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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.

Keywords

Prefrontal cortex; circuitry formation; circuitry maturation; cognitive function; networks; brain imaging; oscillation

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

Schizophrenia is a psychiatric disorder characterized by behavioral phenotypes including positive symptoms, negative symptoms, cognitive impairment, and disorganized speech/

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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; Cornblatt et al., 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 distracted, inflexible, perseverative, and hyperactive (reviewed in Arnsten, 2013).

2.1.1. Definition, anatomical considerations, and connectivity

Definition: The PFC was originally defined as the frontal cortex containing granular layer IV (Fuster, 2008). Based on the cytoarchitecture, Brodmann defined the area praefrontalis as area 11 within the large “regio frontalis”, which included his areas 8, 9, 10, 11, 12, 13, 44, 45, 46 and 47 (Brodmann, 1909; Fuster, 2008; Preuss, 1995; Rose and Woolsey, 1948; Uylings et al., 2003). Upon further analysis of connections and functions, the human/primate PFC consists of a much larger area containing both granular and agranular areas (Table 1). Efforts have been made to define the rodent PFC, but anatomically equivalent regions in rodents are agranular. Thus, after many works comparing between primates and other animals, a more sensible criterion for the PFC that can be extended into other species beyond human/primates has been the distribution of thalamic fibers and as such, the PFC is defined as the part of frontal cortex connected with the mediodorsal (MD) nuclei of the thalamus (Fuster, 2008; Rose and Woolsey, 1948; Uylings and van Eden, 1990; Wise, 2008). In addition to the connections with the MD nuclei, the PFC has connections with diverse brain regions and can be subdivided into several regions that have different connections and functions.

Passingham and Wise, in their recent book (Passingham and Wise, 2014), divided the primate PFC into medial, orbitofrontal, caudal, ventral and dorsal areas (see areas in Table 1). It is a convenient overview, and we will briefly summarize these subregions and their proposed functions in primates. The medial PFC area has connections with the hippocampus, amygdala, and premotor cortex, all of which provide information on behavioral outcomes of previous actions, which would serve as internal signals. The region chooses future actions based on these internal signals. The orbitofrontal PFC area receives sensory stimuli associated with ongoing outside world events, including olfactory, visceral and gustatory information through the insular cortex, and somatosensory and visual information from other cortical regions. In addition, this region has connections with the amygdala that provides updated information on the value of the events. Among these many sensory stimuli, the region evaluates and chooses objects as goals for future actions, based on their associations with outcomes in relation to current needs. These two areas contain both granular and agranular regions. The caudal PFC area has connections with the orbitofrontal PFC area providing learned values for the objects, and with other cortical regions including both dorsal and ventral visual stream, and oculomotor nuclei, all of which provide visual information. Based predominantly on visual information, the region searches for and orients attention towards valuable goals. The ventral PFC area has connections with visual and auditory cortices, orbitofrontal PFC area, and premotor cortex, and generates goals based on visual and auditory contexts. The region also sets abstract goals. The dorsal PFC area has many connections with cortical areas that process visual information as well as orbitofrontal PFC area, ventral PFC area, and premotor cortex. By integrating information from these areas on the recent events, the region generates appropriate goals for current

context and desired outcomes. Based on this framework, they proposed that the overall role of the PFC is to collect information for the current context, goals, and past behavioral outcomes, and to formulate goals, set objects, and make decisions on future actions (Passingham and Wise, 2014).

Primate PFC (Table 2 and Figure 1): The primate PFC can be divided into lateral (divided further into dorsal and ventral regions), orbitofrontal, medial, and cingulate areas, based on anatomical characteristics (Carmichael and Price, 1994; Fuster, 2008; Passingham and Wise, 2014; Teffer and Semendeferi, 2012). The ventrolateral PFC (VLPFC) and orbitofrontal cortex (OFC) predominantly receive inputs from the magnocellular part of the MD nuclei of the thalamus (medial part of MD), while the dorsolateral PFC (DLPFC) mainly receives inputs from the parvocellular part of the MD nuclei (lateral part of MD) (Barbas et al., 1991; Giguere and Goldman-Rakic, 1988; Goldman-Rakic and Porrino, 1985). The anterior cingulate cortex (ACC) has mixed patterns: the dorsal ACC receives inputs from lateral MD, while the ventromedial cingulate receives inputs from medial MD (Giguere and Goldman-Rakic, 1988; Vogt and Pandya, 1987; Vogt et al., 1987). MD neurons mainly target cortical layers III and IV in the PFC, while PFC neurons in deep layers V and VI project back to the MD nuclei (Giguere and Goldman-Rakic, 1988; Xiao et al., 2009). The PFC makes connections with the striatum and thalamus, and each PFC subdivision described below makes a segregated loop involving a combination of the cortex, striatum, and thalamus (Chudasama and Robbins, 2006; Ferry et al., 2000). The PFC also makes connections with other subcortical areas, including the amygdala, hypothalamus, and midbrain (Ghashghaei and Barbas, 2002; Ongur and Price, 2000). The PFC receives fibers from association, motor, and sensory cortices, and makes connections with the cingulate and hippocampus (Barbas, 2007; Barbas and Rempel-Clower, 1997; Rempel-Clower and Barbas, 2000). There is layer preference for these cortico-cortical fibers in targeting (either layers II/III or V/VI, depending on the cortical regions) (Barbas, 2007; Barbas and Rempel-Clower, 1997; Rempel-Clower and Barbas, 2000).

The DLPFC (BA10, 8, 9, 46) mediates many aspects of cognitive/executive behaviors, such as working memory, behavioral inhibition, cognitive flexibility, planning, abstract reasoning, and decision making (Chudasama, 2011; Fuster, 2008; Passingham and Wise, 2014), and plays a role in attention and motivation. To mediate spatial working memory, the DLPFC receives visuospatial inputs from the parietal cortex (Cavada and Goldman-Rakic, 1989a, b), and sends outputs to premotor areas and basal ganglia (Bates and Goldman-Rakic, 1993; Goldman-Rakic, 1987; McGuire et al., 1991a, b; Miller and Cohen, 2001; Selemon and Goldman-Rakic, 1985).

The VLPFC (BA44, 45, 47) is situated at the end of the ventral visual stream, and integrates information for object recognition and form representation (Petrides et al., 2012). This region is important for selecting goal-relevant information (Kaldy and Sigala, 2004; Petrides et al., 2012; Verrico et al., 2014; Wilson et al., 1993). The left side of the VLPFC is also involved in cognitive control of memory (Badre and Wagner, 2007). Furthermore, Broca's area, which includes BA44 and 45 typically in the left hemisphere, is a motor language area (Broca, 1863; Grodzinsky and Santi, 2008).

The OFC (BA47, 11, 12, 13, 14, 10) is involved in sensory integration to represent affective values of reinforcers, decision making and expectations based on reward/punishment, and behavioral flexibility (Murray et al., 2007; Ongur and Price, 2000). These functions are important for associative learning (Ongur and Price, 2000) as well as for reversal learning related to rewards (Bissonette et al., 2013; Chudasama, 2011). This region is also involved in emotional motivation and social behavior (Fuster, 2008) and is implicated in many other cognitive functions (Stalnaker et al., 2015). The OFC can be divided into lateral and medial parts, each having connections with different brain areas (Ongur et al., 2003). OFC has direct and indirect connections with the hippocampus, amygdala and hypothalamus (Esmaeili and Grace, 2013). Recently, the insular cortex has gained much attention since it is a part of the brain network that is important for salience processing, a function that is altered in schizophrenia (Palaniyappan et al., 2013). Although the insular cortex per se may not be included in the PFC, its anterior agranular portion has strong connections with the OFC and can be considered as a part of OFC functionally (Table 1, and see also rodents PFC part).

The medial PFC (mPFC)(BA14, 10, 8, 9, these areas are continuous with either DLPFC or OFC) and ACC (BA32, 33, 24, 25, 26) are situated along the medial wall of the frontal lobe. The medial PFC makes connections with the amygdala and hippocampus, and is important for fear conditioning (Ghashghaei and Barbas, 2002; Ongur and Price, 2000). The ACC is involved in mood, emotional regulation, and social behavior (Fuster, 2008; Passingham and Wise, 2014). The ACC is also involved in error/conflict detection and response selection (Chudasama, 2011; Rushworth et al., 2007). The dorsal part of ACC (BA32) connects with the cortex, and is involved in cognition, whereas the ventral part (BA24) connects with the amygdala, nucleus accumbens, hypothalamus, and insular cortex, and is involved in emotion and reward association (Fuster, 2008; Vogt and Pandya, 1987; Vogt et al., 1987). The paracingulate cortex, including a part of BA32, is involved in theory of mind (Vogt and Paxinos, 2014).

Rodent PFC (Table 2 and Figure 1): There have been lots of efforts to resolve conflicts/confusions regarding regionalization in the rodent PFC (Van De Werd and Uylings, 2014; Vogt and Paxinos, 2014; Watson et al., 2011). The rodent PFC is located over the medial, orbital, and insular surfaces of the rostral cerebral hemispheres and consists of two major frontal areas with which the MD nuclei have connections. One is the medial area in the upper edge and medial surface of the hemispheres (including the frontal area, medial orbital, ventral orbital, prelimbic, infralimbic, and anterior cingulate areas). The other is the inferolateral area in the lower and lateral aspects of the hemispheres, superior to the rhinal sulcus (including the insular, lateral orbital, and frontal areas)(Brown and Bowman, 2002; Dalley et al., 2004). Neither area contains a clear granular layer IV (Wise, 2008). MD neurons send fibers to layers I and II/III of the PFC, while PFC neurons send fibers back to the MD nuclei from deep layers V and VI (Heidbreder and Groenewegen, 2003). Pyramidal neurons in layers V and VI also send axons to other subcortical regions (Gabbott et al., 2005). Like in primates, each region has discrete connections involving different set of subregions of the striatum and thalamus, forming a distinct loops that may be associated with specific functions (Chudasama and Robbins, 2006; Dalley et al., 2004; Ongur and

Price, 2000). There are also cortico-cortical fibers that show layer preference in targeting (Vogt and Miller, 1983).

