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Emotional words induce enhanced brain activity in schizophrenic patients with auditory hallucinations

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Abstract

Neuroimaging studies of emotional response in schizophrenia have mainly used visual (faces) paradigms and shown globally reduced brain activity. None of these studies have used an auditory paradigm. Our principal aim is to evaluate the emotional response of patients with schizophrenia to neutral and emotional words. An auditory emotional paradigm based on the most frequent words heard by psychotic patients with auditory hallucinations was designed. This paradigm was applied to evaluate cerebral activation with functional magnetic resonance imaging (fMRI) in 11 patients with schizophrenia with persistent hallucinations and 10 healthy subjects. We found a clear enhanced activity of the frontal lobe, temporal cortex, insula, cingulate, and amygdala (mainly right side) in patients when hearing emotional words in comparison with controls. Our findings are consistent with other studies suggesting a relevant role for emotional response in the pathogenesis and treatment of auditory hallucinations.

Keywords: Schizophrenia; Functional MRI; Salience; Emotional paradigm; Auditory hallucinations

1. Introduction

Auditory hallucinations (AH) are nuclear symptoms in psychoses. Recently, the whole range of functional imaging techniques has been used to evaluate the functional anatomy of the hallucinatory experience. Several areas have been implicated including the auditory cortex in functional magnetic resonance imaging (fMRI) studies (Woodruff et al., 1995), Broca's area in a single proton emission computed tomography (SPECT) study (McGuire et al., 1993), and subcortical structures in a positron emission tomography (PET) study (Silbersweig et al., 1995). Neurobehavioral covariables such as the response to outer auditory speech (Woodruff et al., 1997), the monitoring of the inner verbal image (McGuire et al., 1996) and the discrimination of inner–outer space (Hunter et al., 2003) have also been evaluated through functional imaging studies.

Although the underlying biological mechanisms remain unclear, AH are thought to be related with the activation of cerebral areas involved in normal

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processing of auditory stimuli. However, some studies also suggest a broader activation of cortical and subcortical areas (Woodruff, 2004). Several neuro-cognitive models have been proposed to explain auditory verbal hallucinations in schizophrenia: abnormal auditory imagery, dysfunction in self-monitoring, or abnormalities in storing and retrieving of memories (Seal et al., 2004).

Emotional response has recently been implicated in the pathogenesis of AH (Kapur, 2003). Moreover, the emotional factor is crucial in cognitive therapy of patients with AH (Freeman and Garety, 2003).

A wide range of neuroimaging paradigms have been used to study emotional response in normal subjects. They have included different sensory modalities and cognitive tasks. Along with classical works in this field (Ekman and Davidson, 1994), most of the studies have used the visual sensory modality through the recognition of facial emotions (Murphy et al., 2003). However, relatively few of them (Maddock and Buonocore, 1997; Isenberg et al., 1999) have used the auditory modality, despite the importance of language in human emotions.

Some studies have shown deficits in patients with schizophrenia in regard to emotional processing in face-recognition tasks, and also with affective prosody (Mandal et al., 1998; Edwards et al., 2002). However, several methodological problems make it difficult to compare results and to identify the specificity, extension and nature of these deficits (Edwards et al., 2002). Some fMRI studies have used paradigms based on face recognition (Schneider et al., 1998; Phillips et al., 1999; Kosaka et al., 2002; Gur et al., 2002); emotionally aversive and non-aversive pictures, including faces (Taylor et al., 2002); and pleasurable or non-pleasurable olfactory (Crespo-Facorro et al., 2001) or visual stimuli (Paradiso et al., 2003). All these studies have generally shown a widespread decrease of brain activation in patients with schizophrenia compared with controls.

As far as we know, no emotion–induction auditory paradigm has been used in a neuroimaging study in patients with schizophrenia, despite the fact that AH are present in 70–80% of such patients (Slade and Bentall, 1988). In this fMRI study, we compared brain activation of patients with AH and healthy controls using a new auditory emotional paradigm especially designed for psychotic patients with AH. The principal aim is to evaluate the response to neutral and emotional words. In global terms, although patients usually experience fear and perplexity towards AH, some comment on them as a pleasurable experience (Sanjuan et al., 2004); further, the familiarity and memory of the stimulus could be important in emotional response. For these reasons, we used a paradigm derived from voices and included some positive-pleasant words.

