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Active hippocampus during nonconscious memories

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Abstract

The hippocampal formation is known for its importance in conscious, declarative memory. Here, we report neuroimaging evidence in humans for an additional role of the hippocampal formation in nonconscious memory. We maskedly presented combinations of faces and written professions such that subjects were not aware of them. Nevertheless, the masked presentations activated many of the brain regions that unmasked presentations of these stimuli did. To induce a nonconscious retrieval of the faces and face-associated occupational information, subjects were instructed to view the previously masked faces and to guess the professional category of each person—academic, artist, and workman. Guessing the professional category of previously masked versus new faces activated the left and right hippocampal formation and right perirhinal cortex as well as bilateral fusiform areas and fronto-temporal areas known to mediate the retrieval of semantic information. These activations within the semantic processing system suggest that conceptual knowledge

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acquired during masking was nonconsciously retrieved. Our data provide clues to an analogous role of the hippocampus in conscious and nonconscious memory.

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1. Introduction

Human long-term memory has been divided into two forms, declarative and nondeclarative memory (Milner, Squire, & Kandel, 1998; Squire, 1992). Declarative memories are experienced consciously whereas nondeclarative memories go without consciousness. Extensive experimental psychological, neuropsychological, and neuroimaging evidence demonstrates that declarative and nondeclarative memory dissociate in their functional characteristics and in their underlying neural substrates. Perceptual priming, conceptual priming, and procedural learning are well-studied forms of nondeclarative memory. They have been dissociated from declarative memory on grounds of three convergent sources of evidence: first, priming and procedural learning are often normal in patients with impaired declarative memory due to medial temporal damage including the hippocampal formation; second, normal subjects exhibit performance dissociations between tests of declarative memory and tests of priming; and third, neuroimaging studies of perceptual and conceptual priming demonstrate modality-specific cortical deactivations and deactivations in amodal language areas, respectively, but no activation changes in the medial temporal lobe including the hippocampal formation (Gabrieli, 1998; Schacter & Buckner, 1998).

Yet, a role of the hippocampal formation in certain forms of nondeclarative memory is suggested by the observation of impaired associative priming in amnesic patients with severe bilateral hippocampal damage. Despite intact word-stem completion priming for single words, such patients exhibited abnormal associative priming with word-stem completion (Gabrieli, 1998; Schacter, 1998; Schacter & Buckner, 1998). Chun and Phelps (1999) found that amnesic patients with hippocampal damage failed to nonconsciously learn the relationships between cues and the context in which they were presented, suggesting a role for the hippocampal region in nonconscious associative memory. Moreover, Curran (1997) found that amnesic patients do not learn higher-order information in a serial reaction time task as well as control subjects. These results suggest that amnesic patients may have an associative learning and retrieval impairment, even when learning and retrieval are nonconscious, supporting the notion that some associative learning and retrieval tasks may depend on the hippocampal formation—irrespective of the subject's level of awareness of learning and retrieval. On the other hand, there are reports of healthy subjects who failed to show associative priming with the stem completion task. Only subjects who were aware that the test items were previously encountered showed associative priming effects (Bowers & Schacter, 1990; McKone & Slee, 1997). These

reports imply that not only intact medial temporal structures but also awareness of the relation between study and test may be necessary for associative priming effects (Schacter, 1998).

We have recently reported that the human hippocampal formation is strongly activated when healthy subjects form new semantic associations among items in declarative memory (Henke, Buck, Weber, & Wieser, 1997, 1999). These results and the above-mentioned findings raise the question of whether the hippocampal formation is even involved in the nonconscious encoding and retrieval of stimulus pairs. We tried to answer this question in the present neuroimaging study with healthy volunteers.

Precautions were taken to exclude both conscious awareness of retrieval and conscious awareness of stimulus perception to avoid the confounding effect of declarative memory. Nonconsciousness of encoding was achieved by brief (17-ms) presentations of the visual stimulus pairs which were immediately preceded and followed by presentations (183 ms) of black-and-white dot patterns (backward and forward pattern-masking). Masking procedures interrupt the processing of the stimulus (Kovács, Vogels, & Orban, 1995; Rolls & Tovee, 1994). The interval between the onset of the stimulus and the mask is critical for the visibility of the stimulus. The briefer this interval is, the less detectable becomes the stimulus. Behavioral evidence indicates that masked words which the viewer cannot consciously perceive may still be analyzed visually, orthographically, phonologically, and even semantically (Cheesman & Merikle, 1984; Dehaene et al., 1998a, 2001; Greenwald, Draine, & Abrams, 1996).

