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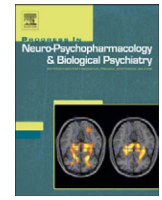

Female specific anterior cingulate abnormality and its association with empathic disability in schizophrenia

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A B S T R A C T

Evidence suggests that impairments of empathy are present in schizophrenia and that such deficits lead to social dysfunction. However, the relationship between brain morphological abnormalities of the disorder and empathic disabilities has not been fully investigated. As the anterior cingulate cortex (ACC) is one of the critical structures for empathy processing, the pathology of this structure might be a major source of social dysfunction, including interpersonal miscommunication in schizophrenia. In addition, as recent studies suggest that different facets of empathic ability depend on different subdivisions of the ACC, pathology of each subdivision would affect the empathic disability of schizophrenia differentially. Structural MRI data were acquired at 3.0 T from 24 schizophrenic patients and 20 healthy participants, and the volumes of ventral and dorsal ACC were measured and compared between the groups. Subjects' empathic abilities were evaluated using a multidimensional questionnaire, the Interpersonal Reactivity Index (IRI). The relationships of structural abnormalities with empathic disabilities were investigated, by correlating ACC subdivisional volumes with each IRI subscale score. Female schizophrenic patients exhibited volume reductions in the ventral ACC bilaterally and in the left dorsal ACC compared with healthy subjects. Schizophrenic patients performed poorly on fantasy and personal distress subscales of the IRI. Furthermore, volumes of the left dorsal ACC were inversely correlated with personal distress subscale scores within female patients with schizophrenia. These results suggest that pathology of specific ACC subdivisions would have an impact on specific empathic disabilities in schizophrenia, with potential gender specificity.

1. Introduction

A deficit in social functioning is one of the most disabling clinical features of schizophrenia and is a significant factor in the resulting social isolation experienced by many with the disorder. One factor leading to social dysfunction is miscommunication with others, which is, at least partially, the result of social cognitive impairments (Lee et al., 2004).

Among social cognitive skills, empathy is critical for human bonding. In brief, this term is generally referred to as the ability of sharing other people's feelings. However, empathy is not considered a unitary psychological process but consists of multiple dissociable components, which include (1) an automatic affective response to another person, by which the other's emotion is shared by the observer, (2) a cognitive capacity to take the perspective of the other person, in which self–other distinction is achieved, and (3) monitoring mechanisms that keep track of the origins (self or other) of the experienced feelings (Decety and Jackson, 2004). Although often used synonymously to theory of mind (ToM), the term "empathy" shall refer to the process of inferring and sharing the emotional experiences of others, in addition to representing what others are thinking. One could say that the ToM represents cognitive facets of empathy, while the "empathy proper" refers to affective facets of empathy. From the viewpoint of such a dichotomy of empathy, one could hypothesize that the neural bases of them would be, at least partially, independent. In fact, dissociations of cognitive and affective empathic abilities were demonstrated among autistic and psychopathic populations (Blair, 2005). Although several reports have suggested affective empathy deficits in schizophrenia, they have not so far been investigated in comparison with cognitive facets of empathy, i.e., ToM. Also no imaging studies have been performed investigating the relationships

Abbreviations: ACC, Anterior cingulate cortex; ACG, Anterior cingulate gyrus; dACC, dorsal anterior cingulate cortex; DSM-IV, Diagnostic and statistical manual of mental disorders, fourth edition; EC, empathic concern; FS, fantasy; IRI, Interpersonal Reactivity Index; NC, normal controls; PANSS, Positive and Negative Syndrome Scale; PD, personal distress; PT, per spective taking; ROIs, regions-of-interests; SCID-P, Structural Clinical Interview for DSM-IV Axis I Disorders—Patient Edition; SCID-NP, Structural Clinical Interview for DSM-IV Axis I Disorders—Nonpatient Edition; SCZ, schizophrenia; SPM2, statistical parametric mapping 2; ToM, Theory of Mind; IQ, intelligence quotient; vACC, ventral anterior cingulate cortex; WAIS-R, Wechsler Adult Intelligence Scale—Revised; WBV, whole brain volume.

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between affective empathy and brain morphological abnormalities in the disorder.

The anterior cingulate cortex (ACC), which is a part of a neural circuit regulating cognitive and emotional processing, is regarded as one of the critical structures for social cognition including empathy (Lee et al., 2004; Amodio and Frith, 2006). The ACC is differentiated from the posterior part of the cingulate cortex on the basis of cytoarchitecture, patterns of projections and functions. In schizophrenia studies, it has been suggested that medial frontal structures including the ACC, are one of the neural underpinnings of social cognitive deficits in the disorder (Yamada et al., 2007; Fujiwara et al., 2007).

Within the ACC, further compartmentalization can be made based on cytoarchitecture and connectivity. Human functional neuroimaging studies have demonstrated that sepa rate areas within the ACC are involved in different aspects of cognition and emotion (Amodio and Frith, 2006). The ACC can be separated into dorsal (dACC) and ventral (vACC) subdivisions (Bush et al., 2000). While the dACC is considered to play a major role in cognitive processing, the vACC is involved more in affective processing (Bush et al., 2000). This distinction might be applicable to the role of the ACC in empathy. Although the ACC is commonly activated in the tasks recruiting the ability of the ToM, as well as in those provoking affective empathy, ToM and affective empathy tasks have been demonstrated to activate different subregions of the ACC (Singer, 2006; Sommer et al., 2007).