We predicted an increased activation of limbic brain regions in both the chronic hallucinators and the controls, when exposed to emotional words compared with when they were presented with neutral words. We also expected a different pattern of activation between patients and controls, reflecting underlying mechanisms that could play a role in the emotional response to AH and, therefore, in their pathogenesis itself.

2. Materials and methods

2.1. Subjects

A group of 22 male psychotic chronic hallucinators were selected out of a sample of 106 patients with AH. All subjects gave written informed consent to participate in the research. The study was approved by the local ethics committee. The characteristics of this sample are described elsewhere (Sanjuan et al., 2004). All of the patients met the following selection criteria for persistent hallucinations:

(a) Voices were not modified in any way by treatment over the course of a year.
(b) Voices were present at least once a day in the last year.
(c) At least two antipsychotic drugs had been tried, at doses equivalent to 600 mg/day of chlorpromazine, in the last year.

For this study, and in order to get a homogeneous group, only patients who heard voices during data acquisition at the end of the fMRI were included ($n = 14$). Three patients were excluded because of gross movement during fMRI data acquisition. Healthy controls were matched by age, gender (all males), laterality (all right-handed) and educational level to the patients. Subjects with a psychiatric history or presence of perceptual abnormalities were not considered as controls. No individual in either group suffered from hearing loss.

The final sample included 11 patients with DSM-IV schizophrenia (American Psychiatric Association, 1994) and 10 healthy controls from a similar ethnic group and educational level. Patients' educational levels were as follows: Illiterate = 1 (9.1%), Primary = 6 (54.5%), Secondary = 3 (27.3%), University = 1 (9.1%). Only one patient was married (9.1%), another one was divorced (9.1%), and nine were unmarried (81.8%). Their ages ranged from 21 to 51 years (mean 38.3, S.D. 7.2), while ages at which patients began to hear AH ranged from 15 to 43 years (mean 23.0, S.D. 10.0). The mean duration of illness was 14.7 years (S.D. = 8.1). All patients were under antipsychotic treatment time of evaluation: 6 (55.5%) under second-generation antipsychotics, and 5 (44.5%) under combined treatment (first- and second-generation antipsychotics).

All patients were clinically assessed with the Global Assessment Scale (GAS) (Endicott et al., 1976), 24-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and Psychotic Symptom Rating Scale (PSYRATS) for AH (Haddock et al., 1999) over the last 24 h. The PSYRATS scale was administered just before data acquisition. The BPRS mean score was 55.2 (range 41–67, S.D. 7.4), the PANSS mean score was 70.8 (range 53–94, S.D. 9.9), the PSYRATS mean score was 28.6 (range 20–34, S.D. 4.4), and the GAS mean score was 38.5 (range 20–45, S.D. 8.5).

At the end of the trial, every patient was asked to score the frequency of voices during MRI, the resemblance of the voices to his own voices, and the level of anxiety. Control subjects were also asked the last question.

2.2. Selection of emotional and neutral words

An emotional response paradigm was designed to replicate those emotions related to hallucinatory experiences. Eighty-two patients with schizophrenia meeting DSM-IV criteria with AH were selected in order to choose words of emotional content specific to their psychoses. All patients were administered the PSYRATS and their discourses about the content of AH were recorded on tape. The recordings underwent transcription. Qualitative data were analyzed using the methodology proposed by Miles and Huberman (1994). Hallucinations based on complex phrases or with neutral content were ruled out. A total of 65 words were chosen based on their frequency, including only those possessing meaning by themselves. They were classified according to the qualitative analysis of their content in five categories: of negative content and imperative tone, insults, of imperative tone, and exclamations related to emotional states and of positive content.

