Functional MRI of Cerebral Activation During Encoding and Retrieval of Words

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Abstract: The aims of the present study were to identify the cerebral structures associated with encoding and retrieval of verbal material. To circumvent the inherent disadvantages of the conventional block designs used in functional magnetic resonance imaging (fMRI), an event-related design compared activation related to randomly intermixed old and new words during recognition. To support the validity of results, both nonparametric analyses in regions of interest (ROI) and statistical parametric mapping (SPM 96) were used. Twelve healthy volunteers, ages 22–35 years, performed three tasks: intentional encoding of words, recognition of old (previously learned) words, and discrimination between words and nonwords, a task to control for visual input and motor output during recognition. Echo-planar magnetic resonance imaging of blood-level, oxygen-dependent, task-related changes was used to compare cerebral activity under active and resting conditions as well as to detect event-related activity within blocks of trials. Comparable results were obtained following nonparametric statistical analysis of selected ROI and SPM. Encoding of words was associated with increased activity in the left inferior frontal gyrus, including Broca's area and in the left parietal association cortex. Event-related data analysis revealed activation of the right medial frontal gyrus, the right anterior cingulate gyrus, and parietal association cortices during recognition of previously presented words. In the lexical decision task, words in comparison with nonwords were associated with activation of the left parietal association cortex. The right medial frontal gyrus, the right anterior cingulate gyrus, and the right parietal association cortex are likely to be involved in episodic memory functions during recognition of previously presented verbal material. The comparison of event-related activation occurring within one trial block instead of among several trial blocks may significantly improve the performance of memory studies. *Hum. Brain Mapping* 8:157–169, 1999. © 1999 Wiley-Liss, Inc.

Key words: verbal memory; episodic memory; word encoding; retrieval; event-related functional magnetic resonance imaging

INTRODUCTION

Brain structures involved in memory tasks

Recent investigations of task-related blood flow increases with positron emission tomography (PET)

and functional magnetic resonance imaging (fMRI) [Grasby et al., 1993; Andreasen et al., 1995b; Andreasen et al., 1996; Fletcher et al., 1997] have provided new information on structures involved in memory subfunctions such as encoding and retrieval. Depending on the tasks used, different brain areas were found to be activated during encoding: the left inferior prefrontal cortex [Demb et al., 1995], the left prefrontal cortex and the medial temporal lobes [Fletcher et al., 1995; Grady et al., 1995; Dolan and Fletcher, 1997], the left prefron-

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tal cortex and the retrosplenial area [Shallice et al., 1994], and the posterior hippocampal formation, parahippocampal gyrus, and lingual and fusiform gyri [Stern et al., 1996]. The left prefrontal cortex has been the most consistently reported region of activation for the different encoding tasks. The following brain areas were activated during retrieval: bilateral precuneus and right prefrontal cortex [Shallice et al., 1994; Fletcher et al., 1995], left prefrontal region, right frontal cortex, biparietal cortices, and cerebellum [Andreasen et al., 1995a]; anterior right prefrontal cortex [Buckner et al., 1995]; dorsolateral prefrontal cortex and anterior cingulate gyrus [Riddle et al., 1993]; prefrontal lobes [Schacter et al., 1996, 1997]; parahippocampal areas [Schacter et al., 1995]; and areas v1 and v2 of the occipital lobes [Le Bihan et al., 1993].

Event-related functional imaging

The level of cerebral activation following a single memory-related event usually ranges below the threshold detected by PET and fMRI. Consequently, the identification of task-related activity is generally performed by comparisons of signal intensities recorded for different trial blocks, i.e., task series with or without assumed cognitive activity in several subjects. However, it has been suggested that the implicit assumption of constant technical conditions and unchanged patient cognitive and mental states for consecutive trial blocks under alternating active and resting conditions might not be accurate. Buckner et al. [1996] and Josephs [1997] have reported fMRI results of serial single trial analyses. These authors note that activation maps for series of single tasks were similar to results obtained for individual trial blocks. It may, therefore, be possible to compare series of individual items, e.g., old vs. new words, within one memory task without requiring indirect comparisons with an assumed nonactive control task. This comparison should allow the identification of some, but not necessarily all, cerebral areas associated with episodic memory functions; other memory-related activities that are common for old and new words may not be detected in this comparison.

The aim of the present study was to identify brain regions associated with intentional encoding and those with retrieval using a verbal recognition task. For analysis of the encoding process, a conventional block design was used comparing the word encoding condition with a resting condition. However, to identify brain structures possibly associated with retrieval, an event-related, item-by-item approach was applied comparing activation associated with old and new items.

Initial event-related analyses of memory tasks have been performed very recently. Schacter et al. [1997] found significant activation of the anterior prefrontal, frontal opercular, medial parietal and visual cortex during true and false recognition when comparing with visual fixation in block and event-related study designs. However, they did not find differences in relation to item types. In an event-related paradigm, Buckner et al. [1998b] failed to find any significant difference between correct judgments to old and new words. In contrast, Buckner et al. [1998c] have reported increased activity in the left and right prefrontal cortex during task blocks with high retrieval success. In an object classification task, Buckner et al. [1998a] observed reduced activity of extrastriate visual cortex, inferotemporal cortex, and left dorsal prefrontal cortex for repeated in comparison with new items. Consequently, there is good evidence that old and new items might cause different activation during recognition in an episodic memory task; however, this has not yet been shown. Thus the major focus of the present study was to investigate whether recently learned words showed different cerebral activation in comparison with new words in a recognition task.

METHODS

Subjects

Twelve volunteers (7 males, 5 females, mean age = 26.5 years; SD = 3.93y range = 22–35y) were recruited from the student population and faculty of the University of Tübingen, Germany. The study was conducted in accordance with the Declaration of Helsinki and after approval of the local hospital ethics committee. Handedness was determined using the Edinburgh Handedness Inventory [Oldfield, 1971]. All subjects were right-handed, i.e., less than five common tasks were performed with the left hand (mean = 1.58, SD = 1.83). No subject had ever changed handedness. Medical and psychiatric histories confirmed that the respective subject suffered from neither physical nor major psychiatric disorders. One female subject had congenital idiopathic nystagmus, which was activated when one eye was closed.