The method to determine awareness is a critical issue in studies of nonconscious information processing. There are two methods to determine the stimulus–mask interval at which the viewer loses awareness of all stimulus properties: the subjective and the objective method. The subjective awareness threshold is based on the viewers' introspective reports of their perceptual experiences. This method has much been criticized as unreliable or even ineffective in preventing awareness of stimulus perception (e.g., Cheesman & Merikle, 1984; Eriksen, 1960; Holender, 1986). Therefore, we use the objective method to determine the awareness threshold in the present study. The objective definition of the awareness threshold relies on the viewers' discriminative capabilities as typically measured in forced-choice tasks concerning visual or semantic characteristics of stimuli. For example, viewers have to decide between a stimulus and a distracter immediately following the masked presentation of the stimulus. The objective awareness threshold is set at the point where the viewers' selection accuracy between the stimulus and a distracter reaches chance. This method safely excludes awareness of stimulus perception, but by its definition it leaves the experimenter without a behavioral indication of nonconscious stimulus processing. In this study, we, therefore, inferred the presence and nature of visual and cognitive processes during stimulus encoding and retrieval from the activation changes in the brain as measured by functional magnetic resonance imaging (fMRI). Functional MRI is a noninvasive technique for localizing regional changes in blood oxygenation, a correlate of neural activity. Most neuroimaging studies aim to identify brain areas whose activation correlates tightly with an aspect of the subjects' behavior. If the logic of neuroimaging is correct, however, it should also be possible to reverse this direction

of reasoning (Dehaene et al., 1998b). Toward this end, face–word pairs were chosen as stimulus material, because the neural pathways involved in word and face encoding and retrieval have been extensively studied in neurological patients and normals with neuroimaging. The expected locations of brain activations indicative of face and word processing and retrieval were determined a priori on grounds of this literature. In addition, we included a conscious encoding and retrieval condition run with the same subjects to replicate the published neuroimaging findings within our paradigm. For conscious encoding, the face–word pairs were presented for 3 s and without masks. The stimulus pairs used for conscious and nonconscious encoding consisted of a face and a written profession typed below the face.

Minutes following nonconscious encoding, a nonconscious retrieval of the faces and associated professions was initiated by presenting the faces again, without masks, with the instruction to guess the professional category of each individual—academic, artist, and workman—and to press one of three keys accordingly. The required translation from the profession (e.g., gardener) to the professional category (workman) was intended to reactivate established semantic rather than visual or phonological face–profession associations. The retrieval instruction for the conscious retrieval condition was to remember the professional category of the presented person.

We attempted to keep the nature of information processing as equal as possible during conscious and nonconscious encoding/retrieval in order to vary the level of awareness of encoding/retrieval alone.

2. Materials and methods

2.1. Subjects

We examined 11 normally sighted, right-handed men (age: 21–29, mean 25.5) without current or past neurological or psychiatric diagnoses. Informed consent was obtained after the nature and possible consequences of the fMRI study were explained. Yet, subjects were not told until the end of the experiment that stimuli were briefly flashed between masks.

2.2. Experimental design

2.2.1. Stimuli

Stimuli consisted of 144 black-and-white full frontal portraits of unknown bald human faces with neutral expressions and without paraphernalia (Kayser, 1984). Stimuli were digitized and degraded in contrast. Next, we selected 10 common academic, 10 artistic, and 10 workman professions. Professions which qualify for more than one of these three professional categories were not considered. The selected professions were assigned randomly and in equal portions to the faces. The professions were typed below the faces (Fig. 1a). The resulting face–profession combinations were then divided into six sets of 24 stimuli. One set of faces was used per condition; sets were balanced across conditions to distribute stimulus generated effects.

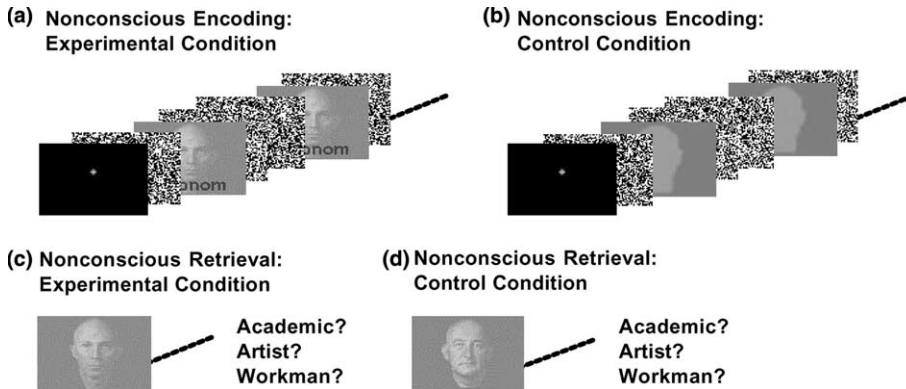


Fig. 1. Experimental design. Example stimuli, visual noise masks, and fixation slides are presented from a stimulation sequence displayed during the fMRI time-series on “nonconscious encoding” ((a) experimental condition; (b) control condition). Following “nonconscious encoding,” the previously masked faces ((c) experimental condition) and new faces ((d) control condition) were presented in the fMRI time-series on “nonconscious retrieval” with the instruction to guess the professional category (academic, artist, workman) of each face. Stimuli are reproduced from the book “Heads” by permission of Kayser (1984).

2.2.2. Behavioral tasks

Data were acquired in four fMRI time-series. For all subjects, the two fMRI time-series on conscious encoding and retrieval followed the two fMRI time-series on nonconscious encoding and retrieval to leave subjects ignorant of subliminal presentations and to avoid visual search during the masked presentations.

