Functional neuroimaging of auditory hallucinations in schizophrenia

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Neuroimagen funcional de las alucinaciones auditivas en la esquizofrenia

Summary

The neurobiological bases underlying the generation of auditory hallucinations, a distressing and paradigmatic symptom of schizophrenia, are still unknown in spite of in-depth phenomenological descriptions. This work aims to make a critical review of the latest published literature in recent years, focusing on functional neuroimaging studies (PET, SPECT, fMRI) of auditory hallucinations.

Thus, the studies are classified according to whether they are sensory activation, trait and state. The two main hypotheses proposed to explain the phenomenon, external speech vs. subvocal or inner speech, are also explained. Finally, the latest unitary theory as well as the limitations the studies published are commented on. The need to continue investigating in this field, that is still underdeveloped, is posed in order to understand better the etiopathogenesis of auditory hallucinations in schizophrenia.

Key words: *Auditory verbal hallucinations. Functional neuroimaging. Schizophrenia.*

Resumen

Las bases neurobiológicas subyacentes a la generación de las alucinaciones auditivas, síntoma paradigmático y angustiante de la esquizofrenia son aún desconocidas a pesar de estar descritas fenomenológicamente con profundidad. El propósito de este trabajo es realizar una revisión crítica de la literatura publicada en los últimos años, centrándose en los estudios de neuroimagen funcional (PET, SPECT, RMf) del fenómeno alucinatorio.

Para ello se clasifican los estudios según sean de rasgo, de estado y de activación sensorial. También se exponen las dos principales hipótesis propuestas para la explicación del fenómeno: lenguaje exterior frente a lenguaje interior o subvocal (inner speech). *Finalmente se presenta una hipótesis unitaria, así como las limitaciones de los estudios publicados. Se plantea la necesidad de seguir la investigación en este campo, todavía en estado incipiente, con el objetivo de comprender mejor la etiopatogenia de las alucinaciones auditivas en la esquizofrenia.*

Palabras clave: *Alucinaciones verbales auditivas. Neuroimagen funcional. Esquizofrenia.*

INTRODUCTION

Hallucinations, perceptions in absence of external stimuli, are one of the most outstanding symptoms and a clear sign of severity of the schizophrenic disorder. Auditory verbal hallucinations are a common and distressing symptom of psychosis and it is estimated that its prevalence in schizophrenic patients is around 70%-80%. However, although it has been described in depth over time, its location and etiopathogeny are still unknown.

Difficulty to specify the neuronal base of hallucinations is partially due to the extraordinary heterogeneity of this subjective mental phenomenon as well as to its transitory nature. Furthermore, this component is found in different diseases such as bipolar disorder (15% of patients report hallucinations), toxic psychoses, or Alzheimer's disease, among others, which makes it difficult to unify its etiology.

Neuroimaging techniques allow for the *in vivo* and non-invasive study of the human brain, which means an important development for the structural and functional study and knowledge of schizophrenia in order to increase knowledge on its neurobiological bases.

These techniques make it possible to measure the cerebral activity *in vivo* during the presence of clinical symptoms such as hallucinations or during a sensorial activation test, and studies of the distribution and occupation of the specific cerebral receptors[1,2].

Structural neuroimaging by computerized tomography (CT) and magnetic resonance (MRI) has made it possible to know structural abnormalities in schizophrenia, retorted and consistent findings, although not specific to this disease, as dilation of the lateral ventricles and reduction of the temporal lobe volume and the amygdala-hippo-

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campal formation. Neuroimaging studies are scarce[3] in the field of hallucinations and even more so if we consider the hallucinatory phenomenon as an isolated symptom of schizophrenia. MRI studies have compared two groups of patients with and without hallucinations to observe possible evidence of the structural base of this symptom, revealing an inverse relationship between the severity of the hallucinations and the volume of the left superior temporal gyrus (Brodman area -BA-22)[4,5], suggesting an abnormal role of the auditory cortex in the development of auditory hallucinations. Other studies with MRI and CT on hallucinations in Alzheimer's disease with subjects who have hallucinations and a control group of patients with this disease who do not suffer hallucinations also observed an increase in the ventricles and greater degree of cerebral atrophy[6,7].

This present review attempts to up-date the latest findings in functional neuroimaging on the hallucinatory phenomenon in schizophrenia as well as to present the neurobiological theories underlying this phenomenon.

