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Functional deficit of the medial prefrontal cortex during emotional sentence attribution in schizophrenia

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ABSTRACT

Background: Functional brain imaging research has already demonstrated that patients with schizophrenia had difficulties with emotion processing, namely in facial emotion perception and emotional prosody. However, the moderating effect of social context and the boundary of perceptual categories of emotion attribution remain unclear. This study investigated the neural bases of emotional sentence attribution in schizophrenia.
Methods: Twenty-one schizophrenia patients and 25 healthy subjects underwent an event-related functional magnetic resonance imaging paradigm including two tasks: one to classify sentences according to their emotional content, and the other to classify neutral sentences according to their grammatical person.
Results: First, patients showed longer response times as compared to controls only during the emotion attribution task. Second, patients with schizophrenia showed reduction of activation in bilateral auditory areas irrespective of the presence of emotions. Lastly, during emotional sentences attribution, patients displayed less activation than controls in the medial prefrontal cortex (mPFC).
Conclusions: We suggest that the functional abnormality observed in the mPFC during the emotion attribution task could provide a biological basis for social cognition deficits in patients with schizophrenia.

1. Introduction

In the last decade a growing body of research demonstrated deficits in social information processing in schizophrenia (Pinkham et al., 2003; Brunet-Gouet and Decety, 2006; Green et al., 2008; Wible, 2012; Green et al., 2015), contributing to impaired verbal communication and social interactions. The mental operations underlying social interactions include processes involved in perceiving, interpreting, and generating responses to the intentions and emotions of other persons (Adolphs, 2003). One of the key aspects of successful social interactions lies in the capacity to accurately recognise the often-subtle emotional cues that are expressed during conversations. Speech can convey emotions through different channels: linguistic and pragmatic information. Linguistic processing involves the semantic integration of words and sentences in order to reconstruct a coherent message, and also relies on phonological and syntactic analysis. The pragmatic information concerns the processing of gestures, facial expressions, and emotional prosody (the melody of speech) that accompanies the oral expression of language. Moreover, schizophrenia is characterized by both emotional and language abnormalities.

Functional brain imaging researches on emotional processing in schizophrenia have already been investigated, with a majority of experiments using basic facial emotion recognition paradigms. Compared with healthy controls, patients had difficulties with emotion perception and showed lower activation in the bilateral amygdala, parahippocampal gyrus and fusiform gyrus, right superior frontal gyrus and right lentiform nucleus (Hempel et al., 2003; Holt et al., 2005; Das et al., 2007; Gur et al., 2007; Li et al., 2010; Satterthwaite et al., 2010; Anticevic et al., 2012). Facial emotion perception is an important domain of social cognition (Green et al., 2005) and impairment in perceiving facial emotion contributes to problems in interpersonal relationships among patients with schizophrenia (Poole et al., 2000). Besides, another research focused on speech prosody recognition (Grandjean et al., 2006). Patients with schizophrenia are often impaired in their capacity to extract non-verbal emotional information from

Abbreviations: BOLD, blood oxygen level dependent; EMO, emotional task; fMRI, functional magnetic resonance imaging; GRAM, grammatical task; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; ToM, theory of mind.

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language (Bach et al., 2009b; Bach et al., 2009a; Edwards et al., 2002; Kucharska-Pietura et al., 2005; Leitman et al., 2005; Mitchell et al., 2004; Brazo et al., 2014).

However few studies have investigated the neural bases of emotion recognition during emotional speech attribution in schizophrenia (Mitchell et al., 2004; Regenbogen et al., 2015). Mitchell et al. (2004) demonstrated that patients with schizophrenia activated the left insula to a greater extent than did healthy controls during a sentence auditory task of attending to emotional prosody. The other functional study evaluated the neural responses of emotional expression using video clips and showed aberrant activation in regions implicated in semantic processing in schizophrenia patients during the neutral speech content (Regenbogen et al., 2015). These studies suggested abnormal neural patterns of language areas during emotional speech and need further investigations.

Besides emotional processing abnormalities, disturbance of language processes has long been reported in schizophrenia. Functional brain imaging studies have demonstrated reduced left and increased right prefrontal cortex (PFC) activation during language tasks in schizophrenia patients, relative to healthy controls (Kircher et al., 2002; Boksman et al., 2005; Dollfus et al., 2005; Dollfus et al., 2008) though some have demonstrated only increased right hemisphere activation with no difference in the activation of the left hemisphere (Sommer et al., 2001). Abnormalities were also found in the brain network involved in semantic processing (Kubicki et al., 2003). These semantic processing deficits do not seem to be dependent on grammatical category of a word, such as nouns, verbs, or adjectives (Rossell and Batty, 2008). However, it is less clear how individuals with schizophrenia process verbal material with emotional valence.