In the experimental condition of the fMRI time-series “nonconscious encoding,” we presented a set of 24 face–profession pairs masked by visual noise patterns to exclude conscious perception of stimuli (see “Masking Paradigm”). The subjective percept of this presentation consisted of moving grains, interrupted by a visual fixation cross (Fig. 1a). In the control condition of this time-series, we maskedly presented a facial contour without physiognomy and with no professions added (Fig. 1b). Subjects did not know that subliminal stimuli were presented. Their percept of the presentation in the experimental condition was identical to their percept of the presentation in the control condition. The instruction for both conditions was to keep attentive and to focus gaze on the fixation cross.

To test for a nonconscious retrieval of the faces and face–profession associations, a second fMRI time-series “nonconscious retrieval” was carried out. In the experimental condition of this time-series, the previously masked 24 faces were presented again, with no professions added and without masks, for 3 s each (Fig. 1c). In the control condition of this time-series, a set of 24 faces that had not been presented previously was shown (Fig. 1d). The task in both conditions was to guess the professional category of each individual—academic, artist, and workman—and to press one of three keys accordingly.

In the experimental condition of the fMRI time-series “conscious encoding,” a further set of 24 face–profession pairs was presented, without masks and without

fixation crosses, each pair for 3 s. Subjects were instructed to watch the faces and to read the professions (incidental encoding). The control condition of this fMRI time-series was the same as the control condition of “nonconscious encoding,” i.e., a masked facial contour was repeatedly presented.

The last fMRI time-series was “conscious retrieval” which tested the retrieval of the faces and face–profession associations. In the experimental condition of this fMRI time-series, the previously presented 24 faces were displayed again (with no professions added), for 3 s each, with the instruction to remember the presented person’s profession, to translate it into the correct higher category—academic, artist, and workman—and to press the designated key accordingly. In the control condition of this fMRI time-series, a set of 24 faces that had not been presented previously was shown, each face for 3 s, with the instruction to guess the professional category of each person.

2.2.3. *Functional MRI design*

Functional MRI data were collected in four time-series (see Behavioral Tasks). Trials were blocked per condition. There were six alternating epochs of 24 s per fMRI time-series; three epochs for the experimental condition and three epochs for the control condition. The six epochs of a time-series alternated according to A–B–A–B–A–B or B–A–B–A–B–A. Eight stimuli were presented per epoch. The delay time between the encoding and the retrieval scans was 5 min. The switch between the task for the experimental and the task for the control condition of “conscious retrieval” was indicated by a briefly flashed signal: “R” for “remember the profession” and “G” for “guess the profession.” The computer-driven stimulation was back-projected with an LCD projector on a screen that subjects could watch through a mirror which was attached to the head coil. Our study protocol was approved by the Human Studies Committee of the Department of Neurology, University Hospital Zurich.

2.3. *Masking paradigm*

An interstimulus forced-choice task remains the “gold standard” for the definition of awareness in experimental psychology (Cheesman & Merikle, 1984; Greenwald et al., 1996; Holender, 1986). Therefore, we chose to assess awareness of stimulus perception objectively. To obviate the need for subjects to be informed of the presence of masked stimuli before the study so that findings would not be confounded by explicit attempts to detect the stimuli, we assessed awareness in a separate group of 14 normally sighted subjects. In this behavioral study, we verified that the forced-choice responses concerning stimulus attributes were at chance following the masked presentation of the stimuli. In the first run of this study, 24 faces were maskedly presented, each followed by the forced-choice between two faces, the stimulus and a distracter. The instruction was to decide which of the two faces had been presented maskedly. In the second run of this study, 24 face–profession pairs were maskedly presented, each immediately followed by the presentation of the stimulus face alone. The task was to guess the professional category—academic, artist, and workman—of each stimulus face and to press one of three designated keys

accordingly. The response was scored as a hit, if the professional category (e.g., workman) of the previously presented profession (e.g., gardener) was selected. The hit rates did not differ from chance in either run (faces: $M = 12.4$, $SD = 1.9$; $t(13) = 0.76$, $p > .05$; professions: $M = 8.3$, $SD = 1.9$; $t(13) = 0.69$, $p > .05$). We, therefore, concluded that the masked stimuli were presented below the objectively defined awareness threshold and decided to use this stimulation sequence in the fMRI experiment. Each stimulus (S) was presented six times within 3 s for 17 ms, visual noise masks (M) were presented for 183 ms, and a fixation cross (F) for 233 ms, in the sequence F–M–S–M–M–S–M–F–M–S–M–M–S–M–F–M–S–M–M–S–M. On questioning at the end of the fMRI experiment, no subject reported to have perceived or even suspected anything else than moving grains during the masked sequences.

2.4. *Technique of stimulus presentation*

The computer-driven stimulation (640×480 resolution, 60-Hz refresh rate, 8-bit color depth) was back-projected with a Sony LCD projector (60-Hz refresh rate) on a screen standing in front of the scanner. Subjects could watch the presentations on this screen through a mirror which was attached to the head coil of the MR scanner.