FUNCTIONAL NEUROIMAGING OF AUDITORY HALLUCINATIONS

The complex neuronal base of auditory hallucinations in schizophrenia has been poorly understood, even though it has been subjected to study since the beginning of psychiatry. During the last decade and thanks to the incorporation of functional neuroimaging techniques, investigations have been initiated that aim to know the neurobiological bases of hallucinations.

As is explained further on, there are two theories on the neuroanatomical substrate of the hallucinatory phenomenon: that of external speech and that of subvocal or inner speech. The external speech theory suggests that the production of auditory hallucinations in schizophrenia is associated to an increase in the activity in the cortical network specialized in audition and in the perception of external speech. In the literature, it is observed consistently that verbal auditory hallucinations are associated to an increase in activity in the primary and secondary auditory cortex, Broca and Wernicke areas, amygdala-hippocampal complex and anterior cingulate cortex[8-12]. Data from different origin suggest it in this way: studies on temporal epilepsy, surgical electrical stimulation or already described disorders by MRI in schizophrenia, associate auditory hallucinations to the left temporal cortex. The inner speech theory would postulate that the auditory hallucination is a product of the incapacity of the schizophrenic patient to control the generation of his own thoughts, these being perceived as foreign. The cerebral areas related with inner speech would be involved[13-14], involving the activation of the left inferior frontal region and the hypoactivation of the supplementary motor area, rostral motor area and medial temporal gyrus.

In 2001 Stephane[15] developed a unitary hypothesis, stating that the dysfunction of the cerebral areas responsible for the generation of speech would be the fundamental mechanism to generate auditory verbal hallucinations in schizophrenia. In this model, which will be explained in detail further on, two phenomena occur parallelly: activation of the perception areas of external language (perceptive component), together with a variable activation of the areas involved in inner or subvocal language (motor component).

The neuroimaging studies performed on the hallucinatory phenomenon can be classified in three ways:

- *Trait studies,* that assess the cerebral functionalism of the hallucinatory component of groups of patients with a positive history of hallucinatory disorder and/or who are actively hallucinating, assuming that the hallucinatory state is continuous and homogeneous and that it persists in the radiopharmaceutical uptake period, although it is very unlikely that this premise is true. Here, both neuroimaging (CT, MRI) as well as functional (SPECT, PET, fMRI) techniques are used.
- *State studies,* that assess the cerebral functionalism of the hallucinatory component of groups of patients who are actively hallucinating at the exact moment in which the hallucination occurs. These studies are more recent and performed thanks to more exact techniques, performed with H_2O-PET and fMRI.
- Finally, there are *stimulation or sensorial activation studies* that assess the cerebral activity during the performance of a specific sensorial task, either by exposure to a certain stimulus or instructions to generate mental images.

In these three types of studies mentioned, the study group (schizophrenic subjects with hallucinations or history of hallucinations) is compared with health control groups or schizophrenics without a history of hallucinations or by retest with the same subjects once the hallucinatory phenomenon has subsided.

TRAIT STUDIES OF AUDITORY HALLUCINATIONS

The trait studies can give us an estimated approximation of cerebral functionalism, however it should be kept in mind that it is unlikely that the hallucinatory phenomenon is stable, homogeneous and persistent in a determined time.

The first study by ^{123}I-IMP SPECT was performed by Matsuda et al[16] in 1988, assessing auditory hallucinations in a patient with alcoholic dependence when he was actively hallucinating and after the hallucinatory symptoms abated, observing an increase in the left superior temporal lobe activity, areas corresponding to the primary and secondary auditory cortex. In 1989, Notardonato et al[17] studied a schizophrenic patient with a history of auditory hallucinations by SPECT, showing an increase in the basal ganglia uptake and in the right temporal lobe.

Musalek et al[18] performed an interesting study by SPECT with ^{99m}Tc-HMPAO, comparing 17 patients with chronic auditory hallucinations and 28 healthy volunteers, showing a superior cerebral regional blood flow in the basal ganglia and decrease in the frontal-lateral, mesofrontal and hippocampal areas. The next year, the same author found similar findings in a group of 28 actively hallucinating schizophrenic patients (17 auditory and 11 tactile) compared with a control group of 28 normal subjects using the same technique, showing that the hallucinations are associated with a bilateral increase in the activity of the basal ganglia and hippocampal regions as well as a decrease in the bilateral activity in the lateral frontal lobes[19].

However, the results of the studies described previously can be biased due to the use of neuroleptics in the group of patients with hallucinations, since it has been described that chronic treatment with neuroleptics increases the regional cerebral blood flow (rCBF) in the basal ganglia[20] or also by the large discrepancy in age with the control group, since age is related with a decrease in rCBF principally in the frontal region[21].

