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ORIGINAL PAPER

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Hippocampal underactivation in an fMRI study of word and face memory recognition in schizophrenia

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Abstract Schizophrenia is a major mental disorder which is characterized by several cognitive deficits. Investigations of the neural basis of memory dysfunctions using neuroimaging techniques suggest that the hippocampus plays an important role in declarative memory impairment. The goal of this study was to investigate possible dysfunctions in cerebral activation in schizophrenic patients during both word and face recognition memory tasks. We tested 22 schizophrenics and 24 controls matched by gender, age, handedness and parental socioeconomic status. Compared to healthy volunteers, patients with schizophrenia showed decreased bilateral hippocampal activation during word and face recognition tasks. The whole brain analysis also showed a pattern of cortical and subcortical hypoactivation for both verbal and non-verbal recognition. This study provides further evidence of hippocampal involvement in declarative memory impairments of schizophrenia.

Key words hippocampus · word recognition · face recognition · schizophrenia

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Introduction

Schizophrenia is a syndrome characterized by several cognitive dysfunctions, one of the most important of which is memory disturbance. Declarative memory, usually divided into episodic (personal events) and semantic (facts), is primarily affected [49]. All processes of declarative memory are impaired in schizophrenic patients, but recognition is the aspect that is least affected [8, 10, 37]. To date, non-verbal memory has not been widely investigated. In a meta-analysis of 70 studies, only 8 reported data on recognition of non-verbal stimuli [2]. However, studies that have assessed non-verbal memory have also found it to be impaired [48], and a recent meta-analysis of 84 studies of recognition memory in schizophrenia found a greater impairment in figural than verbal recognition [37]. In that meta-analysis, data on face memory recognition were reported in only 3 studies.

The understanding of the origin of memory impairment in schizophrenia has been greatly enhanced by the development of structural and functional neuroimaging techniques [49]. Functional studies using SPECT, PET and MRI show a pattern of hypoactivation in the hippocampus and both hypoactivation and hyperactivation in the prefrontal cortex [49]. Beneath the apparent heterogeneity of the published findings on schizophrenia and memory, a consistent, robust pattern of group differences in memory processes is observed. Like neuropsychological studies, functional studies have mainly been performed using verbal tasks. In a meta-analysis by Achim and Lepage [1] only one study used face encoding, and one other used object encod-

ing. Interestingly, though the majority of the studies were performed with verbal stimuli, the right side of the hippocampus was more activated than the left.

In normal subjects, evidence from positron emission tomography (PET) studies showed that encoding of episodic memory involves the left prefrontal cortex, whereas retrieval is accompanied by enhanced right-sided prefrontal activity [15]. Kircher et al. [26] observed that anterior hippocampus is the region involved in both encoding and retrieval. In a review of 275 PET and fMRI studies, Cabeza and Nyberg [7] concluded that there is a clear effect of material lateralization. Objects, faces and spatial stimuli recruited the right temporal medial regions more, and verbal stimuli the left.

The patterns of verbal memory recognition in schizophrenics have been obtained with paradigms contrasting encoding and retrieval processes. The results have shown both increases and decreases in various cerebral regions [21, 23, 41].

Regarding non-verbal stimuli, in a paired object recognition task Lepage et al. [29] found that patients had hypoactivation in the left dorsolateral prefrontal and right inferior prefrontal regions but did not differ from controls in the hippocampal activation. Eyler Zorrilla et al. [14] examined the activation in four cerebral regions: the hippocampus, parahippocampal gyrus, inferior prefrontal cortex and fusiform gyrus during presentation of novel and repeated pictures, finding that repeated pictures produced more activations than the novel ones. Face recognition has mainly been used to investigate visual perception [39] or working memory processing [5, 53].

Voxel based morphometry studies showed that the medial temporal lobe is the most affected region in schizophrenics, and although the left side predominates, the reductions are usually bilateral [4, 42]. It is possible that reductions in the gray matter of the right hippocampus contribute to face recognition deficits in schizophrenic patients.

The novelty of the present study is to explore the cerebral activity of faces and words recognition in the same sample of schizophrenic patients.

In conclusion our aim was to identify the possible impairment of hippocampal structure and function in patients with schizophrenia during the performance of verbal and non-verbal memory task. This could contribute to the hypothesis about the abnormal asymmetry in the pathogenesis of schizophrenia [12]. We hypothesized that the left hippocampus may be disrupted predominantly during verbal recognition and the right hippocampus mainly during non-verbal recognition.

