Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice

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Abstract

In the present PET study we explore some functional aspects of the interaction between attentional/control processes and learning/memory processes. The network of brain regions supporting recall of abstract designs were studied in a less practiced and in a well practiced state. The results indicate that automaticity, i.e., a decreased dependence on attentional and working memory resources, develops as a consequence of practice. This corresponds to the practice related decreases of activity in the prefrontal, anterior cingulate, and posterior parietal regions. In addition, the activity of the medial temporal regions decreased as a function of practice. This indicates an inverse relation between the strength of encoding and the activation of the MTL during retrieval. Furthermore, the pattern of practice related increases in the auditory, posterior insular-opercular extending into perisylvian supra-marginal region, and the right mid occipito-temporal region, may reflect a lower degree of inhibitory attentional modulation of task irrelevant processing and more fully developed representations of the abstract designs, respectively. We also suggest that free recall is dependent on bilateral prefrontal processing, in particular non-automatic free recall.

The present results confirm previous functional neuroimaging studies of memory retrieval indicating that recall is subserved by a network of interacting brain regions. Furthermore, the results indicate that some components of the neural network subserving free recall may have a dynamic role and that there is a functional restructuring of the information processing networks during the learning process. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Learning and memory are fundamental brain functions enabling the central nervous system to encode experiential information and adapt in a non-stationary environment. Learning may be defined as the processes by which the brain functionally restructures its processing networks or its representations of information as a function of experience. The memory trace can then be viewed as the resulting changes in the processing system. From a parallel distributed processing perspective [3] learning in a neural network is a dynamic consequence of information processing and network plasticity. By hypothesis, this is also the case for the human brain [69]. Understanding the functional role of different brain regions in learning and memory is important for the understanding of the brain as a cognitive system [23, 91], including the role of the prefrontal, the anterior cingulate, the medial temporal, and the posterior parietal regions [8, 9, 23, 60, 63, 83, 84, 91].

The medial temporal lobe (MTL) displays rapid plasticity in some classes of synapses and has reciprocal connections with multimodal associative neocortical and subcortical regions, indicating an essential role in long-term memory [21, 83, 98]. Perception and short-term memory are thought to be implemented as distributed activity in the neocortex [18, 28, 50, 51, 52, 83]. If such distributed neocortical activity is to be stored as a declarative long-term memory, the MTL memory system must be engaged at the time of learning [83]. Information initially represented or registered in the neocortex is thought to be bound into a long-term memory trace by the MTL. This initial binding process has been called cohesion or short-term consolidation [60]. Presumably, the neocortex is the final storage site for some forms of declarative knowledge [21, 28, 50–52, 60, 84]. This implies that declarative learning, storage, and memory retrieval

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are dependent on some type of interaction between the MTL and the neocortex.

Attentional processes and working memory interact with certain learning and memory processes [5, 13, 79]. 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 [13, 48, 79]. Performance on a novel task is thought to depend more, and as performance becomes more automatic, less, on attentional and working memory resources [10, 13, 74]. Supposedly some forms of controlled processing are related to working memory representations supported in the prefrontal cortex (PFC, the central executive, [4, 5]) and the posterior parietal regions (the visuo-spatial sketch pad [5]) to bias in favour of task-relevant processing [14]. In addition, it has been suggested that the anterior cingulate cortex (ACC) is related to on-line performance monitoring and error detection [11]. In many functional neuroimaging studies, activation of the dorsolateral PFC is paralleled by activation of the ACC [42]. This indicates a close functional relationship between the ACC and the PFC, and both the dorsolateral PFC and the ACC may subserve executive aspects of working memory [17].

The PFC has been implicated in working memory [28, 29, 36, 41, 44, 72], memory retrieval [63, 81], initiation and execution of complex mnemonic strategies particular in free recall [71, 94], search and retrieval processes [58], and the temporal organization of behavior [28, 29]. It has also been suggested that the PFC participates in the interaction between working memory and long-term memory [4, 14], as well as self-initiated behaviours [26, 68], and central executive functions [5, 17, 62].

The ACC may be an important component of the attention system subserving the selection among competing complex contingencies [20, 34, 74] selective attention [15, 66, 67], attention shifting and top-down-search [46]. Mesulam and colleagues [51, 57, 61] have suggested that the ACC is part of a large-scale attentional network, including the frontal eye fields (FEF) and posterior parietal cortex (PPC). The PPC is interconnected with prefrontal, cingulate, and parahippocampal areas [36]. Parietal regions, including the precuneus, have been activated in both verbal and non-verbal memory retrieval [9, 23, 40, 81] indicating a general role in retrieval. The PPC has also been implicated in visual imagery processes and the use of visual imagery as a retrieval strategy [22, 47, 81], as well as in visuo-spatial attention/cognition [45], especially in co-operation with the PFC and pulvinar [19]. Furthermore, the inferior parietal regions may be related to the representation of the spatial relations between different segments of complex visual designs [47].

Previous PET studies have indicated that practice may induce a functional restructuring of the processing networks [42, 74]. This reorganization of the functional connectivity is most likely related to different adaptive processes, in part related to different demands for attentional and working memory resources. Consistent with this hypothesis, Jenkins et al. [42] and Raichle et al. [74] observed decreasing activity of both prefrontal and anterior cingulate regions as a consequence of practice.

Recently it was hypothesized that the MTL is necessary to bind neocortical representations related to new information and novel non-automatic processes, while the prefrontal cortex is necessary to support the temporal organization of behavior and subserve representations that bias in favour of task relevant processing [13, 14]. Related to the functional changes of the processing architecture, Cohen and O'Reilly [14] suggest two consequences of practice. As automaticity develops, performance will gradually depend less on prefrontal support, and when the neocortical representations are fully developed (as a result of practice), the necessary support of the MTL will diminish.

In order to explore the functional interaction between attentional/control processes and learning/memory, we modified a free recall abstract-design list-learning paradigm sensitive to MTL lesions devised by Jones-Gotman [43]. Our experimental approach was based on the logic described by Raichle et al. [74], i.e., introducing novel material of the same kind as the material just learnt causes reactivation of the regions that showed practice related effects. The PET paradigm of Raichle et al. [74] was modified to include two full repetitions of the basic experimental block. This allowed us to model non-specific time effects and block repetition as confounding covariates in the general linear model [25].

We hypothesized that practice (in this case repeated encoding and recall) would lead to a higher degree of automaticity, i.e., a decreased dependence on controlled and attentional processing. Supposedly this would be reflected in decreased activity of the prefrontal, anterior cingulate, and posterior parietal regions. Furthermore, we hypothesized that repeated activation of the neocortical representations through repeated encoding should strengthen the neocortical interconnections in such a way that the neocortical network eventually could support retrieval less dependent on the MTL. In short, we suggest that some components of the neural network subserving memory retrieval have a dynamic role, and that this will be reflected in the functional restructuring of the information processing network during the learning process.

The results relating to the medial temporal lobe (MTL) are described and discussed in detail in Petersson et al. [69]. In brief, the MTL regions, in particular the right, were activated in NR-RS but not in TR-RS. There were practice related activation decreases in the MTL regions when NR was directly compared to TR or using an interaction approach [70].

2. Materials and methods

2.1. Subjects

Twelve right handed (Edinburgh handedness inventory, [64]) healthy male subjects (mean age = 24 years, range = 22–29 years) were included in the study. The subjects were pre-screened and none used any medication, had a history of drug use (including nicotine), head trauma, neurological or psychiatric illness, or family history of neurological or psychiatric illness. The subjects had one to five years of university level education. The study was approved by the local Ethics and Radiation Safety Committees at the Karolinska Hospital. Informed consent was given by all the subjects. A twelfth subject with partially missing data in the left medial temporal lobe was included in this study.

2.2. PET scanning

Each subject underwent 12 measurements of rCBF with a 3D ECAT EXACT HR PET scanner [96] and bolus injections of [15-O] butanol [7]. The PET scanner was used in 3D-sampling mode producing 60 s tracer uptake images. The different tasks were started at the time of tracer injection and the scanning was automatically initiated when the brain radioactivity exceeded a pre-determined level above background. Scatter correction was made and a 2D-transmission scan was used for attenuation correction (a second transmission scan was performed if the subject left the scanner during the rest period between blocks). Six + two scans were lost for technical reasons in two different subjects, respectively.

2.3. The experimental paradigm

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 separated by 10–30 min of rest when the subjects were allowed to leave the PET scanner (Fig. 1c). Within each block, the subjects were scanned in three different states: reference state (RS), novel recall (NR), and trained recall (TR).