Tasks

Three tasks were used consecutively to assess memory functions: (1) intentional encoding, consisting of the explicit learning of a 20-item word list (task 1), (2) recognition of 20 old words intermixed with 20 new words (task 2), and (3) discrimination of 20 words and

20 nonwords (lexical decision, task 3). Items of different types were randomly intermixed within tasks 2 and 3 (old vs. new; words vs. nonwords, respectively). The items were presented visually on a screen. The tasks consisted of three comparable 20-item word lists, which were balanced for imagery, concreteness, and meaningfulness [Baschek et al., 1977; Oldigs-Kerber et al., 1991]. Nonwords consisted of strings of random letters. To reach equivalent visual stimulation for targets and nontargets, the length of nonword strings was individually matched with words from the list used in the same task. Subjects indicated their decision by pressing a response button in their right hand once or twice. In addition to the number of button presses, the times to the first reactions were recorded. Reaction times for old and new items were not significantly different (old words: 1.33 ± 0.42 , new words 1.32 ± 0.39 mean $\pm$ SD, *t*-test, $P > 0.75$); consequently, these were not used in further analyses.

Task 1 was designed to identify the brain region associated with intentional encoding. The subjects were instructed to learn 20 words for later recognition. Subjects had to press once for every word. Implicit learning of 20 words during a lexical decision task, i.e., word vs. nonword discrimination, was investigated in a pilot study. However, the implicit encoding procedure did not yield a sufficient recognition performance to permit adequate assessment of retrieval during subsequent recognition trials.

A recognition task (task 2) was designed to identify brain areas associated with verbal retrieval. Subjects had to discriminate between old words, i.e., 20 words initially presented in task 1 and 20 new words from a second, comparable word list. The 40 items were presented in random order. Old words had to be indicated by pressing the response button once, new items by pressing twice. This task was designed for event-related, item-by-item analysis to test our major hypothesis that activations related to old and new words can be distinguished within one series of randomly intermixed items. In addition, activation during recognition was compared with activation under a resting condition (see below).

A lexical decision task (task 3), consisting of the discrimination of words and nonwords, was used as the control task for recognition task 2. A series of 20 new words (from a third list) and of 20 nonwords were presented in random order. The subjects distinguished between words and nonwords by pressing the response button once for words and twice for nonwords. The subjects were thus exposed to comparable visual stimuli and responded identically for tasks 2 and 3.

The lexical-decision task might control only for some of the processes that form part of the discrimination of verbal material, since visual input and motor output were comparable in both tasks. It cannot be used to receive activations caused by episodic memory processes by subtracting activations related to lexical decision from activations related to distinction of old and new words. The word-nonword discrimination reflects differences in semantic and lexical decisions, which might at least be partially relevant during discrimination of old and new words. However, activation found to be associated both with discrimination of old vs. new words and with the lexical decision task cannot be easily attributed to memory. Activation found in identical areas in both tasks might be related either to common cognitive processes in episodic or semantic memory function, but it cannot be excluded that such common activation might be related to visual input or conduction of the motor response. Due to this insecurity, we are reluctant to draw conclusions on those activations that are common in both tasks, even though it might be of major theoretical importance which areas might be activated commonly by these different tasks.

To exclude an influence of task performance on cerebral activation, all three tasks were designed to be easy, allowing all subjects to achieve nearly perfect results. Incorrect responses were rare: across the 12 subjects, the maximum number of errors summed across the three tasks was 2. All three tasks were performed in alternating blocks of resting and active conditions (4 plus 4 in task 1, 8 plus 8 in tasks 2 and 3). Every active condition block consisted of five items and, depending on the task, comprised either intermixed old and new words or nonwords and words in random order). Nonactive resting conditions consisted of five strings of seven X for all three tasks (no response was required). All items, i.e., words, nonwords, or strings of seven X, were presented for 10 sec each. Thus every active condition block was presented for 50 seconds and was preceded by a resting condition block of 50 sec duration. Presentation of task 1 required 400 sec, that of tasks 2 and 3, 800 sec each.

Task 3 was always performed first to prevent explicit learning of words during this task. Consequently, the experiments could not be balanced for time effects. However, this should not affect within task comparisons. The subjects were not informed of the fact that the control task was to be followed by a memory task. All subjects gave their prior consent that the details of the study design would be explained on completion of the experiment.

fMRI acquisition

The tasks were consecutively performed in the MR scanner. The subjects were placed in a supine position in the scanner with the head and proximal limb securely fixed to minimize involuntary movements. They were instructed to avoid any eye movements during all functional measurements. The words were projected on a transparent screen that could be observed in a mirror placed in front of the subject's head. All subjects were briefly informed that the purpose of the experiment was to assess cerebral blood flow during cognitive tasks. Whole brain fMRI was performed with a commercial 1.5 Tesla whole body tomograph using an axial multislice echo planar imaging sequence (EPI) with 27 axial slices (4 mm slice thickness, 1 mm gap, 64*64 matrix, field of view (FOV) 192*192 mm, echo time (TE) 46 msec, flip angle 90°, 150 msec acquisition time/slice. Slices were oriented axially. The total acquisition time for 27 slices covering the whole brain was 4.05 sec.

Task 1 was run in a series of 40 repetitive fMRI acquisitions. Task 2 and control task 3 were conducted in blocks of 80 repetitive fMRI measurements (picture presentation and repetition intervals: 10 sec). The acquisition period for each event consisting of the presentation and classification of an item (old or new words, nonwords or strings of seven x) was placed in the last 4.05 sec of each 10-sec presentation interval. Consequently, an EPI scan of the whole brain with 27 slices was acquired for each individual item. The delay between presentation and classification of a new item and item-related signal acquisition (i.e., 5.95 sec) was determined in accordance with McCarthy et al. [1994], who observed that cerebral activation occurred between 6 sec and 9 sec after task onset and declined within a similar period after task completion. We, therefore, assumed activation associated with the perception and classification of each item occurring at the onset of each presentation interval to be detectable at the end of the interval and to be completed prior to the onset of acquisition for the next item (i.e., 16 sec after onset of item presentation). The first acquisition of each block was excluded to prevent confounding by task changes. Data acquisition with double or triple frequency compared to the rate of image presentations might be useful to improve the fit of regressors used to model event-related responses for subsequent analyses (Buckner et al., 1998a,c; Josephs et al., 1997; Schacter et al., 1997). However, the procedure was not suitable for this study due to technical limitations represented by the number of acquisitions in a series processible during a 2-hr session. Two hours was the

maximum time period for the investigation accepted by the subjects.

A corresponding set of T1-weighted spin echo images (repetition time (TR) 600 msec, TE 12 msec with identical slice positions, slice thickness, and FOV) was acquired for the identification of anatomical regions. Anatomic and EPI images had the same orientation (parallel to the AC-PC line) and the same thickness to allow an overlay of EPI images on the anatomical templates. To control for involuntary head movements between individual measurements, anatomical images were repeated at the end of the tasks. In the presence of detected subject motion, the more appropriate set of anatomical images was used for the designation of anatomical regions. In addition, EPI image series were visually checked for possible motion during the scans. Volunteer movement was less than one pixel for all acquisitions.

