An fMRI study of theory of mind in schizophrenic patients with “passivity” symptoms

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Received 21 October 2007; received in revised form 18 January 2008; accepted 21 January 2008
Available online 7 February 2008

Abstract

Several studies have shown that patients with schizophrenia underactivate brain regions involved in theory of mind relative to controls during functional brain imaging. However, in most studies the samples were fairly heterogeneous in terms of clinical symptomatology.

We examined a group of nine patients with first episode or recurrent episodes, who clinically presented with predominant “passivity” symptoms such as third-person auditory hallucinations or delusion of control, using a cartoon-based theory of mind task and compared activation patterns with a group of 13 healthy controls. All patients responded well to antipsychotic treatment and were only mildly symptomatic at the time of testing.

The patient group showed significantly less activation of the right anterior cingulate cortex (ACC) and right insula compared with controls, but greater activation in dorsal areas of the medial prefrontal cortex, right temporal areas and left temporo-parietal junction.

Patients with schizophrenia with predominant “passivity” symptoms and good response to antipsychotic treatment show a markedly diverging pattern of brain activation during theory of mind task performance compared with healthy controls. These findings suggest abnormal activation of those brain areas involved in the evaluation of self-reference during mental state attribution.

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Keywords: Medial prefrontal cortex; Anterior cingulate gyrus; Mentalising; Voice-commenting hallucinations; Passivity symptoms; Delusion of alien control

1. Introduction

The term “theory of mind” (ToM) refers to the cognitive ability to represent own and other persons’ mental states (Premack & Woodruff, 1978). ToM allows one to reflect upon beliefs, desires, intentions, knowledge states, feelings, and necessarily includes the distinction of one’s own from another’s mental state and between reality and appearance. For example, an individual can have a representation of the accuracy of another’s knowledge state, i.e. that someone else may hold a true or false belief about facts (e.g. the location of an object) or the mental state of a third party (e.g. an intentional deception). ToM comprises different levels of complexity, where the true or false belief of an object location is referred to as a “second-order” representation (“I know XY”), and the inference of the belief that a third person plans a malicious act is referred to as a “third-order” representation (“I believe that X assumes that Y wants to cheat on him”) (recent reviews by Brüne & Brüne-Cohrs, 2006; Saxe, 2006).

Since the advent of new brain imaging techniques some 15 years ago, our understanding of how ToM is represented in the brain has leaped forward. Not only has the neural network engaged in ToM tasks been described in great detail (Amodio & Frith, 2006; Siegal & Varley, 2002), the cerebral correlates of ToM subprocesses such as self versus other representation have also been disentangled (Saxe, 2006; Vogele et al., 2001), and differences in activation patterns between related phenomena such as ToM and empathy (Völlm et al., 2006) as well as cognitive versus affective ToM (Hynes, Baird, & Grafton, 2006) have been carved out using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Current empirical evidence suggests that the ToM network entails...
cortical midline structures, particularly the medial prefrontal cortex (mPFC) and the anterior portion of the cingulate cortex (ACC), the precuneus (PC), and outer surface areas of the middle temporal lobes (MT) and superior temporal sulcus (STS), and the temporo-parietal junction (TPJ) (reviewed in Brüne & Brüne-Cohrs, 2006; Saxe, Carey, & Kanwisher, 2004). The mPFC and the ACC are thought to help distinguish self from other, to be engaged in error monitoring and prediction, and to differentiate salient from non-salient stimuli, as well as “decoupling” hypothetical states from reality (Carter, MacDonald, Ross, & Stenger, 2001; Frith & Frith, 2003; Siegal & Varley, 2002). The role of the PC is less well known, but this brain area seems to be important for the experience of agency and self-consciousness (Cavanna & Trimble, 2006; Schilbach et al., 2006). The temporal regions contain mirror neurons that play a decisive role for imitation and learning as well as for the recognition of intentional movements (Gallagher & Frith, 2003; Kourtzi & Kanwisher, 2000). The TPJ comprises an area that contributes to the discrimination of self and other (Gallagher et al., 2000) and is selectively active during task performance requiring the attribution of a character’s true or false beliefs (Decety & Grèzes, 2006; Saxe, 2006; Sommer et al., 2007). In addition, amygdalar and orbitofrontal activity may contribute the affective “tone” to the evaluation of thoughts and intentions (Berthoz, Grèzes, Armony, Passingham, & Dolan, 2006; Grèzes, Berthoz, & Passingham, 2006).

