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Emotional auditory paradigm in neuroimaging: a base for the study of psychosis

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Introduction. Since the arrival of neuroimaging numerous studies have tried to analyze the differences between emotional and non-emotional response. The majority of these studies use visual approach (faces) and begin with data in normal subjects. The present study introduces a new paradigm for the study of emotional response based on auditory approach and designed specifically for the study of psychoses.

Method. The most frequent words heard by psychotic patients with auditory hallucinations were analyzed. They were classified according to five categories which were compared with 13 other words with the same structure but with a neutral emotional valency. This paradigm was applied to see the cerebral activation with functional magnetic resonance imaging (fMRI) in 10 right handed healthy males.

Results. In the preliminary analysis a clear differentiation is observed depending on the type of stimulus applied (emotional or non-emotional), both in the intensity of activation (right and left temporal cortex) as in the activation of specific areas (right precentral and supramarginal gyrus) only with the emotional stimulus.

Conclusions. The present paradigm allows the observation of a differentiation in the cerebral activation to emotional auditory stimulus and could be of utility in the study of psychotic patients.

Key words:
Functional magnetic resonance imaging. Auditory paradigm. Emotional processing. Words.

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Paradigma auditivo emocional en neuroimagen: una base para el estudio de la psicosis

Introducción. Desde la llegada de la neuroimagen numerosos estudios han tratado de analizar las diferencias en la respuesta emocional frente a la no emocional. La mayoría de estos estudios utilizan la modalidad visual (caras) y parten de los datos en sujetos normales. En el presente estudio se presenta un nuevo paradigma para el estudio de la respuesta emocional basado en la modalidad auditiva y diseñado específicamente para el estudio de la psicosis.

Método. Se analizaron las palabras más frecuentes que oían los pacientes psicóticos con alucinaciones auditivas, se clasificaron según cinco categorías y a partir de las mismas se diseñó un tren de 13 palabras emocionales, comparándose con 13 palabras con la misma complejidad sintáctica y con una valencia emocional neutral. Se aplicó este paradigma para ver la activación cerebral mediante resonancia magnética funcional (RMf) en 10 varones sanos y diestros.

Resultados. En los análisis preliminares se observa una clara diferenciación según el estímulo sea emocional o no emocional, tanto en la intensidad de la activación (córtex temporal derecho e izquierdo) como en la activación de áreas específicas (precentral y supramarginal derecha).

Conclusiones. El paradigma presentado permite observar una diferenciación en la activación cerebral de la respuesta a estímulos auditivos emocionales y podría ser de utilidad en pacientes psicóticos.

Palabras clave:
Resonancia magnética funcional. Paradigma auditivo. Procesamiento emocional. Palabras.

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INTRODUCTION

Since the studies of Charles Darwin on the expression of emotions in man and animals[1], many investigators have tried to analyze the biological bases of our emotional response, both from animal research[2] and from the search for biological correlates to the different emotions[3]. Classic theories tried to relate the peripheral changes to stimuli of different emotional content to establish a psychophysiology of the emotions. The arrival of functional neuroimaging through magnetic resonance (fMRI) has opened a new and exciting perspective in this field.

Functional neuroimaging studies can be divided into three sections: those that seek differences in the baseline condition of the subject without subjecting him/her to any stimuli, those that try to capture a specific and special moment of the brain functional activity (as, for example, pressing a button when the subject experiences hallucinations) and those others that try to measure brain functional activity while the subject undergoes a type of stimulus or task.

Thus, within functional neuroimaging, «paradigm» is called the stimulus or task of experimental design in which the subject is repeatedly subjected to two or more situations. During recent years, there have been multiple paradigms for the study of brain activity with very different complexity. These have been divided according to the stimulus modality (motor or sensorial) or the type of cognitive task to be studied. For the extraction of results, these situations normally include the performance of one or more specific functional tasks and the baseline rest situation[4].

However, the analysis of the differences observed in brain activation according to whether the stimulus has an emotional content or is emotionally neutral is one of the areas that generates the greatest interest. In an extensive revision on the subject, Murphy[5] analyzed 106 neuroimaging studies that had focused on analyzing the differences on brain activation observed between emotional paradigms versus non-emotional ones. Almost 90 % (95 papers) of these studies have used the visual stimulus modality, mainly with presentation of emotional expressions in faces or of emotional content images[6-9], the remaining experiments being distributed in auditory (11 studies), olfactory (5 studies), tactile (2 studies), gustatory (2 studies) stimuli and even electric shock and saline injection (1 study each).

