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Reduced white matter integrity as a neural correlate of social cognition deficits in schizophrenia

Jun Miyata [a,*], Makiko Yamada [a], Chihiro Namiki [a,b], Kazuyuki Hirao [a], Teruyasu Saze [a], Hironobu Fujiwara [a], Mitsuaki Shimizu [a], Ryosaku Kawada [a], Hidenao Fukuyama [b], Nobukatsu Sawamoto [b], Takuji Hayashi [a], Toshiya Murai [a]

[a] Department of Neuropsychiatry, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Kyoto 606-8507, Japan
[b] Human Brain Research Center, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Kyoto 606-8507, Japan

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ABSTRACT

Background: The pathology of schizophrenia is thought to involve multiple gray and white matter regions. A number of studies have revealed impaired social cognition in schizophrenia. Some evidence suggests an association of this social cognition deficit with gray matter reductions in 'social brain' areas. However, no study has yet revealed the association between social cognition abilities and white matter abnormalities in schizophrenia patients.

Methods: Twenty-six schizophrenia patients and 27 healthy controls underwent the Perception of Affect Task (PAT), which consisted of four subtasks measuring different aspects of emotion attribution. Voxelwise group comparison of white matter fractional anisotropy (FA) was performed using tract-based spatial statistics (TBSS). The relation between impaired social cognition ability and FA reduction was examined in patients for each subtask, using simple regression analysis within brain areas that showed a significant FA reduction in patients compared with controls. The same correlational analysis was also performed for healthy controls in the whole brain.

Results: Schizophrenia patients showed reduced emotion attribution ability compared with controls in all four subtasks. The facial emotion perception subtask showed a significant correlation with FA reductions in the left occipital white matter region and left posterior callosal region. The correlational analyses in healthy controls revealed no significant correlation of FA with any of the PAT subtasks.

Conclusions: Our voxelwise correlational analysis of white matter provided a potential neural basis for the social cognition impairments in schizophrenia, in support of the disconnection hypothesis.

1. Introduction

Magnetic resonance imaging (MRI) studies on patients with schizophrenia have consistently reported gray matter volume reductions in frontal and temporal cortical regions, medial temporal lobe structures, the basal ganglia, and the thalamus (Ellison-Wright et al., 2008; Shenton et al., 2001). This disorder is thought to arise as a result of disrupted connectivity between these gray matter regions (Friston, 1998). Diffusion tensor imaging (DTI) provides information about white matter tracts and their organization based on water diffusion. DTI enables the detection of subtle white matter abnormalities, and a reduction in fractional anisotropy (FA) implies decreased white matter tract integrity. A number of studies have demonstrated FA reductions in white matter in diverse areas including frontal white matter, the corpus callosum (CC), and the cingulum, in schizophrenia patients (Kubicki et al., 2007; Walterfang et al., 2006). These findings suggest that white matter abnormalities may be an anatomical substrate for the 'disconnection hypothesis' (Friston, 1998) of schizophrenia.

On the other hand, recent neuroimaging and lesion studies have revealed a network of gray matter regions

* Corresponding author. Tel.: +81 75 751 3386; fax: +81 75 751 3246.
E-mail address: miyata10@kuhp.kyoto-u.ac.jp (J. Miyata).

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underlying social cognition. The amygdala and the orbitofrontal cortex have been found to make important contributions to facial emotion expression processing (Adolphs et al., 1994; Hornak et al., 1996): the medial and orbitofrontal cortices play key roles in mentalizing ability, often referred to as the theory of mind (ToM; Baron-Cohen et al., 1994; Fletcher et al., 1995); the temporal pole and the superior temporal sulcus make important contributions to both of these abilities (Brunet-Gouet and Decety, 2006); and the inferior parietal lobe has a critical role in the judgment of agency (Chaminade and Decety, 2002). In regard to schizophrenia, a number of studies of schizophrenia patients have revealed impaired social cognition abilities, and an abnormal hemodynamic response in the brain regions mentioned above during social cognition tasks (Brune, 2005; Brunet-Gouet and Decety, 2006; Mandal et al., 1998). In addition to these functional abnormalities, some studies have revealed associations between impaired social cognition ability and structural abnormalities in gray matter regions critical for social cognition (Fujiwara et al., 2007; Hirao et al., 2008; Yamada et al., 2007).