Each block consisted of six scans, with at least 10 min between scans, in the order: RS1/NR/NR/training period/TR/TR/RS2. During RS, the subjects filled in the contours of simple predrawn designs of the same size as the abstract designs (e.g., squares, circles, triangles, and crosses). The predrawn designs were presented in a matrix and were shown on a monitor (Fig. 1a). Visual feedback of the hand was provided by closed circuit TV and shown on the monitor just below a computer screen (Fig. 1a). The subjects were free to fill in as many contours as they found comfortable. The reference state was chosen to
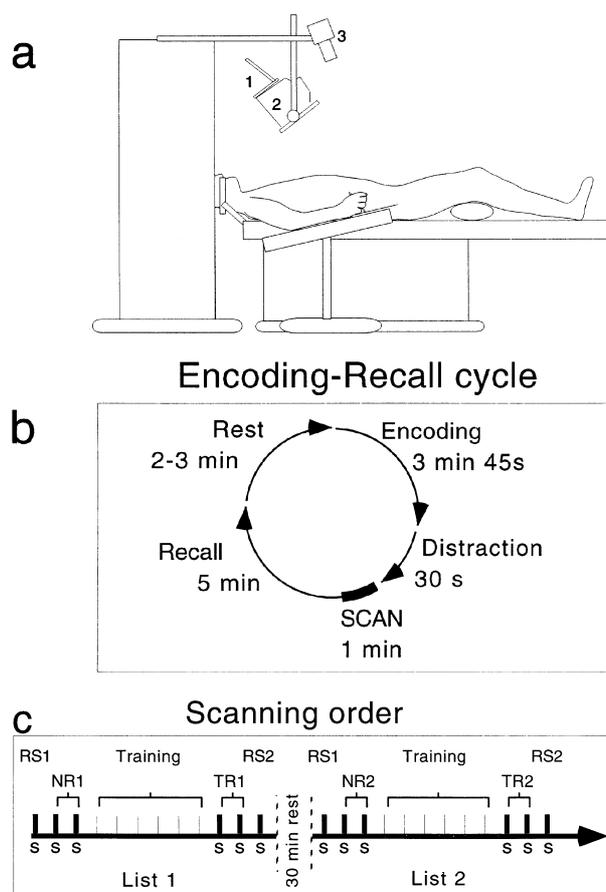

Fig. 1. a. The experimental PET scanner setup. 1 = computer screen for presentation of the abstract designs to be copied during encoding. 2 = monitor for closed circuit visual feedback of the hand. 3 = camera feeding into the monitor in the closed circuit visual feedback. b. The encoding-recall-cycle. During encoding each of the 15 abstract designs were copied one time. Then a distracter text were read during 30 s. Finally, during recall the designs were reproduced as faithfully as possible. c. The scanning order of the 12 scans, 2 reference state (RS), 2 novel recall (NR), and 2 trained recall (TR) scans in each block (bold markings, s = scanning) and the training period (approximately 30 min) of 6 encoding-recall-cycles in each block (thin markings).

match the tasks of interest in visuo-motor co-ordination, and represents a low level reference state. 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. 1b). During encoding a list of 15 separate abstract designs, simple enough to be copied rapidly but sufficiently complex to discourage descriptive naming [43] were shown 15 s each on the computer screen (Fig. 1a). The subject copied each design one time, and all designs were copied with a pen on the same paper. Following encoding the subject read a nonsense text aloud for 30 s in order to prevent recency effects [5]. After this, the recall part started, the bolus injection given and the subject was instructed to start drawing the designs from memory. The subject reproduced the designs as faithfully as possible in

any order during recall. To fully report what had been retained in long-term memory, the subject had 5 min at his disposal to reproduce the designs (only 2–3 min were used). Two different lists of 15 designs 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 (Fig. 1c). The training period consisted of six encoding-recall cycles. Altogether the subject went through 10 encoding-recall-cycles and were scanned on the first two and last two recall-procedures during each block. The time between when the subject was first confronted with the list of abstract designs to the last time during trained recall was approximately 75 min for each list. During the experiment the subjects hand movements were confined to $\approx 12 \times 18$ cm defined by the field of view of the monitor ($\approx 5°$).

2.4. Data analysis

The PET images were realigned, spatially normalized and transformed into a common stereotactic space as defined by the SPM95 template, an approximate Talairach space [87], 3D isotropic Gaussian filtered (14 mm FWHM), proportionally scaled to account for global confounders and analysed with statistical parametric mapping [25]. Non-specific approximately linear monotone time effects and experimental block were modeled as confounding covariates using scan order and block repetition in the general linear model. To test hypotheses about regionally specific condition or covariate effects, estimates were compared using linear contrasts. The resulting set of voxel values for each contrast, a *t*-statistic image SPM[*t*], was voxelwise transformed into a standard normal SPM[*Z*], and thresholded at $Z = 3.72$ (or omnibus significance $P < 0.0001$). This will reduce the number of false positive voxels of activated clusters. The activated regions were then characterized in terms of spatial extent and peak-height of local maxima. All reported *P*-values are corrected for multiple non-independent comparisons based on the theory of differentiable 3D stationary Gaussian random fields [1, 97].

The terms of activation and deactivation are used as synonyms for relative increased and decreased rCBF, respectively. For reasons of portability of data, the tables of local maxima use approximate Talairach designations [87]. In the anatomical description of the activated regions below the SPM[*Z*], thresholded at $Z = 3.72$, was displayed in the Karolinska Computerized Brain Atlas of Greitz (CBA, [38]). The anatomical database of the CBA makes it possible to interactively determine the anatomical structures and Brodmann areas (BA) encompassed by an activated region. Only regions of spatial extent that were significant $P < 0.1$ (corrected) are described. Likewise, only local maxima of significantly activated clusters are reported if the local maxima are significant $P < 0.1$ (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.

In addition, we used an interaction approach to characterize learning related effects (see [70] and discussion below). This approach assesses learning related effects as an interaction contrast in the general linear model. Specifically, data from a state of interest (in this case the recall state, i.e., NR and TR) are related to data from a reference state that is collected in temporal proximity to the state of interest. The RS scans collected before the training period will be denoted RS1 and the RS scans collected after the training period will be denoted RS2. The NR and RS1 scans were acquired before the training period and the TR and RS2 scans were acquired after the training period, and we tested for learning related effects using the contrast [NR-RS1]—[TR-RS2]. In addition, block repetition was included as a confounding covariate. The same significance criteria as described above were used.

The reproduced designs were scored according to: near exact reproduction of the design = 3, close reproduction with one addition, distortion, omission, inversion or rotation of a detail = 2, fair reproduction that contained two of the above mentioned mistakes = 1, anything worse was given 0.

3. Results

3.1. Behavioral data

The performance during novel recall 107 ± 19 (mean $\pm$ SD, maximum obtainable score $= 180 = 15 \times 3 \times 4$), were increased to 178 ± 3 (improvement $P = 0.002$, Wilcoxon signed rank test) during trained recall. During the approximately 80 s from the bolus-injection to the end of scanning, the subjects reproduced 6.2 (± 1.3) designs in NR and 9.3 (± 2.5) in TR. During RS, RS1, and RS2 the subjects filled in the contours of 16 (± 6.9), 15, and 17 simple designs per scan, respectively.

3.2. Regional cerebral blood flow (rCBF) data

3.2.1. Activations in novel recall compared to the reference state

The significant activations (spatial extent) in NR-RS constituted a network of several brain regions (Table 1 and Fig. 2). Deactivations are reported in Table 2.

The prefrontal and anterior cingulate activations ($P < 0.001$) included the bilateral posterior parts of superior-middle frontal (BA 6, 8, extending into the anterior parts of precentral BA 6), the middle frontal (BA 46 and left BA 9, 10, extending into the left superior frontal BA 10), and the inferior frontal (BA 44, 45) regions. The frontal operculum was activated bilaterally (BA 45, 47, 49) extending into the anterior insular cortex

Table 1
Activations in NR-RS. BA = Brodmann area, g = gyrus, l = lobule

Activations in NR-RS Region	BA	x, y, z	Z-score	P-value
Prefrontal cortex				
Middle frontal/precentral g	6 dx	22, −6, 48	8.22	0.000
	6 sin	−24, −10, 40	7.07	0.000
Middle/superior frontal g	10/11 dx	20, 38, −12	4.09	0.044
	10 sin	−22, 46, −8	5.12	0.000
	10/11 sin	−20, 44, −12	5.71	0.000
Middle frontal g	10 sin	−48, 28, 28	5.85	0.000
	47/11 sin	−20, 30, −20	4.04	0.054
	11 sin	−18, 38, −16	4.63	0.01
Inferior frontal g	44 sin	−52, 12, 32	4.77	0.003
	44/45 sin	−54, 14, 4	6.08	0.000
Precentral/inferior frontal g	6/44 sin	−40, −4, 32	5.81	0.000
Anterior insula	14 dx[a]	26, 18, 8	7.94	0.000
	14 sin[a]	−28, 16, 8	6.42	0.000
Frontal operculum	49 dx[a]	24, −6, 20	4.08	0.047
Anterior cingulate cortex	24/32 dx	16, 18, 28	5.23	0.000
	24/32 dx	18, 26, 24	5.06	0.001
	24/32 sin	−8, 16, 36	9.77	0.000
Posterior cingulate cortex	23	−2, −28, 20	5.44	0.000
Parieto-occipital cortex				
Precuneus	7 dx	14, −76, 44	10.77	0.000
	7 sin	−18, −74, 40	9.81	0.000
Superior parietal 1/ superior occipital g	7/19 dx	26, −76, 36	9.81	0.000
Supramarginal/angular g	40139 sin	−32, −46, 28	7.63	0.000
Infero-temporal cortex				
Inferior temporal g	37 dx	50, −62, −20	7.50	0.000
Fusiform g	37 dx	32, −40, −16	5.33	0.000
Fusiform/inferior occipital g/cerebellum	18/19 dx	40, −82, −24	5.06	0.001
Cerebellum		−16, −46, −28	3.95	0.074
		26, −64, −28	6.56	0.000
		−32, −62, −28	6.10	0.000
		32, −40, −28	5.33	0.000
		−34, −44, −28	5.70	0.000
		−48, 70, −28	6.45	0.000
Basal ganglia				
Head of nucleus caudatus dx		10, 12, 16	6.15	0.000
Head of nucleus caudatus sin		−16, 18, 12	5.57	0.000
Midbrain				
Red nucleus		0, −22, −4	5.54	0.000

[a] Refers to the Karolinska Computerized Brain Atlas. The co-ordinates refer to the Talairach space (1988). All P-values are corrected for multiple non-independent comparisons.

(BA 14 and right BA 15). There were also bilateral lateral orbitofrontal activations (BA 10, 11, right $P = 0.08$). The anterior cingulate activation included bilateral BA 24, 32 and 33. In addition, the mid-posterior cingulate cortex was activated bilaterally ($P = 0.01$, BA 23 extending into BA 26/29/30).

