Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 7627–7632, July 1997
Neurobiology

Positron-emission tomography imaging of long-term shape recognition challenges

A. ROSIER*†, L. CORNETTE*, P. DUPONT‡, G. BORMANS‡, J. MICHIELS§, L. MORTELMANS‡, AND G. A. ORBAN*

*Laboratorium voor Neuro- en Psychofysiologie, Universite Catholique de Leuven Medical School, ‡Nuclear Medicine, Center for Positron Emission Tomography, University Hospital, and §Laboratory for Medical Imaging Research, Department of Radiology, University Hospital, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

Communicated by James M. Sprague, University of Pennsylvania, Philadelphia, PA, May 7, 1997 (received for review January 16, 1997)

ABSTRACT **Long-term visual memory performance was impaired by two types of challenges: a diazepam challenge on acquisition and a sensory challenge on recognition. Using positron-emission tomography regional cerebral blood flow imaging, we studied the effect of these challenges on regional brain activation during the delayed recognition of abstract visual shapes as compared with a baseline fixation task. Both challenges induced a significant decrease in differential activation in the left fusiform gyrus, suggesting that this region is involved in the automatic or volitional comparison of incoming and stored stimuli. In contrast, thalamic differential activation increased in response to memory challenges. This increase might reflect enhanced retrieval attempts as a compensatory mechanism for restoring recognition performance.**

Because recognition memory requires judgments concerning the prior occurrence of items, interference with either memory storage or retrieval may impair task performance. Whether such interventions specifically influence the regional cerebral blood flow (rCBF) pattern during recognition is as yet unknown. We addressed this question by challenging a long-term memory task involving the recognition of abstract visual shapes in two different ways: a pharmacological and a sensory challenge.

We chose to use abstract shapes to limit the possible influence of (verbal or visual) semantic associations.

The pharmacological challenge consisted of the presence of the benzodiazepine diazepam during the acquisition of new information. This challenge, selected on the basis of previous reports (1, 2), was optimized in a preliminary study in which we demonstrated that 15 mg of diazepam caused a clear (about 20% recognition deficit) and significant impairment in the delayed recognition of abstract visual shapes (3). Because this anterograde amnesic effect was obtained without concomitant effects on detection, visual perceptual, or discriminative performances, even at peak levels of drug activity (3), it selectively interfered with memory-related processes during the encoding of new information. To examine the specificity of the rCBF changes during an impaired delayed recognition, we selected a second challenge that induced a deficit in recognition performance which was similar in degree to that induced by diazepam. This second, sensory challenge consisted of a shorter stimulus presentation during recognition (4). As with the pharmacological challenge, this sensory challenge did not significantly impair visual perceptual and discriminative performances, and thus its effect was also restricted to memory-related processes.

Hence, this experimental design provided us with the tool to examine whether changes in rCBF during delayed recognition were specifically related to the diazepam challenge during acquisition or whether they reflected a more general degradation in recognition performance, regardless of the primary cause of this impairment.

METHODS

Subjects. Twelve right-handed male students were recruited. They ranged in age from 18 to 24 years and in weight from 64 to 85 kg. They had no illness or history of alcoholism or drug abuse. None had used chronic medication for the last 4 months, or had ever taken benzodiazepines. They were told to abstain from caffeine at least 36 hr before the study, and from food and beverages for at least 3 hr before the experiment, but for no more than 10 hr. They were instructed to avoid the use of alcohol from the day before the study and until at least 24 hr after the end of the session. This study was approved by the ethical committee of the Universite Catholique de Leuven School of Medicine, and all subjects gave their written, informed consent. Subjects were screened for admission during a test session in which they were instructed to memorize a list of 18 abstract stimuli. They were admitted to the study only if their immediate recognition performance exceeded 70%.

Stimuli. White outlines generated with MATLAB using mathematical formulas (5) were adapted to produce angular and asymmetrical closed curves in addition to smooth symmetrical curves (6) (Fig. 1). Two abstract shapes were presented on either side of a fixation point (0.25° diameter) with the stimulus center at a distance of 3.5° or less, in a dimly lit room at a fixed distance of 114 cm. Stimulus position was randomized within a 3.5° circle around the fixation point. Stimulus size was randomly changed and could assume one of four values between 1.5° and 3°.

Tasks. During encoding, 16 stimuli were presented pairwise for 1,700 msec with each pair separated from the following pair by a blank screen (250 msec). Each stimulus was presented four times, twice on the left and twice on the right. Subjects were instructed to memorize the shapes irrespective of sequence, position, or size. Because of the abstract nature of the stimuli and prior screening for association, interaction between novelty effects and storage were minimized (6, 7).

In standard recognition, pairs of stimuli were presented for 1,700 msec during which subjects had to detect the "old" stimulus by pressing the response key on the corresponding side. The intertrial interval was 250 msec. In sensory-challenged recognition, the choice stimuli were presented for only 75 msec, immediately followed by a mask stimulus for 1,625 msec. This mask consisted of a superimposed combination of eight random shapes. The response window and intertrial interval were similar to standard recognition. Each subject performed four recognition tasks (two standard and

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: rCBF, regional cerebral blood flow; PET, positron-emission tomography.

