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Morphology of the orbitofrontal cortex in first-episode schizophrenia: Relationship with negative symptomatology

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Abstract

Different studies have documented OFC abnormalities in schizophrenia, but it is unclear if they are present at disease onset or are a consequence of disease process and/or drug exposure. The evaluation of first-episode, drug-naïve subjects allows us to clarify this issue. Magnetic resonance imaging was performed on 43 first-episode, antipsychotic-naïve schizophrenia patients and 53 healthy comparison subjects matched for age, gender, race, and handedness. Gray matter OFC volumes were measured blind to the diagnoses. As compared to controls, patients had greater volumes in left total OFC ($p=0.048$) and left lateral OFC ($p=0.037$). Severity of negative symptoms (anhedonia, flattened affect, and alogia) positively correlated with both the left lateral (Spearman's, rho=0.37, $p=0.019$; rho=0.317, $p=0.041$; $r=0.307$, $p=0.048$, respectively) and the left total OFC (Spearman's, rho=0.384, $p=0.014$; rho=0.349, $p=0.023$; rho=0.309, $p=0.047$, respectively). The present results suggest that first-episode, antipsychotic-naïve schizophrenia subjects exhibit increased OFC volumes that correlate with negative symptoms severity. The OFC, through extensive and complex interconnections with several brain structures with putative role in pathophysiology of schizophrenia including amygdala, hippocampus, thalamus, DLPFC, and superior temporal lobe, may mediate schizophrenia symptoms such as blunting of emotional affect and impaired social functioning. Although the specific neuropathological mechanisms underlying structural abnormalities of the OFC remain unclear, increased OFC volumes might be related to deviations in neuronal migration and/or pruning. Future follow-up studies examining high-risk individuals who subsequently develop schizophrenia at different stages of disease could be especially instructive.

Keywords: First-onset schizophrenia; Magnetic resonance imaging (MRI); Neuroimaging; Orbital frontal cortex; Psychosis

1. Introduction

Efforts to unravel the precise brain alterations underlying psychiatric disorders in recent years have increasingly employed neuroimaging and neuropathologic techniques. Both neuroimaging and postmortem studies have consistently indicated that schizophrenia is characterized by subtle but significant gray matter abnormalities, particularly affecting frontal and temporal lobes (Shenton et al., 2001). A critical role of prefrontal cortex (PFC) in schizophrenia has also been suggested by a number of neuropsychological studies demonstrating deficits in cognitive domains such as executive functions and working memory (for a review see Elvevag and Goldberg, 2000). PFC is, however, a heterogeneous structure both anatomically and functionally, including dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex, and anterior cingulate. As those subregions appear to be involved in different cognitive processes, it is conceivable to hypothesize that they might be differentially involved in the pathophysiology of schizophrenia.

The orbitofrontal cortex, the ventralmost division of PFC, and its reciprocal connections with several brain structures play

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a major role in a wide range of neuropsychological processes, including coding of interoceptive and exteroceptive information, emotional processing and memory, recognition of reinforcing stimuli, stimulus-reward association, reward-guided behavior, mood regulation, impulse control, and control of autonomic and motor effector pathway (Price, 1999; Zald and Kim, 2001). Some of these processes have been reported to be affected in schizophrenia (Bartels and Drake, 1988; Schneider et al., 1995; Stip, 1996). In animals, OFC lesions are associated with aggressive behavior, appetite disturbances, and social withdrawal (Fuster, 1989; Raleigh and Steklis, 1981). In humans, OFC lesions are associated with different emotional disturbances, including apathy, social withdrawal, socially inappropriate behaviors, impairment in the identification of facial and vocal emotional expression, depressed mood, affective instability, and lack of affect (Grafman et al., 1996, 1986; Rolls, 1996). It is interesting to note that most of these symptoms are related to negative symptomatology commonly observed in schizophrenia. Yet, abnormal social behavior is frequently reported as a premorbid feature of the disease, appearing long before its onset (Walker and Lewine, 1990).

