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ORIGINAL PAPER

^{18}FDG PET study of amygdalar activity during facial emotion recognition in schizophrenia

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Abstract The role of the amygdala during facial emotion recognition (FER) tasks as well as its clinical implications in schizophrenia patients remains unclear. While most of authors have reported hypoactivation, recently it has been suggested that patients may also exhibit hyperactivation. We studied amygdalar response during a previously validated FER task using ^{18}[F] fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) technique in ten right-handed healthy volunteers and 11 right-handed non acute patients with schizophrenia. Both groups underwent two scans on different days in a random order; each consisted of 17 1/2 min of continuous emotional and control tasks. Statistical Parametric Mapping (SPM) 2 analysis with a region of interest approach was carried out. Left amygdalar hyperactivation among the schizophrenia group was shown in both emotional and control tasks when compared to healthy subjects. The right amygdala showed no differential activation in any of the tasks. Patients diagnosed with schizophrenia exhibit a non-task specific amygdalar hyperactivation during a continuous emotional and non-emotional task when compared to matched healthy controls.

Keywords Nuclear medicine · Limbic system · Hemispheric specialization · Positron emission tomography · Emotion · Negative symptoms

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Introduction

The role of the amygdala during the emotional process in schizophrenia remains unclear. The cortical and subcortical brain areas for emotion recognition have been defined, and include amygdala, hippocampus, insula, anterior cingulated cortex, ventral striatum, fusiform gyrus, and orbitofrontal cortex [4, 7, 30] as well as other areas which may play a minor role. Neuroimaging techniques have allowed studying in vivo brain metabolism. A summary of the activation paradigms published on healthy subjects reveals that facial emotion recognition (FER) tasks may act as the most powerful trigger for activation of the emotion network [18]. The amygdala is the brain structure with the largest activation during the FER paradigms [5, 15, 16, 43]

aside from the visual areas. Indeed, several studies have only taken the amygdala into account for their analysis of FER [3, 12] although this limited approach to region of interest (ROI) in neuroimaging studies remains controversial [13, 35]. The main functions of the human amygdala are emotion and vigilance [6], based on its role in automatic evaluation of danger [47], emotion recognition [1, 12, 15, 16] [29, 46] and novelty detection [44]. A lateralized specialization has also been suggested, entrusting novelty awareness to the right side and emotion recognition to the left [3, 28, 40].

Previously, studies in patients diagnosed with schizophrenia with FER paradigms have reported poorer amygdalar activation [2, 9, 17, 36] compared to healthy controls suggesting lack of function correlated with emotional disturbances associated with the disease. However, the results of other studies using different designs and technology ranged from differential activation according to stimuli or clinical features [16, 31, 33, 39] to a pattern of hyperactivation in comparison to healthy controls [19, 20, 24]. Besides the different methodology, among the explanations for these apparently contradictory results, Holt et al. demonstrated a lack of habituation phenomena (adaptative neural response which facilitates the ignoring of repetitive irrelevant stimuli) in temporal lobe structures among schizophrenic patients while passively viewing either emotional or non emotional facial expressions [19].

So far, there have not been studies of FER among schizophrenic patients with ^{18}[F] fluorodeoxyglucose (FDG) PET. Pharmacokinetics of FDG makes it different from other faster time resolution brain imaging techniques, such as fMRI, MEG or $H_2^{15}O$ PET. The metabolism of the tracer (FDG) stops during the glycolytic pathway and essentially remains trapped in the area of active metabolism. This allows the evaluation of the degree of accumulative activation of brain areas for a period of 30 minutes and acquisition of a single image per scan, which would be directly proportional to neural activity. In this sense, FDG technique would be advantageous should the emotion task require some practice and judging emotions with an emotional concomitant that builds over minutes. These characteristics may have prevented its application for the study of emotions, probably due to the previously mentioned habituation phenomena. However, we have recently reported emotion-related left amygdalar activation in healthy volunteers during FER tasks with FDG-PET [11].

The aim of this study is to evaluate the amygdala activation in a sample of patients with schizophrenia and matched healthy volunteers during a FER task and assessed with FDG-PET. We hypothesized that a differential amygdalar activity could be predicted, with hyperactivation among the patients.

