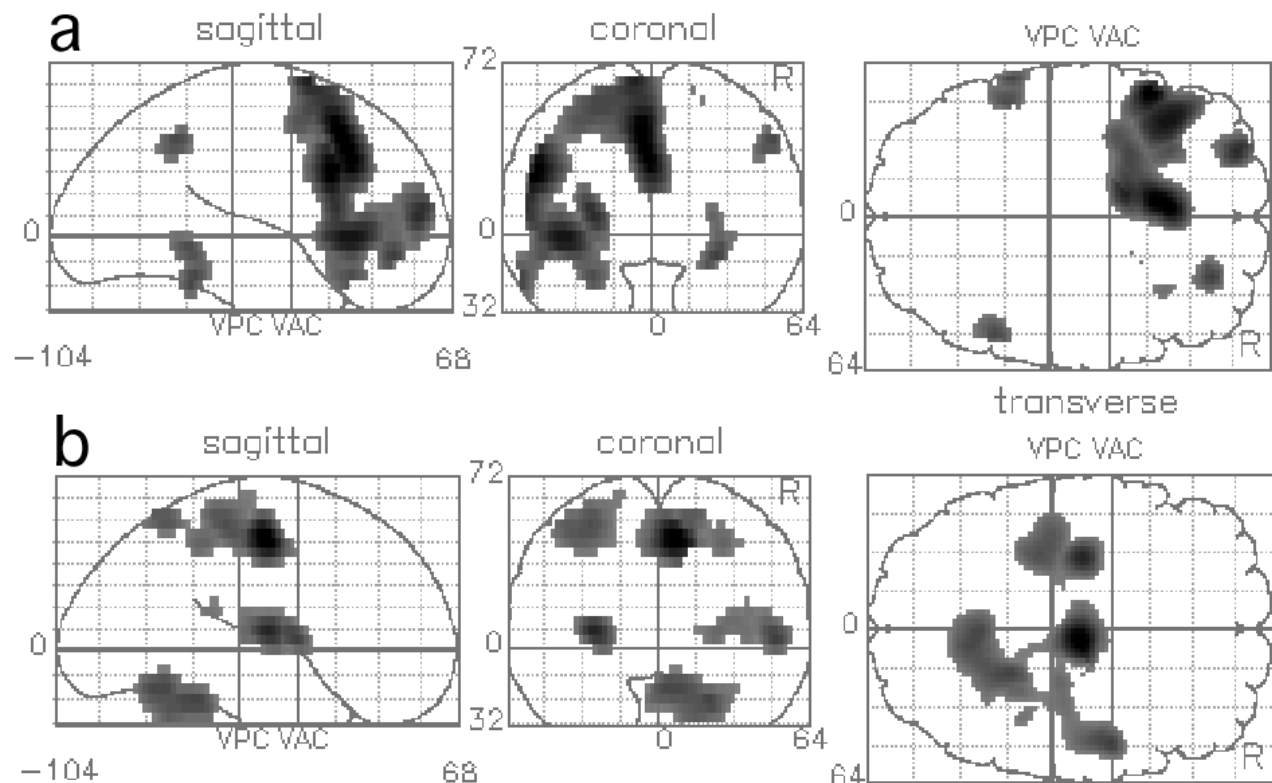


Fig. 8. Learning related modulation of the free-recall network. (a) The pattern of differential significant activation in novel recall vs. trained recall and (b) in trained recall vs. novel recall. The images are thresholded at $Z = 3.09$.

extending to the left superior frontal gyrus (BA 6, 8), and in the left middle-inferior frontal-frontal opercular (BA 44, 45, 47, 49; $P < 0.001$) extending into the anterior insular region (BA 14, 15). Prefrontal decreases were also observed in the lateral orbitofrontal (BA 11; right $P = 0.066$, left $P = 0.085$) bilaterally and a left middle frontal (BA 10; $P < 0.029$) region. In addition, practice related decreases included two smaller left middle-inferior temporal (BA 20, 21; $P = 0.090$; BA 37; $P = 0.079$) and a right inferior parietal region (BA 40; $P = 0.077$).