The parieto-temporo-occipital, infero-temporal and cerebellar activations (right $P < 0.001$, including the right infero-temporal cortex, and the left infrotemporal-occipito-temporal $P < 0.001$) included the bilateral precuncus and superior parietal lobule (BA 7), extending into the superior parts of inferior parietal BA 19, sup-
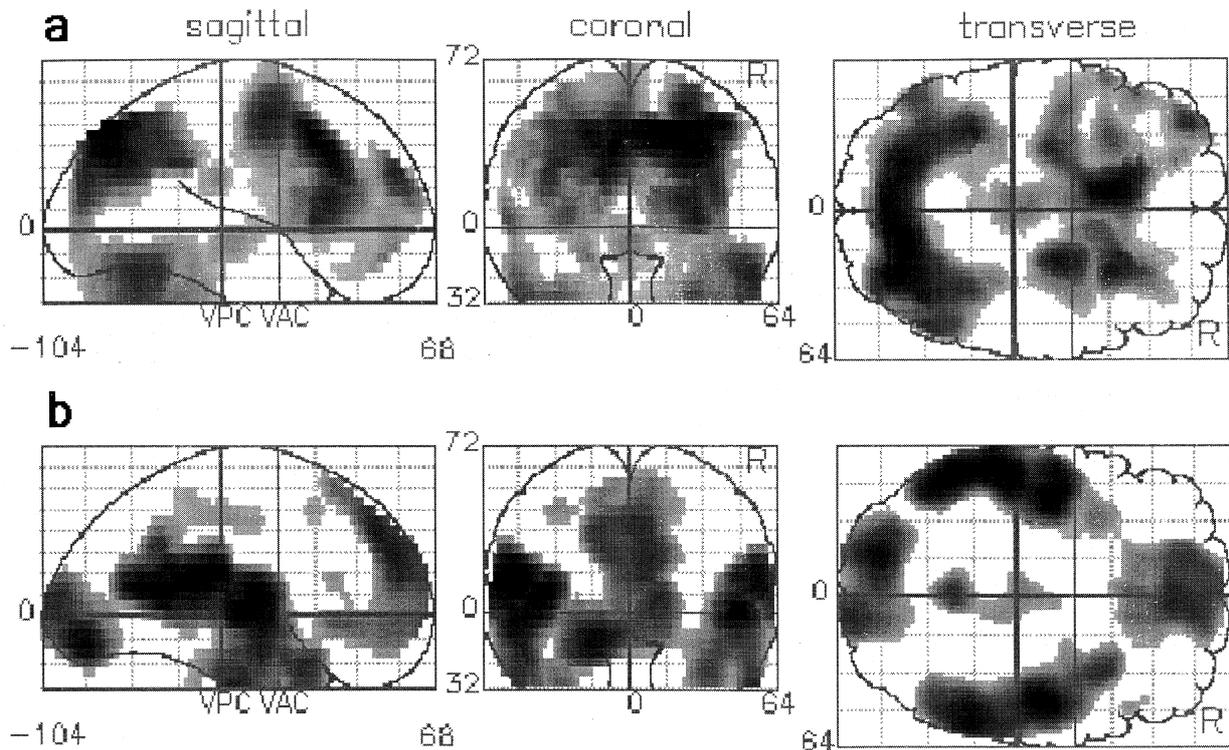
Fig. 2. The pattern of activation in (a) novel recall—reference state, and (b) reference state—novel recall (thresholded at $Z = 3.29$ or $P \leqslant 0.0005$).

ramarginal 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, 37), the posterior parts of inferior temporal gyrus (BA 37) extending bilaterally into the lingual-fusiform (BA 19, 37) and the medial temporal (BA 35, 36, right BA 27, and left BA 28) regions. The occipito-temporal activations extended into lateral and mediolateral parts of cerebellar cortex.

The subcortical activations ($P = 0.003$) included the thalamus bilaterally (in the vicinity of anterior and mediodorsal parts), the pulvinar ($P < 0.08$), and the midbrain (including the mammillary bodies). In addition, the anterior insular activation extended into the caudate and the lentiform nuclei.

3.2.2. Activations in trained recall compared to the reference state

Several brain regions were activated in TR-RS (Table 3 and Fig. 3). Deactivations are reported in Table 4.

The prefrontal and anterior cingulate activations ($P < 0.001$) included the bilateral posterior parts of middle frontal gyrus (BA 6, 8 extending into the anterior parts of precentral BA 6). The right middle frontal activation extended into the right inferior frontal (BA 44), the right frontal operculum (BA 44, 45, 46, and 49), and the right anterior insular cortex (BA 14, 15). There were also bilat-

eral anterior middle frontal activations (BA 46, left $P = 0.05$, BA 10, 46). The anterior cingulate activation included bilateral BA 24 and 32.

The parieto-temporo-occipital activations ($P < 0.001$) included the bilateral precuneus and superior parietal lobule (BA 7) extending into the superior parts of superior-middle occipital gyri (BA 19), the superior parts of right angular-supramarginal gyri (BA 39, 40), and the right inferior parietal lobule (BA 19).

The occipito-temporal, cerebellar, and subcortical activations included (right $P < 0.001$, left $P = 0.001$) bilateral middle parts of the lingual-fusiform (BA 19, 37) extending into the right inferior temporal and right inferior occipital (BA 19, 37) regions and the lateral and medial parts of cerebellar cortex. The subcortical activations ($P < 0.06$) included the bilateral thalamus (left > right, mediodorsal and in the vicinity of anterior thalamus) and the lentiform nucleus (left $P = 0.01$) extended into the caudate nucleus.

3.2.3. Increases in novel recall compared to trained recall

The significantly activated network in NR-TR included several brain regions (Table 5 and Fig. 4).

The prefrontal activation included the bilateral middle frontal/lateral orbitofrontal (right $P = 0.03$, and left $P = 0.01$, BA 10, 11) and the left middle frontal

Table 2
Deactivations in NR-RS

Region	BA	x, y, z	Z-score	P-value
Prefrontal cortex				
Medial superior frontal g	8/6 dx	8, 26, 52	5.03	0.001
	8/6 sin	−14, 28, 48	4.75	0.003
	8/9	4, 42, 36	6.75	0.000
	9 dx	6, 50, 24	6.50	0.000
	9 sin	−16, 48, 32	6.13	0.000
	9/10 sin	−10, 54, 28	6.06	0.000
	10/11	2, 52, −4	5.07	0.001
	10 sin	−6, 58, −4	5.15	0.001
Subfrontal g	24/25	0, 26, −4	5.05	0.000
Middle frontal g	8 sin	−32, 14, 44	4.12	0.041
Inferior frontal g	45 dx	48, 22, 16	4.02	0.057
Paracentral 1	5/31	0, −26, 44	4.38	0.016
Posterior cingulate cortex	23/31	0, −54, 28	6.11	0.000
Temporal and opercular-insular cortex				
Superior temporal g	22 dx	52, −48, 16	8.27	0.000
	22 sin	−50, −54, 8	9.04	0.000
	22 sin	−52, −34, 16	9.14	0.000
	38 dx	34, 10, −20	6.16	0.000
	38 sin	−32, 8, −28	4.92	0.002
Middle/superior temporal g	21/38 dx	38, −2, −16	5.81	0.000
Inferior temporal g	20 dx	52, −22, −28	6.93	0.000
	20 sin	−50, −24, −24	6.27	0.000
Posterior operculum/insula	13 dx[a]	44, −18, 0	8.91	0.000
	13 sin[a]	−40, −12, 8	9.04	0.000
Occipital cortex				
Cuneus	17/18 dx	10, −98, 4	6.41	0.000
Lingual g	18 sin	−18, −86, −12	7.82	0.000

[a] Refers to the Karolinska Computerized Brain Atlas. All P-values are corrected.

($P = 0.004$, BA 9, 46, $P = 0.05$, BA 10). There were also a left frontal opercular/anterior insular ($P = 0.06$, BA 45/49, 14) and small bilateral superior-middle frontal (right $P < 0.09$, left $P = 0.08$, BA 8 and left BA 6) activations.

The left anterior cingulate ($P = 0.006$) was activated in left BA 24 and 32.

The parieto-occipital, temporo-occipital, and infero-temporal activations (right $P = 0.003$, left $P < 0.001$) included the bilateral superior parietal (left > right, BA 7) and the inferior parietal BA 19 extending into the superior parts of angular gyrus (left > right, BA 39). The temporo-occipital and infero-temporal activations (right $P < 0.06$, left $P = 0.009$) included the left inferior occipital and the bilateral middle-inferior temporal BA 37, extending into left middle temporal region (BA 21).

The medial temporal and anterior occipito-temporal activations (right $P = 0.009$, left $P < 0.02$) included bilateral BA 35 and 36, right BA 34, left BA 27 and left BA 28.

3.2.4. Increases in trained recall compared to novel recall

In the TR-NR comparison, a network of several significantly activated regions were observed (Table 6 and Fig. 4).

The opercular, mid-posterior insular and supra-marginal activations (right $P < 0.001$, left $P < 0.001$) included the bilateral perisylvian parts of supramarginal BA 40, the temporo-parietal opercular (BA 43, 50), the mid-posterior insular (BA 13, 14), and the posterior opercular (BA 44) regions extending into the superior temporal regions (BA 41/42/22).

The occipital activations included the right middle lingual gyrus ($P = 0.02$, BA 19/37) and a small left posterior lingual region ($P = 0.08$, BA 18/19). In addition a left pre/postcentral region ($P = 0.06$) was observed.