Materials and methods

Subjects

All patients were recruited from the Hospital Clinic Schizophrenia Program at our center and fulfilled DSM-IV criteria for schizophrenia. The original sample included 14 patients and 10 healthy controls, all young, right-handed men. Of them, three patients were excluded from the analysis because the elevated number of non-responses (more than 50% of total), technical problems, and psychotic relapse after the first scan (which led to change in medication). Thus, final sample was composed of 11 patients and 10 healthy controls. Table 1 shows demographic and clinical data of the sample. Patients were studied while clinically stable and under remission. Remission was considered to apply where there were no hospital admissions during the previous 6 months, no single item of Positive subscale of PANSS over 3 and no total sum of the same subscale over 10 points. Patients were taking atypical antipsychotics: two clozapine, four olanzapine and five risperidone (mean chlorpromazine equivalent dose of 263.6 mg; SD = 86.7). No change of medication or dosage was allowed during the inter-scan time.

Exclusion criteria were current or past history of any psychiatric (including substance abuse), neurological, or major medical conditions. All subjects provided written consent as approved by the local Institutional Review Board. Medical and psychopathologic exploration was carried out on all of them, including SCID-I for DSM-IV disorders and Calgary [34]. Positive And Negative Symptom Scale (PANSS) [22] scale was carried out in the patients group.

Table 1 Demographic and clinical data

	Schizophrenia group ($n = 11$)	Control group ($n = 10$)	P significance
Age (in years)	28.64 (7.1)	27.50 (2.7)	0.638
Time between scans (in days)	27.8 (30.6)	34.9 (29.0)	0.594
Calgary Depression Scale	1.36 (2.3)	0.00 (0.0)	0.098
PANSS—Positive	8.50 (1.7)		
PANSS—Negative	18.33 (9.6)		
PANSS—General	25 (4.3)		

All subjects were right-handed men

Variables are expressed as mean and SD (Standard deviation). Non paired t tests were calculated for all comparison. PANSS means Positive and Negative Symptom Scale

Facial stimuli

Facial images came from a set of 175 black and white photographs of amateur actors in an evoked-emotion performance. These pictures are the property of the *Brain Behavior Laboratory* (University of Pennsylvania) and have been validated for this type of study [14]. Selected pictures included male/female faces with neutral, sad, or happy expressions.

Procedure

Participants were seated comfortably, in a quiet place, one meter in front of a 15 in. screen laptop (Samsung X15plus). SuperLab Pro® (Cedrus, version 2.0.4) displayed the pictures and collected the behavioral data (type of response and time of reaction in milliseconds). Subjects held an optical two-button mouse (Logitec®) in both hands, using either the left- or the right thumb for answering.

Tasks (Fig. 1). Tasks and study design followed the recommendations for facial emotion recognition studies [8] which included low cognitive demand, two conditions per task and limited time of exposure. Participants performed two different tasks on two different days. Each task consisted of rating 300 images, each displayed for 3.5 s for a total of 1,050 s (17 1/2 min) of continuous task. Subjects were instructed to be sure about their responses before answering as rapidly as possible. The Emotional task (ET) consisted of three series of 50 happy and 50 sad faces (men and women in equal number, randomly displayed). The left button defined "sadness" and the right button "happiness". For the Control task (CT), a gender-discrimination task was chosen, in which pictures of 50 men and 50 women with neutral expressions were displayed three times in exactly the same order as in the ET. Right button defined "man" and left button "woman". Tasks were performed alternately between the groups: half of the subjects started with the ET. Before performing the tasks, subjects were trained with a similar ten face tasks, in order to avoid instrumental mistakes. On each button, a hand-drawn icon reminded the subjects of the meaning of the answer in case of need. After finishing the task, subjects rested for 10 minutes before the scans were performed.