Statistical analysis

The difference in activation by old and new words during recognition was expected to be small. Consequently, very high thresholds for statistical significance (e.g., $P < 0.001$ and additional Bonferroni correction) could not be assumed to allow the detection of minor activation differences. To allow detection of minor effects and at the same time to minimize the risk of false positive results, in this study a segmentation technique defining several regions of interest (ROI) was used. Nonparametric statistical procedures were subsequently applied for hypothesis testing, i.e., for the identification of memory-related cerebral activity. ROI-based analysis was chosen because it provides a simple tool that allows averaging signal intensities of specific ROI from different individuals. The nonparametric approach was preferred in the present study because the number of acquisitions available for comparison was low for some tasks, 16 vs. 16 acquisitions for encoding, or for item-by-item comparison of old or new words, respectively. Normal distributions of signal intensities, which are the basis for parametric data analysis, could, therefore, not be assumed. In addition, nonparametric tests are known to be more robust to outliers than parametric tests in the presence of small numbers of items. The disadvantage of a ROI-based approach is that activation can be identified only in areas that have a priori been delineated for hypothesis testing. Consequently, an additional analysis using statistical parametric mapping (SPM) [Friston, 1996] was performed for two reasons: (1) comparison of results with the nonparametric analysis in regions of interest, and (2) identification of additional active

brain areas during encoding and retrieval, which were not included in the ROI-based approach.

Segmentation

For individual evaluations, ROI were defined in each slice and drawn onto the axial T1-weighted images (see Fig. 1). Individual segmentation is an alternative strategy to spatial transformations of several brains onto a common template [Toga and Mazziotta, 1996; Frackowiak et al., 1997]. This strategy has been recommended for a priori hypothesis testing [Tzourio et al., 1997]. The method was chosen in the present study, because reasonable hypotheses regarding anatomy and psychological function could be formulated. ROI were selected to include regions possibly activated by memory or other aspects of the study tasks as, e.g., vision (striate and extrastriate occipital cortex), language comprehension (Wernicke's area and Broca's area), memory (orbitofrontal cortex, prefrontal cortex, anterior cingulate gyrus, parietal association cortex, hippocampus), and motor response (precentral gyrus, supplementary motor area, cerebellum [see Orrison, 1995; Kolb and Whishaw, 1996; Rosenzweig et al., 1996; Frackowiak et al., 1997]). All ROI were large enough to prevent a significant influence to be exerted by small movement artifacts on study results. ROI are depicted in Table I. Figure 1 depicts the segmentation of different brain areas in one subject. Anatomical landmarks described by Mai et al. [1997], Kretschmann and Weinrich [1996], and Talairach and Tournoux [1988] served as the basis for the designation of the ROI.

Nonparametric statistical analysis

In a first step, signal intensities observed for individual pixels during active blocks (tasks 1–3, i.e., learning, recognition, and lexical decision) were compared with signal intensities under the control conditions (presentation of X-strings) using nonparametric rank statistics (Wilcoxon U-test). This was performed individually for all pixels and every subject. Likewise, event-related analyses within active trial blocks were performed to compare the signal intensities associated with old and new words (task 2), or to compare signal intensities associated with words and those with nonwords (task 3). Individual pixels were assumed to be activated in the presence of signal intensities during active trial blocks with significantly greater intensities than those occurring during the control condition (Wilcoxon-Test $P < 0.01$). A similar assumption was made in the event-related analysis of old words associ-

ated with greater signal intensities than new words (or nonwords; tasks 2 and 3). The U-value determined as the threshold for statistical significance depended on the number of activated and control states used for the respective comparisons, i.e., 16 vs. 16 items for task 1, and for event-related analyses of tasks 2 and 3; 32 vs. 32 items for the comparison of active blocks and resting conditions in tasks 2 and 3. It should be noted that information on the absolute differences of signal intensities was not used for comparisons of signal intensities in this rank statistic. Consequently, the statistical analysis is relatively robust to outliers and thus avoids false positive results. In a next step, the number of activated pixels and the total number of pixels were counted for the segmented ROI in all 12 subjects. The proportion of activated pixels in relation to the total number of pixels in the respective ROI was used for further statistical analysis. Using nonparametric analysis of variance (ANOVA), it was determined for every task if the proportion of activated pixels varied for different ROI and different subjects (Friedman two-way nonparametric ANOVA). The proportion of activated pixels served as the dependent variable; ROI represented an independent within-subject factors; individual subjects represented an independent between-subject factor. The Friedman ANOVA assesses the presence of an effect of a variable, e.g., ROI on signal intensities without indicating which ROI cause this effect. In the presence of a significant global effect ($P < 0.001$), a secondary analysis compared the number of activated pixels for all subjects with the mean proportion of activated pixels for all regions in all subjects using Chi²-statistics (df = 1 and $P < 0.001$ for individual comparisons). The described secondary statistical comparison was chosen in accordance with the study hypotheses that activation is greater in some ROI than the average level of activation calculated for the total number of ROI. The usual posthoc test of Friedman nonparametric ANOVA to perform a comparison of activation of every ROI with that of every other ROI was less compatible with the outlined study hypothesis. The present procedure is highly conservative in that only the most activated regions reach significant differences when compared with the mean value calculated for all areas.

Statistical parametric mapping

A second analysis was performed using statistical parametric mapping (SPM 96) [Friston, 1996]. Individual subjects' functional images were corrected for motion and realigned using the first scan of each block of items as the reference. T1 weighted anatomical

Figure 1.