We used a stimulus presentation program of our own devising “Scope” (M. Dürsteler, University Hospital Zürich). Scope was written for the Microsoft Windows operating Systems Windows NT 4.0. It uses routines from the Microsoft Direct Draw SDK Version 3.0A to synchronize the stimulus change with the vertical retrace of the graphic card. The refresh rate of the computer’s graphic card was 60 Hz. At this frequency, our LCD projector synchronized itself to the graphic card’s vertical retrace rate. The shortest presentation time which can be achieved is the time between two vertical retraces which is 16.67 ms with our equipment. The timing of the Scope program was verified with an array of photo transistors sitting on the computer display and with a digital impulse emitted by Scope just after the flipping of the stimuli. Their output was observed on a digital oscilloscope while Scope was running with a sequence of special black-and-white images. Scope’s clock reading was found to be accurate to 1 ms. The synchronization of the LCD projector was examined using a Spectra Pritchard photometer directed to the projection screen. We observed the photometer’s analog output together with Scope’s flipping impulses on a digital oscilloscope while the program was running a sequence of alternating black-and-white images with a presentation time of 16.67 ms per image, i.e., the shortest presentation time which can be achieved. The photometer’s analog output and Scope’s flipping impulses were found to be fully synchronized.

2.5. *Image acquisition and analysis*

Functional T2*-weighted images with a matrix size of 128×128 (voxel size $2 \times 2 \times 4$ mm) were obtained on a GE 1.5 T Signa MR scanner with an echoplanar single shot pulse sequence (EPI) using an axial slice orientation (TR 4 s, flip angle 50° , TE 50 ms, 30 slices of 4 mm). Volumes were realigned to the first volume (SPM99b; Friston et al., 1995a). A mean image was spatially normalized into

stereotaxic space (standard EPI template SPM99b) (Friston et al., 1995b). Data were then smoothed with an 8 mm (FWHM) isotropic Gaussian kernel. Data analysis was calculated voxel by voxel modeling the conditions as stimulus functions—box car function convolved with a hemodynamic response function—applying the general linear model (SPM99b; fixed effects model). The resulting within-subject effects of each subject were then further analyzed in a second level analysis (SPM99b; random effects analysis) to obtain between-subjects effects. The second level analysis accounts for the variance of response from subject to subject. It was also performed voxel by voxel and consists of a one-sample t test upon the computed contrast files of each single subject (Holmes & Friston, 1998; see <http://www.fil.ion.ucl.ac.uk/spm/RFX-poster.pdf>). For the group comparisons of the experimental versus the control conditions the height threshold was set at $T = 4.14$ which corresponds to a p of .001 uncorrected for multiple comparisons. This threshold is justified by a priori predictions of regions with activation increases during the experimental conditions. For the reversed contrasts, control versus experimental condition, we used a corrected height threshold of $p = .05$. The within-subject results were thresholded at $T = 2.35$ ($p = .01$, uncorrected).

3. Results

3.1. Behavioral results

3.1.1. Nonconscious retrieval

Accuracy in guessing the professional categories in the experimental condition (maximal score = 24; $M = 7.09$; $SD = 2.70$) differed neither from chance ($M = 8$; $t(10) = -1.11$; $p > .05$, two-tailed) nor from the performance during the control condition ($M = 8.54$, $SD = 2.29$; $t(10) = -1.09$; $p > .05$, two-tailed).

3.2. Conscious retrieval

Accuracy in remembering the professional categories of faces in the experimental condition (maximal score = 24; $M = 9.72$, $SD = 2.00$) was better than chance ($M = 8$; $t(10) = 2.85$; $p < .05$, two-tailed) and better than accuracy in the control condition ($M = 7.63$, $SD = 1.43$; $t(10) = 2.46$; $p < .05$). The performance in the conscious experimental condition was significantly better than the performance in the nonconscious experimental condition of the retrieval scans ($t(10) = 2.94$, $p = .007$). We were not collecting accuracy measures for face recognition, but the subjects reported after the experiment that they had easily recognized the “old” faces.

3.3. Imaging results

In the following, we report activation changes in the expected brain areas during the four fMRI time-series and draw inferences about visual and cognitive processes during the scans on nonconscious encoding and retrieval. The predicted regions of