The medial PFC (mPFC) is divided into three regions, prelimbic (PL) (middle part of the anterior portion, BA32), infralimbic (IL) (ventral part of the anterior portion, BA25), and anterior cingulate (AC) (dorsal part of the anterior portion, BA24, and both dorsal and ventral parts of the posterior portion) (Chudasama, 2011; Dalley et al., 2004; Heidbreder and Groenewegen, 2003). When BA32, 24, 25 are compared to the primate equivalents, there are both similarities and differences (Vogt et al., 2013; Vogt and Paxinos, 2014). The dorsal regions of mPFC make connections with the dorsal striatum, whereas the ventral regions make connections with the ventral striatum and amygdala. In both cases, the striatum makes connections with the ventral pallidum and the medial part of the MD nuclei of the thalamus, forming the medial network (Ongur and Price, 2000). The mPFC is involved in both cognitive and autonomic visceromotor functions (Murray et al., 2007; Ongur and Price, 2000). The dorsal region is implicated in memory for motor responses including response selection and temporal processing of information, whereas the ventral region is implicated in attention, including attention to stimulus features and task contingencies, attention set shifting, and behavioral flexibility, all of which are important for decision making (Bissonette et al., 2013; Chudasama and Robbins, 2004; Dalley et al., 2004; Heidbreder and Groenewegen, 2003; Vertes, 2006). In addition, the dorsal ACC is involved in social behavior, avoidance behavior, and emotionality (Watson et al., 2011), and the ventral mPFC is involved in fear-related behavior (Watson et al., 2011).

The OFC is divided into medial, ventrolateral and lateral regions (Dalley et al., 2004; Ongur and Price, 2000). These regions have connections with the ventromedial and lateral striatum, which in turn make connections with the ventral pallidum, and the lateral part of the MD nuclei, forming the orbital network (Ongur and Price, 2000). This loop is important for reversal learning and choice involving delayed information (Dalley et al., 2004; Murray et al., 2007; Ongur and Price, 2000). The OFC also has strong connections with the amygdala (Watson et al., 2011). The OFC mediates many aspects of reward association that underlie discriminative behavior (Murray et al., 2007; Ongur and Price, 2000). In rodents, the agranular insular cortex is adjacent to the OFC and situated laterally in the ventrolateral frontal cortex. This region is important for the integration of sensory, autonomic, and visceral information that is transmitted to other PFC subregions (like OFC) and subcortical areas (Gogolla et al., 2014).

2.1.2. Functional subdivisions—Morphological comparisons between primates and rodents, like cytoarchitecture and receptor binding, to identify equivalent regions (Ongur and Price, 2000; Vogt et al., 2013) have revealed differences in their PFCs: e.g., there are no granular areas in rodents, and the primate PFC is spread over to indulge into both lateral and medial surfaces of the hemispheres, but the rodent PFC is not. Therefore, in addition to morphology, identifying functionally equivalent regions together with a connectivity analysis between brain regions may be more appropriate. However, it should be noted that superficially similar behavioral phenotypes may not be equivalent between primates and rodents (Brown and Bowman, 2002; Wise, 2008) and that there are several fundamental differences (Preuss, 1995; Rilling and Insel, 1999; Wise, 2008). Despite of these cautions

and limitations, functionally equivalent regions in the PFC between primates and rodents have been mapped by numerous lesion studies and others (Arnsten, 2013; Heidbreder and Groenewegen, 2003). In Table 2, we summarize the current findings comparing primates and rodents. These should be combined with the efforts to identify equivalent functional assays between humans and animals, e.g., Research Domain Criteria (RDoC), a recent effort by the National Institute of Mental Health (NIMH), which aims to identify behavioral domains that can be studied across traditional definitions of psychiatric disorders (discussed in the last section and Table 7)(Cuthbert, 2014; Insel, 2014). We will briefly summarize functional subdivisions of PFC in a task-related manner.

Working memory involves the maintenance and integration of goal relevant information to guide decision making and behavior (Brown and Bowman, 2002; Chudasama and Robbins, 2006; Fuster, 2008). In primates, spatial working memory is mediated by the DLPFC (Chudasama, 2011), whereas object working memory is mediated by the VLPFC (Verrico et al., 2014). In rats, the mPFC (PL and ACC) is important for spatial working memory.

Reversal learning requires animals to reverse learned associations between actions and subsequent rewards or punishments, and involves behavioral flexibility (Chudasama and Robbins, 2006; Young et al., 2011). In primates, this behavior requires the OFC and ventromedial PFC (VMPFC) (Bissonette et al., 2013; Chudasama and Robbins, 2006), while in rodents, it is mediated by the OFC (Roesch et al., 2009; Schoenbaum et al., 2009; Takahashi et al., 2011b)(all these regions have connections with the amygdala that determines the value of events). Readers are also encouraged to refer to an excellent review on other forms of decision-making tasks including the reinforcer devaluation in which animals adjust to changes in reward value, and the delay discounting in which animals make choices between immediate small rewards and later larger rewards (Chudasama, 2011).

Attention is also a crucial behavior by which animals allocate resources for efficient information processing and focus on more important and relevant environmental events. There are several types of attention, like selective, divided, and sustained attention, each associated with different PFC regions (for review, see Chudasama, 2011). Attention is measured by tasks such as the five choice reaction time task using a touch panel screen for both primates and rodents (Maddux and Holland, 2011). In humans, the DLPFC and ACC are involved in attending to multiple feature attributes (Chudasama, 2011). In rats, the mPFC including the ACC and PL are required for response accuracy. In addition, PL lesions increase perseverative responses, while ventral IL lesions increase premature responses (Chudasama, 2011).

Set shifting requires the recognition of changes in the dimension of cues, inhibitory control, and decision making. There are two kinds of set shiftings in dimension of cues: one is an extra-dimensional shift in which relevant cue is changed from one dimension to another, e.g., from shape to color, and the other is an intra-dimensional in which relevant cue is changed, e.g., from a triangle to a square, but within the same dimension (in this case, the dimension is shape). In primates, the DLPFC and VLPFC are important for extra-dimensional shifts, and the ACC for error/conflict detection and intra-dimensional shifts

(Bissonette et al., 2013). In rodents, the mPFC is important for extra-dimensional shifts and the ACC for intra-dimensional shifts (Bissonette et al., 2013).

Social behavior includes a wide range of behaviors, such as maternal nurturing, juvenile plays among siblings, mating, and aggression. Basic social interactions between adult animals of the same sex require social motivation, recognition of social cues, social memory, processing of reward, fear, and emotions, and decision making (Millan and Bales, 2013). In primates, many brain regions, in particular, the OFC, ACC, amygdala, and hippocampus are involved (Fuster, 2008; Rudebeck et al., 2008), while in rodents, similar brain regions including the OFC and dorsal ACC are involved (Millan and Bales, 2013; Watson et al., 2011).

2.2. Components and connectivity of PFC

Work from the laboratories of Patricia Goldman-Rakic, Amy Arnsten, and many others have shed light on the anatomy and physiology of the PFC (Arnsten, 2013). In particular, primate studies have identified the main cellular components that comprise the microcircuitry supporting working memory as well as the crucial role of neuromodulation. In this section, we will overview the principles of PFC circuitry.

2.2.1. Excitatory and inhibitory neurons: Formation and maturation—There are two major types of neurons that make up the local circuitry in the PFC (Zaitsev and Lewis, 2013): Excitatory neurons that use glutamate as the neurotransmitter make up 70–75% of the neuronal population, while inhibitory interneurons that use GABA as the neurotransmitter consist of 25–30% of neurons in primate brains (Hendry et al., 1987; Hornung and De Tribolet, 1994). During development, excitatory neurons migrate from the subventricular zone to the cortical surface, and mature to form dendrites and synapses (Fishell and Heintz, 2013; Geschwind and Rakic, 2013). Inhibitory interneurons migrate tangentially from the ganglionic eminence to the cortex, and form synapses with pyramidal and other neurons (Marin and Muller, 2014).

There are several subgroups of inhibitory interneurons that make synapses on distinct cellular compartments of pyramidal neurons, major excitatory projection neurons. Fast spiking, non-adapting, parvalbumin (PV)-positive interneurons are one class of interneurons in PFC, comprising around 25% of interneurons in the DLPFC, (Kawaguchi, 1993; Lewis and Gonzalez-Burgos, 2008). They include basket cells, which target the soma and proximal dendrites of pyramidal neurons, and chandelier cells, which target the axon initial segment of pyramidal neurons (DeFelipe et al., 1989; Gorelova et al., 2002; Kawaguchi et al., 1995; Krimer et al., 2005; Lewis and Lund, 1990; Sesack et al., 1998; Williams and Lacaille, 1992; Zaitsev et al., 2005). The PFC also contains regular-spiking, adapting, calbindin/calretinin-positive interneurons that target distal dendrites of pyramidal neurons in layers I and II (Krimer et al., 2005; Zaitsev et al., 2005) as well as somatostatin-positive interneurons that target distal dendrites of pyramidal neurons in layers II, V and VI (de Lima and Morrison, 1989; Fino and Yuste, 2011; Kawaguchi and Kubota, 1996; Lewis and Gonzalez-Burgos, 2008; Ma et al., 2006; McGarry et al., 2010). Another subclass identified recently is a group of interneurons that express 5-HT_{3aR}, a receptor for 5-HT (Rudy et al.,

2011). Since the classification of interneurons is far more complex than described here, a new nomenclature has been proposed based on six axonal features (DeFelipe et al., 2013). Mechanisms determining differentiation of these diverse cell types have just begun to be unveiled (Kepecs and Fishell, 2014).

Many molecular components involved in neurogenesis, cell migration, specific targeting, and specific synapse formation of both excitatory and inhibitory neurons have been identified, some of which have been implicated in schizophrenia (e.g., ERBB4/NRG1, Del Pino et al., 2013; Flames et al., 2004; DISC1, Brandon and Sawa, 2011; some synaptic molecules, Hayashi-Takagi et al., 2014; O'Dushlaine et al., 2011; Pocklington et al., 2014).

2.2.2. Local circuitry formation and maturation—Neurons initially make contacts with many other neurons during development, followed by refinement or “pruning” of connections (Stoneham et al., 2010; Tessier and Broadie, 2009) possibly to enhance the signal to noise ratio during information processing (Collin and van den Heuvel, 2013; Yuste, 2011). Structural and functional remodeling of the circuitry takes place through activity-dependent synaptic maturation (Doll and Broadie, 2014; West and Greenberg, 2011). In addition to synaptic pruning, there are changes in synaptic size and strength at individual synapses (Whitt et al., 2014).

Maturation of PV-positive interneurons depends on inputs from pyramidal neurons (Donato et al., 2013; Fuchs et al., 2007; Kepecs and Fishell, 2014). PV-positive interneurons also control spiking of pyramidal neurons and are strongly interconnected with each other to promote synchronous activity. Through these processes, the circuitry reaches an appropriate excitatory/inhibitory (E/I) balance and forms a functional unit, called a “module.” Molecular mechanisms of how diverse interneuron populations are integrated into the local circuitry have been characterized in detail (e.g., pentaxin, Pelkey et al., 2015).