Radiotracer administration and PET imaging

Before performing the task, capillary blood glucose was obtained from each volunteer in order to exclude hyperglycemia. A peripheral intravenous access was used to administer 8–10 mCi (296–370 MBq) of FDG radiotracer, 60 s after starting the task. Siemens PET-Computed tomography Biograph tomography acquired images 30 min after radiotracer administration. A standard 11-min "HEAD/BRAIN PET-Computed Tomography" routine was performed (1 min for transmission; 10 min of emission). Thirty-five tomographic attenuation-corrected brain sections were obtained (2.47 mm slice thickness). Reconstruction was performed with OSEM algorithm (16 subsets and 6 iterations) with a matrix of 128 × 128 × 35 and 2.6 mm pixel size.

Images analysis

The 35 DICOM images per subject per scan were reconstructed with the MRIcro® (version 1.39) software. Post

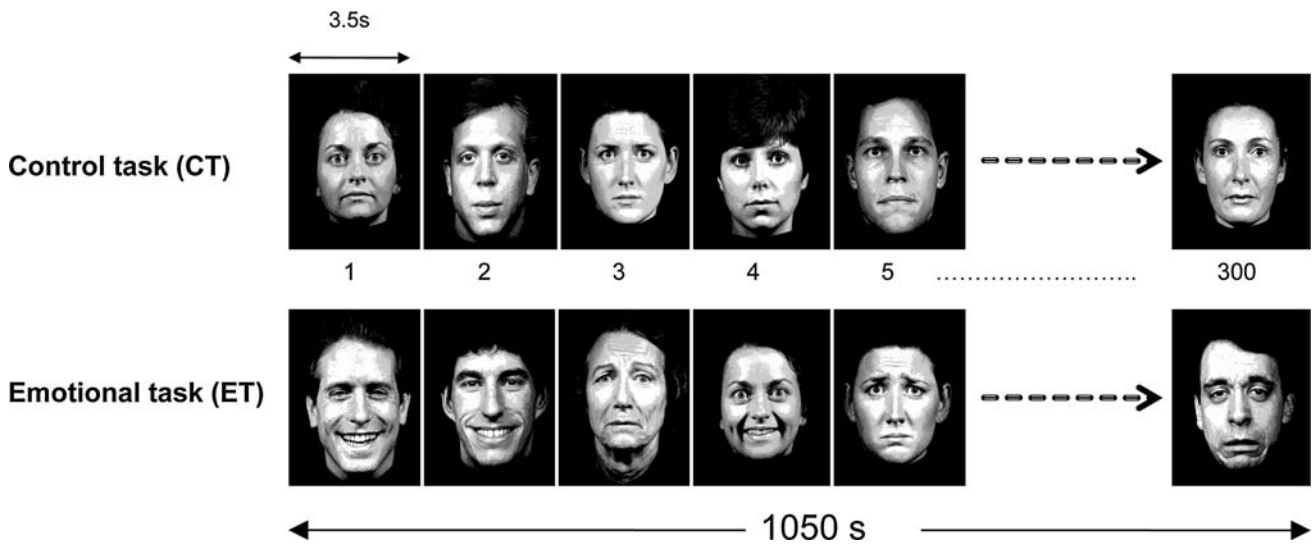

Fig. 1 Emotional task (ET) displayed equally balanced faces of men or woman with either sad or happy expression, while control task (CT) displayed also equally balanced men or women expressionless faces

processing of the reconstructed images was performed using SPM2 tools (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm), functioning with MATLAB® 7.0.1). First, each image was manually reoriented to an SPM PET template and then each pair of ET-CT scans was realigned. Next, realigned images were normalized to PET template. Finally, images were smoothed with a Gaussian kernel of 5 mm of Full Width at Half-Maximum.

The design of the study included two groups and two conditions per subject and one scan per condition. The SPM contrasts were carried out using ANOVA, two-tailed non-paired and paired *t* tests and simple regression (correlation). Both standard proportional scaling for each image to 100 and a threshold (relative global) of 0.5 were applied, without sphericity correction.

A statistical general threshold for the map of significance was fixed in uncorrected $P = 0.005$, with no minimum-activated voxel threshold. Left and right amygdala WFU-Pickatlas [27] masks for the regions of interest (ROIs) were selected for all comparisons in the study. The degree of activation is presented in the tables as normalized "z" format. These specifications are the same that were set in the previous study of technique validation [11].