Sagittal scout image indicating slice positions and segmentation of brain areas in eight horizontal slices (3, 6, 9, 12, 15, 18, 21, 24) beginning with slice 3 (top row middle) and ending with slice 24 (bottom row right); numbers in the horizontal images indicate brain areas: 1,2 orbitofrontal cortex right and left (R,L); 3,4 anterior superior frontal gyrus R,L; 5,6 medial frontal gyrus R,L; 7,8 inferior frontal gyrus R,L; 9,10

Broca's region R,L; 11,12 precentral gyrus R,L; 13,14 supplementary motor area R,L; 15,16 superior temporal gyrus R,L; 17,18 anterior cingulate gyrus R,L; 19,20 caudate nucleus R,L; 21,22 putamen; 23,24 thalamus R,L; 25,26 hippocampus R,L; 27,28 primary visual cortex R,L; 29,30 extrastriate occipital cortex, 31,32 parietal association cortex R,L; 33,34 anterior cerebellum R,L; 37 cerebellar vermis.

images were coregistered to the mean of the corrected functional scans and aligned to the SPM-T1-template in the Talairach space. The calculated transformation matrix was applied to all functional images for spatial

normalisation. Finally, the functional images were smoothed with a 6 mm full-width, half-maximum (FWHM) Gaussian filter. Contrasts were calculated by applying a boxcar function without delay for compari-

TABLE I. Description and function of anatomical regions and fMRI activation in 12 subjects^a

Name of area ^b	Side L/R	Total number of pixels in the area, (mean $\pm$ SD)	Word encoding (task 1): block design: new words vs. baseline	Word recognition (task 2) block design: known and new words vs. baseline	Lexical decision (task 3) block design: words and nonwords vs. baseline	Word recognition (task 2) event-related analysis: known vs. new words	Lexical decision (task 3) event-related analysis: words vs. nonwords
Orbitofrontal cortex (1, 2)	L	347 $\pm$ 137	3.02 $\pm$ 4.03	1.36 $\pm$ 1.1	1.79 $\pm$ 1.38	0.74 $\pm$ 0.60	0.11 $\pm$ 0.21
	R	247 $\pm$ 115	1.62 $\pm$ 1.06	1.70 $\pm$ 1.32	3.49 $\pm$ 3.31	0.76 $\pm$ 0.94	0.09 $\pm$ 0.22
Anterior supe- rior frontal gyrus (3, 4)	L	788 $\pm$ 189	2.15 $\pm$ 1.89	2.63 $\pm$ 3.23	2.43 $\pm$ 1.73	0.86 $\pm$ 0.82	0.18 $\pm$ 0.27
	R	799 $\pm$ 191	1.87 $\pm$ 1.35	3.14 $\pm$ 4.02	3.46 $\pm$ 3.24	0.98 $\pm$ 0.71	0.29 $\pm$ 0.55
Medial frontal gyrus (5/6)	L	963 $\pm$ 179	3.20 $\pm$ 3.46	4.98 $\pm$ 3.74*	5.44 $\pm$ 3.2*	0.90 $\pm$ 0.70	0.26 $\pm$ 0.29
	R	875 $\pm$ 179	2.22 $\pm$ 1.75	5.89 $\pm$ 4.98*	6.19 $\pm$ 5.04*	1.27 $\pm$ 1.23*	0.19 $\pm$ 0.33
Inferior frontal gyrus (7/8)	L	41 $\pm$ 40	5.16 $\pm$ 7.98*	6.61 $\pm$ 5.46	3.35 $\pm$ 3.21	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
	R	33 $\pm$ 39	0.59 $\pm$ 1.11	6.23 $\pm$ 4.75	6.17 $\pm$ 4.38*	0.81 $\pm$ 1.20	0.34 $\pm$ 0.63
Broca's area of inferior frontal gyrus (9/10)	L	299 $\pm$ 72	4.69 $\pm$ 3.89*	4.38 $\pm$ 3.53	4.73 $\pm$ 3.07	0.48 $\pm$ 0.64	0.37 $\pm$ 0.49
	R	292 $\pm$ 65	2.03 $\pm$ 2.73	4.48 $\pm$ 4.22	6.16 $\pm$ 5.5*	0.93 $\pm$ 0.93	0.10 $\pm$ 0.19
Precentral gyrus (11/12)	L	578 $\pm$ 71	4.42 $\pm$ 2.89*	6.10 $\pm$ 3.33*	7.34 $\pm$ 3.85*	0.86 $\pm$ 0.49	0.17 $\pm$ 0.20
	R	638 $\pm$ 118	2.73 $\pm$ 1.93	3.61 $\pm$ 3.30	4.38 $\pm$ 3.66	1.17 $\pm$ 1.02	0.28 $\pm$ 0.40
Supplementary motor area (13/14)	L	378 $\pm$ 111	5.40 $\pm$ 3.69*	6.07 $\pm$ 4.21*	6.98 $\pm$ 4.09*	0.65 $\pm$ 0.59	0.23 $\pm$ 0.38
	R	361 $\pm$ 95	4.29 $\pm$ 3.36*	6.46 $\pm$ 6.25*	8.15 $\pm$ 3.83*	1.03 $\pm$ 0.68	0.19 $\pm$ 0.30
Superior tem- poral gyrus (15/16)	L	209 $\pm$ 51	3.15 $\pm$ 3.62	4.61 $\pm$ 5.12	4.90 $\pm$ 5.3	0.35 $\pm$ 0.63	0.59 $\pm$ 1.16
	R	235 $\pm$ 60	1.88 $\pm$ 1.91	4.46 $\pm$ 5.77	4.27 $\pm$ 6.29	0.97 $\pm$ 0.45	0.25 $\pm$ 0.58
Anterior cingu- late gyrus (17/18)	L	394 $\pm$ 84	1.71 $\pm$ 1.51	3.48 $\pm$ 2.41	3.32 $\pm$ 2.96	1.03 $\pm$ 0.91	0.15 $\pm$ 0.21
	R	364 $\pm$ 82	1.27 $\pm$ 1.33	4.14 $\pm$ 4.62	5.73 $\pm$ 3.86*	1.86 $\pm$ 1.70*	0.20 $\pm$ 0.31
Hippocampus (25/26)	L	135 $\pm$ 38	1.55 $\pm$ 1.37	0.97 $\pm$ 1.05	1.72 $\pm$ 2.1	0.73 $\pm$ 1.40	0.17 $\pm$ 0.57
	R	136 $\pm$ 36	1.93 $\pm$ 1.62	1.22 $\pm$ 1.6	1.73 $\pm$ 2.58	0.59 $\pm$ 0.89	0.00 $\pm$ 0.00
Primary visual cortex (27/28)	L	264 $\pm$ 58	3.32 $\pm$ 3.82	4.87 $\pm$ 5	3.59 $\pm$ 3.33	0.85 $\pm$ 0.62	0.09 $\pm$ 0.17
	R	283 $\pm$ 72	2.51 $\pm$ 2.48	5.58 $\pm$ 6.14*	4.27 $\pm$ 2.82	0.58 $\pm$ 0.43	0.12 $\pm$ 0.25
Extrastriate occipital cortex (29/30)	L	398 $\pm$ 182	2.94 $\pm$ 1.61	5.89 $\pm$ 4.43*	6.55 $\pm$ 4.35*	0.72 $\pm$ 0.50	0.31 $\pm$ 0.48
	R	422 $\pm$ 116	3.10 $\pm$ 2.64	5.84 $\pm$ 4.77*	5.92 $\pm$ 4.09*	0.81 $\pm$ 0.52	0.13 $\pm$ 0.24
Parietal associa- tion cortex (31/32)	L	1016 $\pm$ 160	3.53 $\pm$ 2.8*	6.82 $\pm$ 4.73*	5.00 $\pm$ 2.3*	1.35 $\pm$ 1.07*	0.52 $\pm$ 0.56*
	R	934 $\pm$ 148	2.56 $\pm$ 1.34	6.09 $\pm$ 5.08*	5.34 $\pm$ 5.34*	1.38 $\pm$ 1.15*	0.38 $\pm$ 0.51
Anterior cer- ebellum (33/34)	L	644 $\pm$ 131	2.37 $\pm$ 1.97	5.07 $\pm$ 4.78*	4.13 $\pm$ 4.07	1.04 $\pm$ 1.02	0.27 $\pm$ 0.39
	R	612 $\pm$ 128	2.54 $\pm$ 2	5.73 $\pm$ 6.65*	4.44 $\pm$ 3.44*	0.96 $\pm$ 0.84	0.22 $\pm$ 0.22

