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·Review·

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

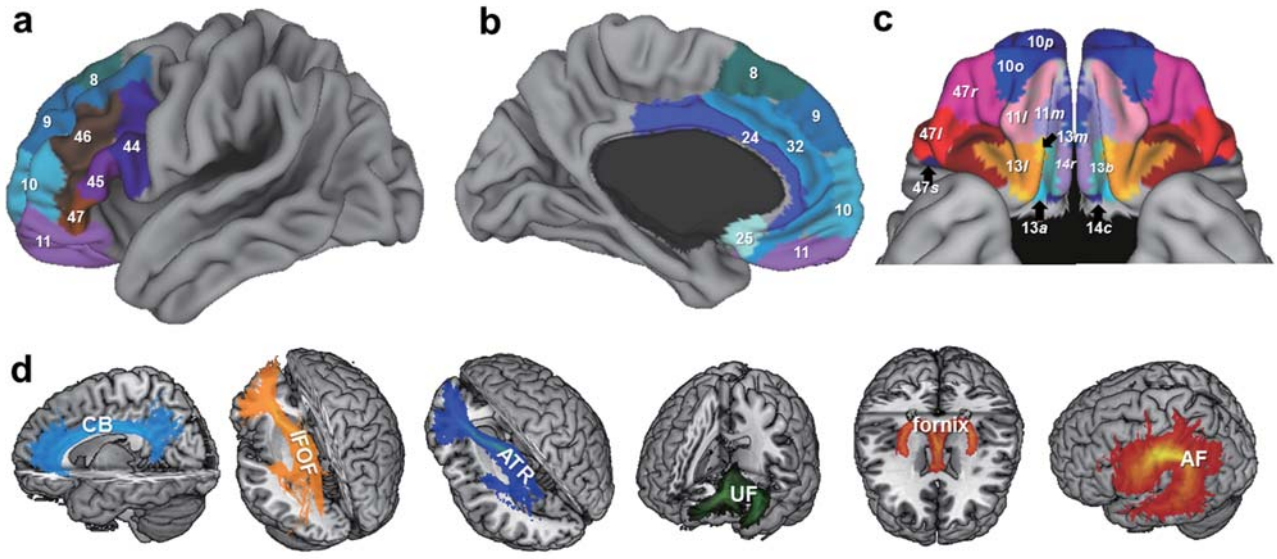

Fig. 1. Architectonic subdivisions of the PFC (a, b, c) and the major PFC white matter tracts involved in schizophrenia (d)[13, 14]. Dorsolateral PFC: lateral area 8, lateral area 9, and area 46; ventrolateral PFC: areas 44, 45, and 47; rostral PFC: area 10; orbitofrontal cortex: areas 11 (11m and 11l), 13 (13a, 13b, 13m, and 13l), 14 (14r and 14c), 10 (10p, 10o), and 47/12 (47/12r, 47/12m, 47/12l, and 47/12s); medial PFC: medial areas 8, 9, 10, 32, 24, and 25. The major white-matter tracts linking the PFC and other brain regions are the cingulum bundle (CB), inferior fronto-occipital fasciculus (IFOF), anterior thalamic radiation (ATR), uncinate fasciculus (UF), fornix, and arcuate fasciculus (AF), all of which are implicated in schizophrenia.

integrity. Since the seminal work[19] in which DTI was first applied to schizophrenia, studies have repeatedly found white-matter pathology in schizophrenia by region of interest (ROI) measures to define the fiber tracts, by voxel-based analysis, and by fiber tractography[20]. A systematic meta-analysis of voxel-based DTI FA studies of patients with schizophrenia revealed significant reductions in the left frontal and left temporal deep white matter[21]. The region in the left frontal deep white matter is traversed by tracts interconnecting the frontal lobe, thalamus, and cingulate gyrus. The region in the temporal lobe is traversed by tracts interconnecting the frontal lobe, insula, hippocampus, amygdala, and temporal and occipital lobes[21]. Similar findings were obtained when analyzing studies on patients with first-episode schizophrenia, in whom reduced FA in the white matter of the right deep frontal and left deep temporal lobes was found[22]. Fiber tracking showed that the main tracts involved are the cingulum bundle (CB), the left inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculus, and the interhemispheric fibers running through the corpus callosum[22]. All of these findings provide evidence for disrupted anatomical connections in the fronto-limbic circuitry, even at the early stages of schizophrenia. Therefore, we focus on several major white-matter tracts linking the PFC and limbic regions, the CB, uncinate fasciculus (UF), and arcuate fasciculus (AF) to understand the clinical correlates of PFC anatomical dysconnectivity in schizophrenia.