Differential activations in trained recall compared to novel recall. Practice related increases were observed (Table 5b, Fig. 8b) in midcingulate-paracentral lobule (BA 24, 31; $P = 0.004$), anterior precuneus (BA 5, 7; $P = 0.057$), right superior temporal gyrus (BA 22; $P = 0.032$), lentiform nucleus ($P = 0.019$), and right cerebellar regions ($P = 0.003$).

Using an interaction approach to learning (Petersson et al., 1999b), that is first relating the effects in NR and TR to the reference condition acquired in temporal proximity, RS1 and RS2 respectively, and then testing the contrast [NR-RS1]-[TR-RS2], the practice related effects were generally similar but less robust compared with the results reported above. This may indicate a lack of sensitivity with this approach in certain circumstances (e.g., the use of a non-ideal reference task; cf. Petersson et al., 1999b for a discussion) and emphasises the importance of choosing a closely matched reference task using the interaction approach.

DISCUSSION

The first experiment of this study and previously reported PET data indicate that several brain regions are modulated by practice, in this case repeated encoding and retrieval. These modulations include decreases in the prefrontal, anterior cingulate, posterior parietal, and medial temporal, as well as increases in perisylvian parieto-temporal, posterior opercular-insular, and occipito-temporal regions (Petersson et al., 1997; Petersson et al., 1999a). The second PET experiment of this study was designed to investigate if these learning related effects are dependent on the material used, pseudo-words in the present experiment, in contrast to visuo-spatial material used in the earlier studies. Free-recall of pseudo-words activated prefrontal, anterior insular/frontal opercular, cingulate, parietal, temporal and cerebellar regions (Fig. 7, Table 4). The general pattern of practice related decreases and increases were similar to the results from the two previous studies and are discussed further in the general discussion below.

The most prominent difference between the present experiment and the previously reported results concerns the MTL and the posterior parietal cortex. In contrast to the previous studies we did not observe any significant differential retrieval related MTL activations in the free-

recall condition compared to the reference condition, neither did we observe any practice related changes in the MTL (even at the relatively sensitive significance level of $Z = 2.33$). This indicates that non-specific (e.g., time) effects, novelty detection, attentional effects, retrieval performance, or retrieval effort are not likely to explain in a simple way the observations in the first experiment of this study or the study of Petersson et al. (1997). This may instead point to a material specific interaction effect. First, pseudo-words lack apparent meaning and may thus be less likely to elicit retrieval-related levels-of-processing effects in the MTL, thought to depend on elaborate processing of meaning, which have been reported (Rugg et al., 1997). Second, several lines of investigation have related the MTL to learning and memory of visuo-spatial material (e.g., Maguire et al., 1996; Maguire et al., 1998; Nadel, 1994; O'Keefe et al., 1998). Thus, the practice related decreases observed in the MTL might be more clearly expressed for meaningful verbal or visuo-spatial material triggering associative processing or the processing of visuo-spatial relations. Some indications that this may be the case come from the comparison of the recall of pseudo-words with the reference task (filling in contours of simple pre-drawn designs). The activity of the MTL was significantly greater in the reference condition compared to both the novel and trained recall condition (RS-NR: $[xyz] = [24-12-12]$, $Z = 5.44$, $P < 0.001$; RS-TR: $[xyz] = [34-10-12]$, $Z = 4.96$, $P < 0.001$; $[xyz] = [22-12-12]$, $Z = 3.83$, $P = 0.096$; $[xyz] = [222-24]$, $Z = 4.24$, $P = 0.023$). From another point of view, these results relate to the discussion of the role of the MTL in novelty processing (cf. the discussion of the first experiment above). Pseudo-words nominally represents novel stimuli compared to the familiar simple pre-drawn designs used in the reference condition. The subjects also practised extensively with the pre-drawn designs before the PET data acquisition session started. Since this was not the case for the pseudo-words, the pseudo-words also represented novel stimuli in the context of the experiment (cf. Dolan & Fletcher, 1997). Consistent with suggestions made in the discussion of the first experiment, it appears that at least some MTL effects are not explainable in terms of novelty processing.