Given that the stimuli pattern for the fMRI experiment lasts 20 s for each block, a total number of 13 words were selected according to their frequency in the recording, and then grouped as follows: four imperative words of negative content, three insults, two words with imperative tone, two exclamations related to emotions, and two words of positive content. For the selection of neutral words, we used data published by Algarabel (1996) in which the rate of psychological interest of 1917 Spanish words was described. Subjective rates were obtained from a group of 2000 subjects (from Valencia and Alicante, Spain) who evaluated words on a scale from 1 to 7. The most relevant item for this study was "pleasantness". Subjects had to answer to which degree the word triggered pleasant or unpleasant feelings, on a scale in which 1 = very unpleasant and 7 = very pleasant. The pleasantness average rate of neutral words was 3.8. The pleasantness average rate of emotional selected words was 1.4 for words of negative content, 1.2 for insults, 1.5 for words with imperative tone, 2.1 for exclamations related to emotions, and 5.8 for words of positive content. Emotional and neutral words' valences were significantly different as shown by a paired *t*-test ($t = -3.09$, $df = 12$, $P = 0.009$). Finally, the total number of syllables ($n = 33$) coincided with the number of syllables in the emotional words ($n = 33$).

For the recording procedure, a professional actor from a specialized center was hired to pronounce the words. He pronounced neutral words using a neutral tone and emotional words using an emotional tone but maintaining voice intensity constant (65 dB).

2.3. Image acquisition

The fMR images were obtained by means of BOLD (*Blood Oxygenation Level Dependent*) (Ogawa et al., 1992) contrast, applying the stimulation paradigm described before. Subjects were binaurally stimulated in two different sessions. Fig. 1 represents the distribution of the blocks for both sessions in time. The activation blocks in the first session consisted of 13 Spanish words containing high emotional content. The second session had activation blocks containing 13 words having neutral or low emotional content.

Four blocks of stimuli, 20 s each, interleaved with another four blocks of rest of 20 s each, were presented to patients and controls (Fig. 1). The acquisition order (emotional and neutral) was randomized to avoid biases (habituation, fatigue, saturation and surprise). Subjects were informed before the test about the two types of words they were going to listen to, and were asked to focus their attention on them. A MR 1.5-Tesla. (Philips Medical Systems, Holland) was used for data acquisition. Patients had earphones adjusted to their heads. These earphones were connected by a pair of air tubes to an external audio CD player.

Images were performed applying a dynamic Echo Planar Imaging T2* weighted sequence (TR = 2000 ms, TE = 50 ms, 5 mm slice thickness with no inter-slice gap, acquisition matrix = 96 × 128, field of view = 220 mm

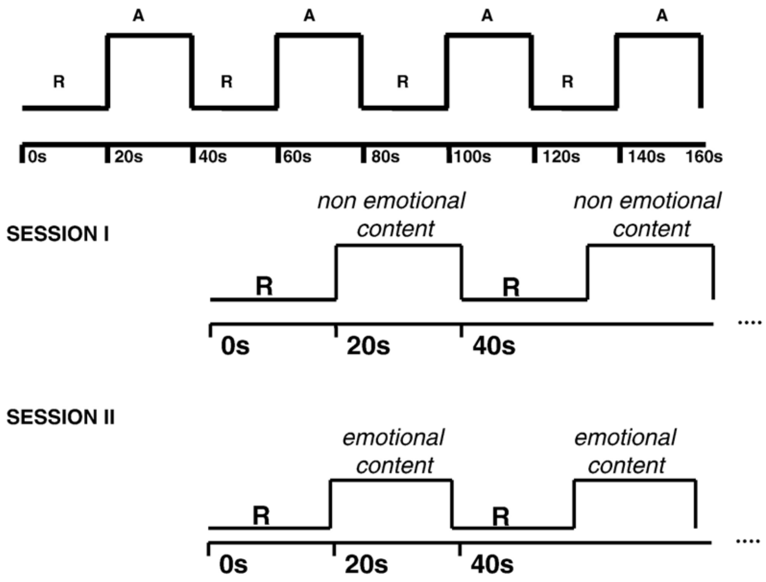

Fig. 1. Stimulation paradigm.

and flip angle = 65°). The voxel size was 3.27 mm × 1.72 mm. The sequence was obtained with spectral suppression. Each dynamic acquisition consisted of 24 contiguous slices parallel to the anterior–posterior commissural plane, covering the whole brain.