2.2.3. Connectivity formation, maturation, and neuromodulation

Connectivity formation: In addition to the local circuitry within the PFC, connections of the PFC with other brain areas are crucial for cognitive function. Imaging studies have demonstrated that in humans, coordinated connections through association pathways are important for several cognitive tasks (Van Essen et al., 2013; Van Essen et al., 2012). In rodents, by taking advantage of readiness for developmental manipulation, many studies have elucidated the connectivity of the PFC underlying cognitive functions (and nowadays, we have more sophisticated methods of circuit manipulation, e.g., optogenetics). For example, gestational administration of the mitotoxin, methyl azoxymethanol acetate (MAM), has been shown to induce developmental disruptions in the brain histologically and neurophysiologically, leading to behavioral deficits similar to those observed with schizophrenia in humans (Lodge, 2013). Anthony Grace's group has characterized this model by *in vivo* recordings of stimulation-induced responses in several brain regions, and has shown that connections among the mPFC, nucleus accumbens, amygdala, and hippocampus are important for motivational drive, context-dependent decision making, and affective processing (Esmaeili and Grace, 2013).

As noted above, connections of the PFC with other areas show some layer preferences in targeting (Fuster, 2008). In addition, cortico-cortical and -subcortical connections have regional preferences as well. For example, in the rat mPFC, the IL and ventral PL areas send more axons to the ventral striatum, whereas the dorsal AC area sends more axons to the dorsal striatum. The dorsal PL area sends axons equally to the ventral and dorsal striatum. The IL and PL areas send axons to the basolateral amygdala, whereas the dorsal AC area does not. All areas send about equal numbers of axons to the lateral hypothalamus (Gabbott et al., 2005). These specific connections ensure specific localization of functional domains in the PFC subregions.

Circuitry maturation: As with the PFC local circuitry, the formation and maturation of connectivity among brain areas also occurs in two phases: the initial formation of connectivity takes place during the prenatal and perinatal periods, followed by a maturation of global circuitry to form functional networks, which continues until young adulthood (Hoff et al., 2013; Uhlhaas and Singer, 2012). The latter process requires modulation involving synaptic plasticity, which would achieve “work together, wire together” by selecting sets of wiring among existing synapses through modulation of synaptic strength. Since long-range connections affect inputs to the local circuitry, the formation and maturation of such connections may be tightly linked to the maturation of local circuitry (Figure 2). The degree of myelination of long-range connections can also modulate the functional strength of the connections as the degree of myelination determines the speed of information transmission along the long-range connections, which in turn affects local circuitry maturation (Nave, 2010). Considering these, myelination of long-range connections and synaptic maturation of local circuitry are most likely interrelated with each other in terms of timing (Nave, 2010)(Figure 2). It is interesting to note that white matter itself also shows plasticity (Fields, 2008). For example, extensive training enhances white matter integrity, even in adults (Bengtsson et al., 2005; McKenzie et al., 2014). It is also interesting that myelination in association cortices continues through mid-late twenties (Hoistad et al., 2009).

The coordinated sequences of biological events during PFC maturation is not yet characterized at molecular and cellular levels in detail (Catts et al., 2013), and comprehensive gene expression studies may give us some insights into the developmental processes that underlie the maturation of PFC local circuitry (Miller et al., 2014). We have begun to clarify these by characterizing a sequence of gene expression patterns during mouse PFC development (Ueda et al., 2015, and Figure 3). The study showed that the developmental processes of PFC proceed sequentially, and interneuron maturation and myelination take place relatively later in the maturation (by postnatal day 35), supporting the idea that myelination is correlated with local circuitry maturation. But even after postnatal day 35, the circuitry is still immature and continues to further mature during adolescence (based on the responsiveness to MK801 injection measured by microdialysis, at postnatal day 42, the PFC does not show the adult like response which is observed at postnatal day 56)(Ueda et al., 2015). The maturation of PFC circuitry is slower than in any other brain regions (e.g., Teffer et al., 2013; Ueda et al., 2015). Even so, the window of plasticity during PFC development (critical period) eventually closes due to various mechanisms (Ko et al.,

2013; Woo, 2014), e.g., the appearance of perineural nets comprised of chondroitin sulfate proteoglycans, nogo receptor/myelin inhibitors, and lynx proteins (Nabel and Morishita, 2013). The duration of plasticity of the circuitry may determine the time period susceptible to various insults during development (Figure 3). Interestingly, social isolation, an environmental insult, during the early phase of development affects myelination, whereas social isolation during the late phase affects the dopamine system, reflecting the timing of specific biological processes taking place (Makinodan et al., 2012; Niwa et al., 2013; Ueda et al., 2015, Figure 3). In primates, development of glutamatergic and GABAergic circuits has been studied, and sensitive periods for vulnerability to schizophrenia have been mapped as well (Hashimoto et al., 2009; Hoftman and Lewis, 2011).

Neuromodulation: In addition to glutamate and GABA, two major transmitters involved in the local circuitry, neuromodulators like norepinephrine and 5-HT, and especially dopamine, are required for network formation and functions. These neuromodulators, through the volume transmission (as opposed to the conventional 1:1 synaptic transmission) modulate neuronal activity in the area more globally. Arnsten's work has provided the evidence on the role of neuromodulator-induced cAMP in regulating local circuitry activity, i.e., changing the gain of the system to optimize goal-directed behavior (dynamic network connectivity, Arnsten et al., 2010; Gamo and Arnsten, 2011). It has also been proposed that the local E/I balance is regulated by neuromodulation (Anticevic et al., 2012). In fact, dopamine modulates fast spiking interneurons through dopamine D2 receptors in postnatal day 45–50 rat brains (O'Donnell, 2010). This D2 receptor activation leads to the attenuation of local excitatory synaptic transmission by recruiting GABAergic activity in the circuitry during and after adolescence (Tseng et al., 2007; Tseng and O'Donnell, 2007a, b). Furthermore, plasticity of the dopamine system itself is modulated by 5-HT (Benes et al., 2000). It is notable that 5-HT_{3aR} is one of interneuron markers (Rudy et al., 2011) and 5-HT has been implicated in modulating neural oscillations (see below).

Distribution of the neuromodulatory system shows region and layer specificity in the PFC, which may vary among species. In human newborns, norepinephrine and dopamine levels are higher in the PFC than in the posterior association cortex, while the reverse is true for 5-HT (Fuster, 2008). After birth, cortical monoamines increase gradually to reach their maximum levels at about 3 years of age, and decline thereafter to settle at adult levels (Fuster, 2008). In primates, the dopamine concentration is higher in layer III than in other layers (Berger et al., 1988; Fuster, 2008; Goldman-Rakic and Brown, 1981, 1982; Levitt et al., 1984; Lewis et al., 1992), while in rats, norepinephrine and dopamine levels are higher in both superficial and deeper layers of the PFC (Berger et al., 1976; Berger et al., 1985; Descarries et al., 1987; Gamo and Arnsten, 2011; Miner et al., 2003).

3. Neurobiological framework for cognitive functions: Functional network formation

Cognitive functions underlying perception, attention, and executive processes are based on the coordinated interactions of large numbers of neurons/modules that are distributed within and across different brain areas. Such interactions are achieved by recruiting several brain

areas to form networks that support certain brain functions and by increasing the coupling among neurons that are functionally relevant for a specific task and reducing the strength of connections that are task irrelevant (neurons that work together become firing together) (Palaniyappan et al., 2013). Importantly, this coupling is transient: the coordination of widely distributed neurons is achieved in millisecond order, forming a large scale of synchronization of neuronal activity and dynamically configured functional networks in the brain (Uhlhaas et al., 2009). In this section, we will overview functional network formation and maturation that support cognitive functions.

3.1. Brain imaging

3.1.1. Functional networks in the human brain—Network formation has been extensively studied in humans using diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) imaging techniques (van den Heuvel and Fornito, 2014). Since neuronal ensembles coordinate brain activity to form synchronized oscillations in the networks, generating small electrical waves that can be recorded by magnetoencephalography (MEG)/electroencephalography (EEG), characterizing the oscillation pattern by these methods is also used to study network formation (Uhlhaas and Singer, 2013, and see below). DTI enables us to gain insights into the structural organization of the brain, such as white matter projections at the microscopic level (Ellison-Wright and Bullmore, 2009; Kubicki et al., 2005), while fMRI measures changes in the local blood flow which correlates with the activity of the brain area (Ogawa et al., 1990; Roy and Sherrington, 1890). Functional MRI also enables us to examine widespread distributions of functional organization in the brain (Greicius, 2008) by characterizing a statistical dependence between spatially distinct neurophysiological signals (correlation of fluctuation/oscillation of the signals) (Friston et al., 1996). Such analyses can be performed during both cognitive task performance and task-free resting states (Fornito et al., 2012; Fox and Raichle, 2007).

Theoretical models have been used to explain how the architectural organization of neural connectivity underlies brain function (Bullmore and Sporns, 2009). One model describes the brain as a graph consisting of nodes (neurons and/or brain regions) linked by edges (interconnecting synapses/axons) (Bullmore and Sporns, 2009). Nodes with a central placement in the network, displaying a high degree of connections and high centrality, are called as hubs (Buckner et al., 2009; Sporns et al., 2007). These brain hubs are individually rich in connectivity and tend to be more densely interconnected among themselves than nodes of a lower degree, suggesting a hierarchical associative organization in human brain networks. These brain hubs together form a central rich club or core (van den Heuvel and Sporns, 2011). Because of their central locations in the overall network, the brain hubs seem to play a pivotal role in global brain communication and serve as putative central points for neuronal convergence and integration of information. These hub nodes emerge and mature during development (node development), and the development of the nodes is coupled with the development of brain functions (see below). Some PFC regions such as the superior frontal area serve as important nodes among the rich club organization, a crucial coordinated structure for network activity in the brain (van den Heuvel and Sporns, 2011).

3.1.2. Networks associated with behavioral mode—There are several networks that are associated with certain tasks, representing the flow of information processing involving several brain areas (Table 3). For example, externally directed cognitions, a set of cognitive processes that involves representing an external source of information to choose a goal or action (e.g., working memory that involves encoding, manipulating, and retrieving information in the service of a goal), are typically associated with activity in a distributed network encompassing fronto-parietal cortical regions. These networks include the fronto-parietal control network (FPCN) associated with functions such as salience processing, the dorsal attention network (DAN) associated with focused attention, and the cingulo-opercular network (CON) associated with executive control functions, all of which include PFC regions (Dosenbach et al., 2008; Dosenbach et al., 2007)(Table 3). There is also a set of brain regions called the default mode network (DMN) that is associated with internally directed cognitions, a set of cognitive processes that involve self-relevant information processing and spontaneous cognition (Buckner et al., 2008; Raichle et al., 2001). DMN activity is high when the mind is not engaged in specific behavioral tasks and is low when the brain is engaged in focused attention on the external environment (Fox et al., 2005). This network includes brain regions centered around the anterior and posterior medial cortex, bilateral temporal lobes, as well as the superior frontal and parietal cortices (Barch and Ceaser, 2012).