Cingulum Bundle

The CB connects paralimbic-neocortical regions and also interconnects limbic structures including the dorsolateral prefrontal cortex (DLPFC), cingulate gyrus, parahippocampal gyrus, and amygdala[20]. The CB is involved in a number of functions, including emotion, self-monitoring, and spatial orientation and memory. By placing ROIs on the CB, Kubicki and coworkers reported reduced FA in the CB in schizophrenic patients compared with controls[23]. This finding has been repeatedly replicated by different methods including ROI analysis, voxel-based analysis, and fiber tractography[23-29]. Decreased FA in the CB has been linked with various cognitive dysfunctions in schizophrenia, such as errors in executive functions relevant to performance monitoring[23], poor general intelligence and working memory[30], impaired Stroop performance[31], and increased saccadic latency[32]. In addition, higher FA in the left CB and left fronto-occipital fasciculus is associated with lower within-individual variability for speed on a computerized neurocognitive battery in healthy controls, but not in patients with schizophrenia[33].

Uncinate Fasciculus

The UF is a bidirectional, long-range white-matter tract that connects the lateral OFC and Brodmann area 10 with the anterior temporal lobes[34]. One would expect that the UF connecting limbic regions to OFCs might be structurally impaired in schizophrenia. However, a recent review of the DTI literature indicates that findings on FA in the UF in schizophrenia are mixed. The UF appears to play either a small role, or no role, in this disorder[34]. Clinical heterogeneity combined with small sample sizes may account for the contradictory results. It is possible that the integrity of the UF is correlated with specific symptoms of schizophrenia. Two studies have shown that the FA values in the left UF of schizophrenic patients with deficit syndromes (such as flattened affect and lack of social engagement) are lower than those of non-deficient patients and controls[35, 36]. In addition, the severity of deficit symptoms is strongly correlated with disruption of the same tract in a group of patients with first-episode schizophrenia[36].

Arcuate Fasciculus

The AF bidirectionally connects the caudal temporal and inferior parietal cortices to the frontal lobe. Due to the fact that this tract connects Wernicke's and Broca's areas, the AF is the major language-processing tract in the brain. Therefore, the integrity of the AF is often linked with the language and thought disturbances in schizophrenia[37]. Although mixed findings have been reported[37, 38], more consistently a reduced FA value in the AF has been found in schizophrenic patients with auditory verbal hallucinations[39-41]. Several studies have also suggested that changes in the integrity of the AF may be relevant to the risk of developing psychosis; decreased axonal or fiber integrity has been reported in the AF of siblings of patients diagnosed with schizophrenia[42, 43]. The disrupted integrity in the AF is consistent with the evidence of language deficits in those at familial or a clinically increased risk for schizophrenia[42].

Several other white-matter tracts connecting the PFC and other regions have also been investigated. These tracts include the fornix, a tract connecting the hippocampus with other regions including the PFC. This tract is important in spatial learning and memory, which are disrupted in schizophrenia. Disrupted integrity of the fornix has been found in a group of patients with schizophrenia, who also showed disrupted functional connectivity between the hippocampus and other regions implicated in episodic memory, such as the medial prefrontal cortex (MPFC)[44]. Another tract that shows FA reduction in schizophrenia is the inferior fronto-occipital fasciculus (IFOF), which connects the occipital, posterior temporal, and orbitofrontal areas[45]. Decreased FA in the left IFOF predicts worse neurocognitive performance both in never-medicated chronic schizophrenia[46] and in adolescents with early-onset schizophrenia[47], as well as predicting empathic impairments in patients with schizophrenia[48]. Other white-matter fiber tracts related to the PFC in schizophrenia include the anterior limb of the internal capsule, the medial portion of which includes the anterior thalamic radiation linking the thalamus and the PFC[49, 50], the genu of the corpus callosum linking the bilateral PFCs[51, 52], and deep white matter within the PFC[53].