Moreover, abundant research has shown that patients with schizophrenia have specific difficulty in inferring what others intend, think, or pretend (Green et al., 2008) and this theory of mind (ToM) impairment probably influences the way schizophrenia patients use language and interpret speech (Brune, 2005). Functional brain imaging research on ToM abilities evidenced lower activation in patients with schizophrenia localized in the cingulate and insular cortex, in the medial PFC (mPFC), and in the left middle/inferior frontal gyrus (Russell et al., 2000; Brunet et al., 2003; Lee et al., 2006). The relationship between emotion processing and ToM has recently been investigated, with some data indicating that these are closely interrelated phenomena (Ochsner, 2008). Decoding of emotions during language communication is thus intermingled with ToM processing.

In this study, the neural bases of emotional sentence attribution were assessed in schizophrenia patients. An auditory task, which has already been validated in healthy volunteers (Hervé et al., 2012), investigated the functional network of emotional processing including verbal information and mental state inference. We hypothesized a functional deficit in a key region, the median prefrontal cortex (mPFC), involved in multiple cognitive processes such as language comprehension, emotion and ToM (Hervé et al., 2012; Beaucousin et al., 2007), in patients with schizophrenia compared to healthy controls during the emotional sentence attribution.

2. Materials and methods

2.1. Subjects

Twenty-one schizophrenia patients, and 25 healthy control subjects, all right-handed were included. Patients were diagnosed with schizophrenia using the DSM-IV criteria established by the MINI PLUS (Sheehan et al., 1998). Demographic and clinical characteristics of the sample are listed in Table 1. Patients and controls presented similar age (Wilcoxon test: $p = 0.67$), gender (CHI2 test: $p = 0.99$), education level (CHI2 test: $p = 0.54$), and handedness scores (Wilcoxon test: $p = 0.89$). The mean of the illness duration was 11.9 years (range: 1–34 years). Each patient's clinical state was evaluated with the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). The patients were required to have been stable on antipsychotic medication for at least two months prior to the study. Daily antipsychotic medication dosage at the time of inclusion was recorded and converted into doses of antipsychotics in chlorpromazine (CPZ) equivalent.

Table 1
Demographic and clinical information of the sample.

	Control subjects $n = 25$	Patients $n = 21$
Age (years)	33.1 (7.3)	33.9 (7.4)
Gender (% males)	76.0	76.2
Handedness [a]	92.8 (14.1)	93.5 (12.3)
Education [b]	52.0	42.9
Illness duration (years)	–	11.9 (7.9)
PANSS Positive score	–	13.6 (5.1)
PANSS Negative score	–	12.0 (4.0)
PANSS General score	–	26.9 (5.7)
Atypical antipsychotic medication	–	18
Typical antipsychotic medication	–	3
Chlorpromazine Equivalent (mg/day)	–	340.3 (253.0)

Numbers between brackets indicate standard deviation.
PANSS: Positive and Negative Syndrome Scale.
[a] Handedness was scored using the Edinburgh Handedness Inventory (Oldfield, 1971).
[b] Percentage of subjects who achieved an educational level superior or equal to the General Certificate of Education A level.

All participants reported French as their mother tongue, had no auditory deficit, and we did not detect any abnormality in the structural scans of any of the included participants. After a complete description of the study, subjects provided written, informed consent according to the Declaration of Helsinki. The protocol was approved by the local ethics board (CPP Nord Ouest, France). The patients with schizophrenia and matched healthy controls were recruited from the Department of Psychiatry of Caen University Hospital and the community, respectively. They received allowance for their participation.

2.2. Tasks

The experimental design was composed of two auditory sentence-classification tasks with actor voices. In one task, referred to as EMO for “emotional”, the participants were asked to classify these sentences, into three different categories on the basis of their emotional content (“anger”, “happiness” or “sadness”). In the EMO task, the sentences contained both lexical and prosodic emotional cues. For instance, “He brought a bunch of flowers on the grave of his daughter” was enunciated with a sad tone.

In the other task, referred to as GRAM for “grammatical”, sentences were classified according to a grammatical feature, the grammatical person of the sentence (1st person, 2nd person, or 3rd person). For example the correct answer to “this morning, at work, I organized my files” was 1st person. The sentences used in the GRAM task were devoid of emotional information, either at the prosodic or lexical level.

Each participant performed two different runs of each task (EMO and GRAM). Each run contained 24 sentences (8 sentences for each categories: anger, happiness or sadness for the EMO task and 1st person, 2nd person, or 3rd person for the GRAM task) and was organized following a slow event-related design, with the different sentences occurring randomly, but in the same order for all subjects. Sentence duration ranged from 2 to 4.5 s (mean $\pm$ sd, EMO: 2.65 $\pm$ 0.49 s, GRAM: 2.64 $\pm$ 0.49 s). After the end of the sentence, the participants had to answer with a 4-button response pad within 3 s. After each sentence trial, the subjects performed a “beep detection task” in order to prevent them from replaying the task during the inter-trial interval. They heard two different tones in random order, separated by 2 to 8 s, and had to respond upon when hearing the lower-frequency tone. The total event duration, including sentence classification plus beep detection, was 14 $\pm$ 2 s (Fig. 1).

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