†To whom reprint requests should be addressed. e-mail: Anne-Marie.Rosier@med.kuleuven.ac.be.

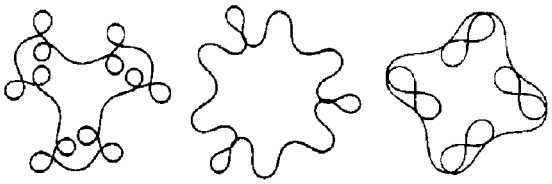

FIG. 1. Three exemplars of abstract stimuli.

two sensory-challenged recognitions). The new stimuli were unique for each recognition task. Each recognition task comprised an equal number ($n = 16$) of old and new stimuli randomized in position and size; these stimuli were also displayed equal numbers of times.

The standard same-different task had a time course similar to the standard recognition task, but the subject had to indicate by key presses whether the two stimuli were the same or not. As an additional control, a sensory-challenged same–different task, exhibiting a time course similar to the sensory-challenged delayed recognition task, was administered to all subjects at the end of the second (placebo) session, i.e., at least 1 month after the positron-emission tomography (PET) session, to avoid interference between stimuli.

In the detection task, subjects had to signal the presence of a random pair of stimuli by pressing both keys simultaneously before the end of stimulus presentation (300 msec). The intertrial interval in the detection task varied randomly between 250 and 850 msec in steps of 200 msec to avoid rhythmic key presses.

Experimental Design. On he first day of the study, subjects memorized a list of 16 shapes. One hour before the presentation of this list, either placebo (20 mg of calcium carbonate, six subjects) or 15 mg of diazepam (mean dosage ± SD = 0.21 ± 0.04 mg/kg, six subjects) was administered orally. Because the metabolic rate may vary independently of the subject's body weight, we opted to use a constant amount of diazepam while limiting the weight range for the participating subjects.

Same–different tasks, detection tasks, and self-rating scales (3, 8) were administered immediately after capsule administration as well as 1 hr later, i.e., at peak levels of drug activity, at which time the subjects learned the shapes. After a 3-day retention interval, subjects completed a PET-rCBF study for delayed recognition. In this PET study, the following tasks were scanned twice, in random sequence: (*i*) standard recognition, (*ii*) sensory-challenged recognition, and (*iii*) fixation. In the fixation task, as in all other tasks, subjects had to fixate a solid white circle in the center of the screen (0.16°). No feedback was given on task performance. To compare drug-challenged and placebo performances within the same subject, and to investigate possible interference with recognition results induced by repetition, or by specific stimuli, all subjects participated in an additional placebo session 1 month after their first session.

PET-rCBF Study. Brain activity was monitored with an ECAT931-08-12 scanner (CTI, Knoxville, TN) as relative changes in local blood flow by using the $H_2{}^{15}O$ method (9). Subjects were immobilized with a foam headholder and a transmission scan was performed to correct for attenuation. Each subject underwent 6 emission scans about 15 min apart. At the beginning of each task, which lasted 2 min, subjects received an i.v. bolus injection of 40 mCi of $H_2{}^{15}O$ (1 Ci = 37 GBq) in 12 sec. The emission scan started when radioactivity reached the brain (usually about 30 sec after tracer injection), and image acquisition lasted for 40 sec. Emission data were reconstructed as 15 planes, parallel to the orbito-meatal line and spaced 6.75 mm apart, by using filtered back projection with a Hanning filter (cutoff 0.5 cycles per pixel). Fixation of the fixation target was controlled by an electro-oculogram.

Statistical Analysis of Performances. Task performances, expressed as the percentage of correct responses, were first normalized by transformation to Z scores and subsequently analyzed with ANOVA, followed by post hoc comparisons for significance (Tukey Honest Significant Difference Test). The mean reaction time was calculated as the average of all reaction times corresponding to trials in which subjects responded within the response window, with the addition of a distinction between correct and wrong responses only for the recognition and same–different tasks. In these analyses, the number of memory tasks was included as a repetitive factor within each subject, whereas the drug/placebo challenge was used as factor between subjects. In addition, because subjects participated in two sessions, additional ANOVAs were performed (*i*) to examine the effect of repetitive sessions on recognition performance and (*ii*) for the diazepam-challenged subjects, to compare placebo recognition performances with those following a diazepam-challenged acquisition within the same subject. Values for d' [$d' = Z$(proportion of hits) − Z(proportion of false alarms)] and response bias [$B = (Z$(proportion of hits) + Z(proportion of false alarms))/2] were calculated according to Signal Detection Theory (10) to control for changes in response preferences.