In addition, globally exploring changes across the entire brain using graph-based network analyses provides a means of searching for possible lesions or alterations in the anatomical connectivity network[17]. By examining networks derived from diffusion imaging data, a longer average path-length and corresponding reduction in global communication efficiency have been found in patients with schizophrenia[11]. Node-level investigation has further revealed altered connectivity centered on frontal association regions[8]. And regional efficiencies in the frontal association cortex are negatively correlated with the severity of symptoms as measured by the Positive and Negative Syndrome Scale[8].

Functional Dysconnectivity Related to the PFC in Schizophrenia

Resting-state functional magnetic resonance imaging (fMRI) and task-based fMRI are often used to make inferences about the connections between brain regions[54]. Using different functional connectivity (FC) analyses, researchers can investigate the PFC-related networks based on single ROIs, specific networks, and whole-brain networks. Abnormal functional interactions between the PFC and widely-distributed regions, such as the parietal cortex, temporal regions, and regions in the default mode network, have been found in schizophrenia both during rest and during several cognitive tasks such as working memory tasks, continuous performance tasks, and reaction-choice tasks (for review, see [55]). Here, we focus on selected networks to illustrate how functional dysconnectivity of the PFC is linked with the impaired cognitive functions and/or the psychotic symptoms of schizophrenia.

Frontostriatal Circuit

Functional dysconnectivity between the PFC and dopamine-regulating regions in the basal ganglia (BG) has been hypothesized to account for two core features of schizophrenia, cognitive deficits and psychosis, based on the dopamine hypothesis of schizophrenia[56], which has been tested in several recent studies[57-59]. Using resting-state fMRI, Salvador *et al.* found increased connectivity between the DLPFC and the BG across low-, medium-, and high-frequency bands, indicating that DLPFC-BG functional dysconnectivity is an abnormal part of the frontostriatal loop in schizophrenia[57]. Yoon *et al.* found task-evoked hyperactivity in the substantia nigra that occurred in association with hypoactivity of the right inferior frontal gyrus (IFG) and the bilateral caudate during a working memory task in a schizophrenic group[58]. They further found decreased FC between the PFC (localized to the right inferior/middle frontal gyrus) and BG regions (substantia nigra and caudate) in patients with schizophrenia while they were performing a working memory task. Similarly, decreased performance-related FCs between the ventrolateral PFC and the bilateral putamen were found during a working memory task, suggesting that weaker frontostriatal connectivity underpins the impaired information retrieval in schizophrenia during working memory performance[59]. Although these studies revealed an abnormality in the frontostriatal circuit in schizophrenia, it is worthy of note that the pattern of abnormality is incompatible: increased FC in the frontostriatal circuit during rest but decreased FC during the task. In order to understand the link between the two types of functional

dysconnectivity, studies measuring resting-state FC and task-state FC in the same individual need to be performed.

Frontotemporal Functional Connectivity

Frontotemporal dysconnectivity has been proposed as a mechanism leading to the psychotic symptoms, especially auditory hallucinations, in schizophrenia. Since the first study suggesting that reduced FC between the left DLPFC and the left superior temporal gyrus was linked to auditory hallucinations in schizophrenia[60], several studies have verified the relationship between frontotemporal functional disconnectivity and auditory hallucinations during different tasks, suggesting a source-monitoring impairment (for review, see[61]). Resting-state FC studies suggest that elevated frontotemporal FC makes auditory hallucinations worse, especially indicated by positive correlations between the reality of hallucinations and the strength of the FC between the left IFG (including Broca's region) and the auditory cortex, posterior temporal lobe, ventral striatum, and anterior cingulate cortex[62]. Based on their recent studies, Hoffman and colleagues proposed a complex functional loop, which includes Wernicke's area and its right homologue, the left IFG, and the putamen, to interpret the generation of auditory verbal hallucinations. In this model, intact FC between Wernicke's area and the left IFG and FC between the left IFG and putamen appeared to allow hyperconnectivity between the putamen and Wernicke's area to be expressed as conscious hallucinations of speech[61]. However, whether the resting-state frontotemporal FC is decreased or increased in schizophrenic patients with auditory hallucinations compared to patients without such hallucinations or healthy participants remains to be determined.