The presence of these distinct networks, each associated with different functions, implies another important notion that network has to be switched around depending on the tasks in which the brain is engaged. In fact, the DMN is suppressed when goal-directed cognitions such as focal attention and working memory are initiated, possibly by reducing goal-irrelevant functions supported by the DMN (Anticevic et al., 2012). Lower DMN activity is associated with successful performance across many stimulus-driven goal-directed cognitive tasks (Anticevic et al., 2012). The presence of an analogous large scale brain network has also been suggested in rodents as well (Becerra et al., 2011; Jonckers et al., 2011).

3.1.3. Mechanisms of network modulation—Recent studies combining pharmacological manipulations and fMRI analysis have identified neurochemical mechanisms underlying these networks in humans (Anticevic et al., 2012). For example, the NMDA receptor antagonist, ketamine has been shown to induce behavioral changes reminiscent of schizophrenia associated behavioral phenotypes both in humans and animal models (Moghaddam and Krystal, 2012), and disrupts FPCN activation and DMN deactivation, resulting in a delay in working memory tasks (Anticevic et al., 2012). On the other hand, monoamines, especially increased dopamine, are associated with stronger positive FPCN-DMN coupling and negative DAN-DMN coupling (Dang et al., 2012). These data suggest that the local E/I balance (mediated by a balance of glutamate and GABA) is critical for interactions between task-based activation and suppression, while long-range neuromodulation may be critical for switching between networks (Anticevic et al., 2012). The latter may involve dynamic network connectivity, actively modulating the strength of excitatory connections via intracellular signaling events within dendritic spines (Arnsten et al., 2010; Gamo and Arnsten, 2011).

These findings suggest a few key principles. First, functional networks are rather dynamic in nature and formation of these dynamic networks likely requires specific neurobiological mechanisms. Second, network performance in certain cognitive functions is determined by the speed of information processing, information transmission, and integration of information. Third, network performance is also determined by the speed of assembly of the networks in a task-dependent manner. All these will be reflected in connectivity and topological measures of networks in brain imaging, which have been related to individual differences in intelligence, performance in specific cognitive domains, information processing speed, and differences in personality traits (van den Heuvel and Fornito, 2014).

3.2. Neural oscillations

3.2.1. Neural oscillations to evaluate brain connectivity—Activity of local brain area and connectivity among local brain areas can be measured by characterizing the fluctuation and synchrony of neural oscillation patterns. Neural oscillations involve synchronization and phase locking of neuronal activities that likely enhance communication among neurons (Fries, 2005; Varela et al., 2001), and are thought to facilitate the transient formation of widely distributed networks that underlie cognitive functions (Varela et al., 2001). This notion is consistent with the finding that neurons participating in the same gamma range oscillatory rhythm synchronize their firings with high precision during visual tasks (Gray et al., 1989). Extracranially recorded EEG and MEG with multi-channels are mainly used for measuring neural oscillation patterns in humans. Neural synchrony can be divided into two types: One is synchrony associated with a local area reflecting the synchronized firings of the neurons in the area, i.e., oscillation amplitude^{*1}, and the other is synchrony in long range reflecting the connectivity among different brain areas, i.e., coherence estimated by the covariance of phase-values between two oscillatory signals (Uhlhaas, 2013; Uhlhaas and Singer, 2013). The latter can also be measured by fMRI as described above, but there are differences between the long range synchrony detected by EEG/MEG and that detected by fMRI, which should be kept in mind especially in translational research (Harris and Gordon, 2015). Oscillations measured by EEG/MEG show more faster responses that directly reflect electrophysiological changes between brain areas, whereas oscillations measured by fMRI show slower components that are correlated with fluctuations of the local blood flow (Harris and Gordon, 2015).

Distinct frequencies of oscillation are involved in different computations as well as coordinations of neural activities (Roux et al., 2012). Local processes tend to be associated with higher frequency oscillations, namely the gamma band (>30Hz), establishing the precise synchronization of distributed neuronal responses, while long-range interactions tend to involve synchrony in lower frequency bands comprised of theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) frequencies (Siegel et al., 2012). The power^{*1} of gamma oscillations is modulated by the phase of theta band oscillations (Canolty et al., 2006) and therefore, theta and gamma band synchronies may contribute to shape the temporal structure of neural activity in the PFC to act as carriers of communications between the PFC and the

^{*1}Oscillation amplitude is a measure of local integration of neural signals, and is an indirect measure of synchrony (Uhlhaas, 2013). Spectral power reflects the amplitude of neural oscillations computed through a time-frequency transformation, which is believed to be more correlated with changes in E/I balance parameters (Uhlhaas, 2013; Uhlhaas and Singer, 2013).

rest of the brain. It has been shown that during the retention period of working memory tasks, there is a change in most ranges of oscillation frequencies, in particular with theta modulations localized to the frontal, hippocampal, and parietal regions (Gevins et al., 1997; Jensen and Tesche, 2002; Sarnthein et al., 1998; Tesche and Karhu, 2000). Furthermore, both power and duration of the theta bands are related to an increase in the amount of information to be retained. Studies that combine EEG and fMRI showed that increased theta oscillations were associated with suppression of the DMN and successful working memory performance (White et al., 2013), implicating that increased theta power may influence top-down modulation of the DMN activity (Liebe et al., 2012). There have been reports demonstrating tight correlations between synchronized oscillations and higher cognitive function by characterizing task-associated oscillations (Singer, 1999; Varela et al., 2001). Therefore, neural oscillations can be used to monitor the status of functional connectivity whose maturation correlates with functional maturation of individual brain.

3.2.2. Neural oscillations in animal models—Study of neural oscillation in humans can be translated into animal study in which we can characterize molecular and cellular mechanisms of oscillations (Gordon, 2011; Uhlhaas and Singer, 2012). In rodents, intracranial multi-channel recordings can measure spike field potentials. Spike field coherence in the gamma frequency range has been shown to be largely confined to the superficial layers in the cortex, namely layers II/III (Buffalo et al., 2011). Furthermore, it has also been shown that fast spiking PV-positive basket interneurons are necessary for the generation of gamma oscillation and that activation of PV-positive neurons enhances gamma oscillation (Cardin et al., 2009) that is associated with cortical activity (Sohal et al., 2009). Therefore, these GABAergic interneurons play a pivotal role in the primary generation of high frequency oscillations and their local synchronization, whereas glutamatergic inputs appear to control their strength, duration, and long-range synchronization (Fuchs et al., 2001). Recently, long-range inhibitory projections originating from GABAergic neurons that terminate selectively on inhibitory interneurons in their respective target areas could also contribute to an important mechanism for inter-regional synchronization (Melzer et al., 2012). Furthermore, the neuromodulatory system plays an important role in the gating of oscillations and synchrony: Gamma oscillations and their synchronization depend critically on the activation of muscarinic (Rodriguez et al., 2004), dopaminergic, and 5-HT receptors (Dzirasa et al., 2013; Dzirasa et al., 2009; Puig and Gener, 2015). All these molecular mechanisms could affect the levels of neural activity, oscillations, and synchronization in the PFC, thereby providing a possible mechanism for mediating inter-regional communication, information selection, and processing involving PFC (Benchenane et al., 2011).

3.3. Development of functional networks

3.3.1. Functional development in human cognition—Human cognitive abilities such as selective attention, working memory, and inhibitory control, take decades to develop (Catts et al., 2013; Dumontheil et al., 2008). For example, in spatial working memory, the strategy of solving the problem is established already by 6 years of age, but the speed of processing continues to improve until 16 years of age (or even older) (Klingberg, 2006). In social behavior, fairly simple social behaviors like joint attention develop by 18 months of

age, and are followed by the development of more complicated ones like pro-social behaviors including fairness and morality that require information processing, recognition of values, and decision making, which develop by 5 years of age. The latter requires several brain areas to be connected and is built upon combinations of previously acquired components of simple social behaviors. Even more sophisticated social behaviors, such as empathy and theory of mind, develop by middle childhood (Happé and Frith, 2014; Korkmaz, 2011). Social communication skills are gradually acquired along these maturation processes.

3.3.2. Imaging studies of development of cognitive function—Imaging studies suggest that functional developments described above accompany network developments in the brain. The foundation of the DMN is already established during the embryonic period with rapid growth in the last trimester, and by age 10, each of the major regions of the DMN is already present (Hoff et al., 2013). However, this is not yet a mature form and during adolescence, the network is further refined and modified, including the transformation of nodes and connections. The modules become increasingly interlinked by the ongoing maturation of long pathways (Hagmann et al., 2010), and nodes become enriched in the PFC (Supekar et al., 2010). Functional coupling of frontal hubs with other brain regions greatly increases during adolescence, implicating the gradual maturation of the frontal areas to become capable of coordinating distributed cortical functions (Hwang et al., 2013; Wu et al., 2013). This pattern of maturation after initial formation of the networks is also observed in inter-network connections: It has been shown that most of connections within the DAN develop during childhood, whereas more extensive inter-network connections develop during adulthood (Farrant and Uddin, 2015). In addition, in 7–9 years old kids, the salience network of the CON has shown to be already active at adult level, while the network becomes connected with the executive networks at older ages (Farrant and Uddin, 2015). Furthermore, inter-network connectivity of the FPCN has been shown to develop during adolescence (Spreng et al., 2013). The rate of maturation is different among functional networks, with networks associated with social, cognitive, and emotion processing developing more slowly than networks associated with motor control and less complex cognitive functions (de Bie et al., 2012; Kelly et al., 2009; Zielinski et al., 2010). Since macroscopic changes like cortical folding are limited after 2 years of age, these network changes are likely due to microscopic changes and/or functional changes (Paus et al., 1999). These might involve events like adjustment of diameter of axons, alignment and packing density of individual axons in the bundles, expansion, strengthening, and elimination of synapses, and myelination.

3.3.3. Neural oscillations and development of cognitive function—Neural oscillations also change during adolescence along with functional maturation. During adolescence, the amplitude of oscillations in the delta and theta ranges reduces (Gasser et al., 1988a; Gasser et al., 1988b; Whitford et al., 2007), while oscillations in the alpha and beta ranges become more prominent. These changes follow a linear trajectory until age 30 (Whitford et al., 2007), and occur more slowly in the frontal than posterior regions (Whitford et al., 2007). Through these processes, cortical networks increasingly express high frequency oscillations with enhanced long-range synchronization (Uhlhaas and Singer,

2011). Therefore brain maturation is accompanied by fundamental changes in the properties of cortical local circuits that in turn promote the precise temporal coding of neural activity over long-range. Such modifications in the amplitude and synchrony of neural oscillations are correlated with improved detection rates and reaction times, basic measurements in cognitive tasks (Uhlhaas and Singer, 2011).

