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Reduced white matter integrity and facial emotion perception in never-medicated patients with first-episode schizophrenia: A diffusion tensor imaging study

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ABSTRACT

Background: Facial emotion perception is impaired in schizophrenia. Although the pathology of schizophrenia is thought to involve abnormality in white matter (WM), few studies have examined the correlation between facial emotion perception and WM abnormalities in never-medicated patients with first-episode schizophrenia. The present study tested associations between facial emotion perception and WM integrity in order to investigate the neural basis of impaired facial emotion perception in schizophrenia.

Methods: Sixty-three schizophrenic patients and thirty control subjects underwent facial emotion categorization (FEC). The FEC data was inserted into a logistic function model with subsequent analysis by independent-samples T test and the shift point and slope as outcome measurements. Severity of symptoms was measured using a five-factor model of the Positive and Negative Syndrome Scale (PANSS). Voxelwise group comparison of WM fractional anisotropy (FA) was operated using tract-based spatial statistics (TBSS). The correlation between impaired facial emotion perception and FA reduction was examined in patients using simple regression analysis within brain areas that showed a significant FA reduction in patients compared with controls. The same correlation analysis was also performed for control subjects in the whole brain.

Results: The patients with schizophrenia reported a higher shift point and a steeper slope than control subjects in FEC. The patients showed a significant FA reduction in left deep WM in the parietal, temporal and occipital lobes, a small portion of the corpus callosum (CC), and the corona radiata. In voxelwise correlation analysis, we found that facial emotion perception significantly correlated with reduced FA in various WM regions, including left forceps major (FM), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), Left splenium of CC, and left ILF. The correlation analyses in healthy controls revealed no significant correlation of FA with FEC task.

Conclusions: These results showed disrupted WM integrity in these regions constitutes a potential neural basis for the facial emotion perception impairments in schizophrenia.

1. Introduction

Schizophrenia is one of the most serious clinical mental diseases, often accompanied by cognitive impairment and severe social disability with a lifetime risk of approximately 0.7% (Tandon et al., 2010). Although the disease results in a heavy social and economic burden, its causes and pathogenesis remain obscure.

Schizophrenia is generally characterized by positive and negative symptoms, poor cognitive ability, excitatory status, and reduced emotional expression. The severity of schizophrenia symptoms can be assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Kay et al., 1988). Literature research suggested that a five-factor model, which consists of positive, negative, disorganized–concrete, excited, and depressed factor, better captured the PANSS structure in patients with schizophrenia (Lancon et al., 2000; Wallwork et al., 2012; Jerrell and Hrisko, 2013a, 2013b). Kohler et al. (Kohler et al., 2000) reported that emotion perception is uniquely associated in schizophrenia with core symptomatology and cognitive domains. Clinically, the ability of facial emotion processing has been found to be a critical factor which predicts clinical treatment outcomes (Mandal et al., 1998a). Li et al. (Li et al., 2012) also suggest that facial emotion perception might be a potential endophenotype of schizophre-

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nia.

Social cognition means the ability to perceive, interpret and regulate responses to emotional information (Green et al., 2008). In addition, much of the information is communicated to us in facial expressions (Fusar-Poli et al., 2009). Facial expressions supply universal signals of emotional tendency and communicate biologically notable information (Ekman, 1993) and the capacity to accurately identify these emotional expressions plays a vital role in facilitating effective communication. Several studies have provided evidence of impaired facial emotion identification in schizophrenia. A recent meta-analysis (Kohler et al., 2010) that pooled data from 86 studies concluded that schizophrenic patients universally have impaired facial emotion perception. However, previous work in this area is confounded by several methodological limitations. First, most facial emotion perception paradigms adopt stimuli that express the full signal strength of a discrete type of basic emotion, which is markedly different from the subtle and ambiguous signal strength of facial expression that is experienced in real-life situations. Second, most previous research recruited chronic schizophrenic patients with several potential confounds, such as medication effects, illness duration, and the psychiatric and medical comorbidities that are related to chronicity of illness (Buckley and Evans, 2006). To reduce these limitations, we applied a standardized facial emotion categorization (FEC) paradigm to never-medicated schizophrenic patients. We hypothesized that impaired facial emotion perception is a trait marker of schizophrenia and that the patients who were in the early stage of illness would also present abnormalities in facial emotion perception.