Additional high-resolution volumetric images were acquired to have an anatomical template of the whole brain. The anatomical high-resolution MR images, necessary for the topographical localization of the activation areas, were obtained with a Gradient Echo T1- weighted sequence (3D volumetric acquisition, TR = 7 ms, TE = 1.88 ms, slice thickness 1.25 mm without inter-slice gap, 256 × 256 acquisition matrix, FOV = 220 mm). A total of 96 slices with a voxel size of 0.86 mm × 0.86 mm were obtained.

2.4. Data analysis

Processing was carried out with the SPM2 (Statistical Parametric Mapping Functional Imaging Laboratory, London) (Friston et al., 1995). Automatic labeling was applied to the following group maps: patients that were presented high-emotional content, patients presented neutral content control subjects presented high-emotional content, and control subjects presented neutral content.

MR images were initially processed to allow voxel-based statistical analyses. Functional images were realigned with subvoxel movement correction. Images were co-registered for every subject so that structural and functional images were situated in exactly the same virtual space. Images were then transformed into standard space, minimizing the least square error that represents the difference between the template image (MNI150, Montreal Neurological Institute) and the subject's image.

Image intensity was smoothed by means of a Gaussian three-dimensional 6-mm kernel, approaching the data to a normal distribution necessary for later statistical tests. Statistical analysis was performed first on each individual subject and also through comparison between subjects (extraction of information and differences in activation between subject groups). The voxel-based parametric maps analysis was performed with one sample *t*-tests from the final sample of 10 control subjects and 11 patients (Random Effects Analyses applied to each group comparison), extracting common features, following the General Linear Model ($df = 9$ for controls, $df = 10$ for patients; *t*-test values, see Table 1).

The False Discovery Rate technique was applied, using the whole brain to address the problem of multiple comparisons, retaining voxels surviving with a value of $P < 0.05$ and a minimum cluster of five voxels.

Areas of activation were delimited with the atlas proposed by Schmahmann et al. (1999). This atlas is included in the software Automatic Area Labeling (Tzourio-Mazoyer et al., 2002), which extracts a table

Table 1
Areas of activation with emotional words, BOLD signal, in hallucinating patients with schizophrenia and controls *

		Controls (n=10)				Patients with schizophrenia (n=11)			
Region	L/R	x	y	z	Z-score	x	y	z	Z-score
Superior temporal gyrus	L	−62	−16	6	4.71				
	R	48	0	−14	4.61	60	−24	−2	4.47
Middle temporal gyrus	L	−60	−38	10	4.63	−54	−12	−12	6.15
	R	64	−48	12	3.83				
Insula	L					−24	24	4	3.03
	R					28	16	−12	4.29
Median cingulate and paracingulate gyri	L								
	R					16	−8	38	3.32
Posterior cingulated gyrus	L					2	−52	28	3.65
	R					4	−36	30	3.04
Amygdala	L								
	R					24	−4	−14	3.75
Inferior frontal gyrus, orbital part	L	−34	28	−12	4.07				
	R					52	38	−8	3.46
Middle frontal gyrus, orbital part	L					−4	56	−8	4.1
	R					38	38	−14	3.73
Superior frontal gyrus, medial part	L								
	R					8	54	34	4.24

* Coordinates are MNI.

with all local maxima of activation and the areas they correspond to in the labeled atlas. If the voxel estimated as active was not in any of the areas labeled, it was assigned to the nearest labeled area. Voxels farther than 4 mm of a labeled area were discarded.