Statistical Analysis of rCBF. Differences in rCBF between conditions were analyzed with statistical parametric mapping software (SPM95, Department Cognitive Neurology, Wellcome). Images were stereotaxically normalized and resliced in planes spaced 4 mm apart and parallel to the AC–PC line to fit the standard planes of the Talairach–Tournoux atlas (11). A Gaussian filter (full width half maximum = 20 × 20 × 12 mm) was used to increase the signal-to-noise ratio and to overcome interindividual variability in brain activity. Data were analyzed in a multi-study design with a study-specific normalization for global activity between subjects and conditions by analysis of covariance (ANCOVA) analysis, including the dual scanning of each task as replicative factor. ANCOVA-corrected rCBF data were compared by using ANOVA with a significance level set at $P < 0.05$ corrected for multiple comparisons for the main effect of recognition (12). Of the brain regions exhibiting significant increases in rCBF during delayed recognition compared with fixation, we excluded motor, premotor, parietal, and early visual regions from further analysis. Based on existing literature on electrophysiological, imaging, and lesion studies (13–23), three regions presumably involved in memory-related retrieval processes were retained: fusiform gyrus (bilaterally) and thalamus. These regions were used as a mask for other subtractions, in which a more liberal threshold ($P < 0.008$) could then be used, corresponding to $P < 0.05$ corrected for the number of foci (three) and the number of subtractions (two) examined.

Anatomical MRI Data. Each subject underwent a high-resolution MRI scan using a 3D-Magnetization-Prepared Rapid Gradient Echo sequence. Acquisition parameters were as follows: 10-msec repetition time, 4-msec echo time, 8° flip angle, 256-mm field of view, and a 256 × 256 acquisition matrix. The three-dimensional volume had a thickness of 160 mm, partitioned into 128 sagittal planes. MRI images of each subject were registered to the corresponding PET images using MIRIT [multi-modality image reconstruction using information theory (24)]. These registered MRI data were then transformed into Talairach space by applying the same transformations as those used to transform the PET images, and an average MRI image was constructed, including the data from all 12 subjects.

RESULTS

Task Performances. After a diazepam-challenged encoding, standard recognition performance was significantly (about 21%) lower than that after a placebo encoding stage (Table 1;

Table 1. Mean performance on control and delayed-recognition tasks for placebo- and diazepam-challenged subjects

	Control tasks		Delayed-recognition tasks	
Challenge	S–D	DET	REC	SCR
Placebo	88 ± 4	85 ± 4	84 ± 6	66 ± 5**
	980 ± 185	*195 ± 62*	*1,282 ± 85*	*1,255 ± 96*
Diazepam	87 ± 4	86 ± 4	63 ± 6*	59 ± 5
	1,210 ± 260	*225 ± 42*	*1,335 ± 85*	*1,113 ± 97*

Performances are expressed as the percentage (± SD) of correct responses. S–D, same–different discrimination; DET, detection; REC, standard recognition; SCR, sensory-challenged recognition. Performances on control tasks were obtained 1 hr after capsule administration; those on memory tasks were obtained after a 3-day retention time. Performance on standard recognition differed significantly between placebo- and diazepam-challenged subjects, as indicated by the asterisk (*, ANOVA, $P < 0.01$). Performance on sensory-challenged recognition also differed significantly from that of standard recognition, only in the placebo group, as indicated by the double asterisks (**, ANOVA, $P < 0.01$). Corresponding reaction times are expressed in milliseconds and shown in italic type.

ANOVA, $P < 0.01$). In the placebo group, the sensory challenge also induced a significantly lower recognition performance (about 18%) compared with standard recognition (Table 1; ANOVA, $P < 0.01$). Hence, as intended, performance on sensory-challenged recognition after a placebo encoding was similar to that of standard recognition in diazepam-challenged subjects.

Comparisons of d' values revealed significant differences (*i*) between placebo and diazepam subjects during standard recognition (ANOVA, $P < 0.001$) and (*ii*) between standard and sensory-challenged recognition in placebo subjects (ANOVA, $P < 0.002$). Among the three challenge conditions, there were no significant differences (ANOVA, $P > 0.8$; Table 2). In contrast, different recognition tasks (standard vs. sensory-challenged) showed no significant differences with regard to response bias within either group, nor were there significant differences between groups for any given recognition task (Table 2; ANOVA, $P > 0.5$). Hence, there was no significant change in the subjects' preferences for particular responses.

For both standard and sensory-challenged recognition, reaction times were similar for diazepam- and placebo-challenged subjects. Although there was no significant consistent effect for either challenge on response latencies, it is noteworthy that the mean reaction time in sensory-challenged recognition in the diazepam-challenged group is shorter than in all other recognition tasks (Table 1).

One hour after diazepam/placebo administration, at peak levels of drug activity and time of acquisition, both groups had similar discrimination and detection performances. Although not significantly different, response latencies were somewhat longer in the diazepam-challenged subjects compared with placebo-challenged subjects (Table 1).