In each condition, amplitude of FDG-uptake in the ROI area was calculated using MRIcro®, in order to calculate percentage of change (%change).

Statistical analysis

All statistics analyses were done using SPSS v12.0 (http://www.spss.com) including descriptive, t-student and χ^2 statistics for time response and accuracy.

Results

Behavioral results

All subjects were highly attentive during the task, as there were no differences in the number of missing responses, ranging from 0.01 to 1.5%. Table 2 shows the intergroup comparison (schizophrenia vs. control group) and Table 3 shows the intragroup comparisons (ET vs. CT) of behavioral data.

Table 2 Behavioral data: intergroup comparison

	Schizophrenia group	Control group	*P* significance
Control Task			
Misattributions (%)	2.0	1.3	0.020
Response time (ms)	927.4 (470.1)	665.5 (238.0)	<0.00001
Emotional task			
Misattribution (%)	6.6	2.2	<0.00001
Response time (ms)	1193.6 (579.4)	903.5 (405.8)	<0.00001

Continuous variables expressed as mean and SD (Standard Deviation). Non paired *t* tests were calculated for the continuous variables, while chi-square value was calculated for the comparison of misattributions. Ms accounts for milliseconds

Table 3 Behavioral data: intragroup comparison

	Control task	Emotional task	*P* significance
Schizophrenia group			
Misattributions (%)	2.0	6.6	<0.0001
Response time (ms)	927.4 (470.1)	1193.6 (579.4)	<0.0001
Control group			
Misattribution (%)	1.3	2.2	0.056
Response time (ms)	665.5 (238.0)	903.5 (405.8)	<0.0001

Continuous variables expressed as mean and SD. Paired *t* tests were calculated for the continuous variables, while chi-square value was calculated for the comparison of misattributions. Ms accounts for milliseconds

Neuroimaging results

In the first analysis, the degree of change of activation between two tasks (ET-CT) and between two groups with an F contrast [(1 −1 0 0] [0 0 1 −1]) were contrasted. A differential degree of activation was observed in the left amygdala [$F = 14.07$; $df_{2,19}$; voxels activated 12; $z = 3.57$; MNI coordinates: −18 −4 −20].

Then each task was contrasted between each of the groups, using a two sample *t* test. When ET was compared, the schizophrenia group showed a left amygdalar hyperactivation compared to the healthy controls (voxels activated = 8; $z = 2.98$; MNI coordinates: −22 −2 −14; %change = 6.7%). When CT was compared, the schizophrenia group also exhibited left amygdalar hyperactivation during the CT (voxels activated = 48; $z = 3.94$; MNI coordinates: −20 −2 −16; %change = 25.4%) compared to the healthy controls. The right amygdala showed no differential activation in any of the tasks. Figure 2 shows the above three afore-mentioned maps of significance.

These results suggested a task-independent hyperactivation among patients with schizophrenia. To confirm this statement, a contrast between all images (ET + CT) of the schizophrenia group versus the control group was preformed. The schizophrenia group exhibited a left amygdalar (voxels activated = 86; $z = 4.64$, MNI coordinates: −20 −2 −14; %change = 4.67%) as well as a right amygdalar hyperactivation (voxels activated = 2; $z = 2.79$; MNI coordinates: 24 −8 −10).