Table 1
Functional MRI results from the group of subjects

Brain region	BA	Coordinates			T value
		x	y	z	
(A) Nonconscious encoding					
L cuneus	17	-12	-94	12	6.3
L s occipital g	19	-14	-92	24	5.6
R lingual g	18	14	-90	-16	5.3
R fusiform/lingual g	19	18	-72	-8	4.7
L fusiform g	19	-40	-70	-20	4.2
L s temp g	22	-56	-40	16	4.2
R i front g	47	44	24	-8	4.3
R i front g	44	46	10	16	4.2
R i front g	45	40	22	4	4.2
(B) Nonconscious retrieval					
R hipp formation		20	-8	-24	4.9
L hipp formation		-22	-4	-28	4.3
R perirhinal		36	-14	-32	7.2
R fusiform g	19	24	-68	-12	6.5
L fusiform g	19	-40	-66	-16	4.4
L fusiform g	37	-42	-50	-24	4.5
L m temp g	37	-44	-66	4	6.0
L m temp g	21	-48	-48	8	5.8
L m/s temp g	21/22	-54	-26	-8	4.8
L s temp g	22	-56	-4	-4	5.2
L s temp g	22	-50	-8	4	5.2
R s temp g	22	58	-40	16	7.4
R i front g	47	50	38	-4	6.2
(C) Conscious encoding					
L hipp formation		-16	-4	-28	5.8
R hipp formation		18	-6	-24	5.8
L lingual g	17	-30	-92	4	5.5
L i occipital g	19	-46	-76	-20	8.5
R i occipital g	18	34	-94	-4	6.4
R i occipital g	19	46	-78	-20	13.9
R i temp/fusiform g	37	44	-58	-24	10.2
L fusiform g	37	-38	-54	-24	8.8
L s temp g	22	-66	-32	-4	4.4
R i front g	47	40	44	-16	5.6
R i front g	44/45	52	24	24	9.1
L i front g	44	-46	14	20	4.6
L i front g	45	-40	20	24	7.7
R s temp g	22	56	-2	-8	-13.4
R cingulate g	31	2	-42	44	-13.4
(D) Conscious retrieval					
R parah g		20	-50	0	6.9
L i temp g	37	-54	-54	-28	4.2

Table 1 (continued)

Brain region	BA	Coordinates			<i>T</i> value
		<i>x</i>	<i>y</i>	<i>z</i>	
R s temp g	22	46	–8	–12	4.7
L i front g	44/45	–44	16	16	4.5
R i front g	47	40	32	–12	4.8

Note. Results of the comparison between the experimental and the control condition of the fMRI time-series are presented in A for “nonconscious encoding,” in B for “nonconscious retrieval,” in C for “conscious encoding,” and in D for “conscious retrieval.” Results are indicated by brain region (column 1), estimates of Brodmann’s area (BA, column 2), and in 3D coordinate space (columns 3–5; *x*, *y*, *z* after standard EPI template SPM99b) (Friston et al., 1995b). The magnitudes of differences in brain activation between conditions are expressed in *T* values (column 6). The height threshold of activation differences resulting from the comparison experimental versus control was set at $T = 4.14$, $p = .001$, uncorrected for multiple comparisons because locations were a priori predicted. The height threshold for the reverse contrasts (control versus experimental; negative *T* values) was set at $T = 13.08$, $p = .05$, corrected for multiple comparisons. L, left; R, right; i, inferior; m, middle; s, superior; front, frontal; temp, temporal; hipp, hippocampal; parah, parahippocampal; g, gyrus.

activation increases in the experimental versus the control condition of each scan were the inferior frontal gyri (BA 44, 45, 47), the temporal lobes (BA 21, 22, 37, 38), and primary and secondary visual cortices (BA 17, 18, 19).

3.3.1. Nonconscious encoding

The comparison between the experimental and the control condition of “non-conscious encoding” maps brain activation changes which underlie the encoding of the faces, the encoding of the words, and the process of associating the faces with the words. This comparison was computed with the data of the whole group. It revealed activation foci in the primary and secondary visual cortices, in the “fusiform face area” (Kanwisher, McDermott, & Chun, 1997; Wada & Yamamoto, 2001) in the right fusiform gyrus, and in the “visual word form area” (Cohen et al., 2000; Dehaene et al., 2001; Fiez & Petersen, 1998; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999) in the left fusiform gyrus (Table 1A), indicating that the masked faces and words were visually analyzed and possibly encoded. There were further activation foci in the right inferior frontal gyrus in Brodmann’s area (BA) 44, 45, 47 and as a trend ($p = .002$) also in the left-side BA areas 44 and 47. These areas have previously been associated with the retrieval of semantic knowledge (Demb et al., 1995; Gabrieli et al., 1996; Kapur et al., 1994; Price, Wise, & Frackowiak, 1996; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). A further activation focus was located in the left superior temporal gyrus (BA 22). The middle and superior temporal gyri have been found to comprise storage sites of associative–semantic and lexical–semantic information (Hodges, Patterson, Oxbury, & Funnell, 1992; Price et al., 1996; Price, Moore, Humphreys, & Wise, 1997; Pugh et al., 1996; Vandenberghe et al., 1996; Warrington, 1975) (Table 1A). The activations in these fronto-temporal regions suggest that the masked words and faces were analyzed up to the semantic level. This contrast does not, however, reveal whether in addition