Table 2. Analysis derived from the Signal Detection Theory comparing standard and sensory-challenged recognition for placebo- and diazepam-challenged subjects

	REC		SCR	
Challenge	d'	B	d'	B
Placebo	1.36 ± 0.30	0.83 ± 0.15	0.54 ± 0.26**	0.75 ± 0.10
Diazepam	0.47 ± 0.28*	0.78 ± 0.12	0.40 ± 0.29	0.82 ± 0.11

Standard recognition (REC) and sensory-challenged recognition (SCR) were measured by d' values and response bias (B). Each value represents the mean of six subjects ± SD. Values for d' during standard recognition differed significantly between placebo- and diazepam-challenged subjects, as indicated by the asterisk (*, ANOVA, $P < 0.001$). Values for d' on sensory-challenged recognition also differed significantly from that of standard recognition, but only in the placebo group (**, ANOVA, $P < 0.002$). Response bias was similar in all conditions (ANOVA, $P > 0.5$).

As tested in the second (placebo) session, the sensory challenge had no effect on the same–different task; performance in the standard same–different task was 88 ± 2% compared with 87 ± 3% in the sensory-challenged same–different task.

PET-rCBF Data. Using data from all 12 subjects, we first identified the cerebral regions exhibiting significantly increased activation during delayed recognition compared with fixation (FIX) by subtracting fixation-induced activation (2 × FIX) from the sum of both types of recognition tasks (REC + SCR; Table 3). Three foci generated by this main subtraction (bilateral fusiform focus, thalamus) were probed in two subtractions: (*i*) [(REC + SCR) − 2(FIX) in placebo subjects] − [(REC + SCR) − 2(FIX) in diazepam subjects], distinguishing between pharmacological conditions, and (*ii*) REC − SCR in all subjects, distinguishing between the two types of recognition tasks (Table 4).

Several brain regions presented a significantly increased blood flow in delayed recognition compared with fixation. An increased activation was observed bilaterally in the occipitotemporal lobe, including fusiform, lingual, and medial occipital gyri, in the superior parietal cortex and in the motor and premotor cortex. Additional foci of unilateral activation included the right cingulate cortex and the posterior thalamus. Finally, activation of the midline cerebellum was observed (Fig. 2 and Table 3).

The left fusiform differential activation in both types of recognition tasks was significantly lower in diazepam-challenged subjects compared with placebo subjects (Table 4, subtraction 1, and Fig. 3). In contrast, differential activation in the posterior thalamus was higher in diazepam subjects (Table 4 and Fig. 3).

Activation in the fusiform foci (left and right) was significantly higher during standard recognition as compared with sensory-challenged recognition, irrespective of the pharmacological condition (Table 4, subtraction 2, and Fig. 3). The opposite tendency was observed in the posterior thalamus, but the latter did not reach the expected level of significance ($P > 0.008$).

Table 3. Shape recognition network

		Coordinates			
(REC + SCR) − 2(FIX)	Side	x	y	z	Z score
Lingual gyrus (BA17/18)	L	−4	−92	−12	7.38
Medial occipital gyrus (BA18)	L	−30	−86	4	6.58
	R	28	−86	8	4.76
Fusiform gyrus (BA19)	L	−36	−68	−16	7.52
	R	36	−74	−16	7.73
Superior parietal cortex (BA7)	L	−24	−62	40	5.39
	R	22	−72	40	6.03
Cingulate cortex (BA32)	R	4	6	44	5.29
Cingulate sulcus (BA24/6)	L	−22	−8	48	5.84
	L	−34	−2	32	4.37
	R	30	−8	48	6.17
Postcentral gyrus (BA4)	L	−36	−28	44	5.14
	R	38	−24	40	4.13
Posterior thalamus		0	−26	4	4.31
Midline Cerebellum		2	−86	−16	7.53

Local maxima ($P < 0.05$, corrected for multiple comparisons) for the main network activated during long-term shape recognition, including all 12 subjects: (standard recognition plus sensory-challenged recognition) versus fixation [SPM contrast, (REC + SCR) − 2(FIX)]. The coordinates (in millimeters) correspond to those in the Talairach space. The indications between parentheses indicate the Brodmann areas. L, left; R, right.

Table 4. Effects of pharmacological and sensory challenges in three cerebral regions

Foci	*Z* score	
	Subtraction 1	Subtraction 2
Fusiform gyrus		
Left (−36, −68, −16)	2.68	4.16
Right (36, −74, −16)	0.73	5.38
Posterior thalamus (0, −26, 4)	−2.78	−1.62

Based on literature data, we selected three foci generated by the main subtraction (REC + SCR) − 2(FIX) to guide the investigation of limited cerebral regions in the *Z* map obtained for the subtraction of the differential activations between drug conditions, [(REC + SCR) − 2(FIX), placebo] − [(REC + SCR) − 2(FIX), diazepam] (subtraction 1), and between tasks, REC − SCR (all subjects; subtraction 2); the three foci are the left and right fusiform focus and the thalamic focus. As a result, a more liberal statistical treshold ($P < 0.008$) could be used. Underlined *Z* scores indicate significant differences at this *P* level. Coordinates for the foci are given in parentheses.

Electro-oculogram (EOG) analysis revealed no differences in the number of saccades between drug conditions for standard and sensory-challenged recognition.