In contrast to object-location recognition experiment and the free-recall of abstract designs in Petersson et al. (1999), the practice related posterior parietal decreases were small, did not include the precuneus or the superior parietal regions, and were localised to the right inferior parietal lobule (BA 39/40). This is likely related to fact that the other two experiments were visuo-spatial in nature while the present paradigm is language oriented. However, the localisation to the right inferior parietal region is puzzling. It has been suggested that the homologous left inferior parietal BA 39/40 subserves the phonological store (Paulesu et al., 1993) of verbal working memory (Baddeley, 1992). Perhaps this indicates that the subject, in addition to a

phonological strategy, initially used a visuo-spatial retrieval strategy, while this was not necessary in the relatively well-practiced state.

The recall performance increased with practice in the present experiment. Given that the regions activated in the relatively less-practised novel recall conditions are engaged in the retrieval process, it is possible that the observed practice related decreases would be more accentuated if performance somehow could have been kept constant. However, some of the observed practise related effects, in particular increases, may be related to the performance increase (e.g., the left pre/postcentral and right cerebellar increases). It was indicated in a similar free-recall paradigm that performance had limited effect on the observed practise related effects (for a more extensive discussion cf. Petersson *et al.*, 1999a). Furthermore, the overall similarities in the pattern of practise related effects in the two experiments of the present study and previous PET studies (Petersson *et al.*, 1999a; Raichle *et al.*, 1994) indicate that performance as an explanatory factor may be limited.

GENERAL DISCUSSION

In the present paper we extend earlier investigations of practice related changes in the functional anatomy during non-motor learning (Raichle *et al.*, 1994) and learning related modulation of functional retrieval networks (Petersson *et al.*, 1997; Petersson *et al.*, 1999a). In two different PET experiments we investigated episodic recognition of object-location relations as well as episodic free-recall of pseudo-words. Even though there are differences in the details, a fairly consistent pattern of learning related modulations is observed in all of these studies. This includes learning related decreases in the prefrontal, the anterior cingulate, the anterior insula/frontal operculum, and posterior parietal regions, as well as learning related increases in perisylvian parieto-temporal, posterior opercular-insular, and occipito-temporal regions. This may indicate that relatively general cognitive processes are reflected in these changes. The detailed differences between the experiments likely represent a mixture of paradigm/task/material specific effects and apparent statistical effects (e.g., false negatives due to lack of statistical power).

Previously these learning related changes have been conceptualised in terms of the interaction between attentional/control processes and learning/memory as well as the development of automaticity or reduced processing complexity (Petersson *et al.*, 1999a). Attentional processes and working memory interact with certain learning and memory processes (Baddeley, 1994; Schneider *et al.*, 1994). In this context, cognitive processes can be divided into controlled and automatic processes. Controlled processes require a higher degree, while automatic processes require a lower