Frontoparietal Functional Connectivity

Functional interactions between the dorsal frontal and parietal regions are engaged by a wide range of higher-level cognitive tasks and are thought to be involved in adaptive task control[63, 64]. In general, greater FC between the dorsal frontal and parietal regions predicts better performance. Disrupted dorsal fronto-parietal FC may account for the impaired executive function and cognitive control in schizophrenia, especially the well-known working memory deficit (for review, see[55, 65]). In addition, the dysfunctional connectivity of the dorsal frontal-parietal network has been correlated with psychotic symptoms such as disorganization[66, 67], which may be due to the disrupted executive function and cognitive control in schizophrenia.

PFC-Hippocampus Functional Connectivity

Disturbed interactions between the PFC and hippocampus have also been proposed to account for the cognitive deficits related to working memory in schizophrenia[68]. Meyer-Lindenberg and colleagues reported persistent undiminished FC between the right DLPFC and left hippocampus in the context of a working memory task in schizophrenia[69]. Benetti and colleagues found that the normal pattern of effective connectivity from the right posterior hippocampus to the right IFG is significantly decreased in both first-episode patients and individuals at high risk for psychosis during a delayed matching-to-sample task, suggesting that a disruption of bottom-up hippocampal–prefrontal integration may be correlated with increased vulnerability to psychosis rather than an effect of chronic illness or its treatment[70].

Medial PFC and the Default Mode Network

The functional connectivity of the MPFC is also involved in psychosis and the cognitive deficits in schizophrenia, due to its role in self-referential mental activity and the organization of thoughts and actions according to internal goals[71]. Hyperconnectivity between the MPFC, a region with reduced task-related suppression during a working memory task, and other regions of the default mode network during both rest and working memory tasks is correlated with the more serious positive symptoms in schizophrenic patients[72]. Moreover, the hyperactivity in the MPFC (reduced task-related suppression) and the hyperconnectivity between the MPFC and the regions of the default mode network during a working memory task are correlated with inferior working memory performance both in schizophrenic patients and their unaffected relatives[72]. These findings suggest that the abnormal MPFC FC may contribute to the disturbances of thought in schizophrenia, impaired working memory performance, and to the risk for the illness[72]. Besides its implications for working memory, the altered MPFC FC is also involved in other cognitive functions. For example, dysconnectivity between the MPFC and the left superior temporal gyrus during a self-other source monitoring task is implicated in the impaired reality monitoring in schizophrenia[73]. And decreased negative connectivity between the MPFC and medial-temporal

regions during perspective-taking has been reported in patients with schizophrenia, and this deficit fully mediates the behavioral impairments in theory of mind in patients[74]. However, similar to other PFC regions, inconsistent findings also exist in the MPFC FC patterns. For example, contrary to hyperconnectivity, a study using an ROI in the ventral MPFC showed decreased resting-state FC between the ventral MPFC and the default mode network regions (such as the anterior MPFC, right middle temporal lobe, hippocampus, parahippocampus, and amygdala) in chronic schizophrenic patients. And the decreased FC between the ventral MPFC and right medial-temporal regions has been correlated with the poorer regulation of emotion[75]. The inconsistency may result from the differences in FC analysis methodology (such as the selection of ROI) and the heterogeneity of schizophrenia.