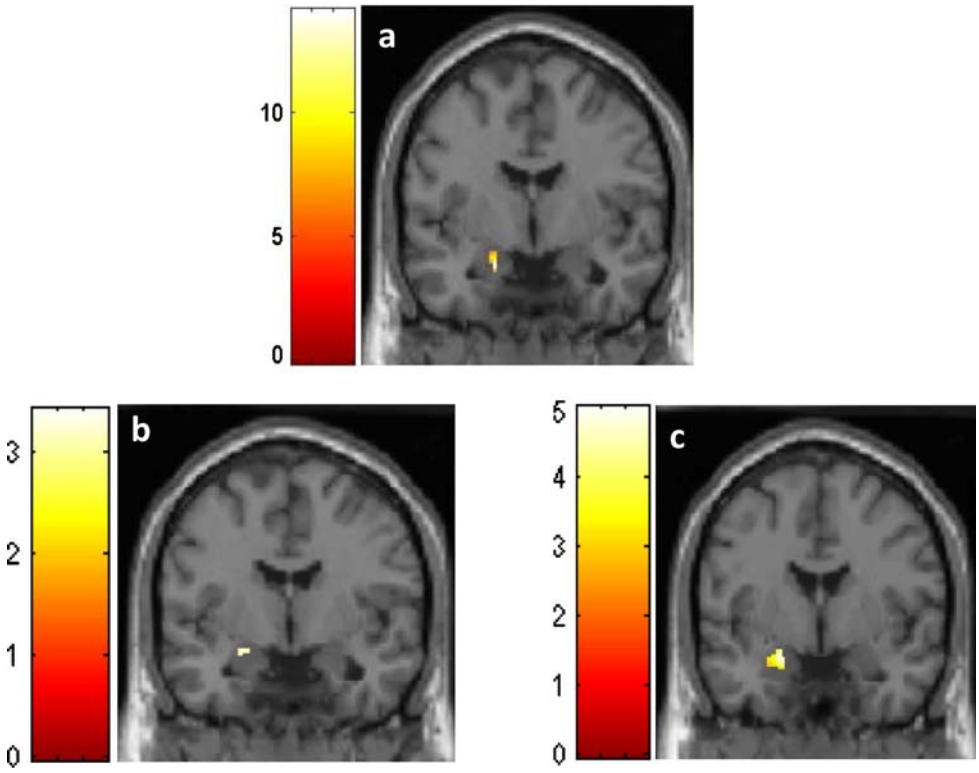

Fig. 2 Left amygdalar hyperactivation in schizophrenic versus healthy controls. (**a**) ANOVA contrast with group × task interaction; (**b**) shows t contrast during the emotional task (ET) between schizophrenic and controls groups and (**c**) shows the t contrast during the control task (CT). The corresponding F or t *score bar* is shown beside each image

In the report that validated this technique and procedure [11], a left amygdalar emotion-specific activation (paired *t* test; ET vs. CT contrast) was reported with the same ten subjects in the control group. We then compared the effect of the task in the schizophrenia group. An ET versus CT paired *t* test contrast among the 11 subjects of the schizophrenia group was performed. No differential activation was observed. The opposite contrast (CT vs. ET) did not show differences either.

Response time (RT) was different among the two groups of subjects and FDG accumulation is proportional to time of activation. Thus, it may be possible that the above results were a consequence of the longer RT. A contrast between mean RT of each image and amygdalar activation, with a simple regression (correlation) was then performed. For the first comparison, all images were selected (EC and CT for the two groups) and no amygdalar activation was observed. The same contrasts were done after splitting by tasks. In this case, neither ET images nor CT images correlated with RT.

Discussion

This study shows a task-independent left amygdalar hyperactivation assessed by FDG-PET in the schizophrenia group compared to a matched control group. The schizophrenia group did not differ in the degree of activation across emotional and non emotional facial recognition tasks. These results could not be attributed to a psychotic or depressive state or to the behavioral data. Patients were under clinical remission of their psychotic symptoms. Depressive symptoms were not more prominent among the schizophrenia group [34]. The behavioral data indicates that the two groups were highly attentive to the tasks. The schizophrenia group exhibited a greater number of misattributions and RT in both tasks, which has been previously reported [8]. However, RT and degree of amygdalar activation were not correlated when analyzed by a direct contrast.

The most interesting finding is the amygdalar hyperactivation during the CT in the schizophrenia group. Indeed, patients exhibited a similar activation when facing emotional and nonemotional tasks. One possible explanation of the results is that patients assess emotionally expressionless faces. In this sense, CT was easier than ET (reduced RT, more accuracy) although the left amygdalar activation was equal among CT and ET in the schizophrenia group. In simpler words, this group would assess for emotional content (or danger, as this is an amygdalar role) where there is none. This would be related to the paranoid symptoms, as the more recent misattribution hypothesis suggests [20]. Indeed, the clear lateralization of the amygdala response would suggest another clue for that. It has been suggested that this hemispheric specialization could be because the right side hemispheric structures focus on novelty and the left side to emotion recognition [40] or due to different rates of habituation of both left and right amygdala [44].