^a Figures in columns 4 to 8 represent the percentages of activated pixels (Wilcoxon test for individual pixels, $P < 0.01$), in 12 subjects (means $\pm$ SD) during different tasks, i.e., encoding (col. 4), recognition of words (cols. 5 and 7), and word nonword discrimination (cols. 6 and 8) depending on analytical strategy. Columns 4–6 represent the results of standard blocked design analysis, cols. 7 and 8 represent results of event-related, item-by-item analysis. Figures of blocked analyses in tasks 2 and 3 are based on comparisons of 32 vs. 32 acquisitions; all other analyses are based on comparisons of 16 vs. 16 items; U-values indicating significant activation of a pixel in Wilcoxon test vary with the numbers of acquisitions. Consequently, proportions of activated pixels cannot be directly compared between both groups of analyses.

^b Numbers in parens refer to positions in Figure 1. L = left; R = right.

* Proportion of activated pixel significantly increased in this area in comparison with mean proportion of activated pixels in all areas ($\text{Chi}^2 > 10.83$, $\text{df} = 1$, $P < 0.001$). To account for multiple testing, an individual P value of $P < 0.001$ was selected as threshold for statistical significance.

son between item types, as the hemodynamic latency is already considered in the measurement design. The scans were defined to the categories in the sequence of the appearance of the preceding stimuli in the trial. A high-pass filter of 200 sec was applied to eliminate low-frequency drifts, and scaling was used for global normalisation. Different acquisitions from one subject were treated as repetitions. The possibility of analysing event-related activation using SPM has only recently been described (i.e., after the performance of our first nonparametric analyses) [Josephs et al., 1997] and was not used in this study. The selected threshold for the detection of activation was $P < 0.01$, which corresponds to the level determined for the assessment of significant activation on a pixel-to-pixel basis in nonparametric analysis. In accordance with the latter analysis, clustering of activated pixels was not required. However, the nominal equivalence of thresholds does not ensure absolute comparability of analyses. A direct comparison of significance level and statistical power between the nonparametric ROI-based analysis and SPM is not feasible because both analyses are based on different statistical assumptions (e.g., regarding the distribution of signal intensities in individual pixels and the reference areas used for comparisons). As mentioned above, for theoretical and practical reasons, the nonparametric ROI-based approach to hypothesis testing was used in this study for the identification of brain structures involved in encoding and retrieval. However, similar results were obtained for both statistical analyses (see below).

RESULTS

Activation during encoding and retrieval

Table I presents an overview of significant activation observed in segmented brain areas and within different tasks following nonparametric analysis of the proportion of activated pixels in 12 subjects. The main focus of the present study consisted of the identification of brain areas activated during encoding and retrieval of verbal information. The results of the present study show: (1) an increased activity of the left inferior frontal gyrus, including the left Broca's area, and the left parietal association cortex during encoding of words (revealed by the comparison of signal intensities occurring during blocks of learning with resting conditions), and (2) the presence of increased activity of the right medial frontal gyrus, the right anterior cingulate gyrus, and both parietal association cortices during recognition of old compared with new words (revealed by event-related, item-by-item analysis ac-

cording to item type). The lexical decision task with similar answer conditions was associated with increased activity of the left association cortex only (when comparing activity associated with words and activity associated with nonwords in an identical event-related analysis, see Table I). These findings suggest that the right medial frontal gyrus, right anterior cingulate gyrus, and right parietal association cortex may be activated during retrieval from episodic memory. It might be possible that the activation of the left parietal association cortex is also related to memory processes that are commonly used in both tasks. There is some good electrophysiological evidence that the left parietal cortex is relevant for old-new discriminations (Rugg et al., 1995). However, due to the inherent limitations of the present design (concerning this issue), it cannot be excluded that the common activation of this area is a consequence of other shared parts of the task, i.e., visual input and/or motor output processing.

Increased activation of the extrastriate occipital cortices during tasks 2 and 3 (block-based comparison of old and new words with the resting condition strings of seven x, or comparison of nonwords and words with the resting condition) might be in agreement with the processing of the image content of the presented words. Activation of the left motor cortex and of both supplementary motor areas (in all three tasks) as well as of the anterior cerebellum (block-based analysis for tasks 2, 3) may well be associated with the required motor response.

Comparisons of nonparametric analysis and statistical parametric mapping

Nonparametric statistical calculations in segmented ROI and parametric analysis with SPM have provided similar results for all comparisons. Areas found to be activated on nonparametric data analysis in segmented ROI (Table I) were also observed to be activated with SPM (Fig. 2). This applies to the comparison of active blocks with the resting condition (old and new words vs. strings of seven x in task 2, general P value $P < 0.01$, no extent threshold; see Table I column 5 and Fig. 2a) and event-related, item-by-item comparisons of old and new words within active blocks in recognition task 2 (see Table 1 column 7 and Fig. 2b). The event-related analysis using both methods also showed significant activation of the parieto-occipital association cortex, right anterior cingulate gyrus, and of the right medial frontal cortex for old vs. new words (comparison of old vs. new words within task 2).

Figure 2.

Cortical projections of cerebral activation in 12 subjects during recognition (task 2) using different strategies of data analysis with SPM (from left to right: right lateral, left lateral, rostral, left medial and right medial view; SPM-Z-maps, $P < 0.01$, single voxels: $k = 1$, $n = 12$). First row (a): block trial analysis corresponding to column

5 in table 1: activation by old words and new words vs. baseline (strings of seven X), second row (b): item-by item comparison corresponding to column 7 in table 1: activation by old words vs. new words.

