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Review

Neural correlates of cognitive deficits across developmental phases of schizophrenia

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A B S T R A C T

Schizophrenia is associated with cognitive deficits across all stages of the illness (i.e., high risk, first episode, early and chronic phases). Identifying the underlying neurobiological mechanisms of these deficits is an important area of scientific inquiry. Here, we selectively review evidence regarding the pattern of deficits across the developmental trajectory of schizophrenia using the five cognitive domains identified by the Research Domain Criteria (RDoC) initiative. We also report associated findings from neuroimaging studies. We suggest that most cognitive domains are affected across the developmental trajectory, with corresponding brain structural and/or functional differences. The idea of a common mechanism driving these deficits is discussed, along with implications for cognitive treatment in schizophrenia.

1. Introduction

Schizophrenia is a psychiatric disorder that affects approximately 1% of the general population (e.g., Saha et al., 2005). It is one of the most debilitating of psychiatric disorders, significantly affecting the lives of patients and their families. While schizophrenia is commonly associated with positive and negative symptoms, cognitive dysfunction is also a core feature of the disorder (e.g., Stone and Seidman, 2016). Importantly, findings suggest that cognitive function in schizophrenia is one of the most critical determinants of quality of life and daily function (e.g., Nuechterlein et al., 2014). Such findings have resulted in a proliferation of research on cognition in schizophrenia, as well as on the underlying cognitive neuroscience of the illness (e.g., Barch and Ceaser, 2012).

Schizophrenia is associated with deficits in several domains of neurocognition including processing speed, attention, working memory, verbal memory and learning, problem solving, and executive functions (e.g., Nuechterlein et al., 2004). Meta-analyses have shown moderate to large effects for impairment in each of these cognitive domains in individuals with schizophrenia (approximately one standard deviation below the mean observed in the general population) (Mesholam-Gately et al., 2009; Fatouros-Bergman et al., 2014; Heinrichs and Zakzanis, 1998; Savla et al., 2013; Schaefer et al., 2013). Similar patterns of cognitive impairment in both recent onset and in chronic medicated patients diagnosed with schizophrenia have also been observed (Czepielewski et al., 2015), as well as between first-episode un-medicated and medicated patients (e.g., Censits et al., 1997; Hill et al., 2004).

In addition, cognitive deficits have been reported prior to the onset of psychotic symptoms (e.g., Jones et al., 1994). Research on family high-risk (FHR) populations also suggests that cognitive deficits may be related to a genetic component of schizophrenia. For example, non-psychotic relatives of individuals with schizophrenia demonstrate deficits with a moderate level of severity compared with healthy controls, particularly in measures of full-scale IQ, vocabulary and word reading, with more modest differences in sustained attention and working memory (Agnew-Blais and Seidman, 2013). Of further note, a recent meta-analysis by Bora et al. (2017) identified deficits in processing information and processing speed in FHR individuals. These investigators observed low performance in accuracy-based tasks as well as deficits in general intellectual ability, verbal learning, planning, and working memory. Neurocognitive impairment is also a robust

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characteristic of clinical high-risk (CHR) individuals, especially those who later convert to psychosis (e.g., Seidman et al., 2016b).

As cognitive deficits remain a core feature of schizophrenia, identifying the underlying neurobiological mechanisms of these deficits is an important area of scientific inquiry. It has been proposed that cognitive disturbances associated with the disorder are likely manifestations of brain abnormalities (e.g., Seidman, 1983). The advent of magnetic resonance imaging (MRI) technology has made it possible to study the brain *in vivo*, and to assess associations between cognitive measures and measures of brain structure, including gray matter volume and white matter microstructure. Brain function can also be assessed using functional magnetic resonance imaging (fMRI) and using electrophysiological responses to stimuli [i.e., event-related potentials (ERPs)]. The culmination of this research suggests that cognitive performance depends on the integrity of brain systems that are distributed and multifaceted (Walter Heinrichs, 2005). The wide array of cognitive domains impaired in schizophrenia, accompanied by the vast and dynamic brain networks underlying these cognitive impairments, presents a challenge for researchers to fully conceptualize neurocognitive deficits in schizophrenia.

In an effort to provide an integrative framework for psychiatry research, the Research Domain Criteria (RDoC) initiative provides an alternative approach to the investigation of psychosis spectrum disorders by integrating information from many levels (e.g., from genomics to circuits to behavior), as well as by examining basic dimensions of functioning that span the full range of human behaviors. The goal of RDoC is to understand psychiatric illnesses in terms of varying degrees of dysfunctions in neural systems underlying cognitive processes.

Building on the efforts of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiatives, the RDoC matrix provides a dimensional approach to the study of genetic, neural, and behavioral features of psychiatric disorders (e.g., Morris and Cuthbert, 2012). The RDoC's integrative model includes neurocognition, social cognition, arousal/regulatory systems, as well as negative and positive valence systems, with a focus on the underlying neural circuits. The neurocognitive system domains of RDoC include: perception, attention, working memory, declarative memory, and cognitive control. By taking a more biologically driven approach, the RDoC framework may help to advance our understanding of complex neurocognitive processes and underlying neurobiological systems that are implicated in schizophrenia.

1.1. Scope of current review

To examine neurocognitive deficits in schizophrenia and their associated neural correlates, this review is selective and uses the integrative framework of RDoC cognitive domains to report findings from neuroimaging modalities, across the different phases of schizophrenia, including chronic, first-episode, and high-risk. As schizophrenia is highly heritable, with first-degree relatives also demonstrating alterations in cognition (e.g., Chen and Faraone, 2000; Keshavan et al., 2005), we will also review selective findings reported in the literature from both clinical and genetic high-risk populations.

Below we review RDoC domains of perception, attention, working memory, declarative memory, and cognitive control across the different phases of schizophrenia, and end with a commentary on the possible implications for cognitive treatment of schizophrenia.