Methods and materials

Participants

Subjects were 24 healthy volunteers (12 male, 12 female) and 22 chronic schizophrenia patients (11 male, 11 female). The patients were recruited from the Psychiatry Service of the Hospital Clinic of Barcelona. The controls were recruited from the community via an advertisement. The patients were diagnosed on the basis of DSM-IV criteria, using the structural clinical interview (SCID), by agreement between two psychiatrists (R.C. and M.B.). Clinical symptoms were rated by using the positive and negative syndrome scale (PANSS) [24]. Schizophrenia subtypes included 18 paranoid, 1 disorganized, 2 undifferentiated and 1 residual. All patients were receiving neuroleptic medication equivalent to a mean of 186.30 mg (SD = 129.76) of chlorpromazine per day (Clozapine = 11; Olanzapine = 4; Aripiprazole = 2; Ziprasidone = 2; Risperidone = 2; Risperidone C = 1). The mean duration of illness was 10.0 years (SD = 5.74).

The control group was matched for gender, age, and parental socio-economic status distribution to the group of schizophrenic patients (Student's *t* test). All patients and volunteers were right-handed. Healthy comparison subjects had no history of mental illness, nor first-degree relatives with psychiatric disorder. Table 1 summarizes the demographic and clinical characteristic of the samples. After a full explanation of the study, all subjects gave written informed consent to a protocol approved by the ethics committee at the Hospital Clinic of Barcelona.

Table 1 Demographic and clinical characteristics of the sample

	Patients with schizophrenia		Normal comparison subjects		
Number of subjects	22		24		
Gender (male/female)	11/11		12/12		
	Mean	SD	Mean	SD	*P*
Age (years)	31.7	6.61	31.7	7.04	0.97
Education degree	5.0	1.23	6.5	0.77	≤0.05
Parental education	4.1	1.75	4.4	1.86	0.60
Duration of illness (years)	10.0	5.74			
PANSS score					
Positive	12.2	4.8			
Negative	21.0	5.9			
General	32.5	9.6			
Total	65.9	17.3			

Positive and negative syndrome scale (*PANSS*). Education level was rated as follows 1 = illiterate; 2 ≤ 7 years (incomplete primary school); 3 = 8 years (complete primary school); 4 = 10 years (incomplete secondary school); 5 = 12 years (complete secondary school); 6 = 17 years (university degree)

Experimental design

The fMRI study consisted of two recognition tasks (words and faces) of material previously seen outside the scanner. The Presentation 0.76 version program (Neurobehavioral System, USA) was used to develop the stimuli task.

During the encoding task, previous to MRI acquisition, the subjects first viewed 2 types of items for the 2 different tasks: 25 words and 25 photos of emotionless human faces (duration, 3000 msec; intertrial interval (ITI) 500 ms). The subjects were not instructed to memorize the items presented but to make a judgment of pleasantness (pleasant/unpleasant?) and to press a response button when the item was considered pleasant. The words were selected from the Lexesp-Corco database, matched for frequency of occurrence in written Spanish [44]. The face photographs (equivalent number of women and men randomly intermixed) were taken from the AR Face database [31]. Approximately 15 min after this study phase, the two experiments of recognition began: 49 verbal stimuli (25 target and 24 non-studied foils) and 49 face stimuli (25 target and 24 non-studied foils) were respectively presented on a screen via a mirror (duration, 3,000 ms; ITI, between 1,000 and 1,500 ms) while fMRI data were collected (see Fig. 1). The stimuli