Despite different lines of evidence supporting a potential role of OFC in the pathophysiology of schizophrenia, only a few neuroimaging studies have examined the anatomical integrity of this structure. They have produced somewhat inconsistent results, with some studies (Chemerinski et al., 2002; Convit et al., 2001; Crespo-Facorro et al., 2000; Goldstein et al., 1999; Gur et al., 2000; Sanfilipo et al., 2000; Szeszko et al., 1999), but not all (Baare et al., 1999; Buchanan et al., 1998; Yamasue et al., 2004), reporting abnormalities in OFC volumes. This apparent discrepancy may be at least partially explained by methodological issues. Firstly, different methods for measuring OFC have been proposed and have reported grossly discrepant values (Lacerda et al., 2003a). Secondly, OFC abnormalities may be specifically related to certain clinical features such as negative symptoms and disturbed social behavior or subgroups of patients (at least one study found volume decrements only in females) (Chemerinski et al., 2002; Crespo-Facorro et al., 2000; Gur et al., 2000). Finally, confounders associated with disease process, drug exposure, and ageing may have hindered significant differences between groups in studies that did not control them. Postmortem neuropathological studies, on the other hand, are faced with additional limitations such as duration of illness prior to death, confounding by concurrent illnesses and perimortem factors (e.g., mode of death, autopsy delay, and tissue processing), diagnosis validity, and availability of enough cases (Harrison, 1999).

Since most neuroimaging studies have examined patients with chronic schizophrenia, the question whether OFC abnormalities occur prior to disease onset or are a consequence of disease process and/or treatment is pertinent. Different lines of evidence have supported the neurodevelopmental hypothesis of schizophrenia (Schultz and Andreasen, 1999; Weinberger, 1995). According to this theory, the symptoms of the disorder are a manifestation of either a dysfunctional neural circuitry resulting from early (pre- or perinatal) deviations (Murray and Lewis, 1987; Weinberger, 1987) or disturbed brain maturational processes such as pruning in late childhood and adolescence (Keshavan et al., 1994), which are largely not apparent until the onset of symptomatology. In vivo MRI evaluation of first-episode, drug-naïve subjects propitiates a privileged opportunity to overcome at least part of the methodological problems present in both postmortem studies and MRI studies examining chronic populations described earlier.

The present study aimed to investigate anatomical integrity of OFC in first-episode, drug-naïve schizophrenia subjects by using a highly reliable and validated method. We were also particularly interested in identifying possible relationships between OFC volumes and symptom severity. We hypothesized that patients would have smaller OFC as compared to healthy controls and that gray matter volumes inversely correlate with negative symptoms (flattened affect, alogia, anhedonia, and avolition) severity. Correlations between OFC volumes and positive symptoms were not predicted in view of inconsistent data in previous literature (Szeszko et al., 1999; Lacerda et al., 2003a,b).

2. Methods

2.1. Subjects

The sample included 43 first-episode, treatment-naïve subjects with DSM-IV diagnosis of schizophrenia (29 males) and 53 healthy controls (34 males). Patients were recruited through the Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center and examined during their first hospitalization, before they were started on antipsychotic drugs. Diagnosis was established using Structured Clinical Interview for DSM-IV — Patient Version (Spitzer et al., 1994). All patients were followed up for at least 6 months to confirm diagnostic stability and obtain additional history. All subjects were given a standard medical examination before the recruitment and provided written informed consent after detailed explanation of the study procedures, which were approved by the University of Pittsburgh School of Medicine Institutional Review Board (IRB). All subjects were physically healthy and did not have a systemic or neurological illness, mental retardation, or head injury. None of the subjects was diagnosed with substance abuse in the previous month or dependence within the previous 6 months. Antipsychotic-naïve status was confirmed based on detailed history taking, collateral information, and diagnostic interviews.

2.2. Clinical ratings

Symptom severity was assessed with Brief Psychiatric Rating Scale [BPRS; (Overall and Gorham, 1962)], Scale for the Assessment of Positive Symptoms [SAPS; (Andreasen, 1984)], and Scale for the Assessment of Negative Symptoms [SANS; (Andreasen, 1983)].

2.3. MRI parameters

All scans were acquired at the MRI Center at the University of Pittsburgh Medical Center with a 1.5-T Signa whole body