2. Perception

2.1. Concept

Perception involves recognizing and interpreting sensory stimuli. Perception is closely associated with attention processes in that perception is the ability to make sense of the surrounding environment, while attention is the ability to concentrate on the perceived stimuli. Perceptual organization involves the processes by which stimuli are structured into coherent patterns such as groups, contours, perceptual wholes, and object representations. Many of the more consistently reported positive symptoms in schizophrenia, including delusions and visual/auditory hallucinations, suggest that the mechanisms underlying perception are potentially compromised. While such deficits are also observed in olfactory and somatosensory perceptual processing in schizophrenia, we will only focus on perceptual organization, and visual and auditory perception.

2.2. Perception in chronic schizophrenia

2.2.1. Behavioral findings

Consistent deficits in visual processing and perceptual organization have been observed in chronic schizophrenia using a number of experimental paradigms, including contrast detection, gestalt processing, and motion perception (e.g., Butler et al., 2008; Silverstein and Keane, 2011). Impairments in perceptual organization have been associated with poor premorbid functioning, poor prognosis, and disorganized symptoms. Auditory perception seems to also be impaired in schizophrenia, whereby patients evince difficulties in discriminating tone and/or rhythm, leading to difficulties in phonological processing and auditory emotion recognition (see Javitt et al., 2015 for a review).

2.2.2. Neural correlates

The underlying neurobiological mechanisms of perceptual processes in schizophrenia have been evaluated using event related potential (ERP) and functional magnetic resonance imaging (fMRI). Silverstein and Keane (2011) conducted a systematic review focusing on neural mechanisms they believed to be specifically implicated in perceptual organization in schizophrenia. In this review, the authors report that imaging studies consistently demonstrate impaired visual perceptual organization in schizophrenia, which is associated with disruption of (1) early visual cortex, such as V1, (2) inferior temporal regions involved in object perception and recognition, (3) parietal regions involved in orienting attention to objects within the surrounding space, (4) frontal regions involved in vision of objects (e.g., anterior portions of the ventral visual pathway including the ventrolateral prefrontal cortex orbitofrontal cortex used for object representation), (5) the P100 (pre-attentional) components of the ERP, and (6) synchronization of oscillations within the beta and/or gamma band (Silverstein and Keane, 2011). Another ERP component used to measure perception is Mismatch Negativity (MMN). MMN reflects the brain's ability to perform automatic perceptual comparisons between consecutive stimuli and is thought to reflect pre-attentive information processing at the level of primary auditory cortex (e.g., Javitt, 2000). This component is widely used to investigate auditory perception impairments in schizophrenia, with reductions in MMN amplitude observed in schizophrenia compared with healthy controls (e.g., Lee et al., 2017).

2.3. Perception in first-episode and high-risk:

2.3.1. Behavioral findings

Behavioral findings suggest that visual perceptual organization does not differ among ultra high-risk, first-episode groups, and healthy controls (e.g., Silverstein et al., 2006), suggesting that these abnormalities may reflect illness progression or associated medication effects. However, differences in auditory perception may also be altered in the earlier phases of the illness (e.g., Lee et al., 2017). In clinical high-risk samples, for example, visual abnormalities strongly predict lower risk of conversion to psychosis, while auditory abnormalities predict higher risk (Lehembre-Shiah et al., 2017).

2.3.2. Neural correlates

fMRI studies of perceptual organization and visual perception in first-episode and high-risk populations are scant, with findings from MMN studies more widely reported. Contrary to what is observed in the chronic phase of schizophrenia, Salisbury et al. (2018) reported no difference between first-episode patients and controls for MMN related to deviants in pitch or duration. In a meta-analysis by Haigh et al. (2017) no significant MMN reduction in first-episode patients to pitch-deviants was observed, however, a small-to-medium reduction to duration-deviants was reported. The authors concluded that pitch deviant MMN is not a candidate biomarker for schizophrenia risk, while duration-deviant MMN may be. Another study by Erickson et al. (2016) investigated MMN as an index of disease risk and progression by conducting a meta-analysis of MMN data in first-episode, chronic, and mixed-stage schizophrenia, as well as in unaffected first-degree relatives, and clinical high-risk individuals. They found that chronic patients evince significantly larger effect sizes for MMN impairments compared to first-episode patients, suggesting that MMN amplitude is associated with disease progression. However, they also reported no association between MMN and duration of illness, suggesting that progressive impairment in patients may not be a linear process. They also observed significant MMN impairments in individuals who were at elevated clinical high-risk for converting to psychosis, with no differences reported in individuals who were at genetic high-risk. Taken together, findings related to MMN impairments in first-episode and high-risk individuals are mixed. Some individual studies have reported no significant differences in first-episode whilst meta-analyses have reported differences in duration deviant MMN for first episode individuals, as well as MMN differences in clinical high-risk.

3. Attention

3.1. Concept

Attention involves several processes necessary for the identification of relevant stimuli, including focusing on some stimuli while ignoring other stimuli (selective attention), and focusing on stimuli until they are processed (sustained attention or vigilance) (Trivedi, 2006). Thus, attention can be considered the gateway for information flow to the brain.

3.2. Attention in chronic schizophrenia

3.2.1. Behavioral findings

There is a great deal of evidence demonstrating that chronic schizophrenia patients experience deficits in both sustained and selective attention abilities (e.g., Hoonakker et al., 2017; Luck and Gold, 2008). Data from the Consortium on the Genetics of Schizophrenia (COGS) revealed that not only are attention deficits reliably detected across cohorts, but they are also relatively independent of current symptom severity and, importantly, they are associated with functional capacity (e.g., Nuechterlein et al., 2015). A meta-analysis of 76 studies measuring attention using reaction time to stimuli also showed that patients with schizophrenia have a slower reactivity than controls (Fioravanti et al., 2012). However, this meta-analysis did not take into consideration the potential effects of deficits in motor speed that may contribute to the differences in reaction time.