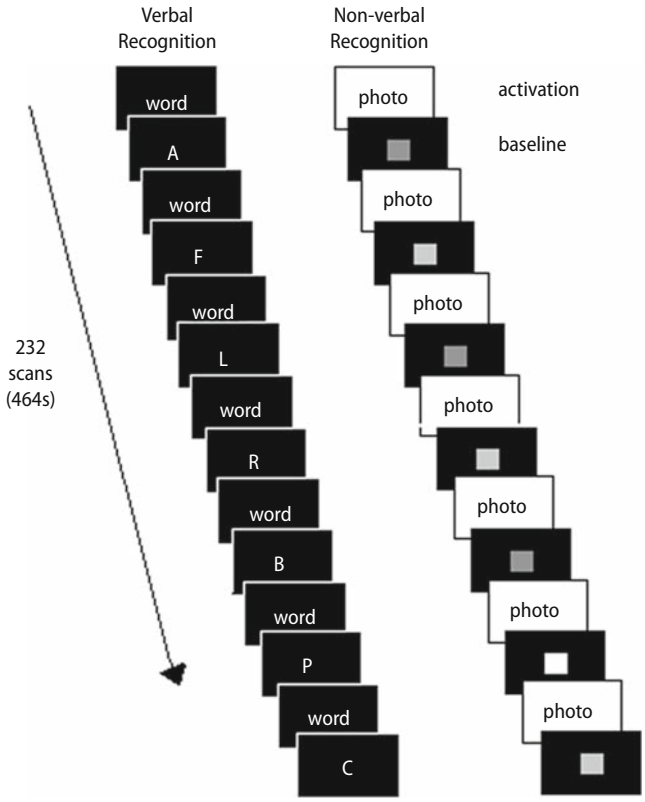

Fig. 1 The experimental design. The *left* stream represents the visual recognition task. The *right* stream represents the verbal recognition task

were back-projected (by a Sanyo Multimedia Prox-III) onto a screen which subject viewed through a mirror located on the scanner's head coil. Subjects' heads were fixed with foam pads to minimize movement during MRI data acquisition. Subjects were also instructed to remain immobile. They had to indicate if the item was the one previously seen (target) by pressing a button with their right hand. The presentation of stimuli (ON) alternated with a low level baseline task (OFF). During baseline of verbal stimuli, white capital letters was shown for 3,000 ms followed by a black screen for 1,000/1,500 ms. Subjects had to respond by pressing a button when the letter A appeared on the screen. During baseline of non-verbal stimuli, coloured screens were shown for 3,000 ms followed by a black screen for 1,000/1,500 ms. Subjects had to respond by pressing a button when a white square appeared on a black screen.

A block design was used in which test items were presented in 14 blocks of 7 items each (32 s/block). Each two blocks presented 2 alternate conditions: 3 target and 4 new stimuli and vice versa. Between each block there was a variable break-time, between 1,000 and 1,500 ms.

MRI acquisition

The study was performed in a 1.5-T MR unit (Signa-Lx, General Electric, Milwaukee, WI) using the blood-oxygen level-dependent (BOLD) fMRI signal. A single-shot gradient echo planar imaging sequence (EPI) was used: TR (repetition time)/TE (echo time) = 2,000/40 ms; FOV (field of view) = 24 × 24 cm, 64 × 64 pixel matrix; flip angle = 90º; slice thickness 6 mm and 20 axial slices per scan.

Before each time series, seven dummy images were collected to achieve scanner equilibrium. These images were excluded from the following analysis. One run consisting of 232 volumes was acquired during each of the two experiments.

Following fMRI scan, a T1-weighted sequence was selected for the acquisition of anatomical images (TR/TE = 12/5.2 ms; TI 300 1 nex; FOV = 24 × 24; 256 × 192 pixel matrix; 1.5 mm slice thickness).

Behavioural data analysis

Three different measures were obtained from both tasks: accuracy (number of correctly identified items), false positives (the number of incorrect "yes" response) and the number of omissions. Reaction time was also measured by calculating the mean reaction time (in milliseconds) for target stimuli. The data of the groups were compared with the Student's *t* test. All statistical analyses were carried out with the SPSS (Statistical Package for the Social Sciences) for windows software, version 14.0.

fMRI data

For image processing Statistical Parametric Mapping (SPM5 Wellcome Department of Cognitive Neurology, London) was used. The images of each subject were corrected for motion and realigned to remove any minor motion-related signal change. All volumes for each subject were normalized into an EPI template supplied with SPM5. During spatial normalization all scans were resampled to 2-mm^3 isotropic voxels. Low-frequency noise was removed with a high-pass filter (128 s) applied to the fMRI time series at each voxel. Finally, the images were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian filter.

Statistical analyses were first performed at a single-subject level. A linear contrast was performed comparing the activation during the novel stimuli and the stimuli previously seen: recognition condition (recognition ≥ novel) for each subject.

Next we performed a group analysis on a second level using the contrast images from the single-subject analysis. We performed a two-sample t test with two different contrasts: schizophrenics > controls and schizophrenics < controls for both fMRI tests (word and face recognition). The height threshold value was set to false discovery rate (FDR) $P < 0.05$ corrected and a cluster extent threshold greater than 20 voxels. First we performed a whole-brain analysis to test all possible differences in cerebral regions. The anatomical location of the cerebral activated areas was determined by the Montreal Neurological Institute (MNI) global maxima coordinates. To identify areas involved with both verbal and non-verbal recognition tasks, we computed a conjunction analysis of the two tasks during activation condition [16]. For this analysis, we applied a threshold of $P \leq 0.001$, uncorrected for multiple comparisons.

