Schizophrenia Research 117 (2010) 31–41

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# Increased amygdala and parahippocampal gyrus activation in schizophrenic patients with auditory hallucinations: An fMRI study using independent component analysis

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ARTICLE INFO

*Article history:*
Received 21 August 2009
Received in revised form 26 November 2009
Accepted 19 December 2009
Available online 13 January 2010

*Keywords:*
fMRI
Brain activity
Independent component analysis
Auditory hallucinations
Auditory emotional paradigm
Schizophrenia

ABSTRACT

*Objective:* Hallucinations in patients with schizophrenia have strong emotional connotations. Functional neuroimaging techniques have been widely used to study brain activity in patients with schizophrenia with hallucinations or emotional impairments. However, few of these studies have investigated the association between hallucinations and emotional dysfunctions using an emotional auditory paradigm. Independent component analysis (ICA) is an analysis method that is especially useful for decomposing activation during complex cognitive tasks in which multiple operations occur simultaneously. Our aim in this study is to analyze brain activation after the presentation of emotional auditory stimuli in patients with schizophrenia with and without chronic auditory hallucinations using ICA methodology. It was hypothesized that functional connectivity differences in limbic regions responsible for emotional processing would be demonstrated.
*Methods:* The present functional magnetic resonance imaging (fMRI) study compared neural activity in 41 patients with schizophrenia (27 with auditory hallucinations, 14 without auditory hallucinations) with 31 controls. Neural activity data was generated while participants were presented with an auditory paradigm containing emotional words. The comparison was performed using a multivariate approach, ICA. Differences in temporo-spatial aspects of limbic network were examined in three study groups.

*Abbreviations:* AH, Auditory hallucinations; MRI, Magnetic resonance imaging; fMRI, Functional magnetic resonance imaging; BPRS, Brief psychiatric rating scale; PANSS, Positive and negative syndrome scale; PSYRATS, Psychotic symptom rating scale; FOV, Field of view; ICA, Independent component analysis; SPM, Statistical parametric maps; BOLD, Blood oxygenation level dependent contrast; MDL, Minimum description length; PCA, Principal component analysis; COI, Component of interest; N.S., No statistical differences; SD, Standard deviation.

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0920-9964/$ – see front matter 
doi:10.1016/j.schres.2009.12.028

*Results:* Limbic networks responded differently in patients with auditory hallucinations compared to healthy controls and patients without auditory hallucinations. Unlike control subjects and non-hallucinators, the group of hallucinatory patients showed an increase of activity in the parahippocampal gyrus and the amygdala during the emotional session.
*Conclusions:* These findings may reflect an increase in parahippocampal gyrus and amygdala activity during passive listening of emotional words in patients with schizophrenia and auditory hallucinations.



## 1. Introduction

Schizophrenia is a psychiatric disorder that alters different psychopathological spheres: cognition thought and affect. Emotional deficits have been considered part of schizophrenia since the early descriptions by Bleuler (Bleuler, 1911). More recently, abnormalities in emotional processing in psychosis have been suggested in different aspects: expression, perception and experience (Trémeau, 2006; Cohen and Minor, 2008; Kring and Moran, 2008). Findings generally indicate impairment in the expression and perception aspects of emotional functioning, but data about experience is less consistent. In a recent meta-analysis, Cohen and Minor (Cohen and Minor, 2008) included 26 published studies employing laboratory emotion induction procedures in healthy controls and patients with schizophrenia. Their findings showed that patients' ability to experience hedonic emotion is preserved, while there is a relatively strong, simultaneously occurring aversive emotion when processing stimuli considered by others to be pleasant or neutral.