degree, of attentional and working memory processing. Automaticity develops gradually as a consequence of practice (Cohen *et al.*, 1990; MacLeod & Dunbar, 1988; Schneider *et al.*, 1994). Performance on a novel task is hypothesised to depend more, and as performance becomes more automatic, less, on attentional and working memory resources. Supposedly some forms of controlled processing are related to the prefrontal cortex (the central executive, D'Esposito *et al.* (1995)) and the posterior parietal regions (the phonological store, Paulesu *et al.* (1993); the visuo-spatial sketch pad Baddeley (1997)) to support task-relevant processing (Ghatan *et al.*, 1998). In addition, it has been suggested that the anterior cingulate cortex is related to attention (Corbetta *et al.*, 1993; Pardo *et al.*, 1991; Pardo *et al.*, 1990; Posner & Petersen, 1990) and on-line performance monitoring and error detection (Carter *et al.*, 1998). It has been observed that activation of the dorsolateral prefrontal cortex is often paralleled by activation of the anterior cingulate cortex (Jenkins *et al.*, 1994). This indicates a close functional relationship between the anterior cingulate cortex and the prefrontal cortex (Duncan & Owen, 2000), and the interaction between the prefrontal and the anterior cingulate cortices may subserve executive aspects of working memory (D'Esposito *et al.*, 1995). The observed practice related decreases may therefore be interpreted as reflecting a gradual development of automaticity (MacLeod & Dunbar, 1988; Petersson *et al.*, 1999a; Raichle *et al.*, 1994). In other words, a decreased dependence on attentional and working memory resources with corresponding changes in activation of the prefrontal, the anterior cingulate, the anterior insula/frontal operculum, and posterior parietal regions. As automaticity develops, performance will gradually depend less on prefrontal and anterior cingulate support, and that the activity decreases in these regions reflect a decrease in processing complexity. This is consistent with the notion of a gradual development of automaticity with practice. As indicated above, this interpretation is related to a suggestion that the different prefrontal processing components involved in retrieval are drawn from the same set of underlying prefrontal sub-processes engaged differentially dependent on the task at hand (Nolde *et al.*, 1998) and the process-context (Wagner *et al.*, 1998a), both internal and external. Furthermore, there also seems to be a general pattern of practice related increases of activity in the auditory, posterior insular-opercular extending into perisylvian supramarginal cortex which may reflect a lower degree of attentional suppression of task irrelevant processing. This pattern of relative increases was less clearly expressed in the second experiment possibly reflecting specific characteristics of the language task used.

In the present study, the prefrontal activation was right lateralised in episodic recognition but bilateral in the free-recall experiment supporting the suggestion that free-recall is dependent on bilateral prefrontal processing (Petersson *et al.*, 1999a). The practice related prefrontal decreases were

bilateral in both recognition and free-recall. However, the prefrontal decreases, similar to the pattern observed in Petersson *et al.* (1999a), were left dominant. This is consistent with the conclusion of Nolde *et al.* (1998) that complex retrieval tasks are dependent on bilateral prefrontal processing, particularly complex cued-recall and free-recall tasks. This may reflect for example initiation of retrieval strategies, self-generation of retrieval cues, selection among candidate responses, and list re-cycling in the case of free-recall, while simple recognition may be based on more heuristic, perceptually related, processes (e.g., familiarity judgement). In the review of Nolde *et al.* (1998) it was indicated that also complex recognition tasks activated the prefrontal cortex bilaterally. Interestingly, a recent multi-study analysis of several episodic recognition studies reported two left prefrontal activations in addition to three dominant right prefrontal activations (Lepage *et al.*, 2000). As a final general conclusion, there are several previous reports indicating that memory retrieval is subserved by a network of interacting brain regions (Nyberg *et al.*, 1998) and the present results indicate that some of the network components may have a dynamic role (Petersson *et al.*, 1999a; Raichle *et al.*, 1994). In other words, there is a functional restructuring of the information processing networks during the learning process. This may reflect changes, directly or indirectly, in local or more long-distance connectivity between regions or network modules (Buchel *et al.*, 1999).

IN CONCLUSION

Learning in a neural network is a dynamic consequence of information processing and network plasticity. The present and previous PET results indicate that practice can induce a learning related functional restructuring of information processing. Different adaptive processes likely subserve the functional re-organisation observed. These may in part be related to different demands for attentional and working memory processing. It appears that the role(s) of the prefrontal cortex and the medial temporal lobe in memory retrieval are complex, perhaps reflecting several different interacting information processes or cognitive components. We suggest that the conclusion of Duncan and Owen (2000) concerning functional neuroimaging and the prefrontal cortex may be extended to the medial temporal lobe. In other words, several of the conceptualisations of prefrontal and medial temporal lobe functions are general in nature making it difficult to generate specific and detailed testable predictions based on explicit models. We suggest that an integrative interactive perspective on the role of the prefrontal and medial temporal lobe is necessary for an understanding of the processing significance of these regions in learning and memory. In order to meet the challenges outlined by Duncan and Owen (2000) it appears necessary to develop more elaborated and preferably explicit computational models for prefrontal and medial temporal lobe

functions in combination with an efficient use and development of functional neuroimaging approaches (Amit, 1998; Arbib, 1995; Horwitz *et al.*, 1999; Ingvar & Petersson, 1999).

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