Functional brain imaging studies into neuropsychiatric disorders such as autism spectrum disorders and schizophrenia have revealed structural as well as functional abnormalities in ToM circuits. In a functional brain imaging study using a task in which mental states have to be inferred from a person’s eye region, patients with autism showed marked underactivation of medial prefrontal areas and the amygdala compared with healthy controls (Baron-Cohen et al., 1999). Similarly, patients with schizophrenia have displayed marked underactivation of brain regions critically involved in ToM performance. Russell et al. (2000), using the same ‘Reading the Mind in the Eyes’ task (Baron-Cohen et al., 1999), found reduced activation during fMRI in the left middle/inferior frontal gyrus and insula (Brodmann areas BA 9/44/45) in five male right-handed patients with schizophrenia relative to seven healthy control subjects. The mean duration of illness was 13 years, and patients were impaired in behavioural performance of the test compared with controls. In a PET study, Brunet, Sarfati, Hardy-Baylé, and Decety (2003) revealed that patients (N = 7) with mixed types of schizophrenia showed rCBF patterns during the attribution of intentions that differed markedly from the pattern of controls. In particular, unlike healthy subjects, patients did not activate the medial prefrontal cortex, but instead, parts of the middle frontal cortex, middle occipital cortex, hippocampus and cerebellum that were qualitatively different from control activations (Brunet et al., 2003). Similarly, in a recent study Lee et al. (2006) found that patients with acute episodes activated areas in the left mPFC to a lesser degree compared with healthy controls subjects in a social cognition paradigm (empathy and forgiveness scenarios); most interestingly, however, activation increased in the patient group upon clinical improvement, and this pattern was associated with improved insight and social functioning suggesting a state effect related to the presence of psychotic symptoms (Lee et al., 2006). This finding was recently supported by Marjoram et al. (2006) who revealed, using a visual joke paradigm where half of the jokes required intact ToM, that relatives of patients with schizophrenia displayed differential activation patterns depending on whether or not they had psychotic symptoms. Those relatives at high-risk of developing schizophrenia activated the right inferior parietal lobule and parts of the prefrontal cortex (particularly BA 8 and 9) less compared with low-risk relatives and healthy controls. Moreover, the high-risk group with psychotic symptoms at the day of scanning displayed activations more similar to patients with manifest schizophrenia than high-risk relatives who had psychotic symptoms in the past (Marjoram et al., 2006).

In spite of growing evidence that thorough clinical subtyping would be more likely to reveal reproducible empirical results (Jablensky, 2006) with regards to the biological underpinnings of schizophrenia, one problem of research into fMRI activation patterns during social cognition tasks is that “schizophrenia” has largely been treated as a homogenous disease entity.

In this study, we were interested in examining ToM task performance in a clinically homogenous group of patients, including patients with first episode and recurrent psychotic episodes, all of whom responded well to antipsychotic treatment and who experienced passivity symptoms including voice-commenting hallucinations, persecutory delusions or “first-rank” symptoms such as thought insertion or thought transference (Frith, 1992). Specifically, we were interested in the question which parts of the “core” neural network involved in ToM – mPFC/ACC, STS, PC, and TPJ – would be distinctly activated in patients with passivity symptoms compared to healthy controls. Our a priori hypothesis was that patients relative to controls would underactivate those brain regions involved in distinguishing self from others, i.e. the mPFC and ACC.

2. Methods

2.1. Participants

Nine patients (six females, three males; eight right-handed, one left-handed) with first episode (N = 6) or recurrent episodes with full remission (N = 3) diagnosed with schizophrenia according to DSM-IV criteria (American Psychiatric Association, 2000) who were treated as in-patients or attended the day-clinic of the local university department of psychiatry and psychotherapy were included. All clinical participants received second-generation antipsychotic medication with a mean chlorpromazine equivalent dose (CPZ; Woods, 2003) of 244.44 mg (S.D. ± 173 mg) per day. The patients’ mean age was 27.89 years (19–38 years; S.D. ± 6.66 years), age of illness onset ranged from 18 to 36 years (mean 25.22 years; S.D. ± 5.69 years), and duration of illness ranged from 0.5 to 13 years (mean 3.00 years; S.D. ± 4.23 years). Four more patients who took part in the study had to be excluded from the statistical analyses due to head movement artefacts in the imaging data.

Thirteen healthy controls (9 women, 4 men; 12 right-handed, 1 left-handed) without a history of psychiatric disorders or first-degree relatives with psychotic illnesses were recruited from the general community. The controls’ age ranged from 22 to 38 years, with a mean age of 26.46 years (S.D. ± 5.30 years). All subjects had normal vision.

The study was approved by the local ethics committee of the University of Bochum. All subjects gave written informed consent. Participants with a history of substance abuse or dependence, traumatic brain injury or mental retardation were excluded from the study.
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