Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia

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Schizophrenia is hypothesized to arise from disrupted brain connectivity. This “dysconnectivity hypothesis” has generated interest in discovering whether there is anatomical and functional dysconnectivity between the prefrontal cortex (PFC) and other brain regions, and how this dysconnectivity is linked to the impaired cognitive functions and aberrant behaviors of schizophrenia. Critical advances in neuroimaging technologies, including diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI), make it possible to explore these issues. DTI affords the possibility to explore anatomical connectivity in the human brain in vivo and fMRI can be used to make inferences about functional connections between brain regions. In this review, we present major advances in the understanding of PFC anatomical and functional dysconnectivity and their implications in schizophrenia. We then briefly discuss future prospects that need to be explored in order to move beyond simple mapping of connectivity changes to elucidate the neuronal mechanisms underlying schizophrenia.

Keywords: prefrontal cortex; schizophrenia; anatomical connectivity; functional connectivity

Introduction

Schizophrenia is a debilitating mental disorder affecting ~1% of the general population, with disturbances of cognitive, social, and behavioral functions. A popular hypothesis for this disorder is that schizophrenia is a “dysconnection” disorder and its symptoms are thought not to be due to a single, regionally-specific pathophysiology but to abnormal interactions between regions[1-5]. Recent MRI studies have provided further evidence for this opinion[6-8]. Among the regions implicated in the pathophysiology of schizophrenia, the prefrontal cortex (PFC) has always been of interest[9], due to changes in neurodevelopment processes, abnormalities in anatomy and function, and its role in the cognitive functions that are impaired in schizophrenia[10]. Recent network analyses based on graph theory have also revealed that the PFC is one of the hub regions affected in schizophrenia[11]. However, no area of the brain acts in isolation. To understand the implications of the involvement of the PFC in schizophrenia, we need to understand the PFC in the context of the brain as a whole. In this review, we summarize the major advances in the anatomical and functional connectivity of the PFC in schizophrenia to generate a clear picture of how PFC dysconnection relates...
to this disorder. Then, we discuss current challenges and future research directions.

**A Brief Introduction to the PFC**

The PFC plays an essential role in the organization and control of goal-directed thought and behavior[12]. Specifically, the lateral PFC is critical for the selection, monitoring, and manipulation of cognitive task sets; the medial PFC is critical for updating these sets; and the orbitofrontal cortex (OFC) is critical for assigning social and emotional meaning to these sets in order to better guide goal-directed behavior[12] (see reference[12] for a detailed introduction to the specific function of each PFC area). Furthermore, the extensive reciprocal connections between the PFC and nearly all cortical and subcortical structures, especially the limbic regions, place it in a unique position to orchestrate a wide range of cognitive and affective neuronal functions[12]. The architectonic subdivisions of the PFC and the major PFC white-matter tracts involved in schizophrenia are illustrated in Figure 1.

Based on the unique role of the PFC in normal functioning, research has linked it with schizophrenia. The major findings in schizophrenia include: spine loss and dendritic atrophy of PFC neurons; smaller PFC grey matter volume; profound dysfunction of the PFC (including deficits in working memory); and changes in gene expression (for review, see[15]). Among these, the changes in microcircuits of the PFC in schizophrenia suggest the possibility of altered connectivity between the PFC and other regions[15].

**Anatomical Dysconnectivity of the PFC in Schizophrenia**

Evidence from myelin pathology in postmortem brain tissue and gene expression profiling has shown that anatomical connectivity might be pathologically changed in schizophrenia[16]. Diffusion tensor imaging (DTI), a new and powerful tool, affords the possibility to explore the anatomical connectivity in the human brain in vivo. By measuring the degree of anisotropy in the random motion of water molecules, DTI can quantify and visualize white-matter fiber tracts[17]. Fractional anisotropy (FA) is the most-commonly used DTI index[18] to examine white matter.