In 1998, in our group, Parellada et al[22] published a study by SPECT with ^{99m}Tc-HMPAO in 25 schizophrenic patients during the acute psychotic episode and a control group. A positive correlation of the positive symptoms was observed, including hallucinatory component evaluated by the Andreasen's scales for the assessment of positive symptoms (SAPS) and the rCBF in the left temporal region.

Another series of studies using PET with F18-FDG performed by the Cleghorn group[23-25] shows disagreeing data, no differences being found in the regional uptake of glucose between the patient group with hallucinations and the control group of patients without hallucinations, but indicating a high correlation with the activity pattern in specific speech centers (right Broca area equivalent with right superior temporal gyrus) in hallucinating patients[23,24]. In any event, there are certain limitations in these studies, such as a reduced sample of patients with hallucinations (11 and 9, respectively), substance abuse and lack of phenomenological description of the hallucinations.

In this way, the presence of auditory hallucinations in schizophrenia has been associated to an increase in cerebral blood flow in the left temporal lobe, although they have not been corroborated in all the studies[25]. It seems that the Cleghorn study[25] contradicts other past studies of his, since it is the only one that maintains a decrease in the activity level in these regions of the auditory sensorial cortex.

STUDIES OF THE AUDITORY HALLUCINATION STATE

The studies of state make it possible to access what is occurring in the hallucination in a specific moment, it being the patient who gives the information on it. Since the hallucinatory phenomenon is transitory, this type of study with «symptom capture» techniques makes it possible to capture the hallucination at the exact time and avoid possible biases arising from the transitory character of the phenomenon.

Using SPECT with ^{99m}Tc-HMPAO in 12 chronic schizophrenic patients with frequent auditory hallucinations and comparing them in a retest 19 weeks later when this state of frequent hallucinations abated completely, McGuire et al[8] obtained a highly significant association of the hallucinations with increase in cerebral blood flow in the Broca area as well as an increase, although not significant, of the left anterior cingulate cortex and left temporal lobe. This suggested that the production of the hallucinations is associated with the increase of the activity in the network of the cortical area specialized in speech. Similar results, although with a smaller sample of five patients, were obtained by Suzuky et al[26] by SPECT with ^{125}I-IMP.

Two studies of a single cases performed by fMRI were published. The first was by Woodruff et al. in 1994[27] with a 48 year old schizophrenic patient who had auditory hallucinations. They observed activation of the middle and right superior temporal gyrus and of the dorsomedial nucleus of the thalamus. In 1999, Lennox et al[28] analyzed a 26 year old schizophrenic patient with a stable pattern of intermittent auditory hallucinations and also reported activity of the right middle and superior temporal gyri as well as of the left superior temporal gyrus, right frontal lobe and right anterior cingulate cortex. Activation of the right superior temporal gyrus precedes (by three seconds) the notification of the presence of hallucinations, corroborating again the hypothesis postulated on the existence of abnormal activation of the auditory cortex in the production of auditory hallucinations.

With greater methodological rigor, Silbersweig et al[29] performed a study of state of auditory hallucinations by PET with H_2O^{15}. In order to capture the hallucinatory moment, there was a button which, when pressed, indicated the onset and end of the hallucination during the performance of the study. Five patients with auditory hallucinations and one patient who had never been treated with visual and auditory hallucinations were evaluated. They presented an increase in the activity of the subcortical nuclei (thalamus and striatal), in the limbic structures (hippocampus) as well as in the paralimbic regions (hippocampal and cingulate gyri, and orbitofrontal cortex) and left auditory temporal cortex. Thus, they postulated that the verbal hallucinations are associated to the activity of the auditory-linguistic association cortices.

In 1999, Dierks et al[11] performed an interesting study using fMRI, adding on to the results of Silbersweig[29]. They found an increase in the blood oxygen level-dependent (BOLD) in the primary auditory cortex (area of the transverse temporal gyrus, a zone called Heschl's gyrus) of the dominant hemisphere, responsible for the hallucinatory experience. Furthermore, they observed an increase in the level of left posterior middle and superior temporal gyri, bilateral hippocampus (related with the recovery of mnesic material), left amygdala (in relationship with the emotional tone associated to hallucinatory component) and frontoparietal operculum (Broca area)

in three patients with paranoid schizophrenia with auditory hallucinations. Through the conclusions, the authors try to provide an integrating view of the clinical features related with hallucinations. They involve the memory of the patient and the emotional reaction caused by the hallucinatory experience. The areas that are activated during the endogeneous hallucinations are the same that are activated in response to a verbal auditory and external tonal stimulus, manifesting that the primary auditory cortex is directly involved in the experience of the hallucinatory phenomenon.