Gold et al. (2007) reported that patients are able to effectively filter distractors when attention is guided by relatively automatic processes (i.e., when the target and distractors are so similar that a random search for the target is necessary), but have more difficulty limiting their search to the target item when attention is guided by more controlled processes (i.e., when subjects are required to search for a well-defined feature that is relatively low in salience). During these controlled trials, patients with schizophrenia show impairments in their ability to guide their attention. These findings suggest that executive control (which we will define in more detail later) may also impact fundamental aspects of attention in schizophrenia.

3.2.2. Neural correlates

During performance of attention tasks, brain activity in patients with schizophrenia differs from that of healthy controls, particularly in regions considered to comprise an attentional network, including the dorsolateral prefrontal cortex (DLPFC), the insula, the anterior cingulate gyrus (ACG), the amygdala, hippocampus, ventral striatum, thalamus and cerebellum (Carter et al., 2010; Liddle et al., 2006). However, as attention is a multi-faceted construct with differential patterns of activation depending upon various aspects that the task engages, inconsistent findings are often noted in the literature (e.g., Carter et al., 2010). For example, patients with schizophrenia display greater cortical activity than controls on less demanding tasks of attention, but less cortical activity than controls on more demanding tasks of attention (Karch et al., 2009). Thus, conflicting findings may be due to the type of attention elicited in the study design.

More specifically, most attention tasks require some aspect of sustained attention that is maintained throughout the performance of a task, as well as require more transient aspects of attention that are engaged during the most crucial moments of a task. To investigate this further, Carter et al. (2010) examined activation in transient vs sustained phases of attention in schizophrenia. Both healthy controls and schizophrenia patients displayed activation in regions of the attentional network, including the anterior cingulate gyrus, DLPFC, insula and inferior parietal sulcus, with the schizophrenia group displaying a greater percentage of active voxels than controls in many regions. However, during transient periods of attention, the schizophrenia group displayed a lower percentage of active voxels than controls. These findings suggest that attention deficits in schizophrenia may be a result of impairments in brain activation associated with transient, attention demanding stimuli, rather than impairments in sustained attention. Such findings may also help to explain some of the inconsistent findings in the literature.

Progressive changes in brain structure over the course of the illness also correlate with attention performance. For example, Andreasen et al. (2011) analyzed brain structural measures at time intervals of up to 15 years after illness onset and found that progressive impairment of brain structure in patients correlated with cognitive impairment, with the largest effects observed for attention, as well as verbal learning, problem solving, and working memory. Of note, frontal, temporal, and parietal white matter loss was associated with poor attention performance, as well as total frontal and total parietal volume reduction. Finally, fronto-temporal white matter has also been implicated in attention deficits in schizophrenia. A study by Singh et al. (2016) using diffusion tensor imaging (DTI) showed significantly reduced fractional anisotropy (FA) values in the uncinate fasciculus compared to controls. In schizophrenia patients, a positive correlation of attention, spatial memory, sensorimotor dexterity and emotion with FA of the uncinate fasciculus was observed.

In addition to MRI measures, ERPs can also shed light on the neural correlates of attention deficits in schizophrenia. The P300 waveform is an ERP that is typically elicited during an auditory or visual attentional task and is thought to reflect processes involved in discrimination of relevant vs non-relevant stimuli. Electrodes covering the central-parietal region of the scalp measure this signal most strongly. Findings of reductions in P300 amplitude and increase of latency in patients with schizophrenia, relative to healthy controls, are quite robust (e.g., O'Donnell et al., 1995; Mathalon et al., 2000; Bramon et al., 2004). P300 amplitude is thought to be related to the amount of attentional resources devoted to the task, whereas P300 latency is thought to reflect stimulus classification/perceptual processing speed (see Earls et al., 2016). Early studies suggest that visual P300 is more sensitive to clinical state, while the auditory P300 is more sensitive to trait (e.g., Duncan, 1988; Mathalon et al., 2000). More specifically, Mathalon et al.

(2000) conducted a longitudinal study of auditory and visual P300 and clinical symptom fluctuations over time and found that both auditory and visual P300 were associated with fluctuations in symptoms but only auditory P300 could be used as a trait marker of schizophrenia. This may suggest that visual P300 is more sensitive to clinical state.

3.3. Attention in first-episode and high-risk

3.3.1. Behavioral findings

Attention impairments are also observed in first-episode psychosis (e.g., Aas et al., 2014). Orellana et al. (2012) suggested that first-episode patients are impaired in sustained attention but not necessarily in selective attention. Interestingly, a genetic predisposition to schizophrenia has been associated with reduced performance in attention (e.g., Birkett et al., 2007). For example, a substantial proportion of nonpsychotic relatives of schizophrenia patients (19–34%) have deficits in attention performance (Chen and Faraone, 2000), suggesting that these impairments may be a suitable endophenotype of schizophrenia. However, it remains unclear whether or not attention deficits are associated with a risk for developing schizophrenia. In a meta-analysis of 9 studies involving clinical high-risk individuals, there were no significant differences found in sustained attention between individuals who convert to psychosis versus those who do not convert (De Herdt et al., 2013). Additionally, a separate meta-analysis showed that individuals who transitioned to psychosis later did not exhibit more severe sustained attention deficits (Bora and Murray, 2014). However, a recent study from the North American Prodrome Longitudinal Study (NAPLS) reported results in juxtaposition to these previous findings. More specifically, Seidman et al. (2016a, 2016b) reported that individuals who converted to psychosis had large deficits in attention compared with controls and had significant deficits in these measures compared to non-converters. Such inconsistencies in findings may be related to the diverse array of attention tasks used and/or to the selection of case and control samples. Further investigation is needed to address these inconsistent findings.