We then conducted a region of interest (ROI) analysis to focus on possible hippocampal differences. We used the WFU-Pickatlas toolbox software for SPM, version 1.02 (Joseph Maldjian, Functional MRI Laboratory, Wake Forest University School of Medicine) to create an ROI including the hippocampus and the parahippocampal structure. Verbal and non-verbal memory related activity was compared using a 2 × 2 factorial design with group and memory task as the two factors. The interaction between groups and memory tasks was calculated by a *t* contrast of the positive and negative effect. The probability threshold was set at 0.005 uncorrected.

In addition, we perform a correlation analysis calculated on a voxel-by-voxel basis with the biological parametric mapping (BPM) software package [9] between the BOLD signals of both tasks separately and regional gray matter concentration in patients and controls. For the difference contrasts, we applied a threshold of $P \leq 0.05$ corrected for multiple comparison.

To assess the relationship between task-related activation and performance, we performed a "simple regression" SPM5 analysis. Task performance was correlated with changes in scaled pixel intensity for each group. In addition, we conducted a "simple regression" analysis to examine the relationship between clinical symptoms and abnormal brain activation in schizophrenia. Fur-

thermore we investigated the relationship between chlorpromazine equivalents and fMRI activity.

Voxel-based morphometry

All MRI images were pre-processed according to the Standard VBM protocol [33] using SPM5, running in Matlab 6.5 (MathWorks, Natick, MA). We first reoriented all images according to the anterior-posterior commissure and then we segment them into gray and white matter and cerebrospinal fluid (CSF). This step comprises a new integrated spatial normalization and segmentation routine. The spatial normalization involves registering each of the images onto the SPM T1 template, whereas the segmentation step uses a priori probability maps to segment tissues. Finally, the GM images were smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel.

We evaluated concentration gray matter differences between groups, using the SPM5 Student's *t* test group comparison. We used the convention that the group comparison results should survive at the corrected false-discovery rate (FDR) *p* value ($P < 0.05$). Moreover, only clusters of more than ten contiguous voxels were considered in the statistical model. We performed ROI analyses using the WFU-Pickatlas toolbox software. For this purpose, we selected different ROI corresponding to the brain structures showing hypoactivation in patients during fMRI.

Results

Memory performance

Performance on recognition was similar in schizophrenic patients and healthy controls in the scanner (see Table 2). However, Student's *t* tests revealed a significant difference in reaction time between patients and healthy subjects in the non-verbal recognition task. Because of software problems, responses were not recorded for three patients.

Table 2 Verbal and visual memory task performance assessed by accuracy, false positives, omissions and mean reaction time (milliseconds)

	Patients with schizophrenia mean (SD)	Normal comparison subjects mean (SD)	*t*	*P*
Verbal task				
Accuracy	20.95 (5.43)	22.38 (2.48)	−1.14	0.25
False positives	1.32 (0.74)	1.42 (1.64)	−0.24	0.80
Omissions	3.11 (5.29)	1.67 (2.46)	1.18	0.24
Reaction time (ms)	1093.15 (303.15)	1012.91 (143.32)	1.14	0.25
Visual task				
Accuracy	14.37 (4.21)	15.08 (3.81)	−0.58	0.56
False positives	4.21 (3.22)	3.75 (2.62)		0.60
Omissions	9.63 (4.15)	8.46 (3.93)	0.51	0.34
Reaction time (ms)	1398.88 (289.35)	1183.33 (169.67)	3.02	0.004*

Milliseconds *ms*
*$P < 0.05$

fMRI results

Examination of the whole brain response during both recognition tasks revealed several foci of decreased activation in patients compared to controls. The between group differences were more striking in face recognition than in word recognition. During word recognition tasks, patients showed significantly lower brain activity than controls in the amygdala, basal ganglia, thalamus, and posterior cingulate gyrus (Fig. 2, Table 3).

Non-verbal recognition elicited less activation in patients compared to controls in inferior frontal gyrus, cerebellum, insula, postcentral and precentral gyrus, cuneus and precuneus, superior frontal gyrus and posterior cingulate gyrus (Fig. 3, Table 3).