Maps of significant differences in BOLD signal in all schizophrenic patients and controls between emotional content stimuli and baseline, and also between non-emotional content stimuli and baseline, were then calculated (Figs. 2 and 3). Corrected values of $P<0.05$

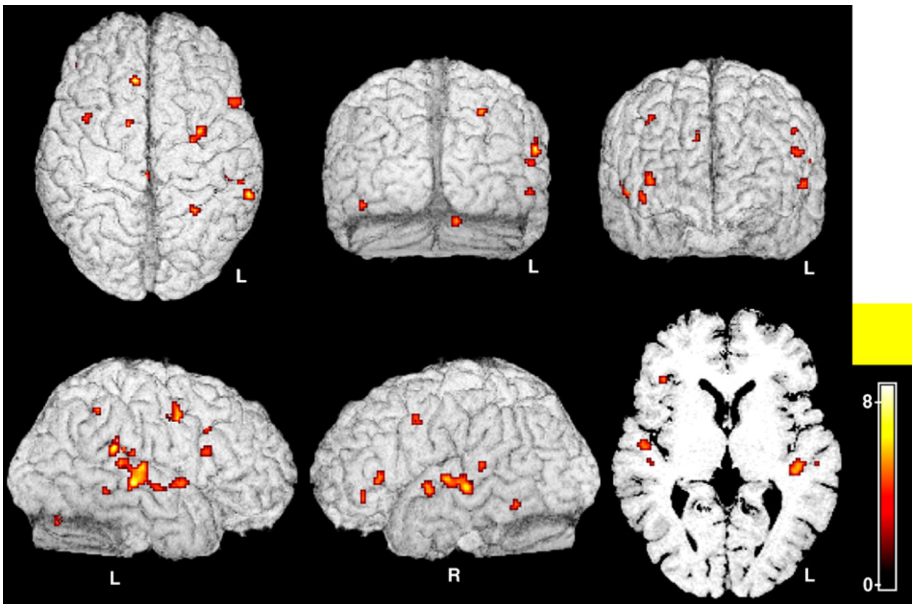

Fig. 2. Activation maps in chronic schizophrenic patients with AH, under non-emotional content stimuli. Areas with functional response are mainly the middle right cingulum, left superior and middle temporal gyri and left precentral area (after P value correction, no suprathreshold voxels were found. Therefore, for illustrational purposes, a $P<0.001$ uncorrected was applied, with minimum voxel size per cluster 5).

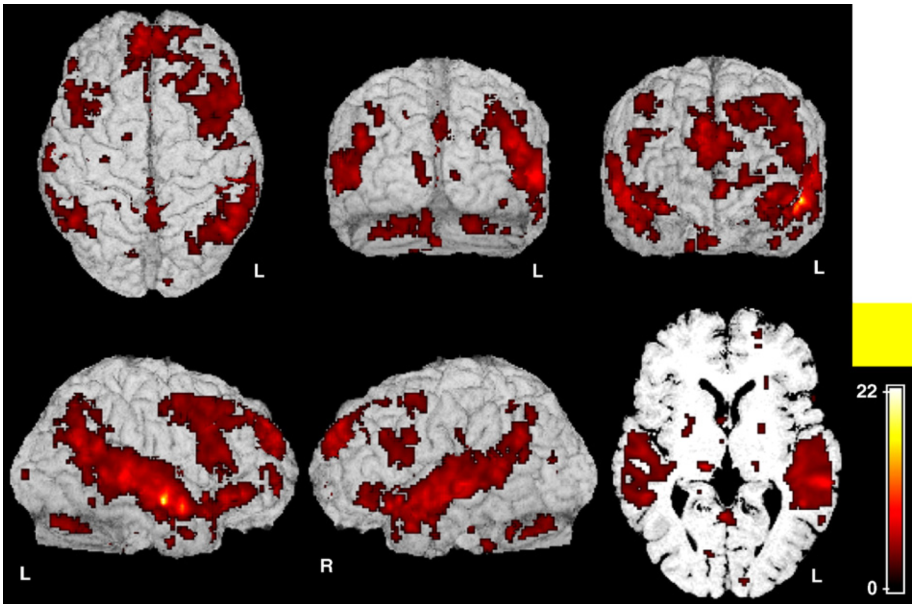

Fig. 3. Activation maps in schizophrenia patients with chronic auditory hallucinations under emotional auditory content. Note the larger activation clusters in the left middle and right superior temporal lobes, right insula and thalamus, and middle and superior frontal lobes (Table 1) ($P<0.05$, FDR-corrected, minimum voxel size per cluster 5).

were applied for controls (emotional and non-emotional paradigms) and patients (emotional paradigm).