However, the anterior cingulate gyrus showed only partial activation on SPM.

From the inspection of SPM images, it might be speculated that parietal and medial parts of the parietal association cortex are independently activated. Different parts of the parietal association cortex have been related to different subfunctions, i.e., the medial part to mental imagery, the lateral part to more abstract semantic processing (see Fletcher et al., 1997). However, both were combined in the ROI approach to increase statistical power in the present study. Further investigations using an equivalent event-related approach might be useful to discriminate the different functions of both areas.

SPM also showed slightly more extended activation as well as small additional spots in the entire brain, which were not included among the possibly relevant ROI. However, the observed minor differences between the hypothesis-oriented, nonparametric data analysis in selected ROI and SPM analyses of the entire brain were not unexpected. They did not exert an influence on the most significant conclusions of this study. The equivalence of ROI-based, nonparametric analysis and SPM was confirmed for all comparisons described in Table I, but was not supported by additional figures due to limitations of place.

DISCUSSION

The major result of the present study is the observation of an increased activation of several brain areas by old in comparison with new words in the present study. To allow the reader to follow the usual sequence

of memory events, the results concerning encoding are presented before the more exciting results during recognition. Then, significant negative results and methodological issues are discussed.

Encoding

The observed activation of the left inferior frontal gyrus, including the left Broca's area, during encoding (block analysis) is in agreement with the known function of these structures in language detection and processing. Activation of the parietal association cortex might reflect high-order processing of information in this brain area. The fact that the extrastriate cortex was not sufficiently activated during encoding to reach significance in comparison with the resting condition during encoding might be attributed to the fact that many of the subjects had used these resting conditions for mental imagery or item repetition. This might have been less relevant during the resting conditions in the recognition paradigm, in which subjects waited for the next items to appear. Depending on the tasks used, the following brain areas were found to be activated during encoding by other authors: left inferior prefrontal cortex [Kapur et al., 1994; Demb et al., 1995; Fletcher et al., 1997], left prefrontal cortex and medial temporal lobes [Grady et al., 1995; Dolan and Fletcher, 1997], left prefrontal cortex and retrosplenial area of cingulum in acquisition of verbal information [Shallice et al., 1994], posterior hippocampal formation, parahippocampal gyrus, and in the lingual and fusiform gyri during picture encoding [Stern et al., 1996]. Furthermore, Tulving et al. [1994b] report the hippocampus, parahip-

pocampal cortex, thalamus, anterior and inferior cingulate cortex, putamen and medial prefrontal cortex to be involved in encoding new pictorial information.

In summary, there is a considerable overlap of results obtained by the present study and other reports. In agreement with most of the above-mentioned authors, left prefrontal activity was observed during encoding in this study. The fact that no brain structure associated with encoding has been identified by all authors might be due to the great variation in the tasks, encoding conditions, and methodology used. The present study used a conservative nonparametric approach to prevent false positive results. However, this might be associated with an increased risk of missing other memory related activation.

Recognition

The major finding of the present study (revealed by event-related analysis of acquisitions related to old vs. new words) is that activation during retrieval of old words from memory was greater in the right medial frontal gyrus, right anterior cingulate gyrus, and both parietal visual association cortices than in other areas. Since the left parietal association cortex was also activated during the lexical decision task (event-related comparison of words vs. nonwords in task 3), its role in episodic memory retrieval could not be clarified. The activation of this area might be either involved in some common memory-related aspects of old-new discrimination (e.g., lexical or semantic processing), or it might be related to other common aspects of both tasks (e.g., visual input or motor output processing). The former is supported by observations of Rugg et al. [1995], who found a relevance of the left parietal cortex in old-new distinctions. However, further study is needed precisely to define the role of this area. The observation of different activations of randomly intermixed item types might be helpful to reach this goal.

The results of the present study confirm the results of other authors, who observed activation of the prefrontal cortex, anterior cingulum, and parietal cortex during memory retrieval using comparable study designs [Riddle et al., 1993; Tulving et al., 1994a; Andreasen et al., 1995a; Buckner et al., 1995; Fletcher et al., 1995, 1997; Grady et al., 1995; Schacter et al., 1996, 1997]. The present results are in accordance with findings reported in the literature suggesting a role of the anterior cingulate gyrus in memory-associated tasks. There is a known relationship among this gyrus, the prefrontal cortex, and parietal association cortex where information may be stored. It has further been

shown to be involved in selection tasks [Raichle et al., 1994]. On the basis of our results, we conclude that the functions of the anterior cingulate gyrus may support the selection of items from episodic memory. The anterior cingulate gyrus might thus be involved in the discrimination of old and new words by supporting either the integration, comparison, transfer or processing of information received from the parietal visual association cortices. The medial frontal gyrus may support the anterior cingulum system in the comparison of old and new information or reflect activation of working memory [Goldman-Rakic, 1990]. Alternatively, both areas might be involved in the control of motor output. A connection between the prefrontal lobe and the parietal association cortex has been postulated by other authors [Goldman-Rakic, 1990; Kesner and Jackson-Smith, 1992]. Using a similar memory task, Schacter et al. [1997] have recently observed the delayed onset of activation in the prefrontal cortex, which might indicate that the prefrontal cortex participates in postretrieval monitoring processes. Further studies are, therefore, needed to clarify the precise function of the prefrontal cortex, as, e.g., in item selection or in maintaining attention, particularly in view of the fact that activation of this gyrus has also been described for other tasks requiring sustained attention.

Relevant negative observations

In contrast to our hypothesis and to findings of other authors, we did not note an increase in activation of the hippocampus or of other temporal structures using the described recognition task (neither in block nor in event-related analyses). Schacter et al. [1996] observed blood-flow increases in the hippocampal formation during conscious recollection of words. Increased activation in parahippocampal areas was found during episodic recognition of objects by Schacter et al. [1995]. Nyberg et al. [1998] recently observed a significant relationship between retrieval success and activation in the left medial temporal lobe. Buckner et al. [1998b,c] also reported a relationship between retrieval success and local brain activation in other brain structures. In comparison with the tasks described by these studies, the present memory task is characterised by a much less complicated task. The subjects rarely made recognition errors and most were able to recall the entire list in a free recall task after completion of the official study. The memory task might thus not have been sufficiently difficult to reveal significant hippocampal activation and to demonstrate detectable differences in activation in other brain areas during retrieval of old and new items. Alternatively, this finding might be

explained by the observation of Squire and Zola-Morgan [1991] that the medial temporal lobe has a less important role when memory is already consolidated. In our task, consolidation may have occurred during the time interval of 20–50 min between encoding and retrieval. Other authors have speculated that the hippocampus is less involved in verbal episodic memory than in spatial memory [Kolb and Whishaw, 1996]. The present verbal recognition memory task may, therefore, be supported by other brain structures that might additionally inhibit this medial temporal lobe structure. Last but not least, technical reasons may be responsible for the described negative results: fMRI slices were relatively large in comparison with the hippocampus and not oriented parallel to the hippocampus. Minor activation might thus have escaped detection. fMRI may be further distorted near the skull base due to severe susceptibility to artefacts in these regions leading to the reduced ability of detecting activation in the orbitofrontal and medial temporal structures. Consequently, the applied technique has to be focused on the hippocampus before any change in activation associated with the present task can be excluded and before task-related causes for the present negative observations can be conclusively discussed.