In the conjunction analysis we found an overlap in activation between the two tasks in right superior frontal gyrus in patients; whereas in controls the convergent activations were found in frontal and occipital regions (Table 4).

We selected the hippocampus and parahippocampus as regions of interest because of their involvement in recognition. Bilateral hippocampal activation was significantly lower in schizophrenics than in the control group ($P < 0.05$, FDR corrected) in a verbal recognition task (see Fig. 4). The left hippocampus showed a significantly greater hypoactivation than the right side: cluster sizes were 264 and 196 respectively.

For the face recognition task, we found also a significant bilateral decreased hippocampal activation in patients compared to controls ($P < 0.05$, FDR corrected). Here, the right hippocampus showed a greater cluster of hypoactivation than the left one. The cluster sizes were 329 and 266, respectively. We found no significant differences in the patients > controls contrast, that is, patients did not present any area of increased activity.

Group × memory task interactions showed a decrease in activation in verbal task < non-verbal task for the schizophrenic group than for controls in the right hippocampus. No significant group x memory task interactions were found on non-verbal < verbal for both group. The correlation analysis between performance and brain activation did not show any

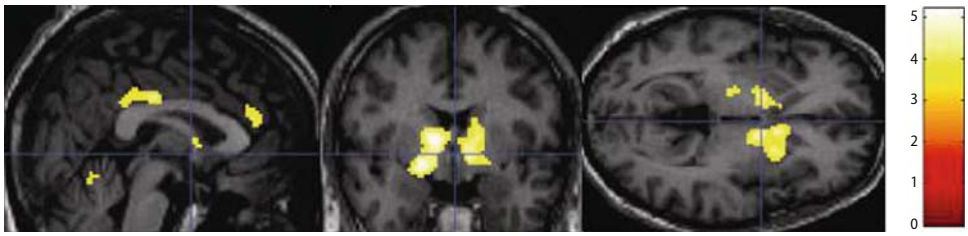

Fig. 2 Views of brain regions showing significant decreases in BOLD activation in patients compared to healthy controls (patients < controls) for word recognition task ($P < 0.05$ FDR corrected)

Table 3 Regions of decreased cerebral activation in patients compared to controls in verbal and non-verbal recognition

Region	Local maxima *x*, *y*, *z*	Hemisphere	Cluster size	BA	*z*
Verbal recognition					
Amygdala	−20 −2 −10	L	290		4.54
Basal ganglia (caudate)	10 8 2	R	396		4.42
Thalamus	18 −12 8	R			4.39
	−10 −24 16	L			4.17
Cingulate gyrus	−2 −20 32	L	44	23	4.30
	−2 −38 28		37	31	3.95
Basal ganglia (putamen)	22 6 −10	R	56		3.95
Non-verbal recognition					
Inferior frontal gyrus	30 22 −8	R	4,750	47	4.31
Cerebellum	−2 −46 −14	L	4,265		4.44
Insula	48 −16 14	R	269	41	3.76
	−52 −32 18	L		42	3.37
Precentral gyrus	50 −6 10	R		6	3.30
Postcentral gyrus	60 −10 14	R		43	3.12
Superior frontal gyrus	−16 54 −2	L	100	10	3.66
Cuneus	−10 −82 34	L	173	19	3.65
Precuneus	20 −56 38	R	100	7	3.59
Cingulate gyrus	−14 30 28	L	50	32	3.53

Local maxima of change in cerebral BOLD were presented in the standard Montreal Neurological Institute (MNI) space. The level of significance was presented at $P < 0.05$ FDR corrected. The BA was determinated by visual inspection using the stereotaxic atlas of Talairach and Tournoux [44]
BA Brodmann's area, *L* left, *R* right

significant results. In addition, we did not find any correlation between the fMRI signal and gray matter of the hippocampus.

In another cycle of analyses, we investigated the relationship between clinical symptoms and fMRI activity. At cluster level there was no significant correlation between the task-related signal changes of the whole brain and both positive and negative symptoms or general psychopathology. Finally, there were no significant relationships between fMRI data and chlorpromazine equivalents.

VBM results

VBM showed a reduced gray matter concentration in the schizophrenic group in the right hippocampus (cluster size = 106; local maxima MNI coordinates = 22 −6 −20, FDR-corrected *P* value at cluster level <0.05) and in left hippocampus (cluster size = 54; local maxima MNI coordinates = −20 −6 −22, FDR-corrected *P* value at cluster level <0.05). Between-group contrasts also revealed decreased gray matter density in schizophrenic patients in the middle and inferior frontal gyrus and insula (Table 5). We found no significant differences in gray matter concentration in the parahippocampus between groups.