The scarce number of studies with auditory modality is striking, above all if we admit the great importance of language and the word in awaking human emotions. The few studies that use an auditory paradigm with emotional response in normal subjects appear in table 1. As can be observed in this table, some studies have sought to provoke different emotions with music[10-12], or noise[13-15] while others have used the presentation of words having different emotional meaning[10-26]. The paradigms used in each one of these studies have been very different and thus it is complicated to compare the results. Some studies have sought to analyze the capacity of identification of the emotional tone (prosody)[16-19] while others have studied the differentiation in the activation pattern according to the type of emotion related with the word[20-26]. In keeping with Maddock[24], the variables that influence the fact that a word may arose an emotion is mainly associated with the emotional value given to it by the subject, to the frequency of its use and to the imagination it can evoke. The complexity (number of syllables) of the word is another factor to consider. These authors found activation in the upper part of the left cingulate cortex in a sample of eight right handed subjects (six women and two men), without being able to observe differences between pleasant stimuli versus unpleasant ones.

All these investigations have great relevance for the study of psychiatric disorders. In very general terms, some authors have stated that all the psychiatric disorders are alterations in emotional activation[27]. Thus, the large amount of studies that use this type of paradigm in subjects with psychiatric diseases[28] is hardly surprising.

Focusing on schizophrenia, many studies have demonstrated deficits in the emotional processing in recognition of faces[29,30], and also some in affective prosody[30]. However, here there are also many methodological problems that make it difficult to compare the results and establish specificity, extension and nature of the deficits[30]. There have also been different functional neuroimaging studies that have gone deeper into the study of these deficits, both in face recognition[31-35] as by pleasant and unpleasant visual stimuli[36]. We have not found any neuroimaging study that uses the auditory modality in the literature. This is particularly striking given that the perceptive disorders these subjects suffer are mostly within this sensorial modality.

This study presents a paradigm based on the audition of words for the study of the differences in brain activation when the content is emotional versus non-emotional. These differences are analyzed with functional neuroimaging (fMRI) and will be validated in healthy control subjects. Our final objective is for this functional neuroimaging model with emotional auditory stimulus to serve to deepen the knowledge of the underlying conditions in patients with schizophrenic psychosis who have auditory hallucinations.

MATERIAL AND METHOD

Elaboration of fMRI paradigm

Selection of words having emotional content for psychosis

So that the selection of the words with emotional content to be specific for psychosis, 82 patients with schizophrenia according to DSM-IV criteria and who had suffered auditory hallucinations according to their clinical record were chosen. All the patients were administered the Spanish version of the PSYRATS scale[37] for hallucinations and the hallucination content were recorded on a tape recording machine. These recordings were transcribed and the most frequently appearing words were analyzed. Hallucinations that were based on complex sentences or had a neutral content were ruled out, selecting words that had meaning by themselves. A total of 65 words were chosen and were grouped according to content in five categories:

- Negative content with imperative tone (for example, get out!, kill him!)
- Insults (for example: good for nothing!, jerk!)

Table 1 **Studies that have used the auditory sensorial modality to analyze the emotional versus non-emotional response in normal subjects**

Author and year (ref.)	Technique	N	Paradigm
			Music
Baker et al., 1997[10]	PET	10	Different types of music
Blood and Zatorre, 2001[11]	fRMI	10	Pleasant music
Blood et al., 1999[12]	PET	10	Pleasant music/unpleasant music
			Noises
Frey et al., 2000[13]	PET	8	Pleasant sounds/unpleasant sounds
Hugdahl et al., 1995[14]	PET	5	Noise/unpleasant tone
Royer et al., 2000[15]	PET	12	Opinion of pleasant stimuli, including auditory
			Words
Imaizumi et al., 1997[16]	PET	6	Identification of the emotion spoken with
Morris et al., 1999[17]	PET	6	Vocalization of emotions
Buchanan et al., 2000[18]	fRMI	10	Voices with different emotional intonation
George et al., 1996[19]	PET	13	Prosody of the words
Schirmer et al., 2004[20]	RMf	24	They heard a series of verbs in which emotional valency was established, the stimulus varied one series with emotional tone and another without it
Philips et al., 1998[21]	fRMI	6	Verbal expression of fear
Royet et al., 2000[15]	PET	12	Opinion of pleasant stimuli, including auditory
Isenberg et al.[22]	PET	6	Neutral and emotional words
Maddock et al., 1997[23]	RMf	7	Words having emotional and neutral content
Maddock et al., 2003[24]	RMf	8	Words with emotional and non-emotional content, analyzing the valency of them. They heard only text, words in sequential form
Tracy et al., 2003[25]	fRMI	15	Emotions, non-emotional words, text plus emotional words, text plus non-emotional words
Goel and Dolan, 2001[26]	fRMI	14	Jokes with humor and without humor

- Imperative tone (for example: do it!, listen!)
- Exclamations related with emotional conditions (for example: fuck!, shit!)
- Positive content (for example: good!, wonderful!).