3. Results

In regard to the questions asked immediately after MR data acquisition, results were as follows:

a) Patients
   - Frequency of voices during the MR experiment: none = 0, some = 4 (36.4%), often = 4 (36.4%), almost continuously = 2 (18.2%), all the time = 1 (9.1%).
   - Resemblance of voices to their own voices: none = 0, a little resemblance = 5 (45.5%), some resemblance = 2 (18.2%), a lot of resemblance = 4 (36.4%), identical = 0.
   - Level of anxiety: none = 1 (9.1%), very little = 2 (18.2%), slight anxiety = 4 (36.4%), moderate anxiety = 3 (27.3%), severe anxiety = 1 (9.1%).

b) Controls
   - Level of anxiety: none = 4 (40%), very little = 3 (30%), slight anxiety = 2 (20%), moderate anxiety = 1 (10%), severe anxiety = 0.

Neutral words against rest baseline patients' group map did not show any activation with the threshold applied ($P<0.05$) when non-emotional words were presented. After application of a less stringent P value ($P<0.001$) in order to see activation trends, main areas involved were left middle and left superior temporal gyrus, middle cingulate gyrus and left inferior frontal gyrus at the orbital part (Fig. 2). When patients were presented high emotional content stimuli, activation survived the $P<0.05$ corrected threshold and was greater both in extent and in estimated activation power. Middle left temporal gyrus was the main involved area. Other areas included right superior temporal gyrus, left and right insula, right median cingulate, right and left posterior cingulate, right amygdala, right and left middle frontal cortex at the orbital part, right inferior frontal cortex at the orbital area, and superior medial cortex (Table 1, Fig. 3).

Activation maps in control subjects did not show striking differences between emotional and non-emotional paradigms. In both conditions, the main areas involved were right and left superior temporal gyri, and right and left temporal gyri, while left inferior frontal gyrus at the orbital part of left insula was activated only with non-emotional paradigm (Table 1).

4. Discussion

The main result of our study is the clearly enhanced activity of the orbitofrontal cortex, temporal cortex, insula, cingulate, and amygdala (mainly right side) in patients when hearing emotional words in comparison with controls. Our finding that the left middle temporal gyrus was the main involved area when patients were presented high emotional content stimuli is concordant with the hypothesis of a reversal of function in schizophrenia in respect of prosody, which is usually considered to rely on the right hemisphere in healthy subjects (Woodruff, 2004). However, activation of the right superior temporal gyrus is probably more related to hallucinations and is concordant with previous reports (Woodruff et al., 1995).

The activations of the insula and orbitofrontal cortex were not surprising since these areas are key regions for the emotional response (Woodruff, 2004) and have also been related to hallucinations (Woodruff et al., 1995; Shergill et al., 2004). Contrary to our predictions, right middle cingulate, and right and left posterior cingulate were activated, but not the anterior cingulate. The activation of the posterior cingulate by threat-related words has been hypothesized to engage episodic memory processes in healthy volunteers (Maddock and Buonocore, 1997). On the other hand, right amygdala's activation has frequently been reported associated with AH and could also be explained as an evocation of the adverse emotional response to these phenomena (Woodruff, 2004).

Recently, several articles have tried to clarify the neural circuits responsible for the processing of personal salience (significance of stimuli to the individual). Bechara et al. (2003) proposed a neurobiological model of endogenous salience by differentiating primary (intrinsic) and secondary inducer processing, although both can overlap. Phan et al. (2004) have supported and extended their model in healthy subjects. Our results are partially concordant with their conclusions. According to these authors, the insula would be responsible for converging both primary and secondary inducer processing. This would be congruent with the relevance of the insula in our schizophrenic patients, since voices heard by subjects probably behaved as primary and secondary inducers in patients and just as primary inducers in controls. It may be that activations in the posterior cingulate and the amygdala reflect the retrieval of emotional verbal memory during an experience similar to the patients' hallucinations. In any case, the self-relatedness of stimuli is probably crucial in emotional processing in patients with schizophrenia. In our paradigm, all the emotional words were self-related and had a strong emotional content.