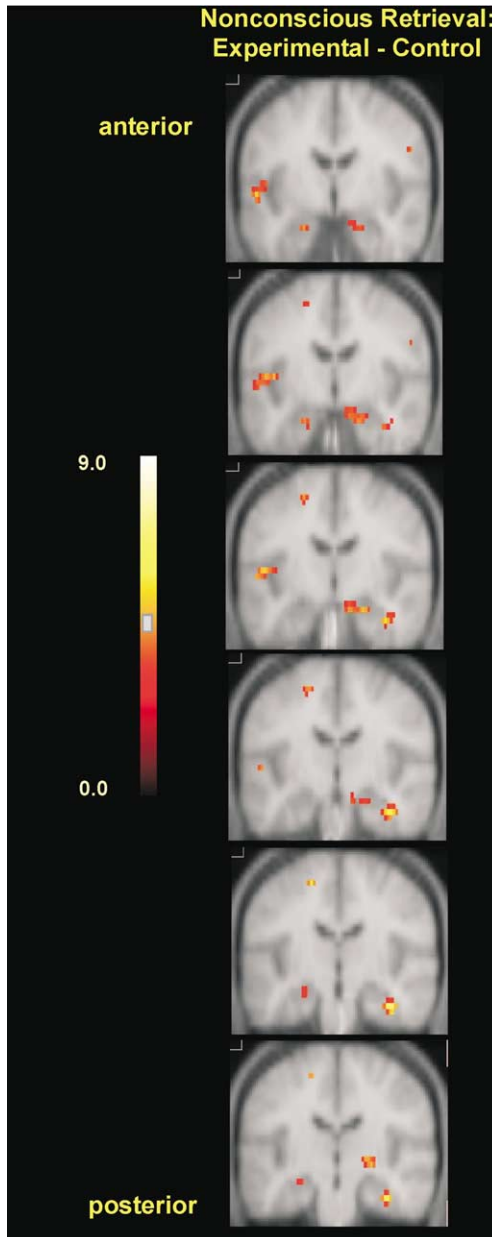


Fig. 2. Locations of medial temporal activations resulting from the comparison experimental versus control condition of the nonconscious retrieval scan. Displayed are functional group data on the group's mean anatomical image which was matched to the functional images and brought into the same stereotaxic space as the functional data. Six consecutive coronal cuts are shown with activation differences displayed as color coded T values (0.0–9.0). The right side of images is the right side of the brain.

semantic associations have been formed between the faces and words. The left anterior hippocampal formation showed a trend toward an increase of activation in the experimental condition ($p = .004$). Differences resulting from the reversed contrast did not reach statistical significance.

3.4. Nonconscious retrieval

The comparison between the experimental and the control condition of “non-conscious retrieval” maps brain activation changes which underlie the retrieval of the faces and face-associated occupational information. This comparison was computed with the data of the whole group. It yielded bilateral activation foci in the anterior hippocampal formation and in the right perirhinal cortex (Fig. 2, Table 1B). This comparison yielded activation foci in the same fusiform areas that had already been activated during the perception of the masked faces and words (Table 1B). This reactivation points to a recovery of faces and possibly associated word forms. Importantly, activation foci were located in the semantic processing system, i.e., in the left middle (BA 21, 37) and bilateral superior temporal gyri (BA 22) (Hodges et al., 1992; Price et al., 1996; Price et al., 1997; Pugh et al., 1996; Vandenberghe et al., 1996; Warrington, 1975) as well as in the right inferior frontal gyrus (BA 47) and—as a trend—in the left inferior frontal gyrus (BA 45 at 0.001; BA 47 at 0.002) (Demb

Table 2
Functional MRI results from the individual subjects

Activated brain region	Nonconscious encoding: experimental versus control (subjects listed by their numbers)	Nonconscious retrieval: experimental versus control (subjects listed by their numbers)
R hipp formation	3, 5, 6, 7	3, 7, 9
L hipp formation	3, 5, 10, 11	1, 2, 4, 6, 9, 10
R parah cortex	2, 3, 4, 5, 6, 7, 9	1, 2, 3, 4, 5, 9
L parah cortex	5, 6, 7, 8,	1, 3, 9, 11
R fusiform g	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	1, 2, 3, 4, 5, 6, 7, 9, 10, 11
L fusiform g	1, 2, 3, 4, 5, 6, 7, 8, 9, 11	1, 2, 3, 4, 5, 6, 8, 9, 10, 11
L i front g	2, 3, 4, 5, 6, 7, 8, 9, 10, 11	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
R i front g	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	1, 3, 4, 5, 6, 9, 10, 11
L m temp g	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
R m temp g	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
L s temp g	2, 3, 4, 6, 7, 8, 9, 10, 11	1, 2, 5, 6, 8, 9, 10, 11
R s temp g	2, 3, 4, 5, 6, 9	1, 2, 3, 4, 5, 7, 8, 11

Note. Displayed are the results from the comparison between the experimental and the control condition of the fMRI time-series on “nonconscious encoding” (column 2) and “nonconscious retrieval” (column 3). Locations of resulting brain activation differences are indicated in the first column. Subjects are individually listed by their code numbers if they showed significant activation differences within the indicated brain region (cut-off: $T = 2.35$, $p = .01$, uncorrected for multiple comparisons because of hypotheses about the expected locations of activations). L, left; R, right; i, inferior; m, middle; s, superior; front, frontal; temp, temporal; hipp, hippocampal; parah, parahippocampal; g, gyrus.

et al., 1995; Gabrieli et al., 1996; Kapur et al., 1994; Price et al., 1996; Vandenberghe et al., 1996). The locations of these activations indicate that additional semantic operations accompanied the guessing of professions for previously masked faces versus new faces. These additional semantic operations correspond either to the retrieval of the previously presented faces alone or to the additional retrieval of face-associated occupational information acquired during encoding.