3.3.2. Neural correlates

Some cross-sectional studies suggest the possibility that P300 may reflect the progressive nature of a pathological process in schizophrenia patients (e.g., O'Donnell et al., 1995; Mathalon et al., 2000). However, only longitudinal studies can provide data to clarify the nature of disease progression. In an attempt to address this, Oribe et al. (2015) found that during a first-episode of psychosis, patients show reduced visual P300 amplitude and delayed P300, with P300 showing progressive amplitude reduction over the course of the illness at 1-year follow-up, suggesting that visual P300 may be a useful biological marker of illness progression. In a meta-analysis of auditory ERPs in first-degree relatives, Earls et al. (2016) showed that P300 amplitude and latency might serve as viable endophenotypes for schizophrenia. Auditory P300 amplitude is also reduced in genetic high-risk groups (e.g., Kim et al., 2018). The auditory P300 can also distinguish clinical high-risk and first-episode individuals from healthy controls, suggesting that these two groups may be characterized by similar deficits in P300 ERPs (e.g., del Re et al., 2015). Auditory P300 abnormalities are also observed in individuals who convert to psychosis compared to those who do not convert (Tang et al., 2017), suggesting that auditory P300 may also be a potential biomarker for conversion. Taken together, these findings suggest that while visual P300 may be a biomarker of disease progression, auditory P300 may be a suitable endophenotype, as well as a potential biomarker for conversion to psychosis.

Gray matter abnormalities have also been associated with impairments in sustained attention in first-episode patients. Salgado-Pineda et al. (2003) reported that gray matter density in the left thalamic nucleus, left angular and supramarginal gyrus, and left inferior frontal and postcentral gyri correlated significantly with performance during an attentional task in patients but not in controls.

4. Working memory

4.1. Concept

Working memory refers to the temporary representation of information that has recently been experienced or recently retrieved from long-term memory storage. The internal representation of this information is transient, but can be maintained for sustained periods of time with the assistance of active rehearsal strategies. Working memory can be subjected to operations that manipulate the information in such a way that it becomes useful for goal-directed or task-relevant behavior. Ultimately, the ability to employ working memory underlies many critical types of human thought processing, such as reasoning, language comprehensive, goal-planning and spatial processing because it provides an interface between perceptive abilities, long-term memory, and action (Baddeley, 2003).

4.2. Working memory in chronic schizophrenia

4.2.1. Behavioral findings

Working memory deficits have consistently been identified as a key feature of schizophrenia pathophysiology (e.g., Forbes et al., 2009; Park and Gooding, 2014). Schizophrenia patients have demonstrated deficits for every component of the working memory model (e.g., phonological, visuospatial, and executive functioning), suggesting that there is not a single component or sub-process of working memory that could be an effective marker for the disorder (Park and Gooding, 2014).

Of further note, despite multiple studies demonstrating significant decreases in IQ in patients with schizophrenia, a meta-analysis conducted in 2009 showed no association between working memory decline and reductions in IQ in patients (Forbes et al., 2009). Working memory deficits also do not appear to be related to severity of positive or negative symptoms (e.g., Forbes et al., 2009; Haenschel et al., 2009; Zanello et al., 2009), nor have they been linked to cumulative antipsychotic medication use (Forbes et al., 2009; Park and Gooding, 2014). This combined evidence has encouraged many to propose that working memory deficits could serve as an endophenotypic marker of schizophrenia, as deficits appear to be more closely related to trait-related aspects of the disorder as opposed to more state-related features of the illness such as cumulative medication dose or illness severity (see Park et al., 2014 for an extensive discussion).

4.2.2. Neural correlates

Reduced activation in the DLPFC during working memory tasks, correlating with poorer performance, has been observed in chronic schizophrenia (Glahn et al., 2005). This hypofrontality is reported in chronically ill patients, as well as in populations of medicated and medication-naïve patients (Barch et al., 2002; Mendrek et al., 2005; Menon et al., 2001). As well as hypo-activation, hyper-activation of the DLPFC has also been observed during working memory in schizophrenia and may depend on the particular conditions of the working memory task (Van Snellenberg et al., 2006). Callicott et al. (2003) investigated patterns of hypo- and hyper-activation of the prefrontal cortex in schizophrenia during working memory. They found that during a working memory task, patients showed both hypo and hyper activation in regions of the dorsolateral prefrontal cortex compared to healthy subjects. However, when groups were subdivided based on working memory performance into healthy subjects and patients with high or low performance, regions of higher prefrontal activation and regions of lower activation were found in the high-performing patients but only regions of lower activation were found in the low-performing patients. The authors concluded that patients with schizophrenia who perform similarly to healthy controls use greater prefrontal resources but achieve lower accuracy (i.e., inefficiency) and that other patients with schizophrenia fail to sustain the prefrontal network that processes the information, resulting in even lower accuracy.

The notion of altered functional connectivity in patients during working memory has also been supported. A study by Ragland et al. (2012) demonstrated that, unlike controls, patients with schizophrenia did not show greater activation in the DLPFC with increased task demand, but instead showed a more diffuse network to meet the same processing demands (Ragland et al., 2012).

Several studies have also shown increased brain activation in areas such as the anterior cingulate cortex and the frontal pole in schizophrenia patients (Glahn et al., 2005), as well as increased functional connectivity between the DLPFC and the hippocampus (Wolf et al., 2009). In fact, abnormal functional connectivity between medial temporal lobe regions, specifically the hippocampus, was evident in a study by Meyer-Lindenberg et al. (2005), where functional connectivity between the hippocampal formation and both the DLPFC and inferior parietal lobe was attenuated in control subjects but not in patients. The authors suggested that the failure to decouple DLPFC-hippocampal activity during working memory tasks may underlie poor performance (Meyer-Lindenberg et al., 2005). In addition to altered fronto-temporal connectivity, schizophrenia patients exhibited decreased connectivity between the PFC and the cerebellum (Schlösser et al., 2003), as well as enhanced connectivity between thalamo-cortical connections (Schlösser et al., 2003) while performing working memory tasks. Taken together, the evidence points to a disruption in frontally-represented top-down executive control, which leads to an increased engagement of other brain regions in order to compensate for increased task demands.