In general, decreased FCs related to the PFC in schizophrenia are often found when a task is performed; however, both decreased and increased PFC functional dysconnectivities are found in schizophrenia during rest. Most of these abnormal FCs are related to the dorsal PFC, although different circuits are involved. These abnormal PFC connectivities have been implicated in the pathophysiology and pathopsychology of schizophrenia, especially the psychotic symptoms and impaired cognitive functions (such as impaired working memory) (Table 1).

Perspectives

Despite the current knowledge on the clinical correlates of PFC dysconnectivity in schizophrenia, many challenges still exist. Here, we list some challenges and express our opinions about how to address these challenges in order to move beyond simple mapping of connectivity changes to elucidate the underlying neuronal mechanisms of the pathogenesis and pathophysiology of schizophrenia.

Fine-Grained Parcellation of the PFC

The PFC has a heterogeneous cytoarchitecture and functions. It is composed of several cytoarchitectonically different subregions involved in a variety of functions and this suggests the existence of functional subregions, such as the superior frontal gyrus[50]. Even though Brodmann-defined brain areas have their unique internal structure, such as the frontal pole (i.e. Brodmann area 10), functional subregions are also suggested due to the distinct anatomical and functional connectivity patterns[46]. Based on the cytoarchitecture, the distribution patterns of multi-receptor, co-activation patterns, and anatomical and/or functional connectivity, each of the PFC regions (DLPFC, ventrolateral PFC, MPFC, OFC, and frontal pole) has been parcellated into subregions[76-82]. These finer parcellation patterns have important implications for identifying the specific functional role of each subdivision in the PFC.

Despite the complexity of functional regions/subregions of the PFC, the existing studies often selected a roughly-defined PFC region to investigate the differences in connection patterns between schizophrenic patients and healthy controls, or interpreted their findings in a way lacking detailed information on the PFC subregions. There is no doubt that new knowledge on PFC dysconnectivity in schizophrenia will be warranted by the next generation of brain atlases, such as the Brainnetome atlas[83], which has

Table 1. Major findings of PFC functional dysconnectivity in schizophrenia

Region-region	Resting-state FC	Task-state FC	Clinical implications
PFC-BG	↑	↓	Impaired working memory
IFG-temporal lobe	unclear	↓	Reality of auditory hallucination
DLPFC-parietal lobe	↑↓	↓	Deficits in executive function and cognitive control (e.g., working memory); psychotic symptoms
DLPFC-hippocampus	unclear	↓	Impaired working memory; psychosis
MPFC-DMN	↑↓	↑↓	Impaired working memory, reality-monitoring, theory of mind; psychosis

BG, basal ganglia; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; FC, functional connectivity; IFG, inferior frontal gyrus; MPFC, medial prefrontal cortex; ↑increase; ↓decrease.

finer parcellation of the PFC and other brain regions[84-87]. On one hand, using a more fine-grained PFC parcellation scheme as a reference for reporting localization results in future studies will be helpful in reducing the confusion in the nomenclature (e.g., lateral PFC, dorsolateral PFC) and make it easier to compare results from different studies, and so will be useful for advancing our understanding of PFC pathophysiology in schizophrenia. On the other hand, it will be possible to identify the neuronal correlates of a specific symptom or an impaired cognitive function with a specific PFC subregion and thus may generate a symptom classification atlas, providing insights into the etiology and pathogenesis of schizophrenia.

However, it needs to be noted that inconsistency exists in the parcellation results obtained by different criteria, methodologies, and imaging modalities. For example, area 44 of Broca's region in the left inferior frontal gyrus can be parcellated into 5 subregions based on its co-activation pattern across different fMRI studies[77], but into 2 subregions based on the distribution pattern of multiple receptors[76], resting-state fMRI-based parcellation[88], and diffusion-weighted tractography-based parcellation[80]. Even using the same methodology, inconsistent findings can be obtained, such as the frontal pole parcellation based on anatomical connectivity obtained by diffusion-weighted tractography[78, 82]. One possible reason for such inconsistency is that there is no standardized protocol to manually identify ROIs of the PFC as targets of the parcellation scheme[55]. Studies are urgently needed to examine the relationships among different parcellation criteria and distinct imaging modalities, and finally achieve a reliable and reproducible map of the human PFC.