In sum, three major developmental processes need to be accomplished for maturation of cognitive functions: (1) acquiring information processing ability (excitatory and inhibitory neurons in the local circuitry with appropriate E/I balance, refinement of the signal to noise ratio, affecting the speed of information processing), (2) brain network formation through activity dependent modification/recruitment of brain areas (enhanced connections and synchrony, affecting the speed of information transmission and the ability of assembling necessary information through interconnecting hub nodes within networks), and (3) establishing ability of efficient network switching (formation of inter-network connections, appropriate neuromodulation, affecting the speed of network engagement). Alterations in any of these processes can lead to defective networks and defective network switching (which can be detected by both brain imaging and oscillation measurement), and are predicted to result in cognitive dysfunctions.

4. Clinical findings: Cognitive impairments and network disturbances

4.1. Cognitive impairments in schizophrenia

Impaired working memory is a fairly recognized endophenotype of schizophrenia and is present even in undiagnosed relatives of patients (Cannon, 2005; Cannon et al., 2000; Cannon and Keller, 2006; Glahn et al., 2003; Lewis and Gonzalez-Burgos, 2008; Park et al., 1995; Snitz et al., 2006; Tuulio-Henriksson et al., 2003). Generalized cognitive dysfunction has been reported among people at high risk for developing psychosis (Brewer et al., 2006), although it is not conclusive whether dysfunction in particular cognitive domains, such as verbal memory, is associated with higher risk (Rajji et al., 2014). The most pronounced deficits observed in the early phase of schizophrenia are in verbal and visual memory as well as in the speed of information processing (Rajji et al., 2009). In the chronic phase of the illness, cognitive deficits appear to become more stable, and cognitive function is generally impaired relative to that in age-matched healthy controls (Harvey et al., 2006). The degree of cognitive alterations correlates with functional outcome in chronic patients (Goldberg et al., 1993; Green et al., 2000; Green et al., 2004; Lewis and Gonzalez-Burgos, 2008; Semkovska et al., 2004), suggesting that the level of spared cognitive function before the chronic phase may determine the degree of functional impairment during the chronic phase.

In the following sections, we will overview the clinical findings regarding disturbances in functional networks in patients with schizophrenia.

4.2. Network disturbances in schizophrenia

Wernicke was among the first to suggest that schizophrenia may involve an anatomical disruption of association pathways (Wernicke, 1885). Bleuler hypothesized that decoupling of psychological processes might be the primary cause of the disease (Bleuler, 1911). Recent progress in dynamic brain imaging technologies and measurement of connectivity has

provided us with new data supporting these old ideas that schizophrenia involves the disruption of pathways connecting various brain regions within neural networks.

4.2.1. Findings in functional brain imaging (Table 4)—Reduced white matter volume has been repeatedly reported as one of structural alterations associated with schizophrenia (Kuperberg et al., 2003; Thermenos et al., 2013; van Haren et al., 2012). Furthermore, altered white matter microstructure of long projections including the uncinate fasciculus, arcuate fasciculus, cingulum, and corpus callosal genu tract, are observed in schizophrenia (Ellison-Wright and Bullmore, 2009; Kubicki et al., 2007). There appears to be compromised PFC activity associated with encoding, maintenance, and response in patients with schizophrenia performing a spatial working memory task (Driesen et al., 2008). For example, patients show a greater decay of blood oxygen level-dependent activity in the PFC than controls during the maintenance phase of the task, which is associated with poor task performance (Driesen et al., 2008). Patients including medication-naïve ones also show hypofrontality and reduced metabolism in the PFC, supporting the idea that the changes are associated with the disorder and are not due to confounding factors, e.g., medications (Callicott et al., 2003; Lewis and Gonzalez-Burgos, 2008; Molina et al., 2005; Weinberger et al., 1992).

Network alterations: Network studies suggest that in schizophrenia, there are reductions in the global communication efficiency, implicating reduced connectivity between more segregated parts of the brain (van den Heuvel and Fornito, 2014) in a wide variety of systems including the FPCN (Repovs et al., 2011), CON (Palaniyappan et al., 2013), DMN (Whitfield-Gabrieli and Ford, 2012), and fronto-striatal (Dandash et al., 2014; Fornito et al., 2013) and fronto-temporal circuits (Hoffman et al., 2011). In particular, frontal and temporal brain regions showed altered clustering (Bassett et al., 2008), longer communication pathways (van den Heuvel and Hulshoff Pol, 2010), and reduced global efficiency (Wang et al., 2012). Furthermore, the strength of connectivity is reduced in PFC regions that are involved in the DMN, especially the infraorbital PFC (Fitzsimmons et al., 2013), and in regions centered around the FPCN, in particular involving the genu, cingulum, and the interhemispheric parietal and occipital tracts, i.e., structures interconnecting the medial regions of the frontal and parietal cortices (Zalesky et al., 2011).

In addition, the centrality of hub nodes is reduced in the medial frontal and medial parietal regions (van den Heuvel and Fornito, 2014), and in the superior frontal cortex, lateral precuneus, and parts of the DMN such as the parahippocampal, inferior, temporal, and cingulate cortices, indicating a less central role for these regions in the networks in schizophrenia brains (Zhang et al., 2012). An altered organization of hub nodes is also observed in schizophrenia including a less prominent role of high degree hub regions in the OFC and parietal cortex and the emergence of non frontal hubs in other brain regions (Bassett et al., 2008; Collin et al., 2013; Zhang et al., 2012). Rich club organization among high degree hub nodes is significantly affected in schizophrenia patients, together with a reduced density of rich club connections that predominantly link the midline frontal, parietal, and insular hub regions (van den Heuvel et al., 2013). This reduction in rich club density was associated with lower levels of global communication capacity (Barch and Ceaser,

2012). These results suggest that a core disturbance in the connectivity and topology of hubs may underlie a wide range of network abnormalities observed in schizophrenia, affecting the functional dynamics and capacity of the brain (van den Heuvel et al., 2013).

Many functional studies have also found changes in a wide variety of systems, many of which involve the PFC (Cole et al., 2011; Fornito et al., 2013; Liang et al., 2006; Zalesky et al., 2011). As stated above, network changes reported in schizophrenia are not merely the result of a relative global reduction in connectivity strength, but likely involve topological changes in the brain networks (Collin et al., 2013) and reduced hierarchical structure, both indicative of a disruption in the organization of connectivity among cortical regions (Bassett et al., 2008).

In schizophrenia patients, a lack of inhibition of the DMN has also been reported (Anticevic et al., 2013; van den Heuvel and Fornito, 2014), with patients not being able to switch appropriately from the DMN to other networks that are necessary for executing certain cognitive tasks such as working memory and attention. These data suggest that both formation and switching of networks necessary for certain cognitive functions are affected in schizophrenia.

Altered connectivity and behavioral outcomes: Connectivity and topological measures have been linked to the severity of positive symptoms, negative symptoms, and cognitive impairments in schizophrenia patients (van den Heuvel and Fornito, 2014). Differences in altered connectivity are associated with differences in symptoms (Meyer-Lindenberg et al., 2006). Moreover, there are also variations in affected connectivity in the brain associated with certain behavioral alterations. For example, the severity of positive symptoms is correlated with *increased* functional connectivity of the mPFC in the DMN (Whitfield-Gabrieli et al., 2009) in schizophrenia, but is also correlated with *reduced* functional connectivity between dorsal regions of the caudate and DLPFC in the first episode of psychosis and in the prodromal period (Fornito et al., 2013). These data suggest that variations in distinct symptom domains may reflect differences in affected neural circuits.

4.2.2. Findings in neural oscillations—Due to the prominent role of gamma band activity in cognitive function, high frequency activity has been characterized extensively in schizophrenia (Uhlhaas and Singer, 2013, 2015). Gamma band amplitude has been shown to be reduced in a wide range of cognitive and perceptual paradigms in schizophrenia, including working memory, executive control, and perceptual processing (Ford et al., 2008; Haenschel et al., 2009; Minzenberg et al., 2010). Of particular importance is that not only the amplitude (reflecting local activity) but also the phase synchrony (reflecting long-range connections) of gamma oscillations is reduced in schizophrenia (Spencer et al., 2003; Uhlhaas et al., 2006): Reduced long-range synchronization would lead to a functional disconnection syndrome (Stephan et al., 2009).

Since gamma oscillation requires the maturation of PV-positive interneurons mediated by NMDA receptors (Cardin et al., 2009), NMDA receptor-mediated maturation of these particular interneurons has been proposed to be a major pathway in schizophrenia pathogenesis (Jiang et al., 2013; Lewis et al., 2012). However, other ranges of oscillations

are also affected in schizophrenia, suggesting more wide spread alterations in brain connectivity in schizophrenia brains (Uhlhaas, 2013; Uhlhaas and Singer, 2015).

5. Neurobiological basis for cognitive impairments in schizophrenia

As summarized in the previous section, schizophrenia shows network disturbances that underlie cognitive impairments. In this section, we will build on the neurobiological processes described in section 2 and 3 to discuss the neurobiological changes in the PFC that are responsible for network disturbances and cognitive impairments observed in schizophrenia.

5.1. Developmental hypothesis of schizophrenia leading to network alterations

Classically, pharmacological studies have predicted the importance of neurotransmitter disturbance in schizophrenia pathogenesis. This includes the hyperdopaminergic hypothesis that hyperactive D2 receptor signaling is responsible for psychotic aspects of schizophrenia (Kellendonk, 2009). Furthermore, since many psychoactive drugs including cannabinoid, amphetamine, and ketamine can induce behavioral phenotypes similar to schizophrenia, disturbance of the pathways involving these drugs may also contribute to the disorder (Moghaddam and Krystal, 2012; Steeds et al., 2015). Especially ketamine, an NMDA receptor antagonist induces behavioral alterations both acutely and chronically in both humans and animals, and has led to the hypoglutamatergic hypothesis (Coyle and Tsai, 2004). Postmortem brain analyses have identified many cell types/processes affected in schizophrenia brains including GABAergic interneurons, in particular, PV-positive interneurons as well as oligodendrocytes/myelination (Akbarian et al., 1993a; Akbarian et al., 1995; Akbarian et al., 1993b; Black et al., 2004; Garey et al., 1998; Glantz and Lewis, 2000; Glausier et al., 2014; Glausier and Lewis, 2013; Lewis et al., 2012; Lewis and Gonzalez-Burgos, 2008; Selemon and Goldman-Rakic, 1999; Takahashi et al., 2011a). Inflammation is also involved in the pathogenesis and progression of the disorder. In fact, microglia activation has been observed in both imaging studies and postmortem analyses (Bergink et al., 2014; Horvath and Mirmics, 2014; Ohgidani et al., 2015). Epigenetic changes that are caused by environmental effects as well as by an adaptation process to situations created by both genetic and environmental insults have also been implicated in schizophrenia (Akbarian, 2014; Hasan et al., 2013). These epigenetic changes may be responsible for some of the gene expression changes observed in postmortem brains. Furthermore, the epigenetic changes have also been detected in peripheral blood samples that may serve as potential biomarkers for schizophrenia (Chan et al., 2014), and analysis of epigenetic changes has now been extended to the analysis of miRNA in peripheral blood samples (Chana et al., 2013). How all these changes associated with schizophrenia occur in the progression of the disorder is still elusive, but during the prodromal period, patients with schizophrenia show some degree of cognitive impairments, suggesting that the alterations are already present before the onset of the disorder.