3.2.5. Increases in novel recall compared to trained recall using the interaction approach

In general, the results using the interaction approach, were similar to the results described above (Table 7 and

Table 3
Activations and deactivations in TR

Activations in TR-RS Region	BA	x, y, z	Z-score	P-value
Prefrontal cortex				
Middle frontal/precentral g	6 dx	24, −8, 52	7.48	0.000
	6 dx	34, −4, 28	5.12	0.001
	6 sin	−42, −10, 36	4.79	0.003
Precentral g	6 sin	−60, −6, 12	4.54	0.008
Middle frontal g	10/46 sin	−38, 46, 24	4.49	0.010
	9/46 dx	28, 30, 24	5.24	0.000
Anterior insula	14 dx[a]	26, 12, 8	6.70	0.000
	14 sin[a]	−26, 10, 8	4.45	0.012
Anterior cingulate cortex	24/32 sin	−4, 10, 40	7.77	0.000
Mid/posterior cingulate cortex	23	8, −28, 20	4.02	0.057
Parieto-occipital cortex				
Precuneus	7 dx	14, −74, 44	10.28	0.000
	7/19 sin	−8, −80, 40	7.10	0.000
Middle occipital g	19 dx	34, −86, 16	5.68	0.000
Supramarginal/angular g	40/39 dx	34, −52, 36	5.81	0.000
Fusiform g	19/37 dx	33, −66, −12	5.11	0.001
Cerebellum		16, −60, −24	7.17	0.000
		32, −54, −28	5.49	0.000
		−26, −58, −28	6.76	0.000
Subcortical activations				
mediodorsal thalamus sin		−8, −16, 4	4.02	0.057
anterior putamen sin		−22, 6, 4	4.43	0.010

[a] Refers to the Karolinska Computerized Brain Atlas. The co-ordinates of the local maxima refer to the Talairach space (1988). All P-values are corrected for multiple non-independent comparisons.

Fig. 5). In brief, the prefrontal activations included the bilateral superior-middle frontal (right $P = 0.005$, left $P < 0.001$, and left $P = 0.05$, BA 10, 11, 46) and the left anterior cingulate (BA 24, 32) regions. The parieto-occipital activations (right $P = 0.02$, and left $P = 0.003$) included left superior parietal (BA 7) and the bilateral inferior parietal lobules (BA 39, 40, extending into right BA 19). The temporo-occipital activations (left $P = 0.10$, and $P = 0.08$) included the left middle-inferior temporal gyrus (BA 37, extending into BA 21). The medial temporal and anterior occipito-temporal activations (right $P = 0.03$, left $P = 0.08$) included the right BA 34 and the right hippocampus proper and the left regions included BA 28 and 36.

3.2.6. Increases in trained recall compared to novel recall using the interaction approach

The opercular, mid-posterior insular and supramarginal activations (right $P < 0.001$, left $P = 0.006$, and left $P = 0.008$) included the bilateral perisylvian parts of supramarginal BA 40, the temporo-parietal

opercular (BA 43, 50), the mid-posterior insular (BA 13, 14), and the posterior opercular (BA 44) regions extending into the superior temporal regions (B3A 41/42/22). The occipital activations included right middle lingual gyrus ($P = 0.09$, BA 19/37), cf. Table 8 and Fig. 5.

4. Discussion

The present PET study explores some functional aspects of the interaction between control/attentional processing and learning/memory. The results are interpreted in the light of several earlier behavioral and functional neuroimaging studies. These interpretations are considered preliminary.

4.1. The prefrontal cortex

The PFC is reciprocally connected to numerous cortical and subcortical structures, including visual, temporal, cingulate, retrosplenial, and posterior parietal
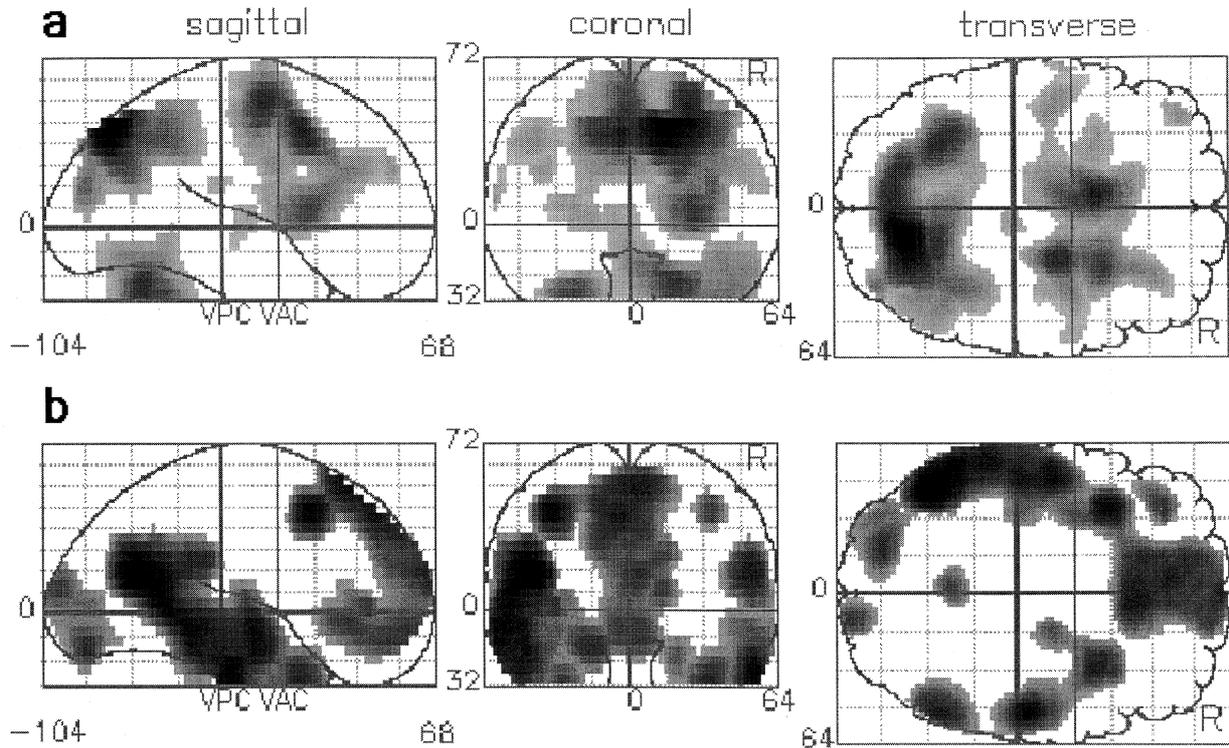
Fig. 3. The pattern of activation in (a) trained recall—reference state, and (b) reference state—trained recall (thresholded at $Z = 3.29$ or $P < 0.0005$).

cortices as well as the MTL and modiodorsal thalamus [29, 36]. The PFC has been implicated in working memory [27, 41, 44, 72], memory retrieval [22, 81, 82, 90], initiation and execution of complex mnemonic strategies [71, 94], search and retrieval processes [58], and the temporal organization of behavior [28, 29]. It has also been hypothesized that the PFC participates in the interaction between working memory and long-term memory [4, 5, 14], self-initiated behaviours [26, 68], and central executive functions [5, 17, 62, 85]. Functional neuroimaging studies of memory suggest an important role of the PFC in encoding and retrieval [8, 23, 63, 91]. The activation of the PFC may be related to retrieval strategies, planning, monitoring and other control processes during retrieval [81] and post-retrieval processing [76].

The reproduction of abstract designs from memory during NR and TR are internally driven and depends on retrieval strategies, attentional processing, executive or supervisory functions like initiation, monitoring, response selection, post-retrieval processing, and the temporal organization of self-initiated output, based on the information retrieved from long-term memory. In contrast, the externally driven reference state RS requires no explicit retrieval strategies or post-retrieval processing, and most likely less monitoring and response selection. In both the retrieval and the reference state, the externally oriented visuo-spatial attention and visuo-motor co-ordination are similar.

In NR-RS, the PFC activation pattern was bilateral, with a tendency for left lateralization in the middle frontal/frontopolar region (including the left BA 10/46). The prefrontal activations in TR-RS were similar, including a left middle frontal activation (BA 10/46). However, there was a right lateralization tendency in TR-RS. These differences were confirmed in the comparison NR-TR. Specifically, practice related decreases (Figs 4 and 5) were observed in the left dorsolateral PFC (BA 9, 46), left middle frontal/frontopolar (BA 10), and bilateral middle frontal/lateral orbitofrontal (BA 10, 11) regions. The changes were greater in the left compared to the right PFC and are consistent with previous PET findings suggesting an important role of the right PFC in retrieval monitoring and verification [81], as well as post-retrieval processing [76]. Retrieval during NR seems to be more dependent on bilateral processing compared to retrieval during TR. This may relate to a proposal [47] that the left middle frontal-frontal opercular region is more involved in the sequential image generation of visual-memory based imagery, while the homologous right area is more related to holistic aspects of this generation process. Another possibility is that the changes reflect re-encoding of the information reproduced from memory in NR, which would be consistent with the hemispheric encoding/retrieval asymmetry model (HERA) [8, 63, 91].

The data are consistent with similar practice related changes previously observed in a verbal learning [74] and a trial-and-error motor-sequence learning paradigm (with performance feedback), where the prefrontal BA 9,

Table 4
Deactivations in TR-RS. All *P*-values are corrected

Region	BA	*x, y, z*	*Z*-score	*P*-value
Prefrontal cortex				
Medial superior frontal g	8/6 dx	4, 26, 52	6.28	0.000
	8/6 sin	−12, 28, 48	5.69	0.000
	8/9	−6, 40, 40	6.27	0.000
	10	2, 62, 16	5.56	0.000
	10	−2, 52, −8	5.38	0.000
Subfrontal g	24/25	0, 28, −4	5.30	0.000
Middle frontal g	618 dx	34, 14, 44	5.37	0.000
	6/8 sin	−36, 12, 44	6.89	0.000
Inferior frontal g	45 sin	−34, 36, 0	5.24	0.000
Posterior cingulate cortex	23/31	−2, −56, 28	5.14	0.001
Right temporo-parietal cortex				
Angular/middle temporal g	39 dx	52, −60, 16	6.25	0.000
Superior/middle temporal g	38/21 dx	32, 8, −28	6.01	0.000
Inferior temporal g	20 dx	52, −22, −24	7.03	0.000
Uncus/hippocampal formation	28 dx	18, −12, −20	4.74	0.004
Left temporo-parietal cortex				
Superior temporal g	22/42 sin	−52, −38, 20	5.79	0.000
	38 sin	−30, 8, −28	4.97	0.001
Middle temporal g	21 sin	−50, −12, −8	6.57	0.000
	37 sin	−52, −54, 8	7.40	0.000
Angular/middle temporal g	39 sin	−42, −64, 16	8.07	0.000
Inferior/middle temporal g	21/37 sin	−56, −40, −8	6.80	0.000
Inferior temporal/fusiform g	20 sin	−50, −26, −20	6.24	0.000
Hippocampal formation		−34, −26, −8	4.41	0.014
Occipital cortex				
Cuneus	18 dx	12, −98, 12	5.19	0.000
Middle/inferior occipital g	18 sin	−30, −88, 4	4.41	0.014
Inferior occipital/fusiform g	19	−18, −84, −16	5.61	0.000

10, and 46 were active in the learning condition but not in the well practiced automatic condition [42]. In line with Cohen and O'Reilly]14], we suggest that, as automaticity develops, performance will gradually depend less on prefrontal support, and that the decreases in prefrontal activity reflect a decreasing dependence on controlled processing. In addition, we suggest that free recall is dependent on bilateral PFC processing, in particular non-automatic free recall.

