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Converging models of schizophrenia – Network alterations of prefrontal cortex underlying cognitive impairments

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ABSTRACT

The prefrontal cortex (PFC) and its connections with other brain areas are crucial for cognitive function. Cognitive impairments are one of the core symptoms associated with schizophrenia, and manifest even before the onset of the disorder. Altered neural networks involving PFC contribute to cognitive impairments in schizophrenia. Both genetic and environmental risk factors affect the development of the local circuitry within PFC as well as development of broader brain networks, and make the system vulnerable to further insults during adolescence, leading to the onset of the disorder in young adulthood. Since spared cognitive functions correlate with functional outcome and prognosis, a better understanding of the mechanisms underlying cognitive impairments will have important implications for novel therapeutics for schizophrenia focusing on cognitive functions. Multidisciplinary approaches, from basic neuroscience to clinical studies, are required to link molecules, circuitry, networks, and behavioral phenotypes. Close interactions among such fields by sharing a common language on connectomes, behavioral readouts, and other concepts are crucial for this goal.

Contents

Abbreviations: BA, Brodmann's area; PTSD, post traumatic stress disorder; GABA, gamma-amino butyric acid; 5-HT, 5-hydroxytryptamine; NMDA, N-methyl-D-aspartic acid; E/I balance, excitatory/inhibitory balance; PFC, prefrontal cortex; MD, mediodorsal; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; PL, prelimbic; IL, infralimbic; PV, parvalbumin; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; MEG, magnetoencephalography; EEG, electroencephalography; FPCN, fronto-parietal control network; DAN, dorsal attention network; CON, cingulo-opercular network; DMN, default mode network; G × E, gene–environment interactions.

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1. Introduction: neurobiology of cognitive impairment as a convergent point to understand schizophrenia

Q3 Schizophrenia is a psychiatric disorder characterized by behavioral phenotypes including positive symptoms, negative symptoms, cognitive impairment, and disorganized speech/behavior (APA, 2014). It typically begins with an onset of psychosis during adolescence to early adulthood. While some patients respond well to currently available treatments, a substantial number remains treatment-resistant, suffering recurrent episodes of psychosis and eventually entering a chronic phase (Lieberman et al., 2008).

Cognitive impairment is considered as a core feature of schizophrenia (Kahn and Keefe, 2013), which manifests even before clinical diagnosis, during the prodromal phase of the disorder (Cornblatt et al., 1998, 2003; Erlenmeyer-Kimling et al., 2000). In fact, Kraepelin originally described the disease as dementia praecox, in which he recognized a generally slow cognitive decline as the hallmark of the disorder, that starts almost a decade prior to the onset of psychosis during adolescence (Kraepelin, 1893). There is heterogeneity among patients in the degree of cognitive changes throughout the course of the disease (Mesholam-Gately et al., 2009). Since spared cognitive function correlates positively with improved prognosis and functional outcome (Bowie and Harvey, 2006a,b; Green, 1996, 2006; Keefe, 2008; Keefe et al., 2007), treatments to enhance cognitive function are an important therapeutic strategy. However, effective pro-cognitive medications have yet to be developed (Geyer, 2010; Geyer et al., 2012). In order to develop such treatments, it is critical to understand the neurobiology underlying cognitive function (Young et al., 2012).

Schizophrenia is currently diagnosed solely by observable phenotypes (APA, 2014) without any reliable diagnostic biomarkers. It is likely that diverse pathogenic pathways are involved in the disorder (Insel, 2010). Since the prefrontal cortex (PFC) is a key brain region involved in cognitive functions (Fuster, 2008), it is possibly a converging biological system underlying cognitive dysfunction in schizophrenia. In this review, we will build a conceptual framework to understand cognitive impairment in schizophrenia. Better understanding of disturbance of brain networks involving PFC at the molecular and cellular levels will hopefully help us to formulate working hypotheses on schizophrenia pathogenesis and pathophysiology that can be tested in animal models and patient-derived materials. The outcomes of those studies will lead to novel therapeutics for cognitive dysfunction in schizophrenia as well as early diagnosis and intervention (Fisher et al., 2013; Lieberman et al., 2008). In this effort, it is crucial to compare human studies and animal works side by side (Sawa and Seidman, 2014). We emphasize that understanding structural and functional similarities and differences between humans and animal models is crucial for having clear perspectives on which aspects of cognitive functions we can (and cannot) model in animals in the context of schizophrenia.

2. Neurobiological framework for cognitive function: PFC

2.1. Structure and functions of PFC

The PFC includes the frontal cortex without motor cortex. It is a key brain region involved in executive functions, such as working memory, attention, and decision making, as well as emotional processing, including affection, emotion, and social behavior (Fuster, 2008). These functions are important in daily living (e.g., Bowie and Harvey, 2006a). Importance of frontal brain is illustrated by the case of Phineas Gage who showed permanently changed personality after a devastating head injury that damaged the frontal area of his brain (Damasio et al., 1994). Subsequently, Jacobson and many other researchers discovered that monkeys with bilateral lesions to the dorsolateral PFC (DLPFC) showed impaired working memory (Jacobsen, 1936, and reviewed in Arnsten, 2013). The monkeys with PFC lesions also tend to be easily

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