The developmental hypothesis of schizophrenia proposes that disruption of early brain development by a combination of genetic and environmental factors (through gene-environment interactions, G X E) increases the risk of later developing schizophrenia (Insel, 2010; Murray et al., 1992; Weinberger, 1996). As summarized in the previous sections, the

development of neural networks and cognitive functions involves many biological processes that can take decades to complete, e.g., the initial formation of connections and circuitries, followed by activity-dependent refinement of these connections. Various insults during early development would make the circuitry vulnerable to stresses during the maturation process (Figure 4). As the PFC has an extended maturation period, a sustained window of plasticity may extend the developmental time window during which these insults further affect the circuitry, making cognitive function particularly vulnerable (Uhlhaas, 2013). Affected processes include: local circuitry formation and maturation including E/I balance, sensory gating, connectivity including myelination, neuromodulation, and activity dependent maturation. All these changes would converge to manifest as network disruption, and as a result, cognitive impairment. Since so many networks necessary for a wide variety of cognitive functions are anchored in the PFC, the manifestations of impairments in the PFC would be diverse. Furthermore, the timing of insults during development may also affect the outcomes of altered networks, e.g., which networks are damaged and how extensive the damage is.

We can characterize the possible chain of events using animal models, namely rodent models with genetic modifications and clarify neuroanatomical changes observed in the PFC of these animals. Some mouse models showing behavioral phenotypes relevant to schizophrenia have shown altered gamma oscillation, supporting that alterations in gamma oscillation may be one of common features in the schizophrenia pathophysiological changes that may be caused by diverse pathogenic pathways (Table 5, and see review Rosen et al., 2015). For example, mice with altered *Nrg1* or *ErbB4* showed alterations in interneuron positioning and gamma oscillation (Del Pino et al., 2013; Fisahn et al., 2009; Yang et al., 2013). When the NMDA receptor was specifically disrupted in PV-positive interneurons, local circuitry formation was perturbed, leading to changes in gamma oscillation and behavior (Carlen et al., 2012). In addition, many paradigms that test G x E have been applied to animal models (e.g., Ibi et al., 2010; Kannan and Pletnikov, 2012; Moreno et al., 2011; O'Leary et al., 2014). Analysis of these models should help us to establish the neurobiological alterations underlying network disturbances and cognitive impairments in the context of the developmental hypothesis of schizophrenia.

5.2. Onset of schizophrenia

Even before the onset of the disorder, patients manifest cognitive decline (Fisher et al., 2013), the feature recognized by Kraepelin. How, then, can we explain the onset of schizophrenia, namely psychotic episodes during the late teens- early twenties, characteristic to schizophrenia? Patients with first episode psychosis show little change in fractional anisotropy in several white matter tracts (Friedman et al., 2008), implicating that there may not be major structural alterations in network connections at the onset of the disorder. The brain changes described above may set up an immature circuitry with reduced information processing capacity, which then manifests as cognitive impairment in the prodromal period of schizophrenia. Additional insults during puberty, such as emotional stress (Niwa et al., 2013), oxidative stress (Emiliani et al., 2014), infection/inflammation (Anderson et al., 2013), and modification of neuromodulators via cannabis use (Bossong and Niesink, 2010; Brown, 2011; Raver et al., 2013), would further burden the circuitry maturation processes. If

the brain is unable to fully compensate for these insults, it may cause system shut down (Figure 4, and see Uhlhaas, 2013). This would create the situation in the brain, like disrupted communications with the hyperdopaminergic status that may be responsible for hallucinations and psychosis that are typically observed at the onset of schizophrenia. However, the onset of psychosis has been difficult to model in mice, since psychosis is defined as the state of loss of contact with reality whose symptoms include hallucinations, delusions, catatonia, and thought disturbances, all of which are difficult to measure in rodents. In fact, positive symptoms of psychosis such as hallucinations and delusions have been modeled in mice as hyperactivity induced after challenging psychoactive drugs, which is clearly not equivalent to e.g., hallucination observed in humans (Takahashi et al., 2011a).

5.3. Chronic phase of schizophrenia

After a recurrence of psychotic episodes, a substantial number of patients sustain their psychiatric symptoms, suffering chronic schizophrenia with variable degrees of wide range of cognitive impairments (Keefe et al., 2007). Imaging data during this phase showed global changes in neural connectivity (Friedman et al., 2008). Furthermore, both white and gray matters, especially cortical thickness have been shown altered in these patients, whose degree of changes may be correlated with their functional status (Kubota et al., 2013; Sasamoto et al., 2014; Ubukata et al., 2013). These patients may show a lack of motivation as well as difficulty in activating task-relevant networks. They may also show an inability to switch networks effectively and efficiently, which may be associated with impaired neuromodulatory mechanisms. Furthermore, when they reach the phase (usually happening later in life), the neuronal system is no longer plastic including myelin and synapses, and phenotypes related to the network alterations (and cognitive impairments) become stable, affecting their everyday-life functioning.

In the chronic phase of schizophrenia, the brain may suffer chronic damage that correlates with stable functional impairments in the networks. These impairments may not manifest as neuronal loss or accumulation of toxic proteins, as observed in neurodegenerative disorders, but may appear as functional neurodegeneration such as changes associated with non-functional synapses and connectivity. There may be some traces of molecular changes implying these conditions in the brains of the chronic phase of schizophrenia (e.g., DISC1 aggregation, Atkin et al., 2012), which may serve as biomarker for chronic schizophrenia. Identification of such traces, if any, and treatment targeting these may be necessary especially for schizophrenia in the chronic stage. Like the onset of schizophrenia, the chronic phase of schizophrenia is difficult to recapitulate in mice.

6. How can we move forward to deal with cognitive impairments in schizophrenia?

Here, we will discuss how we can apply our knowledge in neurobiology to understand altered neural networks underlying cognitive impairments in schizophrenia and how we can develop novel therapeutics for cognitive dysfunction by using available neurobiological materials.

6.1. Approaches for characterizing cognitive functions

6.1.1. Cellular models to characterize predisposition for altered neural networks underlying cognitive impairments—While postmortem brains have been informative in capturing snapshots of disease pathology (McCullumsmith et al., 2014), they may not recapitulate the dynamic aspects of altered neural networks that occur over the course of the disorder. To overcome this issue, samples freshly prepared from patients, such as peripheral blood cells and olfactory epithelial cells, have been used for, e.g., gene expression studies that may reflect different disease states more faithfully as potential peripheral biomarkers for the disease states (Kano et al., 2013; Kurian et al., 2011). Recent advances in induced pluripotent stem (iPS) and induced neuronal (iN) cell technology that can convert somatic cells to neuronal cells allow us to use live neuronal cells derived from patient's somatic cells (Brennand et al., 2014a; Brennand et al., 2014b), including glutamatergic, GABAergic, and dopaminergic neurons. Oligodendrocytes derived from patient's iPS cells (Czepiel et al., 2011) may also be studied to address cellular phenotypes relevant to schizophrenia (Takahashi and Sakurai, 2013). By combining patients' genetic information and their iPS/iN cells, we can analyze cellular phenotypes of a subgroup of schizophrenia patients with defined rare genetic variants (Bundo et al., 2014; Shcheglovitov et al., 2013; Wen et al., 2014). Since this is a subgroup of schizophrenia, it is possible that certain cellular phenotypes identified are associated solely with these particular genetic variation, but it is also possible that some of phenotypes captured in the population might be shared by other schizophrenia patients even without having those genetic variations but with some common downstream mechanisms (Brennand et al., 2014a; Bundo et al., 2014; Wen et al., 2014).

Using these cells, cellular phenotypes such as neurite outgrowth, membrane potential, and synaptic function have been characterized (Pasca et al., 2014). Some of these may indicate the predisposition for altered circuitry activity observed in schizophrenia. Nevertheless, relevant cellular phenotypes can be used for screening of reagents that can normalize the cellular phenotypes. Since the quality of screening depends upon the assay's robustness and relevance to schizophrenia (Stockwell, 2002), it is critical to focus on cellular phenotypes that would have circuitry effects and be amenable to high throughput screening. It would also be helpful to focus on a specific cellular population in order to understand the effects of particular cellular and molecular phenotypes on neural circuits (this is particularly relevant to neuronal cultures differentiated from iPS cells, as they often result in a variable mixture of cell types). In addition to the screening of compounds, iPS and iN cells may be suitable for following the developmental trajectory of cellular and molecular changes relevant to schizophrenia pathogenesis (Brennand et al. 2014), but more knowledge on individual effects of particular cellular phenotypes onto circuitry activity in the brain will be required in order to understand the effects of those changes on the cognitive functions in the context of the progression of schizophrenia.

6.1.2. Animal models to study cognitive impairments—As genetics and other studies have identified many genes and molecular networks involved in schizophrenia, animal models with genetic modifications for those molecules can be used to study cognitive functions supported by brain networks that are difficult to mimic *in vitro*, and to connect the

molecular changes with circuitry alterations and behavioral phenotypes. Animal models can be used to test hypotheses related to genetic and environmental risk factors, and link them to circuitry and behavioral alterations (Mitchell et al., 2013), and are also useful for identifying biomarkers and screening for potential treatments (Mitchell et al., 2013). To use animal models for these purposes effectively, it is important to compare behavioral measures and neural connections in rodents, primates, and humans side by side. Since PFC subregions and their responsible cognitive functions may differ among species, we will need to clarify the similarities and differences in behavioral phenotypes and connectivity/circuitries that are associated with particular behaviors, and understand what we can and cannot model in animal studies. Table 6 summarizes a comparison of behavioral measures among rodents, primates, and humans.