DISCUSSION

The rCBF pattern during the delayed recognition of abstract visual shapes presented both positive and negative regional changes in response to a challenge affecting long-term recognition performance, i.e., a pharmacological challenge with diazepam on encoding and a sensory challenge during delayed recognition.

Given that benzodiazepines reduce cerebral blood flow in several cortical and subcortical structures (25), the following steps were taken to rule out aspecific effects of prior diazepam administration on the delayed recognition activation. First, long-term recognition memory was scanned 3 days after acquisition, a delay allowing a substantial if not total drug clearance (26). Secondly, the pharmacological challenge was not assessed by its effect on the recognition task but by the changes in differential activations between recognition and fixation tasks, removing possible direct effects of diazepam on rCBF. Our data confirm that this strategy was successful because the rCBF during the baseline fixation task was very similar in both diazepam- and placebo-challenged subjects for all foci studied.

Activation of the ventral occipitotemporal cortex, as revealed by the present study, corresponds to the system specialized for object recognition and discrimination in both humans and in monkeys (27–33), and activations in this region fit imaging studies of visual face-, object-, and pattern-matching tasks (13–18). Given the dominant role of the left hemisphere in object recognition, it has been suggested (18) that the right hemispheric contribution becomes crucial when perceptual operations have to be implemented involving corrections, transformation, or rotation of the incoming stimulus. Hence, the strong activation in the right occipitotemporal cortex might also relate to the randomization in stimulus size and position during recognition.

The thalamic activation observed in the present study closely corresponds to the region activated by retrieval in a verbal long-term memory task (ref. 21; *x*, *y*, *z* coordinates = 2, −22, 0 mm). Based on the widespread connectivity between cortical and subcortical structures, it has been proposed that this region is involved in linking distributed neural representations (21), and hence possibly in reactivating the stored information.

Superior parietal activation becomes apparent in tasks involving visuospatial attention requiring either attentional shifts for objects or locations, or requiring sustained attention to peripheral objects (13, 20, 34, 35). Anterior cingulate activation is consistent with its role in attention and the internal generation of motor (or verbal) action and response selection (14, 19, 21, 34, 36).

Surprisingly, no increased activation was observed in frontal or prefrontal cortex during recognition compared with fixa-

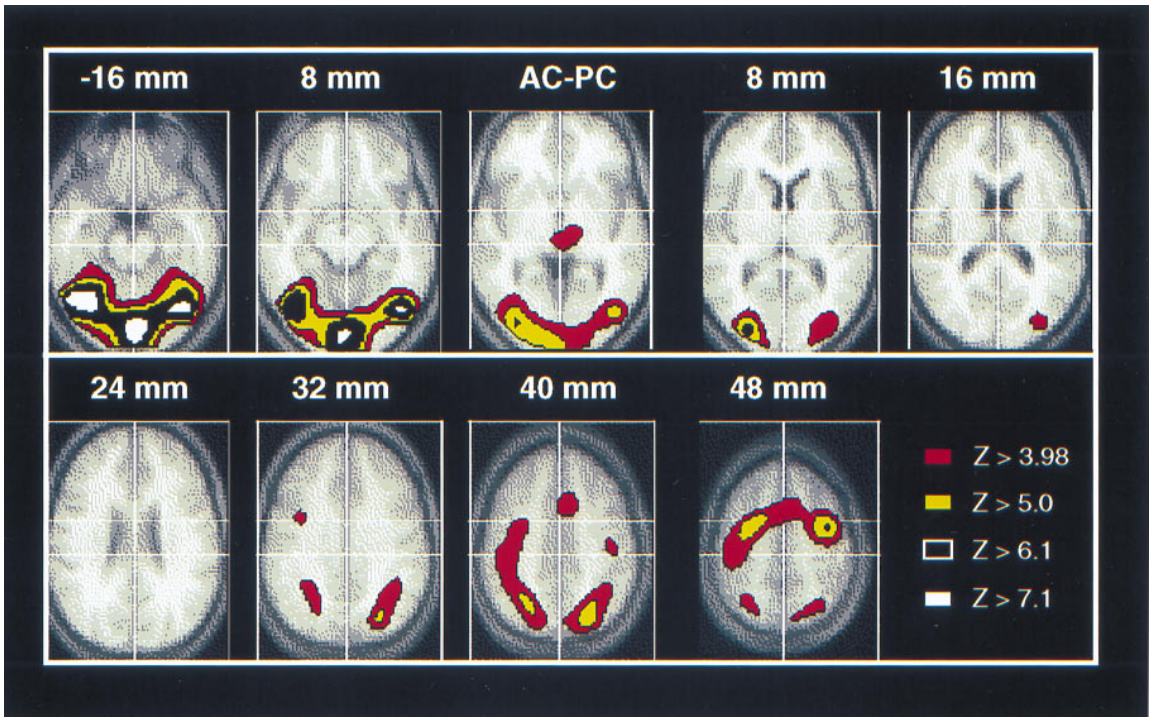

FIG. 2. Statistical parametric maps showing the main pattern of differential activation during recognition compared with fixation [(REC + SCR) − 2(FIX)], including data from all 12 subjects. Maps are shown at 9 horizontal levels (from −16 to +48 mm in steps of 8 mm) superimposed on the average MRI of all subjects. *Z* scores of 3.98, 5.0, 6.1, and 7.1, respectively, correspond to *P* levels 0.05, 10^{-3}, 10^{-4}, and 10^{-5} (corrected for multiple comparisons). The left sides of the images correspond to left sides of the brain.