These data are retorted with another study[9] by fMRI, comparing 4 schizophrenic subjects during periods of hallucinations and in absence of them. They observed activation of the superior or middle temporal gyri (BA 21/22), as Dierks11 and similar to Silbersweig[29], and prefrontal activation during the hallucination period, involving non-dominant primary auditory areas (right side in each subject and bilateral in two of them). It is not possible to make an exact location of the activation, there being marked variations and laterality of the activations, reflecting the different nature of the experience of each individual and the variations of the design of the three studies (both the way the button is pressed as well as the instrumentation that is different). Lennox sustains that there is an abnormal activation of the normal auditory pathways in the hallucinatory experience[9]. These pathways have been described in healthy volunteers by the temporal bilateral activation in response to the presentation of verbal material[30-32].

Absence of activation of the primary auditory cortex after acoustic stimulation in schizophrenic patients with auditory hallucinations has been described in a study with fMRI[12].

In summary, these data suggest that the auditory hallucinations «compete» with external speech in the processing sites within the temporal cortex, there being a physiological competition for a common neurological substrate[9,10]. The consistent activity in the right and left frontal areas (BA 46/47) obtained in Lennox[9] was not observed in the Dierks11 or Silbersweig[29] studies. In a case evaluated by Lennox et al[28], previously commented on, it is shown that the frontal activity was secondary to the temporal activity during the auditory hallucinations. This frontal activity could be related with an emotional response of the hallucination or recovery of the verbal memory, a function that is also associated with the activation of these areas[33,34]. Activity is also not found in the Broca area (BA 44 and 45) in any subject. All these findings do not offer any support to the theory that auditory hallucinations arise from abnormalities of internal or subvocal speech, as has been suggested by different authors[13,14,35].

HALLUCINATORY PHENOMENON STUDIES BY SENSORIAL ACTIVATION TASKS

The investigations performed with stimulation tasks or sensorial activation study the changes in brain activity during the performance of a specific sensorial task. In the schizophrenia area, the studies performed with PET and fMRI by a multicenter team are especially relevant. These studies were focused on understanding the etiopathogeny of the hallucinatory process more than the specific neuroanatomical substrate during the capture of the symptom and are the base of the inner speech theory.

The first studies published by McGuire et al[13,36] evaluated the cerebral processes associated with the autogeneration of speech and verbal images by PET with H_2O^{15}. To do so, they evaluated three groups of subjects (schizophrenic patients with and without a history of auditory hallucinations consistently during the exacerbations of their disease and healthy controls), performing three tasks: one control, another inner speech and another generation of auditory verbal mental images.

The control task consisted in reading groups of words silently, most pejorative, the rest pleasant and neutral. The inner speech task was aimed at mentally reciting, without any articulatory movement, a sentence that began with «you are...» and ended with the words previously shown. And finally, the task of generation of mental auditory verbal images was identical to the previous task, except that it was imagined that it was the voice of another persons aimed against them.

The common areas of activation in the three groups during the tasks of inner speech and auditory verbal imagery were an increase of activity of the left inferior frontal region (Broca area) and decrease in the activity around the right occipital-temporal region. Furthermore, the task of auditory verbal imagery is also associated to a reduction in the posterior cingulate cortex activity. The only differences found were in patients with a predisposition to hallucinations who showed a decrease in the activation of the rostral zone of the supplementary motor area (SMA) and of the left medial temporal gyrus (MTG) when they imagined sentences by the voice of another person. A significant datum is that there were only differences in the group of patients with a history of hallucinations and not between the other two groups (healthy and without hallucinations).

These data are connected, according to McGuire and his team, with the electrophysiological studies that show a reduction in this region of the MTG when the subjects speak aloud[37], also corroborated in phonation studies with monkeys[38] The explanation is that when speech is generated on the left inferior frontal level, information is also sent to specific regions of speech perception (located in the left MTG - Wernicke area) to avoid perceiving inner speech as external speech. The abnormal reduction of the activity in the left MTG when the hallucinating patients mentally articulate foreign words suggests that a defective communication between the areas responsible for the generation and perception of speech could increase the probability of confusing inner speech for external speech and thus contributing to the vulnerability of these patients with hallucinations.