Towards standardized behavioral measures: Recently, efforts have been made to identify equivalent behavioral domains and functional assays between humans and animals, including the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Young et al., 2012). MATRICS addresses many cognitive domains that are affected in schizophrenia, such as attention/vigilance, reasoning and problem solving, executive functioning, reversal learning, working memory, short/long term recognition memory, long term memory and learning, and processing speed (Floresco et al., 2005)(Table 7). From these efforts, CNTRICS evolved to develop cognitive paradigms that can be translated across species (Carter and Barch, 2007). It addresses working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition (Table 7).

Most recently, the RDoC initiative from the NIMH aims to reclassify psychiatric disorders according to basic dimensions of functioning, e.g., fear circuitry or working memory, that may cut across traditional definitions of these disorders (see RDoC at www.nimh.nih.gov for further information). Each behavioral domain is studied across multiple levels of analysis, from genes to neural circuits to behavior in both animal models and humans, assuming that the behavioral domain would share the more or less similar underlying mechanisms among species (Cuthbert, 2014; Insel, 2014). RDoC includes the following domains: Negative valence systems (fear, anxiety, loss), positive valence systems (reward learning, reward valuation), cognitive systems (attention, perception, working memory, cognitive control), systems for social processes (attachment formation, social communication, perception of self, perception of others), and arousal/modulatory systems (arousal, circadian rhythm, sleep and wakefulness)(www.nimh.nih.gov). A comparison among the behavioral domains of above three approaches is summarized in Table 7. These behavioral domains can be applied across species, facilitating the translation of findings from animal studies to potential treatments for humans.

Connectivity: Connectivity should be characterized in conjunction with functions described above. Classically, lesion studies have been used to characterize functional connectivity in rodents and primates. However, since brain areas are connected with each other and each region contains many diverse connections, a lesion in a particular area would affect many

connections, making the interpretation of the studies complicated. In any events, through characterizing PFC functions in rodents (Chudasama, 2011; Chudasama and Robbins, 2006), we can learn the information processing principles in the local circuitry and connections as well as their basic cellular components for circuitry formation and computation. From these rodent studies, we may be able to translate neural and chemical underpinnings of executive functions into primate studies. For humans and primates, imaging studies such as fMRI and PET have elucidated the brain areas responsible for certain behavioral tasks (e.g., Buckholz and Meyer-Lindenberg, 2012). Lesion studies have also been proven to be very informative in human cases (Szczepanski and Knight, 2014).

Since connectivity is a key issue affected in schizophrenia, it is crucial to establish connectivity measurements in animal models. Oscillation analyses coupled with behavioral measurements have been used to correlate brain connectivity with behavioral/cognitive function in animals (Sigurdsson et al., 2010; Suh et al., 2013; Yamamoto et al., 2014). Recent technological advances also allow us to perform brain imaging in small animals with higher resolution (Hoyer et al., 2014). In addition, recent connectome^{*2} efforts have opened up new possibilities to analyze networks more precisely in animal models. For example, the recently published mouse connectome (Zingg et al., 2014) defines subnetworks in the cortex involving three different PFC regions, which closely correlate with functional differences in individual connections. We can combine these with more sophisticated methods like optogenetic approaches and other circuitry specific manipulation methods that enable us to further dissect the functional connectivity for certain behavioral outcomes (Hikida et al., 2013; Parnaudeau et al., 2013).

In addition, the marmoset connectome project has been initiated in Japan (Okano and Mitra, 2014) which may allow us to compare rodents and primates in a more comprehensive manner once whole spectrum of data are collected. Such comparison will require careful functional mapping of brain regions in both rodents and primates. Nevertheless, it is crucial to understand the differences between rodents and primates in order to extrapolate the animal data to humans and vice versa (Chudasama and Robbins, 2006; Keeler and Robbins, 2011).

6.1.3 Theoretical and computational neurobiology to understand network principles—As described above, we now have access to whole range of data including cellular phenotypes, network alterations, and behavioral alterations in animal models. Combined with these, computer simulations and mathematical analysis to enhance modeling of circuitry and information processing will help us to formulate conceptual working principles/hypotheses on how cellular alterations would affect circuitry outcomes. For the modeling, we will also need fine detailed analysis of cells and connections making up networks (Rolls et al., 2008). This approach will become more feasible once we obtain better understanding on connectivity in the whole brain via connectome data. Enhancement of influx of people from these fields will ensure multidisciplinary approaches for psychiatric disorders.

^{*2}A connectome is the set of all neuronal connections. The brain's capacity for neuronal communication and computation power relies on this incredibly complex connectivity architecture.

6.2. Strategy towards developing better therapeutics

Multidisciplinary approaches: Above all efforts will need multidisciplinary approaches and interactions among diverse research groups including basic science and clinical field (Sawa and Seidman, 2014). For example, detailed characterization of clinical features by clinicians who can translate their findings into a language that basic scientists could understand will be necessary, in order to feed clinical findings like certain behavioral phenotypes associated with network alterations, natural course of functional network alterations during the progression of schizophrenia, and comorbidity, into animal and cellular studies. Conversely when we apply therapeutics to humans based on animal findings, we will need appropriate readouts to assess their effectiveness in humans, like brain imaging using specific PET tracers, neural oscillation patterns using EEG/MEG, and behavioral outcomes. Notably, no dysconnectivity phenotypes have yet been translated into a clinically useful predictor (Uhlhaas and Singer, 2012; van den Heuvel and Fornito, 2014).

Population studies like epidemiological studies can also be integrated into these approaches. As McGrath pointed out (McGrath et al., 2013), the epidemiological data from humans can be maximized by combining these with genetic data to gain insights into involvement of G x E in schizophrenia pathogenesis (McGrath et al., 2013). With sufficient resources and technology available, novel hypotheses on how G x E affects network formation and maturation can be tested in animal models, and then translated back again to humans, to further understand schizophrenia pathogenesis and pathophysiology.

Schizophrenia is a disorder entity of diverse pathogenesis: When linking molecules, circuitry, and behavioral phenotypes for therapeutic endeavors, we will need to keep in mind that schizophrenia is a disorder entity that contains psychopathological status with diverse pathogenesis and pathophysiology, and should not be considered as one disorder that can be treated in all patients with the same therapeutics. Subgrouping of patients by measures relevant to etiology should allow us to devise evidence-based therapeutics to that particular populations in a “personalized by etiology” manner (stratification, Gerretsen et al., 2009). Here, there is an urgent need for biomarkers to appropriately stratify patients, perhaps by genetic variations or environmental causes (Prata et al., 2014). As human genetics data have been accumulated and personal genome analysis has become possible using next generation sequencing technology, we may be able to reclassify schizophrenia population into genetically defined groups. If we can identify some specific cognitive impairments associated with network/connectivity alterations in these groups, we could devise therapeutic approaches specifically targeting those. We can use cells derived from people who have those genetic alterations to characterize specific cellular phenotypes and also use mouse models to characterize altered networks and behavioral correlations of the altered networks. All these can be combined with human studies. This comprehensive approach, from cells and animals to humans, should further advance our efforts for therapeutics into the etiology/pathogenesis-driven directions.

Network oriented therapeutic approaches: Once we identify faulty neural networks, developmental processes of network formation, and their working principles, it may be possible to devise network-based therapeutics for schizophrenia. Such therapeutics needs to

be performed while window for the circuitry plasticity is still open, i.e., before the disease progresses into more stable chronic phase. Currently, extensive cognitive remedy or cognitive behavioral therapy (CBT) has been shown to be somewhat effective (Fisher et al., 2013; Mueser et al., 2013), for which both appropriate cognitive assessment and appropriate behavioral readouts for evaluation are necessary. Also, successful CBT requires patient's motivation (Medalia et al., 2014), that may be determined by the degree of spared PFC functions. Repetitive transcranial magnetic stimulation and deep brain stimulation can also be used to modify circuitry, and neural oscillation may be potential readouts (Uhlhaas and Singer, 2013). Neurofeedback (Shibata et al., 2011) directed by fMRI may also have potentials although utilizing fMRI may not be so cost effective for the time being.

Last, but not least, we cannot stress enough that establishing combined approaches and enhancing interactions among all parties involved are imperative in order to lead to successful novel therapeutic approaches for schizophrenia.

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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

List of abbreviations that are defined in the text and used extensively in the text

E/I balance	excitatory/inhibitory balance
PFC	prefrontal cortex
MD	mediodorsal
VLPFC	ventrolateral prefrontal cortex
VMPCF	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 X E	gene-environment interactions

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Highlights

- Prefrontal cortex (PFC) and its connectivity with other brain areas are crucial for cognitive functions
- Altered neural networks including PFC contribute to cognitive impairments in schizophrenia
- Neurobiological events underlying network alteration in schizophrenia are discussed
- Understanding the mechanisms underlying cognitive impairments is crucial for developing novel therapeutics for impaired cognitive functions in schizophrenia
- Multidisciplinary approaches are required for therapeutic endeavor for the disorder

Figure 1. Comparison of the PFC between primates and rodents

The PFC is defined as the frontal cortex that has connections with the MD nuclei of the thalamus. In rodents, the mPFC and ACC are connected with the medial part of MD, whereas the OFC is connected with the lateral part of MD. In primates and humans, the DLPFC and dorsal part of ACC are connected with the lateral part of MD, whereas the ventral part of ACC and OFC are connected with the medial part of MD. Note that in humans, BA24 corresponds to the ventral ACC while BA32 corresponds to the dorsal ACC, and since the areas are concaved anteriorly, BA32 can be seen both superior and inferior to BA24 in this plane of section. BA25, subgenual cingulate, is situated ventrally to these two areas and also more posterior to the plane of section, and cannot be seen. OB: olfactory bulb, CC: corpus callosum.

Figure 2. Maturation of the local circuitry and long range connectivity

The local circuitry consists of excitatory and inhibitory neurons. A triangle is the cell body of pyramidal neurons, major excitatory projection neurons, whereas a circle is the cell body of inhibitory interneurons. Each local circuit is connected with other local circuits via long range connections that are myelinated. Inputs to the area would affect local circuitry maturation. The inputs would also be affected by the degree of myelination, as the degree of myelination determines the speed of neural transmission, affecting the inputs to the local circuitry.

Figure 3. Developmental profiles of mouse PFC

During development of the mouse PFC, many biological processes take place sequentially. First, a subunit switching for the NMDA receptor component, NR2 takes place, followed by the drastic increase of interneuron marker gene expression during postnatal week 2–4. Slightly delayed is the increase of oligodendrocyte/myelin related gene expression, implicating that myelination process may take place by postnatal week 5. But the PFC is not mature functionally based on the responsiveness to MK801 injection. The response becomes adult like at postnatal week 8. During adolescence (postnatal week 6–8), inhibitory neurons and the neuromodulatory system seem to further mature. Social isolation, an environmental insult, performed during postnatal week 3–5 affects myelin formation, whereas that performed during postnatal week 5–8 affects dopamine synthesis via stress response. Interestingly, the different timing of the treatment results in different behavioral phenotypes later in life (Makinodan et al., 2012; Niwa et al., 2013; Ueda et al., 2015).