Reduced cortical thickness has also been observed in the left inferior frontal gyrus, left insular cortex, and left precentral gyrus in schizophrenia patients which was associated with aberrant functional connectivity patterns during working memory tasks (Pujol et al., 2013). Interestingly, a study carried out by Ehrlich and colleagues showed that schizophrenia patients exhibit a differential structure-function relationship to that observed in controls. In this study, healthy control subjects showed strong correlations between working memory ability and lateral prefrontal area. However, the patients exhibited associations within right middle and superior temporal lobe, which the authors interpreted as a possible engagement of a compensatory or alternative network to perform working memory tasks (Ehrlich et al., 2012).

Subcortical structures, specifically the hippocampus, have also been implicated in working memory performance in schizophrenia patients. Reduced hippocampal gray matter volume has been linked to poorer performance on working memory tasks in patients at both early (Guo et al., 2014a, 2014b) and late stages of the illness (Wolf et al., 2008), although with some inconsistencies in findings across studies (Harms et al., 2013). Similarly, reductions in caudate volume have also been linked to compromised working memory performance in schizophrenia (Laywer et al., 2006). Finally, fronto-parietal white matter has been associated with working memory in recent-onset schizophrenia, with FA of the superior longitudinal fasciculus correlating with verbal working memory performance in both patients and controls (Karlsgodt et al., 2008).

4.3. Working memory in first-episode and high-risk

4.3.1. Behavioral findings

At the onset of psychosis, it has been shown that working memory is particularly affected (e.g., Forbes et al., 2009; Mesholam-Gately et al., 2009). For example, a meta-analysis focused specifically on first-episode patients has shown that decline in working memory ability is most evident during transition to illness but once patients enter a more chronic stage of the illness, working memory deficits appear to stabilize and exhibit limited deterioration with illness progression (e.g., Mesholam-Gately et al., 2009). However, both publications stress that there was significant heterogeneity across the studies included, suggesting that the manifestation of illness, as well as methodological considerations (e.g., differential psychometric properties of specific tasks, etc.) need to be considered when interpreting findings (e.g., Forbes et al., 2009; Mesholam-Gately et al., 2009).

Of note, deficits seem to appear within the prodromal period and deteriorate as individuals enter the first-episode of illness (Meier et al., 2014; Wood et al., 2001). Retrospective birth cohort studies have clearly demonstrated premorbid deficits in working memory starting at around 7–9 years of age in those individuals who go on to develop schizophrenia (e.g., Meier et al., 2014; Reichenberg et al., 2010; Seidman et al., 2006). In fact, in the largest study of clinical high-risk subjects to date, the North American Prodrome Longitudinal study showed that those who ultimately convert to psychosis display considerable reductions in working memory abilities compared to controls and non-converters (Cohen's d approximately 0.80) (Seidman et al., 2016b), even after controlling for general cognitive ability and medication exposure.

A few studies suggest that working memory deficits, in general, can best distinguish between prodromal subjects and healthy controls (e.g., Pflueger et al., 2007), as well as between prodromal subjects who ultimately convert to psychosis versus those who do not (Pukrop et al., 2007). Lastly, unaffected, un-medicated first-degree relatives of schizophrenia patients also show reductions, although to a lesser degree in working memory ability, lending more support to the idea that working memory is minimally influenced by medication and may serve as a trait-related marker of the illness (e.g., Agnew-Blais and Seidman, 2013; Seidman et al., 2012; Seidman et al., 2016a; Zhang et al., 2016).

4.3.2. Neural correlates

Functional MRI studies have reported hypofrontality and impaired working memory modulation of fronto-parietal effective connectivity in the early phase of schizophrenia, even with intact working memory performance (Nielsen et al., 2017). Additionally, in a sample of first-episode patients, Tan et al. (2005) reported that *manipulation* of information in working memory is more impaired than maintenance of information in working memory, and this is associated with regions of dysfunctional and compensatory prefrontal responses in the dorsolateral and ventrolateral prefrontal cortex. Reduced cerebellar volume in first-episode patients has also been implicated in poorer performance on working memory tasks (Wang et al., 2017). Reductions in the volume of the anterior cingulate has also been strongly correlated with performance deficits in working memory processes and executive functioning for male, but not female, first-episode patients (Szeszko et al., 2000).

The prodromal phase of psychosis is associated with functional alterations in parietal and temporal networks that subserve visuospatial working memory and which are more evident under high cognitive loads (Fusar-Poli et al., 2010a). Furthermore, clinical improvement in prodromal cases between baseline and one year is associated with a compensatory increase in occipito-parietal activation during visuospatial working memory (Fusar-Poli et al., 2010a).

There is also a large body of evidence demonstrating abnormal activation in unaffected and un-medicated relatives of patients with schizophrenia. Individuals with schizophrenia and their siblings are impaired in their ability to encode the temporal order of items within working memory and such disturbances in working memory and PFC activation may be genetic markers of the vulnerability to schizophrenia (Brahmbhatt et al., 2006). Greater activation in DLPFC in adolescents at genetic high-risk for schizophrenia has been observed during working memory tasks (e.g., Seidman et al., 2006). Further, in a meta-analysis conducted by MacDonald et al. (2009), the authors found that of the five fMRI studies that employed a working memory task, four showed increases in the right dorsal PFC region in the unaffected relatives of patients with schizophrenia (Macdonald et al., 2009). While increased right dorsal PFC activation was the most consistent finding, increased activation in the ventral PFC and reduced activation in the cerebellum was also reported (Macdonald et al., 2009).

In a more recent meta-analysis by Zhang et al. (2016), the authors reported that compared to healthy controls, unaffected relatives also

show reduced activation in the right middle frontal gyrus and the right inferior frontal gyrus, as well as increased activation in the right frontopolar, left inferior parietal lobule, and the bilateral thalamus when performing a working memory task (Zhang et al., 2016).

Taken together, these studies provide evidence for the presence of differential activation patterns in unaffected family members who have an increased genetic risk for schizophrenia. Also, and similar to the patients, these abnormal activations have been interpreted as reflecting a compensatory response to increased working memory load.