Differences resulting from the reversed contrast did not reach statistical significance. Even with a more liberal statistical criterion ($p = .001$, uncorrected) there were only two areas of activation difference possibly corresponding to an activation decrease in the experimental condition—one in the left superior (BA 6) and the other in the left middle (BA 10) frontal gyrus. Thus, we observed no deactivations in regions that may be related to the repeated visual or semantic analysis of the previously masked faces.

3.4.1. Analysis of individual subjects

The comparisons for nonconscious encoding and nonconscious retrieval were looked at within each individual subject ($n = 11$) to find out how consistently subjects contributed to the group effects (Table 2). The hippocampal formation was significantly activated in six out of eleven subjects during encoding and in eight subjects during retrieval. Fig. 3 shows time course data of subject 9 during nonconscious retrieval within a voxel of the head of the left hippocampal formation.

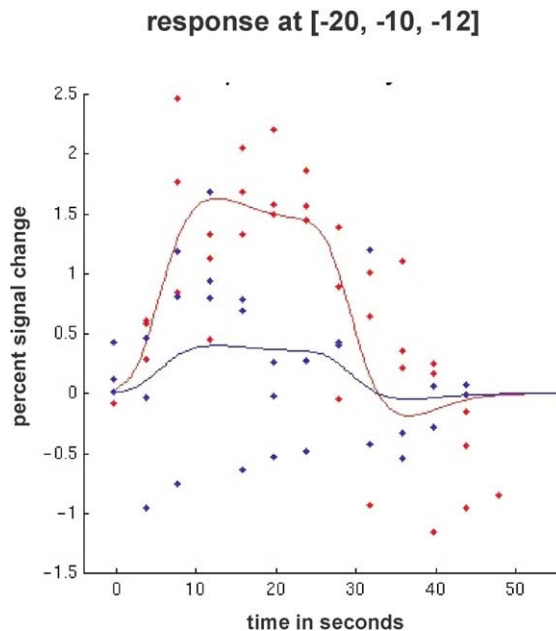


Fig. 3. Time course data of subject 9 during nonconscious retrieval within the voxel at coordinate position $-20, -10, -12$ in the head of the left hippocampal formation. Displayed is the fitted response and the adjusted data over time (in seconds; TR 4 s) for each of the three epochs of the control condition (blue) and the experimental condition (red) of the fMRI time-series on “nonconscious retrieval.”

Parahippocampal areas were activated in eight subjects during encoding and in seven subjects during retrieval. Taken together, ten of eleven subjects showed activation changes in the medial temporal lobe during encoding and during retrieval. The side and location of the significance of activation changes in the medial temporal lobe varied across subjects. This may be due to the nature of the stimulus material which was both verbal (words) and nonverbal (faces) or due to endogenous habitual processing characteristics (e.g., verbal coding or imagery) of each individual subject.

The right fusiform gyrus was activated in all subjects during encoding and in ten subjects during retrieval. The left fusiform gyrus was activated in ten subjects during encoding and retrieval. The left inferior frontal gyrus (BA 45 or 47) was activated in ten subjects during encoding and in all subjects during retrieval. The right inferior frontal gyrus (BA 45 or 47) was activated in all subjects during encoding and in eight subjects during retrieval. Both the left and right middle temporal gyri (BA 21 or 37) were activated in all subjects during encoding and retrieval. The left superior temporal gyrus (BA 22 or 38) was activated in nine subjects during encoding and in eight subjects during retrieval. The right superior temporal gyrus (BA 22 or 38) was activated in six subjects during encoding and in eight during retrieval.

3.4.2. *Conscious encoding*

The comparison between the experimental and the control condition of “conscious encoding” maps brain activation changes which underlie the conscious encoding of the faces and the words, and the process of associating the faces with the words. This comparison with the data of the whole group revealed activation foci within many of the brain regions that had been activated during nonconscious encoding. These activated regions included the right and left head of the hippocampal formation, primary and secondary visual cortices (BA 17, 18, 19), the right and left fusiform gyri (BA 37), the left superior temporal gyrus (BA 22) as well as the left and right inferior frontal gyri (BA 44, 45, 47). Moreover, the reversed contrast revealed two areas where activation was significantly smaller in the experimental than the control condition, namely in the right superior temporal gyrus (BA 22) and the cingulate gyrus (BA 31) (Table 1C).

3.4.3. *Conscious retrieval*

The comparison between the experimental and the control condition of “conscious retrieval” maps brain activation changes which underlie the conscious retrieval of the faces and face-associated occupational information. This comparison with the data of the whole group yielded activation foci in the right parahippocampal gyrus, the right superior temporal gyrus (BA 22), and the right inferior frontal gyrus (BA 47). These results correspond to those from the respective contrast on nonconscious retrieval. In addition, this comparison also yielded significant activation in the left inferior frontal gyrus (BA 44/45), while the activation change during nonconscious retrieval did not quite reach significance in this region. On the other hand, the left and right fusiform gyri exhibited significant activation changes during nonconscious retrieval, but showed only a trend toward an activation change during conscious retrieval (right fusiform gyrus at 0.002; left fusiform gyrus at 0.003) (Table 1D). Differences resulting from the reversed contrast did not reach statistical significance.