Attending to the frequency presented and given that the stimulus pattern for the fMRI experiment should last 20 seconds for each block, a total of 13 words were chosen and were distributed in the following way: 4 negative content imperative words (get out, kill him, hurl yourself down, you will die), 3 insults (whole, good for nothing, jerk), 2 with imperative tone (listen, do it), 2 exclamations related with emotions (fuck, shit), and 2 having positive content (wonderful, good).

Selection of words with neutral content and pairing with those of emotional content

The data published by S. Algarabel in which the indexes of psycholinguistic interest of 1,917 Spanish words are explained was used[38]. This author analyzes different types of indexes of these 1,917 words. These indexes are grouped into two large categories: objective indexes: they refer to the number of letters, number of syllables, written frequency, number of meanings in the Royal Academy dictionary and those called subjective indexes: imaginary, meaningfulness, number of attributes, concreteness, categorizability, familiarity, pleasantness. The first indexes are obtained from the mentioned sources, the subjective ones were obtained from a Valencian and Alicantinian sample of a total of 2,000 subjects who had to evaluate the words on a 1 to 7 scale. The item that interests us most here is that called pleasantness. The subjects should respond to what degree this word aroused feelings of complacence or unpleasant feelings, ranging from 1, very unpleasant, to 7, very pleasant.

The neutral words chosen had to have a syntactic complexity (number of syllables) similar to that of the emotional words, a similar use frequency and neutral or slightly positive score on the pleasantness scale between 3 and 4. We also added that they should never be words that could refer to the subject if they were not common names of objects and simple concepts. The 13 words chosen were: table, liter, case, lamp, wheel, terrace, shoe, mountain, datum, park, meter, novel, drawing. The mean pleasantness index of the neutral words was 3.8. The total number of syllables was the same as in the emotions 33. Joining words whose association had a meaning was avoided.

To make the recording, we used a specialized center, hiring an actor to pronounce the words. The neutral words in neutral tone and the emotional ones with an emotional tone, but with the same intensity of voice (65 bs).

During the fMRI experiment, four blocks with 20 second long stimuli mixed with four more blocks with 20 seconds of rest were presented to the subject. The order of both acquisitions (emotional and neutral) was random to avoid introducing biases (adaptation, tiredness, saturation surprise) due to the order of the auditory stimulus without and with emotional content. The subjects were warned before the test that they would hear these types of words, simply asking them to pay attention to them.

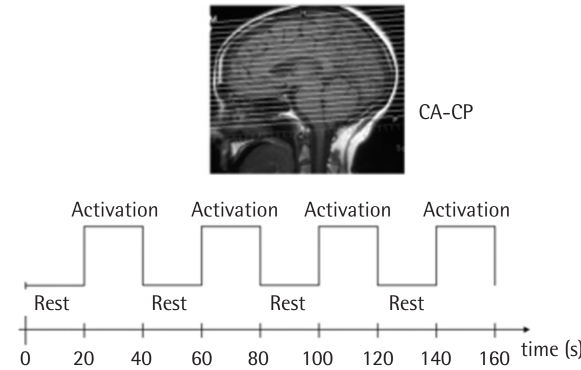

Figure 1 *Distribution in time of eight blocks of stimuli (four activation and four rest).*

Functional magnetic resonance imaging technique

Design

The neuroimaging test consisted in the acquisition of fMRI images by Blood Oxygenation Level-Dependent (BOLD) contrast, using the previously mentioned paradigm, and structured brain images having high spatial resolution to superimpose the activation maps on them.

The subjects were subjected to the block stimulation paradigm, exchanging rest states with auditory stimulation states. Figure 1 shows the distribution in time of the stimulation blocks.

This scheme of blocks was repeated in two sessions for each subject. The first acquisition was the auditory stimulation paradigm with emotional content (sequence groups of 13 words with high emotional content), the second acquisition being without emotional content (groups of 13 words with very low emotional content). Each session consisted in 80 acquisitions of tridimensional data (3D) of the total brain volume, assigning 10 consecutive acquisitions to each activation state (rest and auditory stimulation). finally, a structural volumetric sequence of the anatomical content of the brain was obtained in rest state.