5. Declarative memory

5.1. Concept

Declarative memory is defined as the conscious acquisition, consolidation, and recollection of facts or events. Declarative memory can be divided into two subsystems: (1) semantic memory, referring to our knowledge of the word, and (2) episodic memory, referring to our long-term memory of information related to experienced events and their context. To illustrate these two subtypes of declarative memory, a person would use semantic memory to remember that San José is the capital of Costa-Rica, whereas this same person would use episodic memory to remember details of their last vacation in Costa-Rica (i.e., where did they go, what food did they eat, etc.).

5.2. Semantic memory in chronic schizophrenia

5.2.1. Behavioral findings

Disorganized and abnormal semantic category structure has been observed in schizophrenia during the performance of category verification tasks (e.g., Chen et al., 1994), verbal fluency tasks (e.g., Alexiadou et al., 2018; Allen et al., 1993; Elvevag et al., 2002; Gourovitch et al., 1996; McKay et al., 1996), and categorical sorting tasks (e.g., Lawrence et al., 2007; McKay et al., 1996). However, it is less clear whether semantic priming (i.e., a faster response to a target (e.g., snow) when it is preceded by a semantically related cue (e.g., winter) in schizophrenia is impaired or not. Findings suggest that semantic priming is abnormal in schizophrenia under explicit tasks, but the results are not consistent under implicit conditions (Minzenberg et al., 2002). A meta-analysis has shown no clear evidence for altered semantic priming in schizophrenia in general, although patients with thought disorder show increased semantic priming compared to healthy individuals, but not compared to patients without thought disorder (Pomarol-Clotet et al., 2008). In another meta-analysis, Doughty and Done (2009) observed an uneven profile of semantic impairments in schizophrenia, with large effect sizes for tests of naming and verbal fluency, medium effect sizes for word-picture matching and association, and small effect sizes for categorization and priming tests. The authors concluded that degradation of semantic knowledge may not be sufficient for explaining poor performance during tasks that recruit semantic memory in schizophrenia.

Taken together, these results indicate that schizophrenia patients may show abnormal performance in tasks related to semantic knowledge, but the nature of these abnormalities remains difficult to understand. In addition, there is a great deal of variability among the findings that likely arises from the different tasks and conditions used (e.g., implicit or explicit instruction to memorize the information).

5.2.2. Neural correlates

The N400 is an event related potential that has been established as an index of semantic memory, and its activation is localized to the anterior medial temporal lobes, as well as to middle and superior temporal areas, inferior temporal areas, and prefrontal areas (e.g., Kutas and Federmeier, 2011). Many studies have observed reduced N400 semantic priming effect between unrelated and related targets in schizophrenia, which may reflect a difficulty to activate related concepts in semantic memory in this clinical population (e.g., Condray et al., 2010; Guerra et al., 2009; Kiang et al., 2008; Mathalon et al., 2010; Salisbury, 2008). However, the priming effect of the N400 also seems to be related to the implicit/explicit nature of the task in schizophrenia. In explicit tasks, patients with schizophrenia show a reduced semantic priming effect on the N400 (Kreher et al., 2009). However, during implicit tasks, as a group, schizophrenia patients show a normal N400, while those patients with thought disorder show an increase in semantic priming effect on the N400 (Kreher et al., 2009).

5.3. Semantic memory in first-episode and high-risk

5.3.1. Behavioral findings

Decline in performance during tasks that recruit semantic memory seems to be progressive and accompanied with multiple-episode schizophrenia (Kanchanatawan et al., 2017). At the time of first-episode, verbal fluency seems already to be impaired, however deficits in naming and semantic memory are not necessarily apparent (Kanchanatawan et al., 2017; Mesholam-Gately et al., 2009). Cross-sectional studies have observed poor performance in semantic and verbal fluency in those at clinical high-risk for schizophrenia compared to normal controls (Bora and Murray, 2014; Shin et al., 2016). Further, when compared to controls, siblings of patients with schizophrenia show significantly less word output in the verbal fluency test (Chen et al., 2000). Moreover, ultra-high-risk individuals who convert to psychosis show modest impairments for verbal fluency compared to those who do not convert (Bora and Murray, 2014). Verbal fluency thus seems to be impaired before the first-episode of psychosis, and could be a familial trait marker for schizophrenia. However, the evidence for a broader semantic memory deficit before chronicity of the illness remains scant and further studies are needed to determine whether and to what extent these deficits are present prior to chronicity.

5.3.2. Neural correlates

The literature regarding the N400 in first-episode psychosis and high-risk populations is scant and results are not consistent. For example, Guerra et al. (2009) reported larger than normal N400 amplitude for patients and their unaffected first-degree relatives for related targets, but other studies have reported no significant difference between first-degree relatives and controls (Kiang et al., 2014; Kimble et al., 2000; Pfeifer et al., 2012). While more research is needed, the N400 semantic priming could be a potential biomarker of schizophrenia, as opposed to an endophenotype with a clear genetic connection, which is in line with the lack of clear evidence of broader semantic memory deficits before chronicity of the illness.

5.4. Episodic memory in chronic schizophrenia

5.4.1. Behavioral findings

Episodic memory is generally impaired in schizophrenia (e.g., Achim and Lepage, 2003, 2005; Danion et al., 2007; Lepage, 2007). Moreover, no medication effect, clinical symptoms, nor other impaired cognitive domains (i.e., attention) completely account for episodic memory deficits observed in schizophrenia (e.g., Cirillo and Seidman, 2003). The severity of impairments depends on specific conditions under which patients are encoding or recollecting the information (e.g., Ranganath et al., 2008). For example, schizophrenia patients have moderate impairments in recognition, but large impairments in retrieval performance (e.g., Aleman et al., 1999). Individuals with schizophrenia are also more impaired when they need to memorize relations between items, rather than memorizing items alone (Achim and Lepage, 2003; Guimond et al., 2017; Ragland et al., 2012).

