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Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia

Francesco Benedetti [a,c,e,*], Alessandro Bernasconi [a,c,e], Marta Bosia [a,e], Roberto Cavallaro [a,e], Sara Dallaspezia [a,c,e], Andrea Falini [b,c,e], Sara Poletti [a,c,d,e], Daniele Radaelli [a,c,d,e], Roberta Riccaboni [a,c,e], Giuseppe Scotti [b,c,e], Enrico Smeraldi [a,c,e]

[a] *Department of Clinical Neurosciences, Scientific Institute and University Vita-Salute San Raffaele, Milan, Italy*
[b] *Department of Neuroradiology, Scientific Institute and University Vita-Salute San Raffaele, Milan, Italy*
[c] *C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo), University Vita-Salute San Raffaele, Milan, Italy*
[d] *Dottorato in Neuroscienze e Disturbi del Comportamento, Dipartimento di Scienze Farmacologiche, Università degli Studi di Palermo, Italy*
[e] *National Institute of Neurosciences, Italy*

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ABSTRACT

Background: Patients affected by schizophrenia show deficits in social cognition, with abnormal performance on tasks targeting theory of mind (ToM) and empathy (Emp). Brain imaging studies suggested that ToM and Emp depend on the activation of brain networks mainly localized at the superior temporal lobe and temporo-parietal junction.
Methods: Participants included 24 schizophrenia patients and 20 control subjects. We used brain blood oxygen level dependent fMRI to study the neural responses to tasks targeting ToM and Emp. We then studied voxel-based morphometry of grey matter in areas where diagnosis influenced functional activation to both tasks. Outcomes were analyzed in the context of the general linear model, with global grey matter volume as nuisance covariate for structural MRI.
Results: Patients showed worse performance on both tasks. We found significant effects of diagnosis on neural responses to the tasks in a wide cluster in right posterior superior temporal lobe (encompassing BA 22–42), in smaller clusters in left temporo-parietal junction and temporal pole (BA 38 and 39), and in a white matter region adjacent to medial prefrontal cortex (BA 10). A pattern of double dissociation of the effects of diagnosis and task on neural responses emerged. Among these areas, grey matter volume was found to be reduced in right superior temporal lobe regions of patients.
Conclusions: Functional and structural abnormalities were observed in areas affected by the schizophrenic process early in the illness course, and known to be crucial for social cognition, suggesting a biological basis for social cognition deficits in schizophrenia.

1. Introduction

Defined as the ability to put oneself into the psychological frame of reference of another, so that the other person's thinking, feeling and acting are understood, empathy is a high level process which involves multiple affective and cognitive components, and is unlikely to have a single dedicated brain region. To explore its neural bases, empathy has been dissected into component processes, leading to the identification of core structures including several temporal lobe (TL) regions, the temporo-parietal junction (TPj), medial prefrontal cortex (mPFC), cingulate cortex, and many subregions associated with specific elements of the construct (Farrow, 2007).

Among the core components of empathy, the cognitive ability to represent mental states is usually referred to as theory of mind (ToM) (Premack and Woodruff, 1978), while the ability to infer and share the emotional experiences of

* Corresponding author. Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy. Tel.: +39 02 26433156; fax: +39 02 26433265.
E-mail address: benedetti.francesco@hsr.it (F. Benedetti).

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others and to experience an appropriate emotional response towards others' emotional responses (Lawrence et al., 2004) is usually referred to as affective empathy (Emp). One study in normal subjects using blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) and linking the two processes showed that the functional correlates of these two core components involve the activation of common areas including the TPj, superior temporal lobe, temporal pole, mPFC and orbitofrontal cortex, with activations in other areas being specific for Emp and ToM tasks (Vollm et al., 2006). This suggested that both ToM and Emp depend on the activation of similar brain networks involved in social cognition and perspective taking, which form the basis for making inferences about the mental states of others (Vollm et al., 2006).

Patients affected by schizophrenia are defective in these abilities, showing a domain-wide difficulty with perspective taking that equally affects their appreciation of other people's beliefs, percepts, and emotions (Langdon et al., 2006), and impaired ToM performance with respect to control subjects regardless of the task and independent of the severity of psychopathology, executive function deficit, and general cognitive impairments (Brune, 2005). Patients are aware of their deficits in affective empathy (Montag et al., 2007), which correlate with their performance and influence social functioning (Shamay-Tsoory et al., 2007). These abnormalities have been proposed to underlie specific symptoms of psychosis, such as delusions of persecution and of reference, third-person auditory hallucinations, thought disorder, and negative symptoms (Frith, 1992).