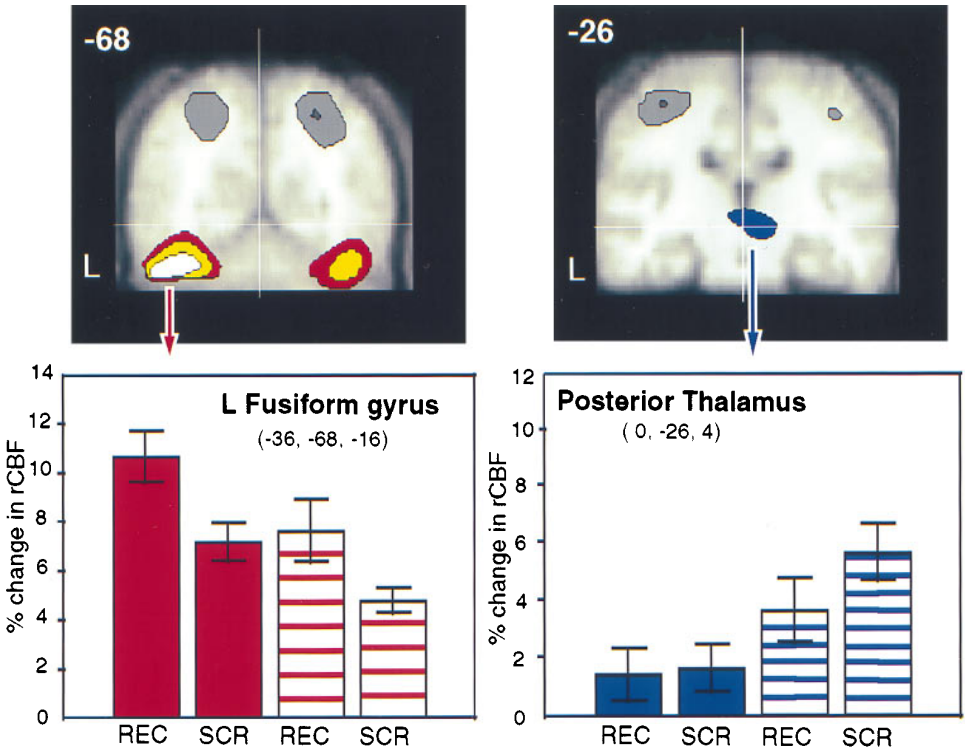

FIG. 3. rCBF profiles for the two regions exhibiting a differential activation between placebo and diazepam conditions: left (L) fusiform gyrus and posterior thalamus. To stress the direction in which activation in these foci varies, the color red is assigned to the fusiform gyrus, exhibiting a significantly higher differential activation in placebo as compared with diazepam conditions, whereas the thalamic focus, displaying the opposite change, is represented in blue. The activated regions, represented by data from the main subtraction (REC + SCR) − 2(FIX), are displayed on coronal sections, taken from the mean MRI data of all subjects after applying the same transformations as those used to transform the PET images into Talairach space. Parietal foci of activation (gray) are indicated only to complete the pattern of regional activation. The color coding on the sections delineates regions with a Z score of >3.98 ($P < 0.05$, corrected for multiple comparisons: blue, red, and light gray), with yellow and dark gray pixels corresponding to $Z > 5.0$ ($P < 0.001$, corrected), and white pixels corresponding to $Z > 6.1$ ($P < 0.0001$, corrected). In each profile, normalized rCBF data are expressed as relative changes by using the fixation task as reference: [recognition − fixation)/fixation] for the standard (REC) and the sensory-challenged (SCR) tasks, and for each drug condition separately (solid bars, placebo; striped bars, diazepam). Error bars represent SDs.

tion, although these regions are known to be involved in both working and explicit long-term memory retrieval (13, 14, 16, 17, 20, 37, 38). A possible explanation for the absence of significant frontal activation in the present study is the absence of verbal associations and possibly the reduced need for monitoring of selections (39–41). A view in harmony with our results has recently been put forward by Mishkin and Murray (30). The absence of significant hippocampal activation during delayed recognition might relate to the long retention time because its role in long-term memory seems restricted to a finite period after the acquisition of information (15, 17, 42–45).

Recognition-induced activation in the fusiform gyrus was significantly smaller during sensory-challenged as compared with standard recognition. Although the total visual stimulation was the same in both types of recognition tasks, presentation of the shapes was of shorter duration in sensory-challenged recognition. The bilateral decrease in fusiform activation is in agreement with single-cell studies showing a sharp reduction in inferotemporal responses by backward masking (4).