4. Discussion

We examined the nonconscious encoding and retrieval of face–word combinations by use of the objective method to determine the awareness threshold of stimulus presentation which excludes an above-chance accuracy in the nonconscious retrieval condition (Cheesman & Merikle, 1984; Greenwald et al., 1996; Holender, 1986; Merikle, 1992). Therefore, the presence and the nature of nonconscious processes during encoding and retrieval were inferred from fMRI signal differences in brain areas which are known to mediate the processing of faces and words. These expected brain areas were verified in two additional fMRI scans on conscious encoding and retrieval within the same subjects.

The expected activation foci were found in both the conscious and the nonconscious conditions of encoding and retrieval. The additional analysis of the individual subjects revealed activation foci in the expected brain regions in most of the subjects during nonconscious encoding and retrieval. The signal difference between the experimental and the control condition was larger during the scan on nonconscious retrieval than during the scan on nonconscious encoding. A likely reason for this variation might be the instruction during the retrieval scan which directed nonconscious processing while the instruction for encoding (“focus gaze on the fixation cross”) left the kind of processing open.

Unfortunately, although our subjects reported to have recognized the “old” faces in the conscious retrieval condition, their conscious retrieval of the associated professions was rather weak. Both of these processes, face recognition and the cued recall of the associated professions, were mapped in the fMRI contrast images. The low performance in the cued recall task, therefore, limits the comparison of the fMRI data from the conscious and the nonconscious retrieval conditions.

We found activation foci in the expected brain regions during the perception of the masked and unmasked face–profession combinations. These were located in bilateral visual areas, in the fusiform gyri (“fusiform face area” and “visual word form area”) as well as in bilateral inferior frontal gyri and left superior temporal areas which are known to mediate the retrieval of associative–semantic and lexical–semantic knowledge. These activation foci indicate that the masked faces and words underwent processing up to the semantic level. Fusiform areas and fronto-temporal regions were again activated later in the conscious and nonconscious retrieval conditions, where subjects were guessing (nonconscious condition) or remembering (conscious condition) the professional categories of the previously presented faces. From these activations in the visual and semantic processing system during the scan on nonconscious retrieval, we are inferring that the subjects had nonconsciously retrieved attributes of the previously presented faces and possibly additional face-associated occupational knowledge presented during encoding. The experimental design and these neuroimaging data do not allow for a distinction between the retrieval of facial information and face-associated occupational information because these components were mapped in the same contrast. The neuroimaging data do not allow conclusions to be drawn about how precisely the retrieved conceptual knowledge matched the information displayed during nonconscious encoding. Unfortunately, this experiment lacks behavioral data indicative of the presence and

nature of nonconscious retrieval processes. In the absence of such direct evidence for nonconscious retrieval processes, we present indirect evidence, namely neuroimaging results which we interpret based on previous knowledge about the functional neuroanatomy of face and word processing. A contamination of activations by conscious rather than nonconscious information processing can be excluded in this study because we used the objective method to determine the awareness threshold.

Importantly, the left and right hippocampal formation and right perirhinal cortex were significantly activated during nonconscious retrieval. There was also a trend toward left hippocampal activation during the nonconscious encoding of the face–profession combinations. Given the important role that the hippocampal formation has for conscious forms of memory, its activation during nonconscious processing suggests that it was involved in the nonconscious memory processes. This finding provides the first positive evidence for a role of the human hippocampal formation in a form of nonconscious learning and retrieval. As stated above, the design of this study does not permit differentiation of which of the task components had triggered activation in the medial temporal lobes. Further studies will pin down those components of nonconscious encoding and retrieval which drive activation in the medial temporal lobe.

A reason for the hitherto sparse evidence for a role of the hippocampal formation in nonconscious forms of memory might have been the kind of tests commonly used to assess nondeclarative memory. Unlike most priming tasks which engender the reprocessing of isolated single items, the recall tasks often used to assess declarative or episodic memory require the retrieval of spatial, temporal, and semantic associations. Therefore, by their nature most priming tasks are unlikely to challenge the typical functions of the human hippocampal formation. Such qualitative differences between tests of declarative and nondeclarative memory naturally engage different brain systems. In the present study, both the retrieval task used for conscious and the retrieval task used for nonconscious retrieval triggered the retrieval of faces and in addition induced a cued retrieval of face-associated occupational information. Also, the reported findings of impaired implicit memory in amnesic patients with medial temporal damage stem from studies with relational learning and retrieval tasks (Chun & Phelps, 1999; Curran, 1997; Gabrieli, 1998; Schacter, 1998; Schacter & Buckner, 1998). Our findings of medial temporal activations during nonconscious encoding and retrieval in healthy subjects complement these results in amnesic patients. Together with these observations in clinical groups, our data in healthy subjects provide clues to an analogous role of the hippocampus in conscious and nonconscious memory (Eichenbaum, 1999).

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