Discussion

Our results show altered patterns of cerebral activation in recognition in schizophrenics for both verbal and non-verbal material.

In the whole brain analysis, the differences between patients and controls were more striking for face recognition than for word recognition. These differences cannot be attributed to task difficulty, because patients and controls performed similarly in both tasks. The lack of differences in memory performance is in agreement with previous neuropsychological lit-

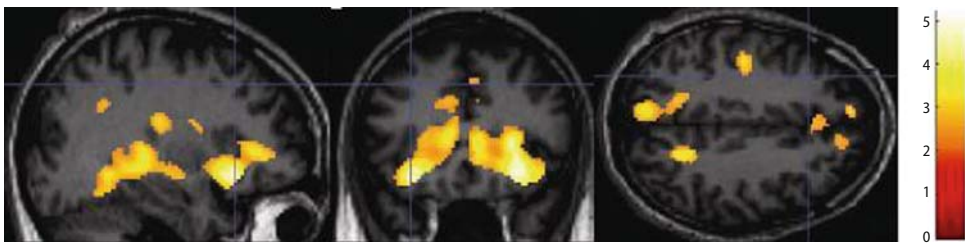

Fig. 3 Views of brain regions showing significant decreases in BOLD activation in patients compared to healthy controls (patients < controls) for facial recognition task ($P < 0.05$ FDR corrected)

Table 4 Conjunction analysis results of verbal and non-verbal memory tasks. The level of significance was presented at $P < 0.001$ uncorrected

Region	Local maxima *x*, *y*, *z*	Hemisphere	Cluster size	BA	*z*
Conjunction analysis in patients					
Superior frontal gyrus	12 22 50	R	332	8	4.86
Conjunction analysis in controls					
Lingual gyrus	26 −94 −6	R	4,987	18	7.83
Inferior occipital gyrus	−32 −92 −8	L		18	7.10
Inferior frontal gyrus	32 24 −4	R	8,283	47	7.03
Middle frontal gyrus	52 28 34	R		9	6.03
Cingulate gyrus	6 −28 30	R		23	5.81
Superior frontal gyrus	8 20 50	R	2,047	8	6.44
Medial frontal gyrus	2 28 44	R		8	5.78
Precuneus	22 −66 34	R	423	7	4.18
Superior occipital gyrus	30 −70 30	R		19	3.92

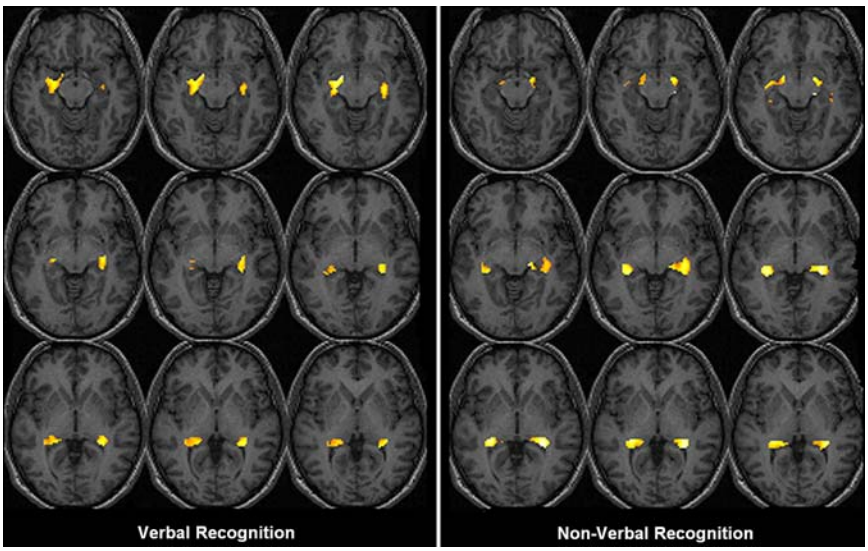

Fig. 4 Region-of-interest (*ROI*) analysis showing the clusters of hippocampal activation difference (schizophrenics < controls) in verbal and non-verbal recognition task (memory activation task > control task) ($P < 0.05$ FDR corrected). The right side of the image corresponds to the right side of the brain. The results are overlapped in a normalized T1 control brain

Table 5 VBM results

Region	Local maxima *x*, *y*, *z*	Hemisphere	Cluster size	BA	*z*
Middle frontal gyrus	−40 50 −14	L	450	11	4.20
Inferior frontal gyrus	−18 12 −20	L		47	3.55
Insula	42 18 4	R	357	13	3.88
Inferior frontal gyrus	50 26 −4	R		47	3.74

Areas of gray matter reduced concentration in schizophrenics versus healthy controls at a *P* (FDR) corrected level of 0.05
BA Brodmann's area, *L* left, *R* right

erature in the sense that recognition is a memory process usually preserved in schizophrenia [49].