In addition, there were bilateral frontal eye field (FEF, BA 6, 8) activations in both NR and TR. The FEFs have been associated with visual attention and visually guided behavior [51, 57, 61], and a network consisting of the FEF, the ACC, and dorsolateral PFC have been implicated in top-down-search and attention shifting [46]. The activity of the FEFs were greater in NR than in TR.

4.2. The cingulate cortex

In many functional imaging studies in which the dorsolateral PFC is activated, there is a parallel activation of the ACC [42]. This suggests a close functional relationship between the ACC and the PFC. There are also functional neuroimaging data indicating that the dorsolateral PFC and the ACC co-operatively subserve executive aspects of working memory [17]. Furthermore, the ACC may have an important functional role in the attention system [73] supporting selection among competing complex contingencies, on-line performance monitoring, error detection, selective attention [11, 15, 20, 66, 67], and in conjunction with the PFC and the FEF, attention shifting and top-down-search [46]. The mid-cingulate region has been associated with suppression of inappropriate responses during self-paced tasks [32, 33] and the posterior cingulate cortex has been related to sensory evaluative functions and visuo-spatial awareness [93].

The ACC was activated in both NR and TR, consistent with its suggested role in attention, performance monitoring, and top-down internal search. The mid-posterior cingulate was activated in NR-RS but not in TR-RS, perhaps reflecting a greater need to suppress task-irrelevant responses in NR compared to TR. The activity in

Table 5
Local maxima of significant activation in NR-TR, listed as local Z-maxima

Activations in NR-TR Region	BA	x, y, z	Z-score	P-value
Superior/middle frontal g	6 dx	22, 4, 36	3.93	0.077
	6 sin	−26, −4, 44	3.94	0.075
	10/11 dx	22, 40, −12	4.55	0.008
	10 dx	24, 38, 0	3.96	0.071
	10/11 sin	−18, 44, −12	4.94	0.001
Middle frontal g	10 sin	−34, 52, 20	4.09	0.045
	9/45 sin	−44, 22, 28	4.54	0.008
	11 sin	−18, 28, −20	4.08	0.046
Anterior insula	14 sin[a]	−28, 24, 16	4.09	0.045
Frontal operculum	44 sin	−32, 6, 32	4.06	0.051
Anterior cingulate cortex	24/32 sin	−8, 20, 36	5.07	0.001
	24/32 sin	−14, 28, 20	4.31	0.020
Parieto-occipital cortex				
Superior/inferior parietal 1	7/40/19 dx	40, −66, 44	4.21	0.029
	7/40/19 sin	−38, −66, 40	5.23	0.000
Inferior parietal 1	39/19 dx	36, −72, 28	4.79	0.003
Angular g	39 sin	−36, −64, 36	5.23	0.000
Angular/middle temporal g	39 sin	−30, −48, 28	4.98	0.001
Occipito-infero-temporal cortex				
Inferior temporal/fusiform g	37 dx	54, −48, −20	4.13	0.040
	19/37 sin	−54, −64, −16	4.33	0.018
Inferior temporal g	19/37 sin	−46, −76, −20	4.14	0.037
Medial temporal cortex				
Parahippocampal g	28/34 dx	20, −12, −28	5.26	0.000
	36 dx	30, −28,20	4.85	0.002
Parahippocampal/fusiform g	36 sin	−34, −28, −20	5.15	0.001

[a] Refers to the Karolinska Computerized Brain Atlas. The co-ordinates of the local maxima refer to the Talairach space (1988). All P-values are corrected for multiple non-independent comparisons.

ACC was greater in NR compared to TR (Figs 4 and 6). Similar practice related changes in the ACC have previously been observed [42, 74]. This is consistent with the notion of a gradual development of automaticity, i.e., a decreasing demand for attentional and different prefrontal control processes [13, 14, 79]. The dynamic changes paralleled each other in the PFC and the ACC, lending further support to the observation of a close functional relationship between activations in the PFC and ACC [42] and the suggestion that both the dorsolateral PFC and the ACC subserve executive aspects of working memory [17].

4.3. The occipito-parietal cortex

The posterior parietal cortex (PPC) has been implicated in memory function and parietal regions have been activated in both verbal and non-verbal memory retrieval [9, 23] indicating a general role in retrieval. The PPC in co-operation with the PFC has been related to visuo-spatial attention/cognition [19], 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 [22]. In addition, the inferior parietal lobule has been associated with the representation of spatial relations between different segments of complex visual designs [47].

In NR-RS, the precuneus, the superior parietal, and the superior parts of inferior parietal and superior-middle occipital regions were activated bilaterally. Similar, but more medial and right lateralized, activations were observed in TR-RS. During recall, the subjects were engaged in internally generated complex responses, i.e., visual-memory based image generation, demanding response selection, focused and sustained visuo-spatial attention, as well as working memory resources relating to the visuo-spatial sketchpad [5]. Both visuo-spatial attention and visuo-spatial sketchpad functions have
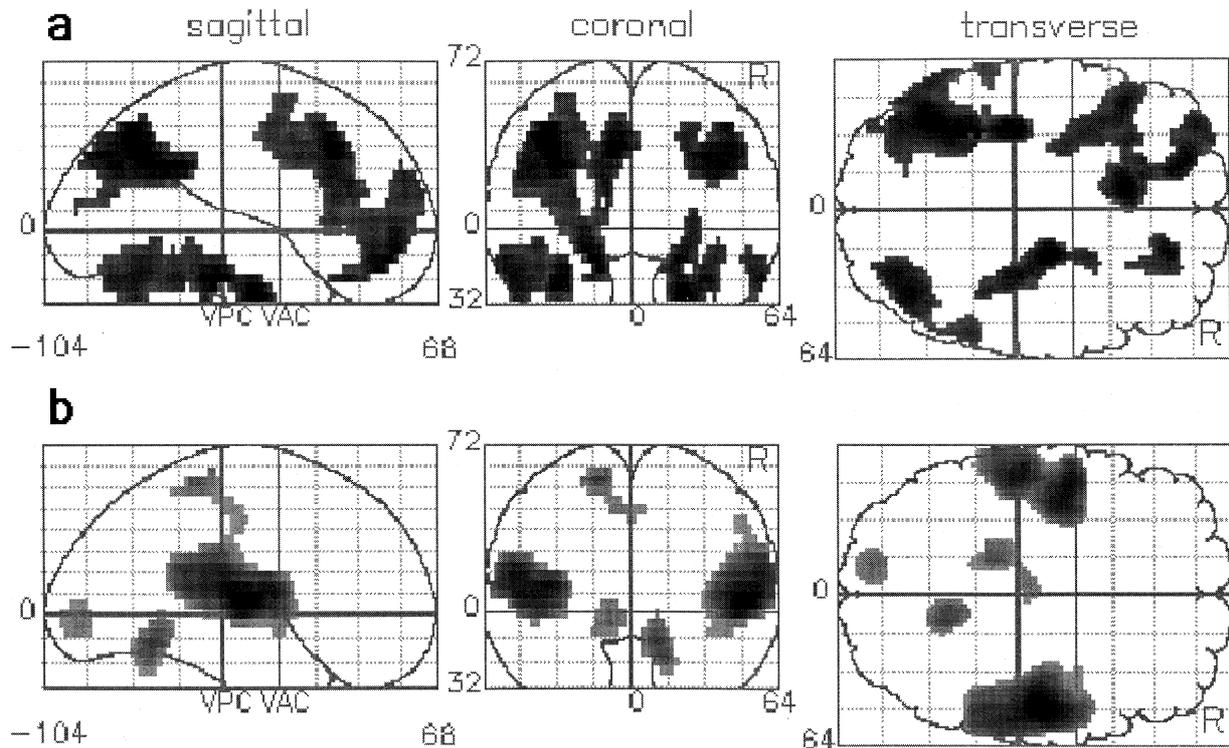
Fig. 4. Practice related changes seen in (a) novel recall—trained recall, and (b) trained recall—novel recall (thresholded at $Z = 3.29$ or $P \leqslant 0.0005$).

Table 6
Activations in TR-NR

Region	BA	x, y, z	Z-score	P-value
Posterior insular operculum	13/16/50[a] dx	−38, −8, 12	5.82	0.000
	13/16/50[a] sin	−46, −4, 8	5.77	0.000
Superior parietal/postcentral	5/7 sin	−16, −38, 56	4.35	0.017
Superior temporal g	41/42/22 dx	48, −18, 4	6.88	0.000
Occipital cortex	41/42/22 sin	−52, −26, 16	5.68	0.000
Lingual g[a]	18/19 dx	10, −56, −12	4.56	0.007
Lingual g	18 sin	−12, −88, −4	3.83	0.106

[a] Refers to the Karolinska Computerized Brain Atlas. All P-values are corrected.

been associated with activity in the PPC [9, 41, 66, 72, 73]. The PPC activations, in particular the activation of the precuneus, are consistent with the use of visual imagery as a retrieval strategy. Confirming the tendency for right lateralization in TR, practice related decreases were greater in the left than the right superior-inferior parietal areas. In other words, the right posterior parietal region continued to be active also after practice (Figs 3 and 7). This is consistent with lesion and functional imaging data indicating a right lateralization of the visuo-spatial attention network [61, 66, 73].