Anatomical Basis of Abnormalities in PFC Functional Connectivity in Schizophrenia

The anatomical substrate of functional connectivity has been an active topic of research. By measuring resting-state FC using fMRI and anatomical connectivity using DTI tractography in the same individuals, spatial consistency between anatomical and functional connectivity has been reported in some networks, such as the default-mode network (e.g., between the MPFC and the posterior cingulate cortex), the salience-processing network, and bilateral parietal–frontal task-activation networks in healthy populations[89-91]. Critically, connections among a spatially distributed and topologically central collective called the “rich club” are central to the integration of information among the different functional networks of the human brain[89]. These studies showed that FC is constrained by anatomical connectivity; however, they are not isomorphic. In general, FC is more prevalent than anatomical connectivity. And FC is context-dependent and easily changed, but anatomical connectivity is relatively stable[92]. Researchers have also begun to seek to understand the anatomical basis of aberrant FC in schizophrenia by combining DTI with fMRI. Both decreased and increased FC have been found in patients who show impaired integrity of white-matter tracts or altered structural network topology (for review, please see [92-94]). Decreased structural interconnectivity among rich club hubs (including the bilateral precuneus, superior frontal cortex, superior parietal cortex, and insula) may underlie the broad range of functional network abnormalities in patients with schizophrenia[95], and this may result in the altered functional dynamics and impaired global brain functioning. Although these findings are important, some open questions remain, such as whether anatomical dysconnectivity and functional dysconnectivity in schizophrenia share common biological substrates (e.g., common genetic factors); whether anatomical dysconnectivity and concomitant changes in FC in schizophrenia develop with progression of the illness; how increased FC between regions along with deficits in anatomical connectivity in schizophrenia can be understood; and whether increased functional connectivity has implications for the pathophysiology of schizophrenia or merely results from artifacts in different analyses applied to DTI and fMRI. All of these questions need to be explored. In addition, technical challenges, such as how to resolve crossing fibers and how to better detect relatively small fiber bundles[94], need to be solved.

Genetic Basis of the PFC Dysconnectivities in Schizophrenia

Impaired PFC function and structure have been found more frequently in unaffected relatives of schizophrenic patients, such as unaffected monozygotic twins, than in control individuals without such a family history[96]. This suggests that dysfunction of the PFC in schizophrenia may be controlled by genetic factors. However, it is unclear that PFC dysconnectivity in schizophrenia is also influenced