In principle, the shorter duration can also interfere with the switching of attention between the two shapes presented in the recognition tasks. During recognition, subjects need to direct their attention toward the peripherally presented choice stimuli. In standard, but not in sensory-challenged recognition, subjects may perform multiple attentional redirections to the choice stimuli before selecting their response. Because response latencies were similar in both types of recognition tasks, it seems unlikely that attention switching differed between the two types of recognition tasks. Even so, the limitations on attentional shifts will only further reduce the effective processing time of the shapes and thus can only exacerbate the response reductions observed when only a single stimulus had to be processed. On the other hand, because a decrease in activation in the left fusiform cortex after a diazepam challenge occurs in both types of recognition tasks, it might reflect the impaired memory storage induced by this pharmacon.

Thus, activation in the left fusiform cortex decreased with either challenge. Because a diazepam challenge impaired memory storage itself, whereas the sensory challenge affected the visual input necessary for comparison with the stored information, we suggest that this region functions as a locus for the matching, either automatically or volitionally (46), of incoming and stored stimuli. This is in perfect agreement with earlier studies suggesting left fusiform involvement in object recognition (18). Interestingly, this left fusiform focus mirrors a focus in the right hemisphere found to be involved in the temporal comparison of successive stimuli, which also entails a matching process (ref. 19; x, y, z coordinates = 40, −62, −12 mm). It is noteworthy that the right fusiform cortex is differentially active during delayed recognition but that this differential activation remains unaltered by the pharmacological challenge. This is consistent with the view indicated above that this right-sided activation might primarily reflect the transformations performed on the incoming stimuli.

The increase in posterior thalamus differential activation observed after diazepam administration is consistent with this region's role in reactivating stored information (14, 21). Indeed, it might reflect stronger or more frequent retrieval

attempts. This might also explain why a diazepam challenge increased the posterior thalamic activation more than the sensory challenge because only the former affected the memory storage.

The mechanisms through which diazepam impairs long-term memory storage are as yet unknown. The present study limited the visualization of its effect to selected regions activated during long-term recognition memory for abstract shapes, but other cerebral regions may be affected as well, although the visualization of these effects will require other tasks. The present study focused on two regions, fusiform cortex and thalamus, whose involvement in recognition processes has been demonstrated both by electrophysiological (27–29, 31–33) and imaging (13–21, 23) studies, and by lesion studies relating damage to either of these structures to impaired memory performance (22, 33).

In conclusion, PET-rCBF imaging reveals two contrasting changes in the long-term memory network that is active in the delayed recognition of abstract visual shapes. The first concerns the left fusiform gyrus, in which differential activation is significantly decreased after either memory challenge. Because a challenge to either memory storage or recognition produces similar effects in this region, we suggest that this region may be involved in matching stored and presented stimuli during recognition. The second change concerns the posterior thalamus, where memory challenges enhance the differential activation during recognition. Activation in the posterior thalamus is suggestive of stronger or more frequent retrieval attempts in an effort to reactivate the stored information.

We thank M. De Paep, C. Fransen, S. Vleugels, M. Heroes, T. De Groot, D. Crombez, W. Costermans, J. Nuyts, and R. Vandenberghe for technical assistance, and Dr. R. Saunders, S. Raiguel, and R. Vogels for comments on the manuscript. We are much indebted to Prof. R. Frackowiak for making the SPM software available and to Prof. P. Suetens for providing us with the MIRIT software. This study was supported by IUAP22-Vision and Memory, and by Grants 9.0007.88, 3.0043.89, 3.0095.92, 3.0227.95 (G.O.), and S2/5-AV-E131 (A.R.) from the Research Council-Flanders. A.R. and P.D. are postdoctoral fellows. L.C. is a research assistant of the Research Council-Flanders.