4.4. The occipito-temporal cortex

Functionally the visual system has been divided into two interacting processing pathways, the spatially-oriented dorsal or occipito-parietal stream, and the object-oriented ventral or occipito-temporal stream [92]. The occipito-parietal and the occipito-temporal processing networks were activated in both NR and TR.

The infero-temporal cortex projects to several structures outside the visual cortex, including the PFC and MTL [88]. Experimental evidence indicate that the occi-

Table 7
Local maxima of significant activation when comparing NR with TR, using the interaction approach, listed as local Z-maxima

Activations in [NR-RS1]-[TR-RS2]

Region	BA	x, y, z	Z-score	P-value
Superior/middle frontal g	10/46 dx	24, 40, 4	4.95	0.001
	10/11 dx	16, 40, −12	4.57	0.007
	10 sin	−22, 46, 0	4.81	0.002
	10/46 sin	−34, 52, 20	4.14	0.037
Anterior cingulate cortex	24/32 sin	−12, 20, 32	5.55	0.000
	24/32 sin	−14, 28, 20	5.53	0.000
	24/32 sin	−18, 24, 0	5.00	0.001
Parieto-occipital cortex				
Superior/inferior parietal 1	7/40 sin	−38, −62, 28	3.96	0.068
Inferior parietal 1/Angular g	39 dx	44, −70, 32	4.58	0.007
	39 sin	−38, −62, 28	4.71	0.004
Medial temporal cortex				
Parahippocampal g	28/34 dx	20, −12, −28	4.93	0.001
	36 sin	−32, −26, −20	4.18	0.031
Occipito-temporal and infero-temporal cortex				
Fusiform g	37 sin	−56, −60, −16	3.97	0.064
Inferior temporal g	20/37 sin	−56, −36, −12	3.86	0.094

[a] Refers to the Karolinska Computerized Brain Atlas. The co-ordinates refer to the Talairach space (1988). All P-values are corrected for multiple non-independent comparisons.

Table 8
Activations in [TR-RS2]—[NR-RS1]

Region	BA	x, y, z	Z-score	P-value
Posterior insular operculum	13/16/50[a] sin	−38, −10, 12	5.04	0.001
	13/16/50[a] sin	−46, −4, 8	5.77	0.000
Superior temporal g	41/42/22 dx	48, −16, 4	6.22	0.000
	22 dx	52, −36, 16	5.60	0.000
	41/42/22 sin	−52, −26, 16	5.33	0.000
Inferior parietal 1	40 dx	46, −20, 40	3.97	0.065
	40 sin	−46, −30, 44	4.00	0.058
Lingual g[a]	18/19 dx	12, −58, −12	3.84	0.101

[a] Refers to the Karolinska Computerized Brain Atlas. All P-values are corrected.

pito-temporal route is involved in object recognition [92] and that the inferior and middle temporal cortex participates in both visual perception and visual memory function [47, 54, 55, 88]. Electrophysiological studies indicate that the response patterns of inferior temporal neurons in adult monkey can change as the result of training [77, 88]. Furthermore, it has been suggested that the input from the MTL to the inferior temporal cortex is of critical importance for learning and maintaining non-consolidated representations [55, 77].

The infero-temporal and occipito-temporal regions were activated bilaterally in NR-RS, consistent with the role of these regions in the representation of complex visual patterns and visual memory function. Similar regions, less pronounced and with a tendency for right lateralization were activated in TR-RS. In contrast, the right mid lingual/fusiform activation was more pronounced in TR-RS. Consistently, increased activation in NR compared to TR were seen in the left inferior temporal/inferior occipital, the right inferior temporal
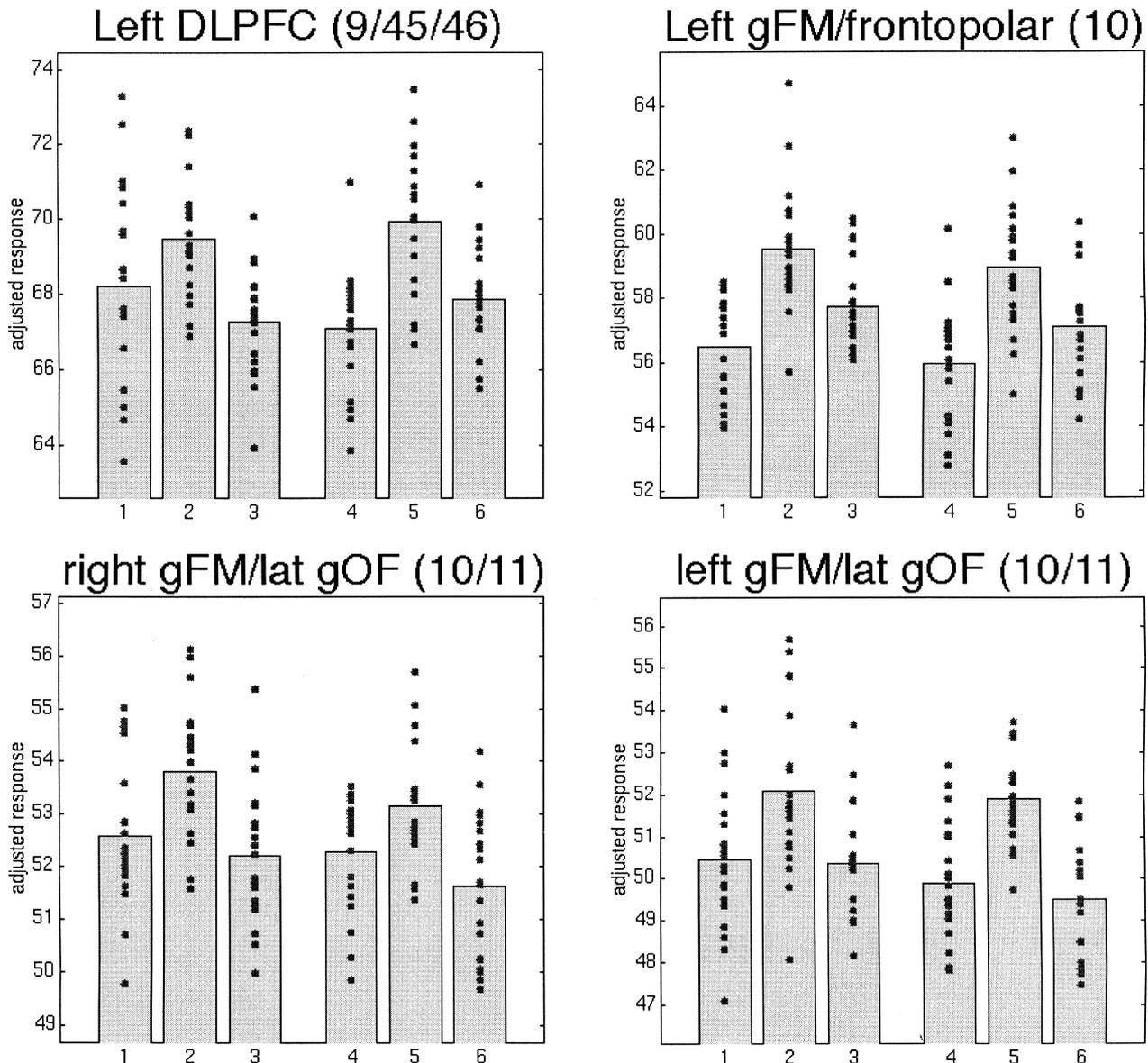
Fig. 5. The adjusted activity in the prefrontal cortex as it varies over the different states in the two blocks (see Fig. 1c for the basic experimental paradigm). The relevant Brodmann areas are given in parenthesis, DLPFC = dorsolateral prefrontal cortex, gFM = middle frontal gyrus, lat gOF = lateral orbitofrontal region. 1–3 = first block, 4–6 = second block. 1, 4 = Rd, 2, 5 = NR, 3, 6 = TR.

region (left > right), and the right occipito-temporal region (BA 18/19) in TR-NR. The increase of activity in the right mid occipito-temporal region, in TR, may indicate more fully developed visual representations of the abstract designs.

4.5. The anterior insular/frontal opercular cortex

Almost all of the cortical and subcortical connections of the insula are reciprocal. The anterior insular connections include visual inferotemporal, temporopolar, perihippocampal cortices, and mediodorsal thalamic nuclei. The anterior and mid cingulate cortices connect

reciprocally most prominently to the mid portion of the insular cortex. There are also widespread intrainsular connections which interconnect the various sectors of the insular paralimbic regions [53]. A visual representation has been described in the anterior insula, and the insula has been hypothesized to have a role in learning and memory [53].