by genetic factors, due to the lack of twin and family studies that focus on functional or anatomical connectivity. Nevertheless, in healthy populations, pedigree studies have found evidence that genes control the functional and anatomical connectivity of the PFC[97, 98]. For example, Karlsgodt *et al*. found that the integrity of several white-matter tracts related to the PFC (anterior limb of the internal capsule, CB, superior fronto-occipital fasciculus, and superior longitudinal fasciculus) is heritable; furthermore, the integrity of the superior longitudinal fasciculus (a primary frontoparietal connection) shares genetic factors with performance of working memory, a heritable trait relevant to schizophrenia[97]. This evidence suggests that PFC functional and anatomical connectivity may be candidate endophenotypes of schizophrenia[99]. Therefore, some studies have sought to link PFC functional and anatomical connectivity with susceptibility genes for schizophrenia using a strategy called as imaging genetics. For instance, Liu *et al*. reported that the catechol O-methyltransferase (*COMT*) val158met polymorphism significantly modulates prefrontal-related FC within the default mode network because COMT plays a unique role in regulating prefrontal dopamine levels[100]. Liu *et al*. found that the functional and anatomical connectivity of the thalamus to the prefrontal cortex is impacted by *DISC1* (Disrupted-In-Schizophrenia 1) Ser704Cys[101]. Wang *et al*. found that carriers of the *KIBRA* (kidney and brain expressed protein) C-allele have a smaller gray-matter volume in the MPFC and bilateral dorsal anterior cingulate cortices and show higher functional synchronization in the same regions than T-allele homozygotes[16]. Given the complexity of the molecular genetics of cognitive function subserved by the PFC and the complexity of the genetic etiology of schizophrenia, understanding the mechanisms by which genetic variations that are associated with risk for schizophrenia impact PFC functional and anatomical connectivity remains a clinically important challenge. Some efforts have been made by exploring how interactions of multiple genes from the same signaling pathway (e.g., *COMT* and *DRD2* interaction[102]) affect resting-state FC. However, more data from imaging genetics in patients are needed. In addition, studies with non-invasive neuroimaging technologies, such as fMRI and dMRI, cannot clearly elucidate whether PFC dysconnectivity is related to the etiology of schizophrenia and how genes, the brain, and the disorder interplay. Genetically-modified animals are considered good models for the solution of these issues and some efforts are in progress[103]. By using genetically-modified mouse models of schizophrenia, researchers will be able to go beyond neuroimaging to look into the underlying mechanisms with disease-specific behavioral tests as well as gene-specific histological examinations, using interactive investigations that are not possible in human studies. Neuroimaging studies on genetically-modified mouse models of schizophrenia are likely to realize a relatively seamless translation of findings to this disorder, since neuroimaging allows the same biological target to be investigated in both humans and animals. Several novel genetic modification technologies have been developed recently. The CRISPR-Cas9 method is a breakthrough that can rapidly and efficiently generate transgenic mice with multiple modified alleles by direct injection of both single-guide RNA and mRNA encoding Cas9 into embryos[104, 105]. Using this novel technology, known schizophrenia-associated mutations can be introduced into mice and their effects on the brain investigated. Several genome-conserved, specified, and verified genetic mutations associated with the PFC and schizophrenia, such as *COMT*(Val158Met) and *DISC1*(Ser704Cys), may be candidates for this novel technology.

PFC Connectivity-Guided Non-invasive Brain Stimulation for Schizophrenia

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation and transcranial direct-current stimulation, have been shown to play a role in the non-invasive treatment of schizophrenia, especially for auditory hallucinations[106]. However, researchers have always been concerned about the precision of these techniques and their influence on other brain regions or networks[107]. A promising direction is to combine them with neuroimaging techniques in the context of the Brainnetome atlas. This atlas, with details of the subregions in the PFC and their connectivity patterns, will provide an accurate guide for the location of brain stimulation techniques and *a priori* knowledge of the possible effects of simulating a specific brain region. The combination of brain stimulation and neuroimaging techniques makes it possible to identify the causal effect of brain stimulation on brain activity of

interest in the stimulated region, which has important consequences for the interpretation of the effects of such stimulation. And this combination also provides a particular window into the effects of focal brain stimulation on remote, functionally connected brain regions[108]. In addition, armed with knowledge of the putative causal interactions among brain regions obtained by effective connectivity analyses (e.g., dynamic causal modelling[109]), it is possible to test the behavioral relevance of an effective fMRI connectivity network underlying a cognitive process by using brain stimulation to stimulate the regions identified by effective connectivity[107]. These advances will shed light on the causality behind the PFC dysconnection and symptoms/impaired cognitive functions in schizophrenia, and provide objective valuation for the non-invasive treatment of schizophrenia.

In summary, the variability in the PFC dysconnectivity patterns across patients is associated with the severity of both cognitive impairments (such as impaired working memory) and cardinal symptoms (such as auditory verbal hallucinations), suggesting that these distinct patterns of connectivity might differentially contribute to schizophrenic symptoms. However, the current roughly-defined PFC subregions hamper precise location of these impairments and symptoms. Future studies with fine-grained parcellation of the PFC may provide a clearer understanding of the PFC in schizophrenia. Furthermore, the anatomical and genetic bases of PFC dysconnectivity in schizophrenia need to be determined. The causality behind the PFC dysconnection and symptoms/impaired cognitive functions in schizophrenia needs to be clarified. Further understanding of the implications of PFC dysconnectivity for schizophrenia may benefit from the integrated knowledge in the Brainnetome atlas, multimodal imaging techniques, imaging genetics, and genetically-modified animal models in the framework of the Brainnetome[83].

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