Block-based and event-related analyses

The comparison of block-based and event-related analyses was not the primary goal of the present study. A direct comparison of block-based and event-related analysis for identical cognitive processes is, therefore, not possible. However, block designs were included in tasks 2 and 3 to assess the validity of the event-related approaches, e.g., differences revealed by the event-related analysis of old and new words are more likely to be detected in areas with increased activity during retrieval of verbal material in comparison with the resting condition. (If only one condition leads to activation in one area, but not the second one, this area is likely to be activated in both blocked and event-related comparison; if one area is activated by both conditions, this area is more likely to show differences between two conditions than areas that show no activation when they are compared with the resting condition using a block design.) However, the event-related comparison is prone to miss those brain areas that may be relevant for retrieval, but are equally relevant for old and new items, e.g., neural correlates of retrieval mode and effort. An overlap of relevant brain areas became apparent in the event-related comparison of activity associated with old vs. new words. The observed significant increase in activity associated

with old in comparison with new words in the medial frontal gyrus and in the parietal association cortices corresponded well with regions significantly activated by old and new words when compared with the resting condition (block analysis, see Table I). This was less pronounced for the activation of the anterior cingulate gyrus, where significantly greater activation occurred in association with old than with new words (event-related analysis); the increase in activity in this area compared with the calculated average for all areas in the block analysis (blocked comparison of old and new words vs. resting condition) was only slightly increased in relation to the average for all ROI (4.14% vs. 3.89%) and failed to reach statistical significance.

Indirect comparisons of the statistical power of event-related and block analyses were possible in the present study. All block-based analyses detected a greater number of activated brain areas than both event-related analyses, even though for the block analysis of encoding vs. the resting condition and for the event-related analyses, the same number of events was used for statistical analysis (16 vs. 16 each). However, even if an identical number of acquisitions had been used for all comparisons, the cognitive processes compared during event-related analyses and the processes compared using block analyses would have remained different, thus preventing direct comparisons of block and event-related analyses.

A series of studies by Schacter et al. [1996, 1997] showed activation associated with false retrieval in a block PET study that could not be reproduced using event-related fMRI with intermixed item types. The fact that we observed differences between item types might be attributed to explicit learning that resulted in near perfect recognition and very few errors, thus allowing the detection of differences in the event-related analysis. In contrast, Schacter et al. [1997] used nonstudied semantic associates to obtain an adequate number of errors for correlation with retrieval success in a later analysis.

Methodological limitations and conclusions

We observed activation of various brain structures during encoding and retrieval using the described hypothesis-oriented, nonparametric analysis of activation in selected regions of interest. Comparable results were obtained following nonparametric analysis in segmented regions of interest and SPM analysis, which confirms the validity of both approaches. For researchers interested in methodological issues of image analysis, the fact that both approaches provided similar results might be of interest. However, we may have

missed other brain regions involved in memory tasks with the conservative ROI-based approach. In accordance with this assumption, we found more extended and additional small activation in all three tasks using SPM. A nonparametric approach was selected because it allowed the use of an event-related or item-by-item method of image analysis within a memory task; due to the low number of items for comparison in the event-related related analysis (i.e., 16 vs. 16) the use of a parametric analysis did not seem adequate initially. However, our results showed SPM to be robust regarding this statistical problem. Later memory studies might be less stringent with a view to the selection of statistical significance levels and the application of nonparametric analyses, thus increasing the statistical power of image analysis. SPM appears to be a valid tool for these purposes. However, it might be argued that activation observed with SPM by overlying series of acquisition images from several subjects onto a common template might not easily be attributed to small brain structures as, e.g., the amygdala. Consequently, the described nonparametric statistical approach may serve as an adequate alternative to SPM in the hypothesis-guided identification of activation in small regions of interest and small samples of subjects, as well as for samples of subjects in whom normalisation to a common template is not adequate due to increased sulcal variability [Mega et al., 1998].

Our selection of the term “event-related” to describe certain analyses might be criticised by others. The term “event-related” was chosen in (at least partial) agreement with electrophysiological notation: acquisitions were related to different event types as, e.g., the classification of old or new items and subsequently selectively averaged and compared according to the assumed cognitive process. However, in the present study only one acquisition was performed for an individual event. In contrast, other authors have attempted to monitor cerebral activity during the entire event [e.g., Jacobs et al., 1997a,b; Schacter et al., 1997; Buckner et al., 1998]. These time-course measurements of event-related activity were also referred to as event-related fMRI by these authors. The present approach might, therefore, preferably be called item-related fMRI to prevent confusion. However, we were hesitant to propose this new and somewhat unusual designation.

We are aware of the fact that the applied tasks and control conditions are not the only ones suitable in the assessment of encoding and retrieval. Encoding of words and recognition of previously presented words are complex processes, of retrieval from memory being only one aspect. At present, a single fMRI study can, therefore, not answer all questions or examine all

subfunctions. However, we assume that future memory studies can be considerably simplified when event-related activation is compared within one trial block instead of between several different trial blocks.