The anterior insula and frontal operculum were activated bilaterally in NR-RS, while these activations were light lateralized in TR-RS. The left anterior insula/frontal operculum (Fig. 6) was more active in NR than TR. This is consistent with the known anatomical connections of the insular cortex. Specifically, the left anterior insula

left ACC (24/32)
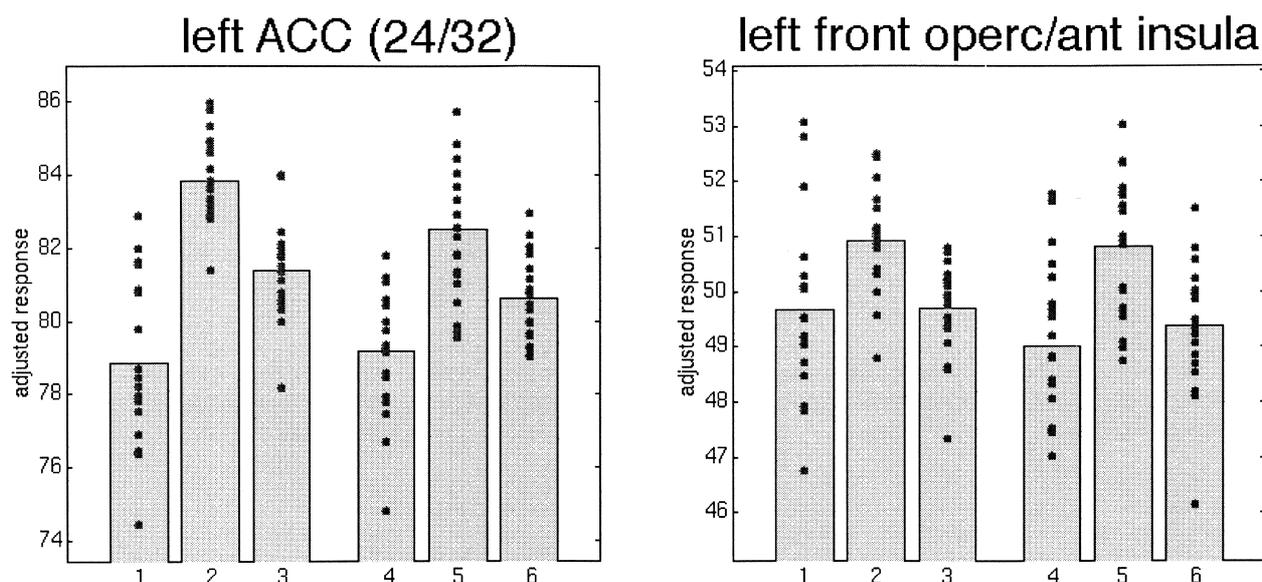

left front operc/ant insula

Fig. 6. The adjusted activity in the left anterior cingulate (ACC) and left anterior insular-frontal opercular cortex (front operc/ant insula) as it varies over the different states in the two blocks. The relevant Brodmann areas are given in parenthesis. 1–3 = first block, 4–6 = second block. 1, 4 = RS, 2, 5 = NR, 3, 6 = TR.
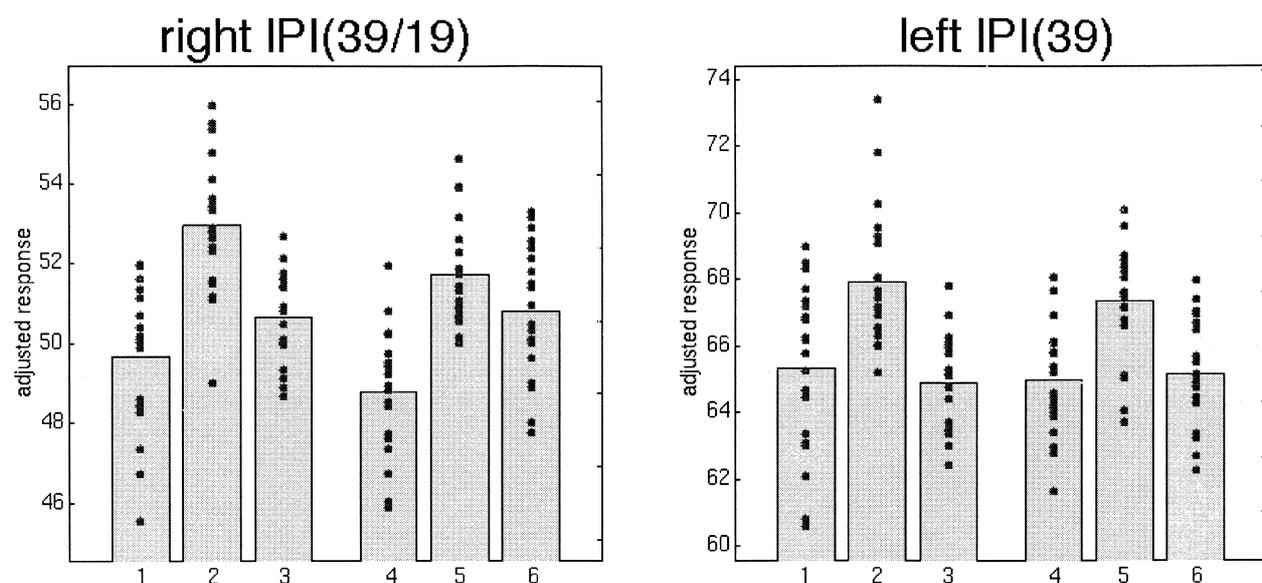
right IPI(39/19)

left IPI(39)

Fig. 7. The adjusted activity in the posterior parietal cortex as it varies over the different states in the two blocks. The relevant Brodmann areas are given in parenthesis, lPI = inferior parietal lobule. 1–3 = first block, 4–6 = second block. 1, 4 = RS, 2, 5 = NR, 3, 6 = TR.

is connected to the left anterior cingulate, left medial temporal, and left infero-temporal regions, all of which were more active in NR compared to TR.

4.6. The medial temporal lobe

The MTL memory sytem may subserve conjunctive learning, i.e., the binding of distributed representations supported or registered in different neocortical association areas, and it has been suggested that the MTL has

an important role in the rapid acquisition of knowledge for long-term integrative learning, the creation of flexible relational representations, and memory consolidation [21, 50, 59, 83, 89]. The fact that memory deficits are more severe when the parahippocampal regions are included in experimentally induced MTL lesions provide evidence indicating that the parahippocampal cortex support memory processes independent of the function of the hippocampus proper [98]. This underlines the importance of a multifunctional perspective on the MTL [30, 31,

91]. For example, the parahippocampal cortex has been related to visuo-spatial memory function [86] and the retrieval of object-location conjunctions [65]. However, the precise role of the MTL and the different sub-regions of the MTL in information processing, learning, memory consolidation, and retrieval are not known [23, 60, 83, 84, 91].

The MTL network may serve as a convergence zone, rapidly storing arbitrary associations or conjunctions of information, binding different distributed neocortical representations active at the time of encoding. It is unlikely that the MTL store all of the detailed information in a memory trace. Instead, the MTL may store a retrieval key or pointer, so-called chunking [95]. The rapid synaptic plasticity of the MTL may be necessary for the encoding of retrieval conjunctions, which support the retrieval and initial stabilization of distributed dynamic neocortical states (i.e., the quasi-stable or transiently stable neuronal firing pattern), representing memory traces, during retrieval. Retrieval may initially depend on a process of neocortical-MTL interaction, in which prefrontal regions initiate internal search, support retrieval strategies, as well as monitoring, control, and post-retrieval processing. This is consistent with functional neuroimaging studies indicating that declarative or episodic memory retrieval is subserved by networks of interacting brain regions, including the PFC, the ACC, and the PPC [23, 52, 91] as well as the MTL [30, 65, 69].

It has been suggested that the interaction between the MTL and the neocortex is dynamic, changing as a function of repeated activations, i.e., repeated learning or encoding [14, 60, 83, 84], representing the dynamic consequence of repeated information processing and network plasticity [69]. Interestingly, artificial neural network models of long-term memory reorganization indicate the possibility and importance of a dynamic relationship between the neocortex and the MTL. In these models, long-term memory reorganization occur as a consequence of repeated activations of the memory representations [2, 50, 75].

We have previously reported that the MTL regions were active in NR (right > left) but not in TR [69]. Consistent with the suggested dynamic relationship between the neocortex and the MTL, the activity of the MTL is lower in the well-practiced TR state compared to the less practiced NR state [69]. This indicates an inverse relation between the strength of encoding and the activation of the MTL during retrieval [52]. Recently, similar results were reported using an episodic verbal retrieval task. In this study, the left MTL was more active in the less practiced memory state compared to the well-practiced (repeated encoding) memory state [56]. These results were re-confirmed in the present report, using the interaction approach.

Interestingly, Cohen and O'Reilly [14] have proposed that the role of the MTL and the PFC changes during learning. They suggest that the PFC and the MTL are more active in the novel untrained state compared to the trained state. The PFC, because of the greater dependence on controlled processing (in co-operation with the ACC), actively supporting task-relevant processing, performance monitoring, and inhibiting task-irrelevant processing. The MTL memory system, because of the greater dependence on rapid learning, binding, and stabilization of distributed representations in the neocortex. Furthermore, they suggest that, as a result of practice, the performance of a task becomes less dependent on the MTL memory system and the attentional/working memory resources of the PFC, and we would like to add the ACC and PPC.

4.7. Subcortical activations

Medial diencephalic damage to the anterior or mediodorsal thalamus or the mammillary bodies is sufficient to cause amnesia [49, 98]. The mammillary bodies receives afferent projections from the hippocampal formation via fornix and sends efferent projections to the anterior thalamic nuclei via the mamillothalamic tract. There is also direct projections from the MTL to the anterior and mediodorsal thalamus [98]. In addition, the mediodorsal thalamus has strong anatomical connections with the PFC [29, 37]. Important common projection targets of the anterior/mediodorsal thalamus, and the MTL include venteromedial and dorsolateral PFC. This allows for interaction between the anterior/mediodorsal thalamus and the MTL in establishing long-term memory and, through the PFC-projections, the temporal organization of behavior at the time of encoding and retrieval [98]. Consistent with the important role of these structures in long-term memory, there were bilateral activation in the vicinity of the anterior and mediodorsal thalamus in both NR and TR, and bilateral activation of the mammillary bodies in NR-RS.

4.8. The cerebellum

The cerebellum may be an essential node in networks subserving cognition, learning, and memory [78]. Functional neuroimaging data are consistent with this suggestion [9]. Neuroanatomical data indicate that the associative and paralimbic cortical regions are recurrently connected to the cerebellum. This cerebro-cerebellar system include for example PFC, PPC and parastriate visual association areas, temporal and cingulate cortices, as well as the MTL and the mammillary bodies [78]. Consistent with the role of cerebellum in memory retrieval, the cerebellum showed bilateral activations of in both NR-RS and TR-RS.

