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Research report

Abnormal white matter connections between medial frontal regions predict symptoms in patients with first episode schizophrenia

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ABSTRACT

Introduction: The medial orbitofrontal cortex (mOFC) and rostral part of anterior cingulate cortex (rACC) have been suggested to be involved in the neural network of salience and emotional processing, and associated with specific clinical symptoms in schizophrenia. Considering the schizophrenia dysconnectivity hypothesis, the connectivity abnormalities between mOFC and rACC might be associated with clinical characteristics in first episode schizophrenia patients (FESZ).

Methods: After parcellating mOFC into the anterior and posterior part, diffusion properties of the mOFC-rACC white matter connections for 21 patients with FESZ and 21 healthy controls (HCs) were examined using stochastic tractography, one of the most effective Diffusion Tensor Imaging (DTI) methods for examining tracts between adjacent gray matter (GM) regions.

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Results: Fractional anisotropy (FA) reductions were observed in bilateral posterior, but not anterior mOFC-rACC connections (left: $p < .0001$; right: $p < .0001$) in FESZ compared to HCs. In addition, reduced FA in the left posterior mOFC-rACC connection was associated with more severe anhedonia-asociality (rho = −.633, $p = .006$) and total score (rho = −.520, $p = .032$) in the Scale for the Assessment of Negative Symptoms (SANS); reduced FA in the right posterior mOFC-rACC connection was associated with more severe affective flattening (rho = −.644, $p = .005$), total score (rho = −.535, $p = .027$) in SANS, hallucinations (rho = −.551, $p = .018$), delusions (rho = −.632, $p = .005$) and total score (rho = −.721, $p = .001$) in the Scale for the Assessment of Positive Symptoms (SAPS) in FESZ.
Conclusions: The observed white matter abnormalities within the connections between mOFC and rACC might be associated with the psychopathology of the early stage of schizophrenia.

1. Introduction

Clinically, a majority of patients with early stages of schizophrenia, a population frequently referred to as first episode schizophrenia (FESZ), demonstrate positive symptoms such as hallucinations and delusions. Negative symptoms also exist in the early stage of the illness, although are observed less frequently in FESZ than in chronic schizophrenia populations. Aberrant salience has been proposed as an important mechanism in the production of psychotic symptoms such as delusions and hallucinations (Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011). Inappropriately excessive salience attached to external events is thought to be associated with delusions, while such salience when attached to self-generated responses may contribute to hallucinations (Kapur, 2003). The anterior cingulate cortex (ACC) is a part of the 'salience network' (Seeley et al., 2007), and it has been suggested that dysfunction of this network may result in misattribution of salience to ordinarily inconsequential events, which might in turn result in hallucinations and/or delusions (Kapur, 2003). Furthermore, auditory verbal hallucinations are associated with functional abnormalities in the ACC (Allen et al., 2007), and other neuroimaging studies have reported reduced activity in the ACC in schizophrenia patients exhibiting delusions (Blackwood et al., 2004; Erkwoh, Sabri, Steinmeyer, Bull, & Sass, 1997; Lahti et al., 2006). Meanwhile, it has been posited that abnormalities in the orbitofrontal cortex (OFC) may be mediating symptom misattribution by conferring aberrant salience to perceived symptomatology (Shad, Muddasani, & Keshavan, 2006). Of interest, a PET study of schizophrenic patients with hallucinations reported increased activation in the OFC (Silbersweig et al., 1995) which provides further evidence that the OFC might be involved in generating this positive symptom. In addition, delusion misattribution in patients experiencing the first episode of psychosis was associated with cortical thickness in the OFC (Buchy et al., 2012) also providing evidence for the association between delusions and abnormalities in the OFC. These previous studies suggested ACC and OFC to be associated with the psychopathology of hallucinations and delusions.

On the other hand, patients with schizophrenia, starting from the early stage of the illness, also show abnormal emotional responses and an increased difficulty with social interaction, suggestive of abnormal emotional processing. It has been proposed that the OFC and ACC play distinct, but complementary, roles in mediating normal patterns of emotional and social behavior (Rudebeck, Bannerman, & Rushworth, 2008; Rudebeck, Behrens, et al., 2008). Among the OFC sub-regions, the medial OFC (mOFC) is activated by emotional stimuli (for a review see Phan, Wager, Taylor, & Liberzon, 2002), while the posterior OFC may function as a general significance detector that particularly responds to salient and behaviorally relevant events in the environment (Diekhof, Falkai, & Gruber, 2011). For the ACC sub-regions, the rostral part of ACC (rACC) is the affective sub-region of ACC and is primarily involved in assessing the salience of motivational and emotional information and regulating emotional responses (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Bush, Luu, & Posner, 2000). Previous studies have suggested that close functional relationships exist between the mOFC and rACC (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Goldstein et al., 2007), as well as between the posterior OFC and the ventral cingulate cortex (Elliott et al., 2002). Therefore, we focused our analysis on the white matter (WM) properties in the connections between functionally related regions of the mOFC and rACC, in an effort to understand the structural connections underlying the salience network and the pathophysiology of positive and negative symptoms in schizophrenia.

The dysconnectivity hypothesis of schizophrenia proposes that schizophrenia results from poor or mis-wired anatomical connections between distinct brain regions, leading to functional disintegration (Foucher et al., 2005; Konrad & Winterer, 2008; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Postmortem and genetic studies have provided evidence for anatomical dysconnectivity and myelination abnormalities in schizophrenia (Davis et al., 2003; Segal, Koschnick, Slegers, & Hof, 2007). We hypothesize that the WM connections between the mOFC and the rACC will be abnormal because of the functional cooperation between the mOFC and the rACC in many important cognitive processes