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REFERENCES

- Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, Watkins GL, Boles Ponto LL, Hichwa RD. 1995a. Short-term and long-term verbal memory: a positron emission tomography study. *Proc Natl Acad Sci* 92:5111–5115.
- Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Boles Ponto LL, Hichwa RD. 1995b. Remembering the past: two facets of episodic memory explored with positron emission tomography. *Am J Psychiatry* 152:1576–1585.
- Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Boles Ponto LL, Watkins GL, Hichwa RD. 1996. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci* 93:9985–9990.
- Baschek IL, Bredenkamp J, Oehrlé B, Wippich W. 1977. Bestimmung der Bildhaftigkeit (I), Konkrettheit (C) und der Bedeutungshaltigkeit (m') von 800 Substantiven. *Z experimentelle angewandte Psychol* 24:353–396.
- Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Reiche ME. 1995. Functional anatomical studies of explicit and implicit memory retrieval tasks. *J Neurosci* 15:12–29.
- Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR. 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci* 93:14878–14883.
- Buckner RL, Goodman J, Burock M, Rotte M, Koutstaal W, Schacter D, Rosen B, Dale AM. 1998a. Functional anatomic correlates of object priming in humans revealed by rapid presentation event related fMRI. *Neuron* 20:285–296.
- Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte M, Rosen BR. 1998b. Functional-anatomic study of episodic retrieval: II. selective averaging of event-related fMRI trials to test the retrieval success hypothesis. *Neuroimage* 7:163–175.
- Buckner Koutstaal W, Schacter DL, Wagner AD, Rosen BR. 1998c. Functional anatomic study of episodic retrieval using fMRI: I retrieval effort versus retrieval success. *Neuroimage* 7:151–162.
- Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JDE. 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci* 15:5870–5878.
- Dolan RJ, Fletcher PC. 1997. Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388:582–585.
- Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RSJ, Dolan RJ. 1995. Brain systems for encoding and retrieval of auditory-verbal memory: an in vivo study in humans. *Brain* 118:401–416.
- Fletcher PC, Frith CD, Rugg MD. 1997. The functional neuroanatomy of episodic memory. *TINS* 20:213–218.

- Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC. 1997. Human Brain Function, New York: Academic Press.
- Friston KJ. 1996. Statistical parametric mapping and other analyses of functional imaging data. In: Toga AW, Mazziotta JC (eds). Brain Mapping: The Methods. New York: Academic Press, pp 363–386.
- Goldman-Rakic PS. 1990. Cortical localization of working memory. In: McGaugh J, Weinberger NM, Lynch G (eds): Brain Organization and Memory. New York: Oxford University Press, pp 285–298.
- Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, Pietrini P, Schapiro MB, Haxby JV. 1995. Age-related reductions in human recognition memory due to impaired encoding. *Science* 269:218–221.
- Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ. 1993. Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* 116:1–20.
- Josephs O, Turner R, Friston K. 1997. Event-related fMRI. *Hum Brain Mapp* 5:243–248.
- Kapur S, Craik FIM, Tulving E, Wilson AA, Houle S, Brown GM. 1994. Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. *Proc Natl Acad Sci* 91:2008–2011.
- Kesner RP, Jackson-Smith P. 1992. Neurobiology of an attribute model of memory: role of prefrontal cortex. In: Gormezano I, Wasserman EA (eds): Learning and Memory: The Behavioral and Biological Substrates. Hillsdale, NJ: Erlbaum.
- Kolb B, Whishaw IQ. 1996. Fundamentals of Neuropsychology. New York: Freeman.
- Kretschmann HJ, Weinrich W. 1996. Dreidimensionale Computergraphik neurofunktioneller Systeme. New York: Thieme Verlag.
- Le Bihan D, Turner R, Zeffiro TA, Cuénod CA, Jezard P, Bonnerot V. 1993. Activation of human primary visual cortex during visual recall: a magnetic resonance imaging study. *Proc Natl Acad Sci* 90:11802–11805.
- Mai JK, Assheuer J, Paxinos G. 1997. Atlas of the Human Brain. New York: Academic Press.
- McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder F, Goldman-Rakic P, Shulman RG. 1994. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc Natl Acad Sci* 91:8690–8694.
- Mega MS, Thompson PM, Cummings JL, Back CL, Xu ML, Zohoori S, Goldkorn A, Moussai J, Faibanks L, Small GW, Toga AW. 1998. Sulcal variability in the Alzheimer's brain: correlations with cognition. *Neurology* 50:145–151.
- Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E. 1996. Activation of medial temporal structures during episodic memory retrieval. *Nature* 380:715–717.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9:97–113.
- Oldigs-Kerber J, Adamus WS, Kitzinger M. 1991. Zur Beeinflussung von verbalen Lern- und Gedächtnisprozessen durch Anticholinergica am Beispiel von Scopolamin. Ein pharmakopsychologischer Beitrag für die neuropsychologische Praxis. *Z Neuropsychol* 2:29–40.
- Orrison WW. 1995. Atlas of Brain Function. New York: Thieme Verlag.
- Raichle ME, Fiez JA, Videen TO, MacLeod AMK, Pardo JV, Fox PT, Petersen SE. 1994. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 4:8–26.
- Riddle W, O'Carroll RE, Dougall N, Van Beck M, Murray C, Curran SM, Ebmeier KP, Goodwin GM. 1993. A single photon emission computerised tomography study of regional brain function underlying verbal memory in patients with Alzheimer-type dementia. *Br J Psychiatry* 163:166–172.
- Rosenzweig MR, Leiman AL, Breedlove SM. 1996. Biological Psychology. Sunderland, MA: Sinauer.
- Rugg MD, Cox CJC, Doyle MC, Wells T. 1995. Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia* 33:471–484.
- Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS. 1996. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc Natl Acad Sci* 93:321–325.
- Schacter DL, Reiman E, Uecker A, Polster MR, Sheng Yun L. 1995. Brain regions associated with retrieval of structurally coherent visual information. *Nature* 376:587–590.
- Schacter DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR. 1997. Late onset of anterior prefrontal activity during true and false recognition: an event related fMRI study. *Neuroimage* 6:259–269.
- Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RSJ, Dolan RJ. 1994. Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature* 368:633–635.
- Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. *Science* 253:1380–1386.
- Stern CE, Corkin S, Gonzales RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. 1996. The hippocampal formation participates in new picture encoding: evidence from functional magnetic resonance imaging. *Proc Natl Acad Sci* 93:8660–8665.
- Talairach J, Tournoux P. 1988. Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Verlag.
- Toga AW, Mazziotta JC. 1996. Brain Mapping: The Methods. New York: Academic Press.
- Tulving E, Kapur S, Markowitsch HJ, Craik FIM, Habib R, Houle S. 1994a. Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition. *Proc Natl Acad Sci* 91:2012–2015.
- Tulving E, Markowitsch HJ, Kapur S, Habib R, Houle S. 1994b. Novelty encoding networks in the human brain: positron emission tomography data. *NeuroReport* 5:2525–2528.
- Tzourio N, Petit L, Mellet E, Orssaud C, Crivello F, Benali K, Salamon G, Mazoyer B. 1997. Use of anatomical parcellation to catalog and study structure-function relationships in the human brain. *Hum Brain Mapp* 5:228–232.