The supplementary motor area (SMA) is involved in the initiation of movements, including speech articula-

tion[39]. This area is also activated in patients with amputated limbs, creating the phantom limb phenomenon. On the other hand, abnormal activations of this area can cause unintentional movements, for example activation of the phonatory muscles, recorded in some studie[40,41] that are produced during the verbal auditory hallucinations and that are characteristic of inner or subvocal speech. The alterations of the SMA described in schizophrenic patients with a history of hallucinations can reflect confusion in the origin of instructions for the autogeneration of speech.

The hypoactivity of these two regions (MTG and SMA) is understood as a reflection of the confusion in the generation and perception of speech of patients with a history of hallucinations in regards to the controls and schizophrenic patients without a history of hallucinations.

These same findings have been retorted in studies[14,35] performed with fMRI. Eight schizophrenic patients with a history of auditory hallucinations and six control subjects were evaluated where they performed inner speech and auditory verbal imagery tasks, observing that the schizophrenic patients showed a less activation than the controls in the areas involved in the self-monitoring of speech when they performed inner speech tasks.

Three other studies[10,12,27] have been performed by fMRI. Woodruff et al. observed maximum activation of the middle and superior temporal gyri (MTG/STG), corresponding to the BA 21 and 22 areas and the BA 42 areas and also dorsomedial thalamus during hallucinations. Activation of the right MTG coincided with the activation induced by external speech in the non-hallucinatory state. David et al[12] studied a case of a history of intermittent and chronic hallucinations (both auditory as well as visual) in periods of exacerbation and remission of the hallucinations, exposing it to visual and auditory stimuli intermittently. The presence of auditory hallucinations decreased the response in the STG and MTG to the auditory stimulation. In 1997, Woodruff et al[10] extended these findings with a trait and state study. The findings are consistent with the hypothesis that auditory hallucinations «compete» with the external speech in the processing sites within the temporal cortex[9,10,12].

These studies are consistent with the notion that auditory hallucinations are associated with alterations in the cerebral areas related with the defective monitoring and mental production of inner speech[13,14,35,36,42,43].

Unitary hypothesis

In a recent review, Stephane et al[15] unified both hypothesis on the origin of verbal auditory hallucinations. They did an exhaustive review on neuroimaging (functional and structural) as well as electrophysiological (transcranial magnetic stimulation), electromyographic and postmortem pathology studies.

They conclude that, in the primary disorder, there would be a dysfunction of the cortical networks responsible for the generation of speech in which an activation in parallel would take place: that of the perceptive component (areas responsible for the perception of external speech would be activated) and that of the motor component (with a variable activity in the areas responsible for the subvocal speech.

The activation of the areas of external speech perception would be responsible for the hallucinatory experience, according to the data suggested through the functional neuroimaging and electrophysiology studies. The studies that support the activation of the areas responsible for subvocal language come from the electromyographic studies (muscular activation that precedes the moment in which the patient reports the hallucinatory experience and that is detected by recording of the activity of the lower lip and chin) and studies that record non-audible vocalizations by microphones located in the larynx.

METHODOLOGICAL LIMITATIONS

In spite of assuming the difficulty in the study of such a transitory and complex phenomenon as is the hallucinatory experience, many of the studies evaluated lack a series of methodological limitations that we summarize in the following.

There is a limited sample, and many studies are published based on single cases. In addition, a lack of a control group is observed: both a healthy control group as well as schizophrenic patients without a history of hallucinations, so that it is not possible to exclude the possibility that the differential activation observed in these investigations is related to schizophrenia, that is, to the disease itself, or to the medication and not to the tendency of the schizophrenic patient to hallucinate. It is necessary to discard the general psychosis factor of the hallucinatory phenomenon specifically. Furthermore, we often find an inadequate control group. Some which have a control group use those that have great heterogeneity in relationship with age, causing a significant bias. On the other hand, there is significant variety in the techniques used. The comparisons with other studies show inconsistencies due to the different techniques used, both in relationship with the instrumentation (PET, SPECT, fMRI) as well as the radioligands and imaging analysis methods. Finally, we observed a variety of designs (trait studies compared to those of state) that are not always clinically comparable.

CONCLUSIONS

In the last two decades, we have seen a significant advance in the knowledge of the neurobiological substrate of the verbal auditory hallucinations, thanks essentially to the functional neuroimaging techniques.

The present literature reviewed suggests that a dysfunction of the neuronal networks responsible for the generation of speech by an activation in parallel of the perception areas of external language (auditory-linguis-

tic cortex) and the motor areas involved in the subvocal speech would be involved in the etiopathogeny of the hallucinations.

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