Thus, further investigation, focusing on differential functions of each ACC subdivision, would give new insight into the role of the ACC in the empathic impairment of schizophrenia. In addition, it could shed light on the neural underpinnings of multi-faceted social (including interpersonal) dysfunctions in schizophrenia.

Study aim was to investigate the relationships between structural abnormalities of ACC subregions and empathic disabilities in schizophrenia. Our a-priori hypotheses in our current study were; (a) The volumes of each ACC subdivision would be decreased in schizophrenics compared to healthy controls; (b) Impairments of both cognitive and affective empathy would be found in the schizophrenia subjects. Alternatively, discrepancies of impairments of these two aspects could be observed; (c) Volume reductions of ACC subdivisions would be associated with empathic ability deficits in schizophrenia. In particular, within ACC subdivisions, vACC and dACC, volumes would be correlated with affective and cognitive empathy, respectively.

2. Methods

2.1. Participants

The schizophrenia group comprised 24 patients (only one male patient was an inpatient and the rest were outpatients) who had been referred to the Psychiatric Department of Kyoto University and who met the criteria for schizophrenia, as assessed by structural clinical interview for DSM-IV Axis I Disorders—Patient Edition (SCID-P, Version 2.0). Fourteen subjects were diagnosed as having the paranoid subtype of schizophrenia, five as having the disorganized subtype, three as having schizoaffective disorder and two as having schizophreniform disorder. All patients were receiving antipsychotic neuroleptics (seven were taking only atypical neuroleptics, two were taking only typical neuroleptics and fifteen were taking combinations of these), and haloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia (American Psychiatric Association, 1997; Woods, 2003). All patients were physically healthy at the time of scanning and psychological evaluation. None had a history of head trauma, neurological illness, serious medical or surgical illness or substance abuse. The comparison group consisted of 20 healthy individuals (10 men and 10 women) who matched the schizophrenia group for age and education level. None of them had history of neurologic or psychiatric illness. The structural clinical interview for DSM-IV Axis I Disorders—Nonpatient Edition (SCID-NP, Version 2.0) was used to assess the presence or absence of DSM-IV Axis I disorders. Additionally, no patients or control subjects had first degree relatives with a history of psychotic episodes. After a complete description of the study to the subjects, written informed consent was obtained. This study was granted approval by the Committee on Medical Ethics of Kyoto University.

2.2. MRI acquisition

2.2.1. Image acquisition

All participants received MR scans using a 3.0-T whole body scanner equipped with an 8-channel phased-array head-coil (Trio, Siemens, Erlangen, Germany). The scanning parameters for the three-dimensional magnetization-prepared, rapid-gradient echo (3D-MPRAGE) sequences were as follows: echo time (TE) = 4.38 ms; repetition time (TR) = 2000 ms; inversion time (TI) = 990 ms; field of view (FOV) = 256 × 256 mm^2; resolution = 0.94 × 0.94 × 1.0 mm^3; 208 axial slices of 1.0 mm thickness. To increase the signal-to-noise (S/N) ratio, we scanned all subjects three times and made average images from these three images using statistical parametric mapping 2 (SPM2) software. (http://www.fil.ion.ucl.ac.uk/spm).

2.2.2. Volumertic analyses for ACC subdivisions

The averaged 3D-MPRAGE images were realigned parallel to the anterior–posterior commissure line and analyzed using MRIcro software (Nottingham, UK). MRIcro permits the manual tracing of regions-of-interests (ROIs) and gives an automatic estimate of their

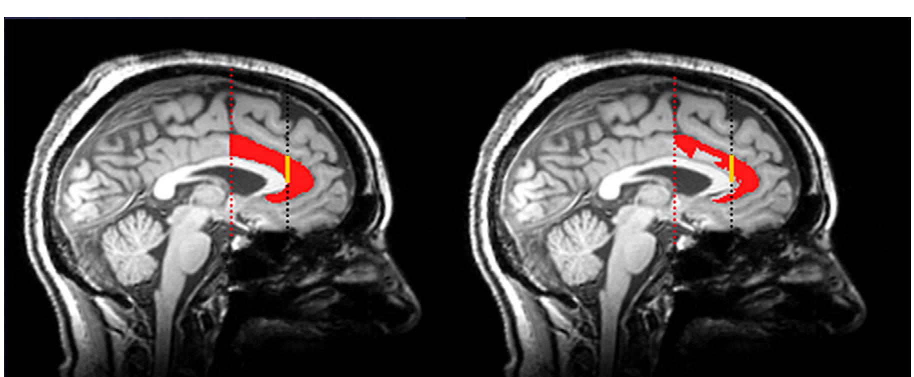

Fig. 1. An example of the ACC subdivisions. The left column presents the anterior cingulate gyrus including subcortical white matter. The right column presents the gray matter components of the left image. The vertical red dotted line represents the posterior border of the ACC region. The vertical yellow line represents the border of ventral and dorsal ACC subregions. As such “ventral ACC” in our definition includes both the ACC sections anterior and ventral to the corpus callosum.