Increasing evidence indicates disruption of connectivity as a primary abnormality in schizophrenia (Stephan et al., 2009; Davis et al., 2003) and suggests that alterations in white matter (WM) may be the core basis for the disconnection (Takahashi et al., 2011). Since the impairments in WM may play a fundamental role in the neurobehavioral presentation of schizophrenia, studying the WM is critical to understanding the neurobiological mechanism of schizophrenia. Diffusion tensor imaging (DTI) has been widely used to investigate the information of WM based on water diffusion. DTI makes it possible to detect subtle WM abnormalities, and a reduction in fractional anisotropy (FA) implies reduced WM integrity. Several lines of research have identified the alterations of WM in frontal and temporal brain areas and tracts such as the cingulum bundles, uncinate fasciculi, internal capsules and corpus callosum to be associated with schizophrenia (Kubicki et al., 2007). These findings show that networks of WM may be impaired in schizophrenia, with the potential for “disconnection” (Friston, 1998) of the gray matter regions, which they connect (Ellison-Wright and Bullmore, 2009). On the other hand, recent neuroimaging studies have indicated a network of gray matter regions underlying facial expression processing, including the amygdala, fusiform gyrus and inferior frontal cortex (Hornak et al., 1996; Morris et al., 2009). Besides these functional abnormalities, several studies have revealed associations between facial emotion perception defects and structural abnormalities in gray matter regions responsible for facial emotion perception (Fujiwara et al., 2007a; Yamada et al., 2007). Considering the complexity of facial emotion perception, which needs the coordinated functioning of a widely distributed network of gray matter regions, facial emotion perception impairments may be caused by the disruption of connection between gray matter regions. To date, however, the correlation between impaired facial emotion perception and WM impairment has been little examined in schizophrenic patients.

A few pioneering studies have begun to investigate this potential association. Fujiwara et al. (Fujiwara et al., 2007a), using a region of interest method, did not reveal a correlation between impaired emotion perception and FA reduction in the anterior cingulum bundle in chronic schizophrenia. Nevertheless, FA reduction in the left occipital WM region and left posterior callosal region was revealed to be associated with the facial emotion perception defects (Miyata et al., 2010) in chronic schizophrenia. Even less investigated is the association between DTI measures and facial emotion perception in first-episode schizophrenia. In the present study, we recruited first-episode schizophrenic patients in a relatively larger sample than those used in previous studies, to examine voxel-based correlation analysis. We also explored correlations between the five-factor model PANSS and both FA values and FEC performance.

2. Materials and methods

2.1. Subjects

The study protocol was approved by the Medical Research Ethics Committee of Nanjing Brain Hospital. Written informed consents were obtained from all participants prior to the magnetic resonance scanning. Sixty-three never-medicated Chinese patients (44 males) with a first episode were recruited at the Nanjing Brain Hospital from February, 2014 to March, 2015. Patients were diagnosed using Structured Clinical Interview for DSM-IV Patient Edition (SCID-I/P), and met the criteria for schizophrenia. The patients had a mean $\pm$ SD age of 24.0 $\pm$ 5.9 years (range, 17–44), a mean $\pm$ SD duration of illness of 10.8 $\pm$ 9.1 months (range, 1–24), and a mean $\pm$ SD education of 12.3 $\pm$ 3.1 years (range, 2–20).

Thirty healthy volunteers (17 males) were recruited by advertisements in the local community. Current mental status and personal or family history of any mental disorder were assessed by a research psychiatrist. None of the controls presented a personal or family history of psychiatric disorder. The controls had a mean $\pm$ SD age of 22.1 $\pm$ 3.5 years (range, 18–31) and a mean $\pm$ SD education of 13.9 $\pm$ 2.8 years (range, 9–20).

General inclusion criteria for all the groups included (1) aged 15–45 years, (2) right-handed, (3) an ability to understand the survey instructions and contents. General exclusion criteria included a history of significant head injury, seizures, cerebrovascular disease, other neurological disease, impaired thyroid function, learning difficulties, and DSM-IV criteria of alcohol or substance abuse or dependence in the past year.

2.2. Assessment

2.2.1. Psychopathological assessment in patients

Two specialists who were unaware of the purpose of the study rated the patient’s psychopathology using PANSS on the day of the DTI test. The PANSS provided the total score and five factor scores including positive (delusions, hallucinations, grandiosity, and unusual thought content), negative (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity, and motor retardation), disorganized/concrete (conceptual disorganization, difficulty in abstract thinking, and poor attention), excited (excitement, hostility, uncooperativeness, and poor impulse control), and depressed factor (anxiety, guilt feelings, and depression) (Wallwork et al., 2012).

2.2.2. Facial emotion categorization (FEC)

A computer-based task to measure FEC was the same as described in a prior study (Huang et al., 2011). It consisted of four practice trials, followed by 60 trials of the actual task. In each trial, a black-and-white still photograph of a woman’s face appeared on the screen. The photographs that were used in this paradigm were comprised of five levels of facial expression: Level 1 represented 100% happy and 0% angry emotions; Level 2 represented 75% happy and 25% angry emotions; Level 3 represented the ambiguous image, with 50% happy and 50% angry emotions; Level 4 represented 25% happy and 75% angry emotions; and Level 5 represented 0% happy and 100% angry emotions (Fig 1). Details of the morphing procedure are described elsewhere (Pollak and Kistler, 2002). The participants were asked to indicate which emotion (i.e., either happy or angry, forced-choice response) best described the facial expression of the woman in the