1. Ghoneim, M. M., Hinrichs, J. V. & Mewaldt, S. P. (1984) *Psychopharmacology* **82,** 291–295.
2. Hommer, D., Weingartner, H. & Breier, A. (1993) *Psychopharmacology* **112,** 455–460.
3. Rosier, A., Vogels, R. & Orban, G. A. (1996) *NeuroReport* **7,** 1899–1904.
4. Kovács, G., Vogels, R. & Orban, G. A. (1995) *Proc. Natl. Acad. Sci. USA* **92,** 5587–5591.
5. Zahn, C. & Roskies, R. (1972) *IEEE Trans. Comput.* **21,** 269–281.
6. Vandenberghe, R., Dupont, P., Bormans, G., Mortelmans, L. & Orban, G. A. (1995) *NeuroImage* **2,** 306–313.
7. Tulving, E., Markowitsch, H., Craik, F. I. M., Habib, R. & Houle, S. (1996) *Cereb. Cortex* **6,** 71–79.
8. Bond, A. & Lader, M. (1974) *Br. J. Med. Psychol.* **47,** 211–218.
9. Fox, P. T., Mintum, M. A., Raichle, M. E., Miezin, F. M., Allman, J. M. & Van Essen, D. C. (1986) *Nature (London)* **323,** 806–809.
10. Johnson, K. O. (1980) *J. Neurophysiol.* **43,** 1771–1792.
11. Talairach, J. & Tournoux, P. (1988) *Co-planar Stereotaxic Atlas of the Human Brain* (Thieme, New York), p. 122.
12. Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D. & Frackowiak, R. S. J. (1995) *Hum. Brain Mapp.* **2,** 189–210.
13. Courtney, S. M., Ungerleider, L. G., Keil, K. & Haxby, J. V. (1996) *Cereb. Cortex* **6,** 39–49.
14. Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L. & Petersen, S. E. (1991) *J. Neurosci.* **11,** 2383–2402.
15. Kapur, N., Friston, K. J., Young, A., Frith, C. D. & Frackowiak, R. S. J. (1995) *Cortex* **31,** 99–108.
16. Moscovitch, M., Kapur, S., Köhler, S. & Houle, S. (1995) *Proc. Natl. Acad. Sci. USA* **92,** 3721–3725.
17. Roland, P. E. & Gulyás, B. (1995) *Cereb. Cortex* **5,** 79–93.
18. Sergent, J., Ohta, S. & MacDonald, B. (1992) *Brain* **115,** 15–36.
19. Orban, G. A., Dupont, P., Vogels, R., Bormans, G. & Mortelmans, L. (1997) *Eur. J. Neurosci.* **9,** 246–259.
20. Corbetta, M., Miezin, F. M., Shulman, G. L. & Petersen, S. E. (1993) *J. Neurosci.* **13,** 1202–1226.
21. Fletcher, P. C., Frith, C. D., Grasby, P. M., Shallice, T., Frackowiak, R. S. J. & Dolan, R. J. (1995) *Brain* **118,** 401–416.
22. Aggleton, J. P. & Mishkin, M. (1983) *Neuropsychologia* **21,** 189–197.
23. LaBerge, D. & Buchsbaum, M. S. (1990) *J. Neurosci.* **10,** 613–619.
24. Maes, F., Collignon, A., Vandermeulen, D., Marchal, G. & Suetens, P. (1997) *IEEE Trans. Med. Imaging* **16,** 187–198.
25. Matthew, E., Andreason, P., Pettigrew, K., Carson, R. E., Herscovitch, P., Cohen, R., King, C., Johanson, C.-E., Greenblatt, D. J. & Paul, S. M. (1995) *Proc. Natl. Acad. Sci. USA* **92,** 2775–2779.
26. Clark, W. G., Brater, D. C. & Johnson, A. R. (1988) in *Goth's Medical Pharmacology*, ed. Bircher, S. (Mosby, St. Louis), 12th Ed., p. 835.
27. Sáry, G., Vogels, R. & Orban, G. A. (1993) *Science* **260,** 995–997.
28. Fahy, F. L., Riches, I. P. & Brown, M. W. (1993) *Exp. Brain Res.* **96,** 457–472.
29. Kobatake, E. & Tanaka, K. (1994) *J. Neurophysiol.* **71,** 856–867.
30. Mishkin, M. & Murray, E. A. (1994) *Curr. Opin. Neurobiol.* **4,** 200–206.
31. Nakamura, K. & Kubota, K. (1996) *Behav. Brain Res.* **77,** 53–77.
32. Colombo, M. & Gross, C. G. (1994) *Behav. Neurosci.* **198,** 443–455.
33. Vogels, R., Saunders, R. C. & Orban, G. A. (1997) *Eur. J. Neurosci.* **9,** 229–245.
34. Vandenberghe, R., Dupont, P., De Bruyn, B., Bormans, G., Michiels, J., Mortelmans, L. & Orban, G. A. (1996) *Brain* **119,** 1263–1276.
35. Posner, M. I. & Petersen, S. E. (1990) *Annu. Rev. Neurosci.* **13,** 25–42.
36. Pardo, J. V., Fox, P. T. & Raichle, M. E. (1991) *Nature (London)* **349,** 61–64.
37. Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S. J. & Dolan, R. J. (1993) *Brain* **116,** 1–20.
38. Kapur, S., Craik, F. I. M., Jones, C., Brown, G. M., Houle, S. & Tulving, E. (1995) *NeuroReport* **6,** 1880–1884.
39. Petrides, M. (1991) *Proc. R. Soc. London Ser. B* **246,** 293–298.
40. Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M. & Houle, S. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 2016–2020.
41. Petrides, M. (1996) *Semin. Neurosci.* **8,** 57–63.
42. Zola-Morgan, S. M. & Squire, L. R. (1990) *Science* **250,** 288–290.
43. Squire, L. R. (1992) *Psychol. Rev.* **99,** 195–231.
44. Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O. & Raichle, M. E. (1992) *Proc. Natl. Acad. Sci. USA* **89,** 1837–1841.
45. Alvarez, P. & Squire, L. R. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 7041–7045.
46. Baddeley, A., Lewis, V., Eldridge, M. & Thomson, N. (1984) *J. Exp. Psychol.* **113,** 518–540.