5.4.2. Neural correlates

Many studies have suggested that episodic memory impairments in schizophrenia are related to dysfunction in prefrontal and medial

temporal lobes, especially in the hippocampus (e.g., Achim and Lepage, 2005; Ranganath et al., 2008). Consistently less prefrontal activation in patients with schizophrenia compared to controls is observed in the DLPFC and ventrolateral prefrontal cortex during both encoding and retrieval (Ragland et al., 2009). More specifically, the DLPFC seems to be a key region for relational encoding of long-term episodic memory, and plays an important role in the deficits of such encoding processes in schizophrenia (Guimond et al., 2017; Lepage et al., 2006; Ragland et al., 2012). Reduced activity in the hippocampus also seems to play a role in the deficits for recognition of associations in schizophrenia, but not for recognition of item-specific information (Ragland et al., 2015a). In general, lower prefrontal cortex and hippocampal volume have also been associated with impaired episodic memory performance in schizophrenia (Baare et al., 1999; Seidman et al., 1994). Similar findings in cortical thickness have also shown that the prefrontal and the medial temporal cortices are thinner in schizophrenia patients with more severe verbal episodic memory deficits (Guimond et al., 2016a; Hartberg et al., 2010).

Of further note, studies of white matter highlight a differential role for frontal and parietal regions in episodic memory in schizophrenia. More specifically, Green et al. (2016) observed that for patients, but not controls, episodic memory encoding correlated with white matter volume in the orbitofrontal cortex and increased radial diffusivity in the fornix, whereas episodic memory retrieval correlated with WM volume in posterior parietal cortex. These findings suggest a differential role for frontal and parietal WM in encoding and retrieval during working memory.

5.5. Episodic memory in first-episode and high-risk

5.5.1. Behavioral findings

Deficits in episodic memory appear to already be present at first-episode of psychosis (e.g., Aas et al., 2014; Kanchanatawan et al., 2017; Mesholam-Gately et al., 2009). First-episode patients show impairments in both item-specific and relational encoding of the information (Greenland-White et al., 2017). The overall level of episodic memory impairments seems stable during a period of 10 years following a first-episode of psychosis, but individuals who have psychotic relapse during the first year show larger decreases over time for the encoding measure of episodic memory (Barder et al., 2013).

Deficits in episodic memory are also present in clinical high-risk populations (e.g., Seidman et al., 2016b). Episodic memory impairments have also been reported in ultra-high-risk individuals for psychosis who later develop a psychotic episode, which is in line with the fact that this deficit is apparent before the full expression of the illness (Brewer et al., 2005). Seidman et al. (2016a, 2016b) also noted larger episodic memory deficits in clinical high-risk who converted to psychosis compared to those who did not convert. Even when adjusting for age, education, symptoms, antipsychotic medication, and overall neurocognitive performance in the other domains, verbal learning in episodic memory seems to be the only specific neurocognitive domain that predicts transition to psychosis in clinical high-risk individuals (Carrion et al., 2018). Interestingly, clinical high-risk individuals also show relational episodic memory deficits, but no impairments in item-specific episodic memory (Greenland-White et al., 2017). This finding could reflect underlying neurodevelopmental abnormalities that are associated with relational episodic memory which are present prior the conversion to psychosis and could be a potential endophenotype of schizophrenia (e.g., Lepage et al., 2015).

5.5.2. Neural correlates

First-episode psychosis patients show normal activation of many brain regions while performing an episodic memory task. However, abnormal activation has been observed in the hippocampus and surrounding medial temporal region for the encoding of arbitrary pairs (e.g., Achim et al., 2007). Hippocampal volume is also positively correlated with verbal episodic memory ability in first-episode schizophrenia individuals (Guo et al., 2014a, 2014b; Hasan et al., 2014). Moreover, during successful encoding in episodic memory, first-episode patients demonstrate reduced functional coupling from the seed in the medial temporal regions to the occipital and frontal regions (Haut et al., 2015). Patients with a first-episode of psychosis also exhibit abnormal brain activity in frontal, temporal, and parietal regions when they recollect past events related to new information (Guimond et al., 2016b).

During episodic memory encoding, those at clinical high-risk who later convert to psychosis demonstrate greater connectivity between the hippocampus and prefrontal cortex, and less connectivity between perirhinal and parahippocampal cortex seeds and occipital and parietal regions (Haut et al., 2015). A recent study also observed a specific correlation between cortical thickness in the temporal lobes and verbal episodic memory in first-degree relatives of individuals with schizophrenia (Fernandez et al., 2018). Left anterior hippocampal hypo-activations and right anterior hippocampal hyper-activations have been observed in unaffected relatives and may suggest an influence of schizophrenia-related genetic liability factors (Pirnia et al., 2015).

Together, these findings suggest that abnormalities in brain regions related to encoding in episodic memory precede the onset of psychosis among individuals at clinical high-risk for schizophrenia

6. Cognitive control

6.1. Concept

Cognitive control (or executive function) involves a range of functions, including goal maintenance, adaptive or reactive control, and performance monitoring (e.g., Lesh et al., 2011). Cognitive control is thus required for maintaining appropriate behavior during interference in a given situation. Cognitive control, however, is not restricted to a particular cognitive domain as it is essential for many cognitive processes, including attention, task switching, cognitive inhibition, error detection, response conflict, memory, and cognitive flexibility (e.g., Miller and Cohen, 2001).

6.2. Cognitive control in chronic schizophrenia

6.2.1. Behavioral findings

Cognitive control is a broadly impaired cognitive feature of schizophrenia (e.g., Lesh et al., 2011). It is also implicated in many of the cognitive impairments observed in schizophrenia. Impairments in this domain may lead to rigid behavior with an inability to respond in a flexible manner to changing situations. Such deficits have been associated with social isolation, poor interpersonal relationships (e.g., Bozikas et al., 2006), reduced quality of life (e.g., Addington and Addington, 2000), and low self-esteem (e.g., Wang et al., 2013).