Acquisition of MRI images

Data acquisition of magnetic resonance superconductor 1.5 teslas (Philips Intera 1.5, Holland) was performed by a clinical team. The patients were given headphones connected by air tubes with an audio CD reproducer. Using these headphones, the patients were isolated from the noise inherent to the fMRI experiment while they received the auditory stimulus. The auditory stimulus test that they were going to hear was previously described to all the subjects. The studies were acquired with the standard quadrature head coil.

For the acquisition of the functional images, the following sequence was used: T2* weighted EPI dynamic sequence of fMRI (multicut 2D sequence; TR: 2,000 ms; TE: 50 ms; 5 mm cut thickness without separation between cuts, acquisition matrix: 96×128; field of vision (FOV): 220 mm; excitation angle: 65º). Voxel size was 3.27×1.72 mm. Sequence was acquired with spectral suppression of fat to minimize artifacts by chemical displacement. Each one of these dynamics had 24 contiguous cuts with a parallel orientation to the anterior commissure-posterior commissure line, with a coverage of all the intracranial CNS.

To study the functional activation, a total of 80 dynamics were acquired (2 seconds long each one) with a global duration of the sequence of 160 seconds. Every 10 ones of these dynamics formed a block. During the experiment, four blocks in rest state and four during activation were alternately studied.

The anatomical structural image necessary for topographic localization of the activation areas was obtained with the T1 weighted gradient echo sequence (volumetric 3D acquisition; TR: 7 ms; TE: 1.88 ms; cut thickness: 1.2 mm without separation between cuts; acquisition matrix of 256×256; FOV: 220 mm). With this sequence, all the intracranial nervous system is acquired with 96 cuts. The voxel size was 0.86×0.86 mm. Duration time of this sequence was 280 seconds.

Data analysis

Based on the images obtained from the structural MRI and fMRI, an initial preprocessing was performed to improve the images in order to adequately perform the statistical analysis pixel to pixel.

The fMRI and structural images were coregistered in such a way that the anatomical areas coincided in both image modalities. In the fMRI images, a realignment was also done with correction of subvoxel movement to eliminate the effects associated with the involuntary movement of the head during the fMRI study. Realignment of the dynamics was performed according to a reference volume. After, the images were transformed to a standard space by minimization of the quadratic error that represents the difference between the template image (MNI350, Montreal Neurological Institute) and study image. This transformation was done beginning with the structural image of each subject. The intensity of the normalized images was softened based on a tridimensional Gaussian nucleus to optimize the signal to noise ratio[39], the data approaching a convenient normalized distribution for the statistical tests that were subsequently performed.

The statistical analysis consisted in the study of a single subject and the intersubject comparison (extraction of data and differences on the activation in the two paradigm groups). The analysis of the parametric maps was done with t-tests studies of a sample based on 10 healthy subjects (analysis of groups of subjects, by an Random Effects Analyses, voxel by voxel, to obtain the characteristics of common activation, according to the MLG through the SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience)[40].

The results were filtered with the False Discovery Rate technique with a corrected $p < 0.1$ and minimum threshold of a group of five voxels (groups less than five voxels were eliminated).

The activation areas were defined by Automatic Area Labeling[41]. Using the Wfu_pickatlas software[42] mask images were obtained of each one of the regions. These were filtered for the parametric images of the test for stimuli with emotional content and the test for stimuli without emotional content, finally counting the number of active voxels.

RESULTS

Activation maps for each non-emotional/emotional paradigm were obtained from the images of the group of 10 control subjects (figs. 2 and 3). It can be observed in figure 2 how the activation is mainly located in the superior temporal gyrus when stimuli with words without emotional content are used. When the auditory stimulus is done using words with high emotional content, areas of activation were obtained in similar regions, but with a greater extension than in the case of the non-emotional paradigm, mainly in the middle and superior temporal gyrus. The meaning for the active areas in these regions reached very significant values (corrected $p < 0.001$).

When auditory stimuli were used with emotional content, a statistically significant supplementary activation was seen in the right post-central area and in the right supramarginal gyrus that did not occur with stimuli without emotional content.