4.9. Deactivations and inhibitory attentional modulation

During an attention demanding task it is functional to facilitate task-relevant and suppress task-irrelevant processing. Deactivations may reflect suppression of neural activity in task-irrelevant modalities [39, 42] or gating of task-irrelevant information [12]. In a visual processing task, Haxby et al. [39] observed deactivations including the auditory, the perisylvian inferior parietal, the mid-posterior cingulate, and the posterior insular areas. Similar deactivations were observed in a visuomotor task and in addition the medial frontal-orbitofrontal and the temporopolar regions were deactivated [34]. Very similar patterns of deactivation have been observed in other attention and working memory demanding tasks [6, 16, 35, 42]. A similar pattern of deactivation was also observed in NR and TR (Table 2, 4, and Figs 2b, 3b, and 8).

The interpretation, of at least parts of this deactivation pattern, as reflecting top-down attentional inhibitory modulation of task-irrelevant processing is consistent with the results of a recent meta-analysis indicating that rCBF decreases in task-irrelevant modalities during visual information processing include primary and association auditory, posterior opercular-insular, as well as perisylvian inferior parietal regions [80]. In a recent PET study, we focused on the question of top-down attentional facilitation of task-relevant and suppression of task-irrelevant processing [33]. The results indicate that both facilitatory modulation of task-relevant and suppressive modulation of task-irrelevant processing are important for the performance of attention and working memory demanding tasks.

Most likely, the need for attentional suppression is greater during novel recall compared to trained recall, indicating a higher degree of automaticity in TR. Based on this, we expected a pattern of deactivation in NR-TR similar to the one described above. In fact, the complete deactivation pattern described in the metanalysis of Schulman et al. [80] is reproduced in NR-TR (Table 6, and Figs 4b and 8).

4.10. Functional neuroimaging and learning related effects

One problem in the study of learning processes is that learning related changes may parallel non-specific time effects not necessarily related to learning. There are several ways of handling this problem. One strategy for separating learning from non-specific time effects is to explicitly model the non-specific effects, i.e., to incorporate time as a linear or non-linear confounding covariate in the statistical model. To the first order of approximation, it may be hypothesized that the non-specific time effects are monotone and sufficiently well approximated by a linear confound or possibly non-linear of low polynomial order. An alternative strategy is to use an interaction approach, i.e., learning effects are assessed with an interaction contrast in the general linear model. This approach relates data from a state of interest to data from a reference state that is collected in temporal proximity to the state of interest. This depends on the assumption that the non-specific time effects influences both the state of interest and the reference state approximately equal. In general this may not be the case (e.g., the task of interest may be very much less boring compared to a simple reference task etc.). In addition, learning related
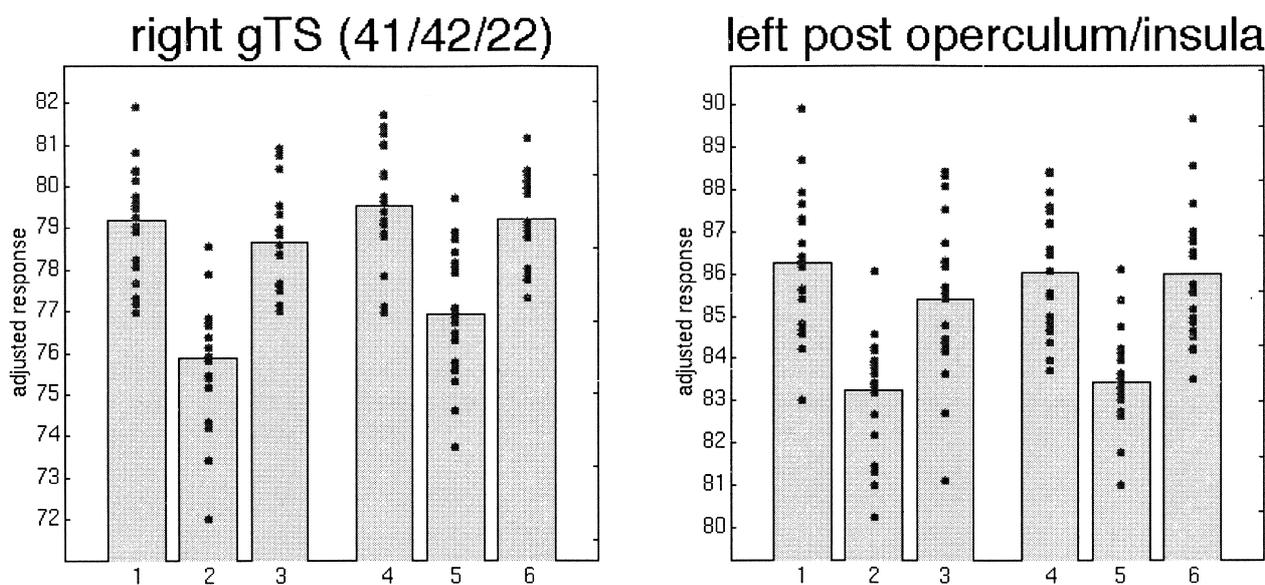

Fig. 8. The adjusted activity in the auditory and posterior insular-opercular cortex as it varies over the different states in the two blocks. The effects were bilateral. The relevant Brodmann areas are given in parenthesis, gTS = superior temporal gyrus, post = posterior. 1–3 = first block, 4–6 = second block. 1, 4 = RS, 2, 5 = NR, 3, 6 = TR.

effects of interest may also affect the reference state and would thus disappear in the interaction contrast.

Our experimental approach was based on the logic described by Raichle et al. [74], i.e., the introduction novel material of the same kind after the first learning block causes reactivation of the regions that showed practice related effects in the first block. This is illustrated in Figs 5–8. Specifically, all local extrema in the NR/TR comparison showed the same general pattern of activation over the two blocks, i.e., the changes seen in the first block were replicated in the second block (there were no significant differences between the NR/TR comparison from the first and second block, $P > 0.6$).

We modified the PET paradigm of Raichle et al. [74] to include two full repetitions of the basic experimental block. This allowed us to model non-specific approximately linear monotone time effects and block repetition as confounding covariates in the general linear model. Our paradigm is not optimized for an interaction approach, but allowed also for this approach. Overall the two approaches yielded similar results (Table 7) with three notable exceptions. Using the linear confound approach there were practice related effects (NR-TR) in the FEF, left anterior insula/frontal operculum, and bilateral inferotemporal/occipitotemporal. Using the interaction approach, these regions except the left inferotemporal/occipito-temporal were absent. One possibility is that this reflects non-linear non-specific time effects in these regions that are not sufficiently well-modeled with the linear confound approach. On the other hand, differentiating the reference state RS into RS1 and RS2 to use the interaction contrast may decrease the signal to noise, thus reducing the detection sensitivity. A third possibility, is that the interaction approach controls for some aspects of procedural or other forms of learning that also affects the reference state.

A second problem in the study of learning related effects is that learning or practice has effects on the performance of a task. There are several ways to control for performance differences. One approach is to use prompted or time-scheduled responses, i.e., controlling the number of responses during scanning. This usually implies that the subjects, after learning or practice, spend less time engaged in task relevant processing and there is an increased risk that the subjects become engaged in task irrelevant processing. Another approach is to try to control the time spent in task relevant processing, which may imply a greater number of responses. We chose the later strategy, using a free recall paradigm in which the subjects were fully engaged in task relevant processing during the whole scanning period. As a consequence, the subjects reproduced more designs during TR than in NR. In order to test if there were brain regions that correlated with the number of designs reproduced in NR and TR, respectively, during the scanning interval, we used this behavioral measure as a covariate of interest. Positive correlations, in NR, were observed in motor regions (light precentral gyrus BA 4/6, [52,4,12], $Z = 4.33$, $P = 0.05$, right lentiform nucleus, [20, −6, −4], $Z = 3.80$, $P = 0.28$), a low-level visual area (right inferior occipital region, BA 18/19, [40, −86, −16], $Z = 3.59$, $P = 0.48$), and the lower part of the left inferior parietal region just superior to the Sylvian fissure (BA 40, [−40, −38, 24], $Z = 4.25$, $P = 0.06$). In TR, positive correlations were only observed in the right inferior frontal region (BA 47, [44,22, −4], $Z = 3.99$, $P = 0.19$). All the other positive correlations in NR or TR corresponded to P-values $\geqslant 0.82$. There were no negative correlations in NR ($P \geqslant 0.9$). However, in TR, the right superior anterior insula/frontal operculum correlated negatively with performance ([28,10,20], $Z = 4.41$, $P = 0.04$; all other negative correlations $P \geqslant 0.88$).

In summary, there was very limited overlap between areas that correlated with performance and regions that showed practiced related changes. The only possible exception being the small posterior perisylvian region of the left inferior parietal lobule. However, this local maximum is almost 2 cm away from the closest local maximum in the activated left auditory/opercular-insular/perisylvian inferior parietal cluster in TR-NR. These results indicate that the major part of the practice related changes observed are not related to performance differences in a simple straightforward manner. In addition, the results indicate that the pattern of performance correlations changes as a function of learning.

Conclusions

In the present PET study we explore some functional aspects of the interaction between attentional/control and learning/memory processes. We used two different approaches to analyse learning related effects. The major part of the effects observed were independent of the method used. The results indicate that automaticity, i.e., a decreased dependence on attentional and working memory resources, develops as a consequence of practice. This corresponds to the practice related decreases of activity in the prefrontal, anterior cingulate, posterior parietal regions. In addition, the activity in the medial temporal regions decreased as a function of practice. This indicates an inverse relation between the strength of encoding and the activation of the medial temporal lobe during retrieval [52]. Furthermore, the pattern of practice related increases of activity in the auditory, posterior insular-opercular extending into perisylvian supramarginal cortex may reflect a lower degree of attentional suppression of task irrelevant processing, while the practice related increase in the right mid occipito-temporal region may indicate more fully developed representations of the abstract designs. In addition we suggest that free recall is dependent on bilateral prefrontal processing, in particular non-automatic free recall.

The present results confirm previous functional neuroimaging studies of memory retrieval indicating that recall is subserved by a network of interacting brain regions. Furthermore, our results indicate that some components of the neural network subserving free recall may have a dynamic role and that there is a functional restructuring of the information processing networks during the learning process.

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