Moreover, non-human primate studies have also reported selective left amygdalar hyperactivation [32] evaluated with FDG PET. Indeed, a lack of habituation phenomena among patients diagnosed with schizophrenia [19, 21] has recently been reported. However, the different rates of habituation cannot be directly tested with this study design. A selective left hemispheric dysfunction in schizophrenic patients during FER tasks has been also suggested [17, 25, 39] although not all reports agreed [16, 24]. The task-content independent left amygdalar hyperactivation found would represent a trait among the schizophrenia group. Our sample only included chronic patients in clinical remission, with few psychotic symptoms.

So far [2], comparative neuroimaging studies during FER tasks between patients diagnosed with schizophrenia and healthy controls have reported amygdalar hypoactivation [9, 17, 36, 37], hyperactivation [19, 21, 24, 38], differential activation due to the kind of emotion displayed [39] or clinical features ranging from paranoia [31, 33, 42] to flat affect [16]. This study cannot be easily compared to the previous ones, because of the difference between fast resolution techniques used so far and the FDG PET and because we decided to include only stable patients, in order to study an illness trait rather than state/psychosis phenomena. Studies by Holt [19, 21], with repetitive stimuli and the time course response assessed with fMRI which show lack of habituation phenomena and hyperactivation in the limbic areas could resemble our methods and results. The limbic area would be hyperactivated even when no emotional judgment is done. In this particular scenario, and although FDG-PET should not be considered as a first line technique in emotion research, this study provided evidence for supporting a global unspecific hyperactivity among in schizophrenia, compared to the general population.

Although the proposed left amygdalar hyperactivation as an illness-trait related to the danger awareness (or emotional process of nonemotional content) is highly attractive, other explanations should be explored. For instance, our results could be also attributed to a broader face perception dysfunctional processing [10]. Indeed, patients with schizophrenia have an abnormal pattern of scanning faces [23, 26], and it has been suggested that the failure on FER performance is caused by a broader cognitive dysfunction rather than specific emotional disturbances [41, 45]. In our study, there was no formal assessment of cognitive function. However, all the previous studies would not have explained the clear hemispheric specialisation we found, as a broader dysfunction should be probably expressed as a bilateral abnormal pattern. This study only assessed the amygdala via ROI, so it would be feasible that other brain areas may have been as much active as amygdala during the task. The whole brain approach was not followed, because of the sample size (which may have induced type 1 errors) and mainly, because this technique was designed and validated for exploring only the amygdalar activation [11]. Again, it could be argued that the sample size would have prevented the finding of differences in the ET-CT contrast among the schizophrenia group. However, it is an unlikely explanation, as we reported differences with the same contrast and settings with an even more reduced sample of ten healthy subjects. Gur et al. [16] have recently suggested that limbic hyperactivation during FER would be responsive of the flat affect. Beyond the different methodological approach (4T fMRI, evaluation of four different emotions and block and event related design), the sample studied has also predominant negative symptoms which could have led to the observed amygdalar hyperactivation. The approach based on clinical features would require further research.

Other limitations of the study should be taken into account. The highly restrictive inclusion criteria could limit the generalization of the results, as only right-handed males were included. We believe that further studies with larger and more heterogeneous samples will be necessary to confirm our results. The content of the emotional task, including only sad and happy faces, would also limit the brain areas activated. Different areas are activated when angry/sad/fear faces are displayed although amygdala is always largely activated [5]. The role of medication in these results would represent another limitation. Drug-induced sedation could have affected RT. Although this should be taken into consideration, it seems an unlikely explanation, as the number of responses and correct responses were very high among the two groups.

In conclusion, left amygdalar activation in response to the facial recognition task is independent to emotional content in patients diagnosed with schizophrenia and assessed with FDG PET. It could be an illness trait which could be related to the misattribution and paranoid symptoms, although future research is warranted.

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