Most previous studies using emotional paradigms in patients with schizophrenia show a decrease of activation in comparison with controls (Schneider et al., 1998; Phillips et al., 1999; Crespo-Facorro et al., 2001; Gur et al., 2002; Kosaka et al., 2002; Paradiso et al., 2003). Our results based on an auditory emotional paradigm showed the opposite. There could be two main reasons for these differences: differences in the stimuli and in the samples.

Differences in the stimuli: Most previous studies have used a visual modality with paradigms of emotional faces (Phillips et al., 1999; Gur et al., 2002; Kosaka et al., 2002) or pleasant and unpleasant pictures (Taylor et al., 2002; Paradiso et al., 2003). Visual stimuli are more likely to be influenced by attention bias, which is frequent in patients with schizophrenia (Salgado-Pineda et al., 2004). Moreover, auditory emotional stimuli could be more appropriate to activate emotional response in schizophrenia because of the symptom profile. This could be especially true since in our study the emotional words are taken from the most frequent emotional voices.

Taylor et al. (2002) found that patients had greater activation of the medial prefrontal cortex when viewing pictures from the International Affective Picture System. Reduced or enhanced activity could be related to the emotional intensity of the stimuli. In other words, there could be a trend to have polar responses: little activation with normal social cognition tasks (Russell et al., 2000) and too much activation if the intensity or self-relatedness of the emotional stimuli is strong enough.

Differences in the samples: All the patients in our study suffered chronic and persistent AH. All had a high score on positive symptoms. Our patients' BPRS scores (mean = 56) are much higher than in other neuroimaging emotional studies such as those of Phillips et al. (1999) (mean = 23) and Taylor et al. (2002) (mean = 39).

Previous data in other studies are concordant with Bleuler's cardinal feature of schizophrenia, blunted affect (Lane, 2003), showing a decrease in brain activation or anhedonia (Crespo-Facorro et al., 2001). However, this decrease in brain activation cannot explain positive symptoms. The functional enhanced activation of our patients could be directly related to the emotional response to positive symptoms. Our findings suggest the importance of emotional response in the development and treatment of psychotic symptoms (Birchwood et al., 2000; Garety et al., 2001; Freeman and Garety, 2003). They may explain the observation of worsening psychoses in high expressed emotion families in schizophrenia (Falloon, 1988).

Our data are of interest in light of Kapur's recent proposal on the possible mechanism of action of antipsychotics (Kapur, 2003). Kapur postulated that in psychosis a dysregulated dopamine transmission leads to an aberrant assignment of salience to external objects or internal representation. Antipsychotics are efficacious in psychosis because they "dampen salience" of the subjective experience of delusion and hallucinations. It is noticeable that all the patients of our sample have persistent AH in spite of having been treated with antipsychotics for a long period. It could be possible that patients stabilized with antipsychotics would not have had this enhanced activation effect.

It was of interest that when neutral stimuli were applied, no clear activation was found. A reason for this could be that patients were being continuously activated by their own voices. If we reduce the threshold of significance, an activation of the left temporal lobe appears. This attenuation of response to neutral auditory stimuli had already been described in the study of David et al. (1996).

A limitation of our study is that these results are generalizable to schizophrenic patients with persistent auditory hallucinations and not to schizophrenia or psychosis as a whole group. It will be important to replicate this study in less severely ill patients and those who have never experienced hallucinations. Schizophrenic patients with a clinical history of hallucinations also need to be investigated using these paradigms before and after stabilization of hallucinations.

In conclusion, our findings suggest an enhanced activation of the limbic and frontal brain areas in persistently hallucinatory patients using a specific self-related auditory emotional paradigm. These findings may help us in our understanding of the dysfunction of the emotional response in schizophrenia.

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