During word recognition, patients underactivated the amygdala, basal ganglia, thalamus, and posterior cingulate gyrus compared to controls. Similar patterns of activation were found in a PET study by Ragland et al. [40], who suggested that the strategic processes for organizing encoding and subsequently facilitating retrieval were impaired. Although we selected a task with emotionless human faces in order to focus on memory performance alone, like earlier studies of emotional memory [27, 43] we observed hypoactivity in the amygdala. The basal ganglia are mainly involved in working memory functions [8, 30], but our findings suggest that they are also involved in the neural activity underlying declarative memory. Our patients presented hypoactivation in the thalamus and cingulate gyrus compared to controls. Both regions have been previously described as abnormal in schizophrenia [11, 18, 21, 29].

As regards the medial temporal lobe, in the verbal tasks schizophrenics presented lower bilateral hippocampal activation than controls. These results agree with previous fMRI studies: a PET study reported reduced hippocampal activation during conscious recollection of studied word in schizophrenic patients [19], while another fMRI study also found that schizophrenics showed less bilateral hippocampal activation during a verbal task [23].

In our study, recognition-associated activity was not consistently localized to either the anterior or the posterior region of the hippocampus [17]. Moreover, the hippocampal activation deficit in patients cannot be attributed to their performance during the task, as both groups had similar results on the tests. These findings suggest that impaired hippocampal activation may be partially compensated by another memory strategy (e.g., familiarity).

As regards hemispheric predominance, though the decrease in hippocampal activation was bilateral, we found greater left hemispheric impairment in word recognition. Verbal memory impairment has been consistently associated with left temporal lobe damage, while non-verbal memory deficits have occasionally been observed in right temporal lobe damage [38]. The factor analysis (group × memory task) confirmed a greater decreased in activation in schizophrenic group than in controls in the right hippocampus in verbal < non-verbal memory task contrast. In schizophrenia, decreased activation has been found in the right hippocampus [19], in the left hippocampus [40] and bilaterally [23]. From the structural point of view, voxel-based morphometry studies coincided that there is left hemisphere predominance in hippocampal gray matter reduction [22].

In the non-verbal task, we also found differences between groups in inferior frontal gyrus, cerebellum,

insula, postcentral and precentral gyrus, cuneus and precuneus, superior frontal gyrus and posterior cingulate gyrus. At the behavioral level, the good performance of both groups during the non-verbal memory recognition paradigm indicated showing that they were attending to the stimuli. However, patients were slower to process facial recognition, suggesting differences in the levels of mental effort made by the two groups in this situation. Nevertheless, covariating the contrasts between groups for reaction time, the discriminating variable, the results did not change.

Our findings agree with reports in the literature which have demonstrated "task-related hypofrontality" in schizophrenia. Abnormal prefrontal cortex activity in schizophrenia during visual recognition paradigms is well documented [19, 28]. These prefrontal findings are also consistent with a recent meta-analysis of episodic memory which identified the left prefrontal region as the most compromised in schizophrenia during retrieval tasks [1]. The schizophrenic group showed less activation in the cerebellum than controls. Structural abnormalities of this structure have been related with dysfunctions in motor control and coordination [5, 34]. In our study, the level of performance was similar for both groups in all variables considered, except for reaction time during visual task, which was slower in patients. The pattern of cerebral and cerebellar hypoactivity may explain the slowness of their performance.

The hypoactivity observed in the insula in the patient group might be interpreted as an effect of the disease. Insular volume reduction has been widely reported [48]. It has been suggested that signal reductions in bilateral insula are associated to impaired recognition of facial expression [49]. The cuneus and precuneus have also been implicated in retrieval success [15, 17]. The cingulate gyrus has been more frequently related to a deficit in visual encoding [28], though its involvement in retrieval processes has also been reported [1].