Neuroimaging studies have been performed to evaluate emotional disturbances in schizophrenia using different stimuli (mainly visual, but also auditory, olfactory and combined). Aleman and Kahn (Aleman and Kahn, 2005) proposed that emotional disturbances and the dysfunction of brain circuits may be at the core of schizophrenia, specifically in the amygdala and prefrontal cortex. Structural and functional magnetic resonance imaging (MRI) studies have focused mainly on the limbic and paralimbic areas (amygdala and prefrontal cortex), and have suggested that abnormalities in the amygdala may account for deficits in emotional processing. Supportive evidence for structural abnormalities comes from the bilateral reduction of amygdala volume in schizophrenia patients (Wright et al., 2000; Lawrie et al., 2003; Garcia-Marti et al., 2008) and populations at risk of developing schizophrenia (Van Rijn et al., 2005). Functional MRI (fMRI) studies have also demonstrated abnormal amygdala activity. Some showed decreased amygdala reactivity to emotional faces (Schneider et al., 1998; Phillips et al., 1999; Taylor et al., 2002; Gur et al., 2002; Hempel et al., 2003; Paradiso et al., 2003; Takahashi et al., 2004; Seiferth et al., 2009; Kang et al., 2009), while others found the opposite (Kosaka et al., 2002; Holt et al., 2005; Taylor et al., 2005; Holt et al., 2006; Gur et al., 2007; Sanjuán et al., 2007; Hall et al., 2008). These contradictory results may be explained by methodological differences in the task procedure (Hempel et al., 2003). While studies in which subjects passively viewed faces (Kosaka et al., 2002; Holt et al., 2005; Holt et al., 2006) or listened words (Sanjuán et al., 2007) found increased amygdala activation, those in which subjects were asked to actively identify the exact nature of the emotion expressed and to discriminate facial affect shown decreased activation (Paradiso et al., 1999).

Although most neuroimaging studies of emotional processing in schizophrenia have focused on the amygdala, other brain structures involved in emotion regulation (insula, anterior cingulate and orbitofrontal cortex) may also be affected (Phillips et al., 2003). Because the amygdala is strongly connected to the prefrontal areas and the anterior cingulate gyrus, the neural interactions between these regions, as evaluated by fMRI, may demonstrate functional disconnectivity. The problem of multiple areas involved in emotional processing can be solved by independent component analysis (ICA). This approach is a model-independent multivariate statistical computational technique designed to extract spatially independent and temporally synchronous activity patterns in brain regions, giving functional covariance in brain regions (Sambataro et al., in press). This method lets the definition of functional connectivity network in several diseases. Some studies have applied ICA to fMRI data in schizophrenia in order to separate data into maximally independent groups and successfully identify different activation networks (Calhoun et al., 2001; Demirci et al., 2008; Garrity et al., 2007).

Disturbances in emotional processing have been related to the origin of the hallucinations (Sanjuán, 2006; Aleman and Laroi, 2008). Cutting (1990) proposed that prosodic deficits contribute to the misattribution that appears to occur in auditory hallucinations in psychosis.

In a previous study, we obtained evidence of enhanced activation of the limbic and frontal brain areas in a small group of persistent hallucinatory patients using a paradigm based on passive listening to emotional words. These areas included the frontal lobe, temporal cortex, insula, cingulate gyrus and amygdala (mainly right hemisphere regions) (Sanjuán et al., 2007). The results of this study suggested a relevant role for emotional response with regard to the neural basis of auditory hallucinations. However, a limitation was that the study did not include a control group of patients without hallucinations, which would enable stronger conclusions about the specificity of the enhanced frontolimbic activation for hallucinations (Allen et al., 2008).

Some functional neuroimaging studies of patients with auditory hallucinations have consistently observed activity in the temporal lobe, particularly in superior temporal gyrus, as well as subregions of the supratemporal plane such us planum temporale or Heschl's gyrus, during auditory hallucinations (Allen et al., 2008).

The present study has two principal aims. First, we aim to analyze differences in functionally connected networks between control subjects and patients with schizophrenia during passive listening to an emotional auditory paradigm using an ICA approach. Secondly, we aim to compare patients with schizophrenia and auditory hallucinations with non-hallucinatory patients.