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ScienceDirect
Schizophrenia Research 105 (2008) 165–174
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Theory of mind and frontal lobe pathology in schizophrenia: A voxel-based morphometry study

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Received 26 March 2008; received in revised form 14 July 2008; accepted 20 July 2008
Available online 5 September 2008

Abstract

Impaired ability to infer the mental states of others (theory of mind; ToM) is considered to be a key contributor to the poor social functioning of patients with schizophrenia. Although neuroimaging and lesion studies have provided empirical evidence for the neural basis of ToM ability, including the involvement of several prefrontal and temporal structures, the association between pathology of these structures and ToM impairment in schizophrenia patients is less well understood. To address this issue, we investigated structural brain abnormalities and ToM impairment in patients with schizophrenia, and examined the relationship between them. Twenty schizophrenia patients and 20 age-, sex- and education-matched healthy participants underwent magnetic resonance imaging (MRI) and were examined for ToM ability based on the revised version of the "Reading the Mind in the Eyes" (or Eyes) test [Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The 'Reading the Mind in the Eyes' test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241–251]. Voxel-based morphometry (VBM) was performed to investigate regional brain alterations. Relative to normal controls, schizophrenia patients exhibited gray matter reductions in the dorsomedial prefrontal cortex (DMPFC), left ventrolateral prefrontal cortex (VLPFC), ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), right superior temporal gyrus (STG) and right insula. The patients performed poorly on the Eyes test. Importantly, poor performance on the Eyes test was found to be associated with gray matter reduction in the left VLPFC in the patient group. These results suggest that prefrontal cortical reduction, especially in the left VLPFC, is a key pathology underlying the difficulties faced by schizophrenia patients in inferring the mental states of others.

Keywords: Schizophrenia; Social cognition; Theory of mind; Eyes test; Voxel-based morphometry; Frontal lobe

1. Introduction

Among the varieties of social cognition, the ability to infer the mental states of other individuals, often referred to as a "theory of mind" (ToM; Premack and Woodruff, 1978) or "mentalizing" (Frith et al., 1991), is

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doi:10.1016/j.schres.2008.07.021

considered to be critical to achieve successful social interactions. ToM ability has been widely investigated in individuals with neuropsychiatric disorders, including schizophrenia, who have substantial difficulty in maintaining interpersonal relationships. Previous behavioral studies on ToM in schizophrenia patients have indicated that these patients are impaired, to varying degrees, in their ability to appropriately infer the beliefs, intentions or feelings of others (Brüne, 2005; Frith and Corcoran, 1996).

Meanwhile, recent neuroimaging and lesion studies have provided converging evidence for the neural basis of the ToM ability. Neuroimaging studies in normal subjects have revealed that the processing of ToM tasks involves mainly the medial prefrontal cortex (MPFC), the orbitofrontal cortex (OFC), the amygdala, the temporal poles and the superior temporal sulcus (Brunet-Gouet and Decety, 2006; Frith and Frith, 2003; Gallagher et al., 2000; Vogeley et al., 2001). On the other hand, lesion studies indicate the involvement of the MPFC, the OFC (Stone et al., 1998; Stuss et al., 2001) and the amygdala (Adolphs et al., 2002; Stone et al., 2003).

At the same time, brain magnetic resonance imaging (MRI) studies have demonstrated multiregional brain alterations in schizophrenia patients. Disproportionate gray matter (GM) reductions in a variety of prefrontal and temporal subregions have often been reported in previous structural MRI studies using manual volumetry (Shenton et al., 2001; Suzuki et al., 2005). Voxel-based morphometry (VBM; Ashburner and Friston, 2000) is a novel automated imaging analysis method for exploring regional GM alterations throughout the whole brain. In a recent meta-analysis of VBM studies in schizophrenia patients, the most consistent findings were of GM reductions in the left medial temporal lobe, left superior temporal gyrus, left medial frontal gyrus, left inferior fontal gyrus and right superior temporal gyrus (Honea et al., 2005).

These regional brain alterations have been found to be related to the symptoms (Sanfilipo et al., 2000) and cognitive impairments (Antonova et al., 2004) observed in schizophrenia patients. Although associations between the abnormalities in the prefrontal cortex and the impairments of attention, working memory and executive function have been demonstrated in schizophrenia patients (Gur et al., 2000; Seidman et al., 1994; Szeszko et al., 2000), the relationship between regional brain alterations and social cognitive impairments remains unclear (Pinkham et al., 2003).

Since prefrontal and temporal structures have been demonstrated to be involved in ToM ability, one could assume that the neuropathological basis of ToM impairment in schizophrenia patients would lie within these brain regions (Brunet-Gouet and Decety, 2006; Lee et al., 2004; Pinkham et al., 2003). However, to date, few studies have investigated ToM abilities and structural brain alterations in patients with schizophrenia simultaneously. In previous studies, we reported an association between amygdalar volume reduction and impaired facial emotional recognition (Namiki et al., 2007), and the relationships between structural abnormalities in the MPFC or the anterior cingulate cortex and impaired ability to infer the feelings of others in social situations (Fujiwara et al., 2007; Yamada et al., 2007), in schizophrenia patients. In line with these studies, the current study aimed to further elucidate the relationship between ToM impairments and structural brain alterations in schizophrenia patients. We applied an advanced ToM task and optimized VBM based on high-resolution structural MRI to the same subjects with schizophrenia, and investigated the interrelationship between them.

Our hypotheses were: (1) that brain alterations would be present in multiple cortical regions in schizophrenia patients, and that these would include the brain areas underpinning ToM ability; (2) that schizophrenia patients would present specific ToM impairments; and (3) if the two above-mentioned hypotheses are true, that we should find a specific association between alterations in specific brain structures and ToM impairments in schizophrenia patients.

2. Materials and methods

2.1. Participants

The schizophrenia group comprised 20 patients (10 men and 10 women, all right-handed), referred to the Department of Psychiatry, Kyoto University Hospital. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV (SCID). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). All patients were receiving antipsychotic medication [typical ($n=2$), atypical ($n=15$), typical and atypical ($n=3$)] and were physically healthy at the time of scanning and cognitive tests. None had a history of neurological injury or disease, medical diseases or substance abuse that may affect brain function.

The comparison group comprised 20 healthy individuals (10 men and 10 women, all right-handed) who were matched to the schizophrenia group with respect to age, sex and education level. They were also evaluated on the basis of SCID and had no history of neurological or psychiatric