With regard to hippocampal activation during the non-verbal memory task, bilateral hippocampal activity was significantly lower in patients than in controls. To our knowledge this is the first study of emotionless face recognition memory to show differences in hippocampal activity in schizophrenia. Other studies exploring non-verbal memory recognition have focused more on the prefrontal region [20, 29]. The difference between patients and controls were more striking for face recognition, this result was also substained by group by task interaction analysis where the right hippocampus was more decreases in verbal < non-verbal task for the schizophrenic group than for controls.

To identify areas involved with both verbal and non-verbal memory tasks we computed a conjunction analysis. In both groups we observed two main regions that showed convergent activation. One area was localized in primary and associative visual regions involving the lingual gyrus, this is in agreement with the fact that both words and faces were visually presented [28]. The other area of coincidence was observed in the prefrontal cortex with right hemisphere predominance. The activation of this area was probably reflecting the retrieval component of the memory tasks [35].

We found no correlation between clinical variables (positive, negative and general symptoms as well as chlorpromazine equivalents) and abnormal brain activation in the patient group. These findings are consistent with a meta-analysis [2] of memory impairment in schizophrenia which reported that clinical variables, except negative symptoms with frontal lobe dysfunction, did not appear to influence the magnitude of memory impairment. Regarding pharmacological data, we can not exclude the impact of antipsychotic medications on memory performance in persons with schizophrenia, but our analysis did not provide support for the argument that medication is a modulator of memory in the treatment of schizophrenia spectrum disorders [47].

Because functional brain activity could be related to reduction in the structures considered, a separated voxel-based analysis was conducted to evaluate the possible gray matter density reduction in these regions. The ROI analysis revealed decreased gray matter density in the bilateral hippocampus, middle and inferior frontal gyrus and insula. Evidence of structural abnormalities in these regions has frequently been reported [4, 36, 45], though the involvement of these abnormalities in functional hypoactivation remains unclear. In our study, other regions presenting hypoactivation did not show gray matter reduction. Furthermore to assess the relationship between hippocampal structural and functional results we performed a BPM correlation analysis. We did not find any significant association between functional activity and hippocampal gray matter concentration.

Regarding memory impairment in schizophrenia, while a verbal recognition deficit has been confirmed in a large meta-analysis [10], few studies have focused on non-verbal recognition deficit in this population [6, 48, 50]. The recognition function is supported by two different processes: recollection and familiarity [52]. Recollection is conceived as the retrieval of source information, while familiarity as the feeling experienced during item exposure. In schizophrenia the recollection process seems to be impaired [1], though familiarity may be sufficient to support recognition memory.

Regarding neuroanatomical theories, Cirillo and Seidman [10] claimed that the pattern of memory deficits in schizophrenia could be explained by dysfunctions in two regions: the prefrontal cortex and the hippocampus/parahippocampus. The prefrontal cortex may be involved in attending and organizing information, and the hippocampus in the consolida-

tion of information for later recall. Impaired verbal declarative memory may be due to medial temporal lobe abnormalities [10]. Our results agree with this hypothesis: we found abnormal activity in this region, specifically in the bilateral hippocampus, as well as abnormalities in its structures. In the case of non-verbal declarative memory, most of the studies in normal controls report the involvement of frontal-temporal network in face recognition ability [25, 32]. Schizophrenic patients unsuccessfully recruit the medial temporal lobe but do not constantly show a decreased activation of prefrontal regions [20, 29]. Our analysis of the activity is in agreed supports this model, revealing the consistent involvement of the frontal-temporal regions in recognition memory deficit of schizophrenia.

This study had some limitations. First, we used a heterogeneous sample composed of patients with different subtypes of schizophrenia and treatments. Consequently we can not isolate the treatment effects in cerebral activation. The most suitable sample would be non-treated patients at the first episode, but this type of patients produces several MRI artefacts due to the excessive movements.

Secondly, the selected paradigm did not comprise either encoding and retrieval conditions. We decided to include only the recognition process because our objective was to assess the hippocampal lateralization in two different recognition tasks.

Finally, this study is based on a block design. If we had used an event-related design we would have separated the neural activity and well differentiate the processes of recollection and familiarity. We would also have identified the differential involvement of anterior and posterior hippocampal regions.

To summarize, schizophrenic patients showed abnormal fMRI patterns of hypoactivation in bilateral hippocampus during both verbal and non-verbal memory recognition tasks. There was a slight trend towards left-verbal and right-visual hippocampal hypoactivity in patients. These findings may indicate that in schizophrenia the hippocampal role in memory is relatively specific regarding the type of material.

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