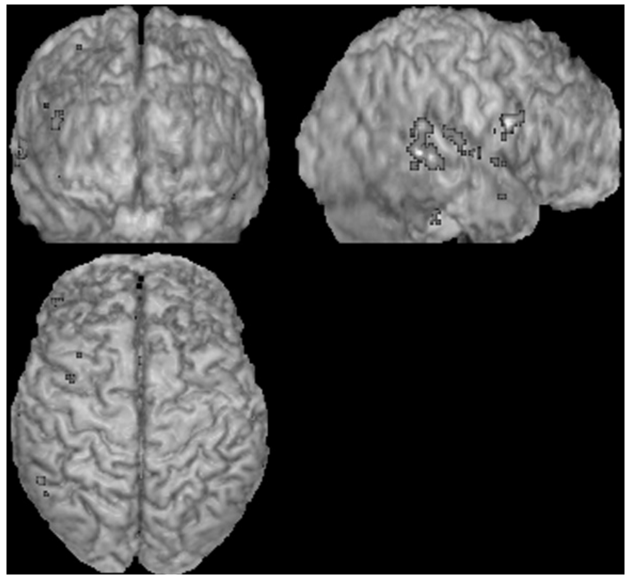

Figure 2 *Auditory activation in 10 controls with stimulation of words without emotional content.*

DISCUSSION

This present article aims to present a new paradigm of emotional versus non-emotional auditory stimulation for the study of emotional reactivity in psychotic patients, showing preliminary data of fMRI in normal subjects. As we mentioned in the introduction, the studies reviewed on the subject have very different methodologies and thus the results are

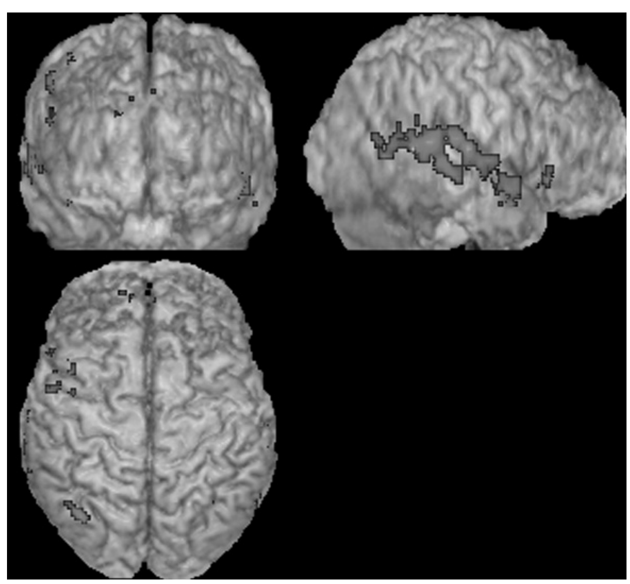

Figure 3 *Auditory activation in 10 controls with stimulatin of words with emotional content.*

not comparable. The paradigm that we present herein has important differences in relationship with those previously used by other authors. The selection method of the neutral words (non-emotional) was similar to that performed by other authors, especially to that used by Maddock et al.[24], although the subjects were not asked to evaluate the neutrality of these words, but rather they were selected from the data of the general population. However, the emotional words were selected based on the conversation of psychotic patients with auditory hallucinations and not from the general population nor from the previous signaling of the valency of pleasantness given by the study subjects. This determined that the words chosen had very specific characteristics. Thus, compared with other studies, the emotional words of our paradigm have the following differential characteristics: *a)* they have a syntactic meaning by themselves; *b)* all refer to the person; *c)* they express, without possibility of ambivalency, a strong affective content that is reinforced by a clear emotional tone (prosody), and *d)* as in most of the studies, there is no differentiation between whether the content of the words is pleasant or unpleasant; it is aimed to analyze the emotional filter that may be done by the psychotic patient and this may be altered both in positive and negative words.

We believe that this paradigm that is especially designed to analyze the emotional response of the psychotic patients may maximize the possible differences in emotional processing of language.

The initial results in normal subjects show a clear differentiation in cerebral activation between emotional and non-emotional words. The large increase in the activation of the temporal areas, an increase that is more marked in the right hemisphere, calls our attention in the first place. It must also be stressed that the areas of the right hemisphere as the supramarginal gyrus and the post-central area are only activated with emotional stimuli. Although these results are only preliminary and require greater analysis, they are coherent with the results of other authors[18,23,25] and indicate that the paradigm described may be useful for the discrimination of the circuits involved in the emotional response to auditory stimuli.

If, as Maddock[24] states, memory may play a very important role in the activation of these circuits, it can be expected that when psychotic subjects with auditory hallucinations listen to words that have a relationship with their hallucinations, this differentiation would be more greater. We hope to verify the certainty or non-certainty of this hypothesis in future studies.

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