Figure 4. What might be happening in the PFC during development/maturation that leads to schizophrenia phenotypes?

Development of neural circuitry/networks that support cognitive functions occurs over decades. If the process proceeds without any issues, healthy network is formed to support everyday life in society. However, several genetic and environmental insults make vulnerable circuitry with somewhat impaired cognitive functions. The vulnerable circuitry, which has unbalanced excitatory/inhibitory activity (E/I), aberrant dopamine (DA) system, and reduced signal to noise (S/N) ratio, can be further impaired by synaptic stress and inflammation during adolescence, resulting in network disturbances and system failure, that lead to the psychosis/onset of the disorder.

Table 1

PFC subdivisions in primates and rodents

		Brodman area	Areas	Connections	Proposed functions	Rodents**
Granular	caudal	8	cPFC	OFC Cortex	Searching for goals	
	lateral	9	dPFC	Cortex OFC	Generating goals based on recent events	
	mid lateral	46		Premotor cortex		
	Postero lateral	9/46				
	ventral	45, 47	vPFC	Cortex Amygdala	Generating goals based on external stimuli	
	orbital	11, 13, 14	OFC	mPFC Amygdala Cortex	Choosing objects based on outcomes	
Agranular	dorsomedial	9		Hippocampus Amygdala	Choosing actions based on outcomes	
	polar	10	mPFC	Premotor cortex		
	lateral	13, 14 Agranular insular cortex	OFC	Cortex Gustatory input Piriform cortex	Choosing objects based on outcomes	OFC Agranular insular cortex
	medial*	24 (AC) 25 (IL) 32 (PL)	mPFC	Hippocampus Amygdala Premotor cortex	Choosing actions based on predicted outcomes	24 (AC) 25 (IL) 32 (PL)

Modified from The Neurobiology of the Prefrontal Cortex by Passingham and Wise (Passingham and Wise, 2014).

* Cingulate cortex is a cortical region superior to the corpus callosum, which spreads over from anterior to posterior brain. Cingulate can be subdivided into 3 regions, anterior, middle, and posterior, which have distinct connections and functions. The anterior portion, BA24, 25, and 32, is included into the PFC. These subdivisions were first identified in primates, but have since been identified in rodents as well (Vogt and Paxinos, 2014).

** There are no granular regions in rodent PFC.

Abbreviations used are: cPFC, caudal prefrontal cortex; dPFC, dorsal prefrontal cortex; vPFC, ventral prefrontal cortex; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; AC, anterior cingulate; IL, infralimbic; PL, prelimbic.

Comparison of subdivisions and functions of PFC between primates and rodents (Chudasama, 2011; Chudasama and Robbins, 2006; Fuster, 2008)

Table 2

Human/primates	BA47, 11, 12, 13, 14, 10	BA14, 10, 8, 9	BA32, 33, 24, 25, 26	BA10, 8, 9, 46	BA44, 45, 47
	Orbitofrontal	Medial¹	Cingulate²	Dorsolateral	Ventrolateral
Functions	<ul style="list-style-type: none"> Decision making Reward/punishment Flexibility Reversal learning Solving conflict Emotional motivation Social behavior 	<ul style="list-style-type: none"> Fear conditioning 	<ul style="list-style-type: none"> Solving conflicts Reward based learning Set shifting Attention Error detection Decision making (cost-benefit analysis) Mood Emotional regulation Social behavior Fear conditioning 	<ul style="list-style-type: none"> Working memory Suppression Flexibility Switching Set shifting Planning Guessing Attention Response selection Reasoning Decision making (accuracy, impulsivity) Motor planning Motivation 	<ul style="list-style-type: none"> Working memory Motor language (Broca's area)
Rodents ³	Orbitofrontal	Medial PFC (IL, PL)	Anterior cingulate	Medial PFC (IL, PL) and anterior cingulate	
	<ul style="list-style-type: none"> Reward association Flexibility Reversal learning Social behavior 	<ul style="list-style-type: none"> Fear conditioning 	<ul style="list-style-type: none"> Solving conflicts Set shifting Attention Decision making (cost-benefit analysis) Emotional regulation Social behavior Fear conditioning 	<ul style="list-style-type: none"> Working memory Inhibitory control Flexibility Set shifting Attention Incentive learning Response selection Decision making, (accuracy, PL; impulsivity, IL) 	

¹These are continuous structures that spread over the DLPFC and OFC.

²BA 23, posterior cingulate cortex, is not part of the PFC, and is unique to primates (Vogt and Paxinos, 2014).

³ We emphasize that areas listed for rodents are functionally similar to some human/primate areas, but not necessarily all areas, nor they necessarily are responsible for the same functions. For example, it is difficult to match BA24, 25, 32 of primates with those of rodents anatomically (see also Figure 1). There may also be heterogeneity in the area along the anterior-posterior axis in rodent brains (Wise, 2008).

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Table 3

PFC and imaging studies (van den Heuvel and Hulshoff Pol, 2010)

Network	Functions	Brain areas
Default mode network	Anti-correlated with fronto- parietal regions associated with cognitive control; deactivated during demanding cognitive tasks directed towards external stimuli (Fox et al., 2005) Linked to self relevant, internally directed information processing, introspective processing	Anterior and posterior medial cortex Temporal lobes Superior frontal cortex Inferior temporal cortex Posterior cingulate cortex Retrosplenial and lateral parietal cortex Medial PFC Parahippocampal gyrus,
Cingulo-opercular network	Maintenance of cognitive set over an extended period during performance of externally focused cognitive tasks (Dosenbach et al., 2008), interception, salience processing	Anterior PFC Dorsal ACC Thalamus Anterior insula/frontal operculum
Dorsal attention network	Focused attention on external stimuli (Fox et al., 2005)	Intraparietal sulcus and posterior parietal lobe Dorsolateral PFC Insula
Fronto-parietal control network	Executive cognitive control processes (Vincent et al., 2008)	Dorsal frontal cortex Dorsolateral PFC Intraparietal sulcus and inferior parietal lobe Precuneus and middle cingulate cortex

Bold regions are in PFC

Table 4

Network disturbances in schizophrenia (Griffa et al., 2013; Uhlhaas and Singer, 2013; van den Heuvel and Fornito, 2014)

	Methods	Reported changes associated with schizophrenia
Structural	DTI sMRI	Increased segregation and reduced global communication efficiency Alterations in hub/node formation and rich club organization *
Functional	fMRI PET	Less connections among more segregated brain regions Decreased hub/node formation, rich club organization *
	MEG/EEG	Reduction of gamma band (amplitude and synchrony) Increased delta and theta oscillations and reduced alpha band power Deficits in phase locking of evoked oscillations in the alpha and gamma bands

sMRI: structural MRI.

* Highly connected and highly central neocortical hub regions play a key role. These brain hubs form a rich club organization characterized by a tendency for high degree nodes to be more densely connected among themselves than nodes of a lower degree (van den Heuvel and Sporns, 2011).

Functional measures are perhaps a more specific index of state-related changes in brain functions, more closely tracking the onset and offset of symptom appearance, while structural measures are more stable and thus may be related to more enduring illness characteristics (van den Heuvel and Fornito, 2014).

Table 5

Mouse models with construct validity showing alterations in networks

Mouse models	Etiology	Network alterations	Behavioral alterations (ones correlated with altered networks)
NMDAR deficient mouse using PV-Cre	Synapse Glutamate Interneurons	(Carlen et al., 2012; Billingslea et al., 2014) gamma oscillation, forebrain	Habituation Working memory Associative learning Self care Social behavior
<i>ErbB4</i> deficient mouse	Synapse Glutamate Interneuron migration	(Del Pino et al., 2013; Hou et al., 2014) gamma oscillation, PFC	Locomotor Emotional response Social behavior
MAM treated mouse	Glutamate	(Lodge et al., 2009) gamma oscillation, mPFC and hippocampus	Latent inhibition
Inactivation of MD thalamic nuclei	PFC	(Parnaudeau et al., 2013) MD-PFC synchrony	Working memory Flexibility Reverse learning
Cannabinoid treatment	Synapse	(Raver et al., 2013) cortical oscillation	Working memory
22q11.2 deletion mouse	Diverse	(Sigurdsson, 2010) hippocampus-PFC synchrony	

See also (Rosen et al., 2015).

Table 6

Cognitive functions and testing in primates vs. rodents (Sarnyai et al., 2014)

	Working memory	Attention vigilance	Verbal learning and memory	Visual learning and memory	Reasoning and problem solving	Speed of processing	Social cognition
Human (Nuechterlein et al., 2004)	WCST WMS-III	CPT-IP	Hopkins Verbal Learning Test	BVMT-R	Maze WCST Tower of London	Trail making test BACS	MSCEIT
Primates	Delayed response task (Wimmer et al., 2014)	5-CSRT (Spinelli et al., 2005)	N/A	Paired associative learning (Schneider et al., 2013)	Set shifting (Dias et al., 1996)	5-CSRT (Spinelli et al., 2005)	Facial recognition (Parr, 2011)
Rodents	Radial arm maze (Crusio et al., 1993)	5-CSRT (Chudasama and Robbins, 2004)	N/A	Novel object recognition (Bevins and Besheer, 2006) Visual discrimination (Bussey et al., 2012)	Visual discrimination and reversal (Bussey et al., 2012) Cross maze set shifting task (Yawata et al., 2012)	5-CSRT (Chudasama and Robbins, 2004)	Social interaction Social recognition (Nadler et al., 2004)

WCST: Wisconsin Card Sorting Test

WMS-III: Wechsler Memory Scale®-3rd Edition

BACS: Brief Assessment of Cognition in Schizophrenia

CPT-IP: Continuous Performance Test-Identical Pairs

BVMT-R: Brief Visuospatial Memory Test-Revised

MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test

5-CSRT: 5-choice serial reaction time task

Table 7

A comparison of behavioral domains in MATRICS, CNTRICS, and RDoC.

MATRICES	CNTRICS	RDoC
Attention/vigilance Reasoning and problem solving Executive functioning Processing speed Working memory Reversal learning Short and long term recognition memory Long term memory and learning	Attention/vigilance Reasoning and problem solving Processing speed Working memory Verbal learning and memory Visual learning and memory Social cognition	Cognitive systems Attention Perception Working memory Cognitive control Positive valence systems Reward learning Reward valuation Negative valence systems Fear Anxiety Loss Systems for social processing Attachment formation Social communication Perception of self Perception of others Arousal/modulatory systems Arousal Circadian rhythm Sleep and wakefulness