Studies of the neural basis of these deficits focused on single components of empathy. A recent review by Brunet highlighted the importance of PFC, anterior cingulate cortex and amygdala for social cognition (Brunet-Gouet and Decety, 2006). Using a task in which mental states are inferred from a person's gaze direction, patients with schizophrenia showed a reduced activation of middle/inferior frontal gyrus and insula (Russell et al., 2000). Lower levels of activation in the left mPFC have been reported in a social cognition paradigm involving exposure to affective empathy and forgiveness scenarios (Lee et al., 2006). Lower activation in prefrontal structures has been reported during attribution of intentions (Brunet et al., 2003). Using a task addressing ToM abilities (exposure to cartoons depicting social interactions) patients showed lower activation in cingulate and insular cortex, and higher activation in mPFC, temporal structures, and TPj (Brune et al., 2008). Abnormalities in neural response to visual jokes requiring intact ToM have also been described in relatives of patients (Marjoram et al., 2006), who are known to share deficits in ToM abilities with patients (Janssen et al., 2003).

Structural magnetic resonance imaging (sMRI) studies using voxel-based morphometry (VBM) showed that the above mentioned brain structures demonstrate progressive reduction in density and volume of grey matter soon after onset of schizophrenia (Honea et al., 2005), thus suggesting a neurodegenerative basis for abnormal performance and neural responses (Farrow, 2007).

The purpose of the present study is to evaluate with BOLD fMRI and VBM sMRI the brain neural and structural correlates of ToM and affective empathy in schizophrenia, linking the two processes within the paradigm of (Vollm et al., 2006). We hypothesized that the tasks would cause different neural responses between patients and healthy controls in the brain areas mentioned above, and that these areas would have different grey matter volume across the two participant samples.

2. Methods

2.1. Participants

Twenty-four patients (14 males and 10 females; 3 left-handed) with chronic schizophrenia, and 20 similar-aged controls (7 males and 13 females; 1 left-handed) were studied. Exclusion criteria were mental retardation, substance abuse within the past 3 months, history of major unstable physical illness and other psychiatric comorbidities. Patients were biologically unrelated, clinically stabilized outpatients meeting DSM-IV criteria for chronic schizophrenia (Structured Clinical Interview for DSM Disorders; subtype: undifferentiated $n=9$, paranoid $n=13$, disorganized $n=2$) who were responders to typical and atypical antipsychotics in monotherapy (clozapine $n=9$, risperidone $n=11$, aripiprazole $n=2$, haloperidol $n=2$). Doses had been stable in the 3 months before enrollment and remained unchanged.

All data were collected in the same day. Symptoms severity was rated on PANSS (Kay et al., 1987). Handedness was assessed with the Edinburgh inventory (Oldfield, 1971). BOLD fMRI and volumetric T1-weighted sequences were acquired in the afternoon. After complete description of the study to the subjects a written informed consent was obtained. The local ethical committee approved the study protocol.

2.2. Cognitive activation paradigm

A visual activation paradigm comprising a series of comic strips, each depicting a short story, was used. The fMRI task was derived from (Vollm et al., 2006). Stimuli were presented in blocks. There were four categories of stories: Theory of Mind (ToM), with one character whose intentions had to be inferred by the subject; Affective empathy (Emp), with interactions between two story characters which required the participant to empathize with the protagonist to be understood; and two control conditions based on the comprehension of physical causality, with one or two characters. Each condition was presented twice, in a random order, so that the task consisted of eight blocks. In each block five different comic strips (three pictures each) depicting a short story were presented. Each picture was shown for 3 s in the centre of the screen, and then a picture showing two possible outcomes of the scenario were shown for a further 8 s. Participants were required to make a choice between the two story endings using a button box. Only one of the outcomes represented a plausible story ending. At the beginning of each block, a short question introducing the block, designed to engage the corresponding mental construct in the participant, was shown. Responses were recorded for all trials, and failure to respond during the 8 s response window counted as an absent response. The total duration of the task was 13 min. Each block lasted about 1 min and 37 s, with minor differences due to random interstimulus interval. For a complete description of the tasks and sample pictures, see (Vollm et al., 2006).