Considering the complexity of cognitive functions such as social cognition, which requires the coordinated functioning of a widely distributed network of gray matter regions, it is possible that social cognition impairments may be caused by disrupted connectivity between gray matter regions. To date, however, the association between impaired social cognition and white matter abnormality has been little examined in schizophrenia patients. To the best of our knowledge, an earlier study by our research group (Fujiwara et al., 2007) was the first to investigate this potential association. This study, which used a region of interest (ROI) method, did not reveal an association between impaired emotion attribution performance and FA reduction in the anterior cingulum bundle in schizophrenia.

To fully investigate such an association, a correlational analysis in the whole brain is necessary. In the present study, we employed the Perception of Affect Task (PAT; Rau, 1993), a test battery that encompasses a broad range of social cognitive factors, such as perspective taking and empathy. To perform voxelwise correlational analysis, we employed a recently developed technique called tract-based spatial statistics (TBSS) (Smith et al., 2006). TBSS maps each subject's DTI data onto a common white matter tract center ('skeleton'), and is robust to registration confounds. We hypothesized that impaired emotion attribution task performance in patients would have a positive correlation with FA reduction in white matter that connects gray matter regions relevant for social cognition. To explore if the individual difference in social cognition task performance among the normal population has neural correlates in white matter, we also performed a correlational analysis of healthy controls.

2. Materials and methods

2.1. Subjects

Twenty-six schizophrenia patients, diagnosed based on the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), were studied. None of the patients had comorbid psychiatric disorders. All patients were receiving antipsychotic medication. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess the severity of clinical symptoms. Twenty-seven healthy controls, matched with the patient group in age, sex, handedness and education levels were recruited. The controls had no history of psychiatric illness, as determined by the non-patient edition of the SCID, and there was no history of psychotic disorders among their first-degree relatives. Exclusion criteria for all individuals included a history of head trauma, neurological illness, serious medical or surgical illness, and substance abuse. These patients and healthy controls partially overlapped with participants in our earlier studies (Fujiwara et al., 2007; Miyata et al., 2009). All participants were physically healthy at the time of scanning and psychological tests. After receiving a complete description of the study, all participants gave written informed consent. The study design was approved by the Committee on Medical Ethics of Kyoto University.

2.2. Psychological tests

To confirm the participants' basic visuoperceptual ability for facial stimuli, a short version of the Benton Facial Recognition Test (BFRT) (Benton et al., 1983) was used. Participants were asked to match the faces of identical individuals from six choices, which were shown in varying views and light conditions.

For the assessment of the participants' social cognition ability, we administered the PAT battery, which examines the ability to attribute emotions to facial expressions and to protagonists in complex social situations. The PAT battery comprises four subtasks designed to separately assess verbal, visual, and verbal–visual processing abilities.

Subtask 1 involved matching of verbally described social situations with verbal emotion labels. Short stories describing emotional situations were presented. From a list of seven emotion labels (happiness, sadness, fear, anger, disgust, surprise, and neutral), participants were asked to choose the one that best matched the feeling of the main protagonist in each situation.

Subtask 2 involved matching of emotional facial stimuli with verbal emotion labels. Participants were provided with the same emotion label list as subtask 1, and were requested to choose the most appropriate labels for presented emotional facial stimuli, selected from the Picture of Facial Affect series (Ekman and Friesen, 1976).

Subtask 3 involved matching of verbally described social situations with emotional faces. Participants were presented with the same short stories as in subtask 1. They were provided with a list of seven facial expressions of an individual from the Picture of Facial Affect series and were asked to choose the facial expression most appropriately matching the feeling of the main protagonist.

Subtask 4 involved matching of emotional faces with nonverbal social situations. Seven photographs of social situations were provided. A human figure representing one of the seven emotions was indicated by an arrow in each photograph. The faces of these figures were not visible. The same facial stimuli used in subtask 2 were presented, and participants were asked to choose the most appropriate human figure.

Each subtask consisted of 35 stimuli, five items for each of seven emotions. These subtasks were performed in this fixed order for all participants.