6.2.2. Neural correlates

Cognitive control requires the coordination of multiple brain regions, including the DLPFC, medial frontal cortex (including the anterior cingulate), and parietal regions (see review by Lesh et al., 2011). The DLPFC is thought to be involved in maintenance of rules for action and response selection (Asaad et al., 2000). The anterior cingulate is implicated in response conflict and signals the DLPFC when control-related activity should be increased to improve performance (Egner and Hirsch, 2005), while parietal regions allow the DLPFC to shift attentional focus and provide information for learned stimulus–response pairings (Miller and Cohen, 2001). Interestingly, a meta-analysis of 41 neuroimaging studies of cognitive control in schizophrenia revealed reduced activation in patients within these regions, including the bilateral DLPFC, anterior cingulate, and mediodorsal thalamus (Minzenberg et al., 2009).

The DLPFC, superior parietal cortex (SPC), and anterior cingulate seem particularly important when participants are required to respond

to a probe based on a preceding cue (Smucny et al., 2018). Reduced brain activation in the left DLPFC in schizophrenia has been associated with cognitive control demand during encoding (Ragland et al., 2015b). It has been further suggested that when cognitive control is impaired, it may be more difficult to spontaneously use effective encoding strategies (Brigham and Pressley, 1988). Striatal activation is also implicated in cognitive control. For example, Ceaser and Barch (2016) reported greater prefrontal, as well as striatal, activity in patients during cognitive control tasks compare to healthy controls.

Functional and structural connectivity associated with cognitive control have also been examined, with reports of lower fractional anisotropy in the right anterior limb of the internal capsule, the right thalamus, and the right corpus callosum, as well as lower functional activation in a frontal-thalamic-cerebellar network in patients during a Stroop task (Wagner et al., 2015). Finally, to investigate network connections underlying cognitive control, Ray et al. (2017) observed greater network functional connectivity in the frontal parietal network in schizophrenia patients during cognitive control tasks.

6.3. Cognitive control in first-episode and high-risk

6.3.1. Behavioral findings

Evidence suggests that early developmental processes are associated with impairments in cognitive control. A meta-analysis by Mesholam-Gately et al. (2009) showed that impairments in executive function were already present during the first-episode. A recent study by Gay et al. (2017) examined the effects of early neurodevelopmental markers on cognitive control and reported interactions between neurological soft signs (NSS) and anterior cingulate morphology, between NSS and handedness and between anterior cingulate morphology and cerebrospinal fluid volume on cognitive control tasks. This supports the hypothesis that cognitive control impairments in patients with schizophrenia may be a final common pathway of several early neurodevelopmental mechanisms.

Cognitive control deficits during childhood have also been associated with increased risk for schizophrenia (e.g., MacCabe, 2008). For example, young relatives who later develop the disorder are more likely to have impairments in cognitive control during childhood (Keshavan et al., 2005). Such deficits are also evident in first-degree relatives of individuals with schizophrenia. More specifically, MacDonald et al. (2003) demonstrated that genetic liability is associated with deficits in context processing. A follow-up study by Delawalla et al. (2007) demonstrated significantly greater errors in siblings as well as increased activity throughout the cognitive control network compared with controls. Other measures of cognitive control, such as the Stroop test (e.g., Filbey et al., 2008) and the antisaccade task (e.g., (Calkins et al., 2004), have also been associated with genetic liability.

6.3.2. Neural correlates

During an fMRI task, first-episode patients showed impaired cognitive control that was associated with reduced activation of the DLPFC (Yoon et al., 2008). Furthermore, patients did not engage in the same fronto-parietal network as healthy controls under conditions requiring high cognitive control. DLPFC connectivity was also associated with increased symptoms of disorganization and poorer psychosocial functioning in first-episode individuals.

For clinical high-risk individuals, Morey et al. (2005) observed intermediate performance between healthy controls and first-episode patients, with the high-risk group showing smaller differential activation in frontal regions (including the anterior cingulate, inferior frontal gyrus, middle frontal gyrus) compared to the control group. Additionally, functional activity during cognitive control has been associated with reduced activations in clinical high-risk individuals compared with healthy controls in the ventral and dorsal striatum, and in the DLPFC, inferior frontal gyrus, anterior cingulate and cuneus (Colibazzi et al., 2016). Furthermore, cognitive control related activations in the DLPFC of CHR individuals who convert to psychosis are smaller compared to non-converters (Colibazzi et al., 2016). A review by Wood et al. (2007) noted that impairments in prefrontal cognitive functioning, and the underlying neurobiological abnormalities, provide the most likely marker of risk for conversion to psychosis. Finally, in a genetic high-risk sample, Becker et al. (2008) demonstrated that although behavioral performance on cognitive control tasks was similar for relatives of schizophrenia patients and controls, relatives showed increased activation in the right dorsal and ventral PFC, left parietal cortex, as well as significantly decreased activation in the left dorsal PFC.

Taken together, these findings demonstrate that high-risk individuals have difficulty activating cortical networks underlying effective cognitive control. These findings further suggest the potential role of abnormalities in these networks as a marker for psychosis risk.

7. Implications for treatment

Targets for treatment are also an area of scientific inquiry that is crucial for alleviating the symptoms of schizophrenia. In the future, perhaps the development of new treatments will not only ameliorate aspects of psychosis but also act as preventive measures in those at high-risk for developing schizophrenia. It is noteworthy also that antipsychotic medication has been shown to be effective in ameliorating positive symptoms, but negative symptoms are less responsive to such medications and there is scant evidence that such medications can enhance cognition in schizophrenia (e.g., Barch, 2010; Genevsky et al., 2010; Minzenberg and Carter, 2012; Yang et al., 2017).

It is possible that the underlying brain mechanisms of positive symptoms and cognitive deficits are different. The lack of a clear pharmacological agent that could improve cognitive deficits in schizophrenia, and the strong association between cognitive deficits and poor functional outcome, has led to the development, in recent decades, of psychosocial treatments aimed at improving cognition in schizophrenia. More specifically, in recent years, psychosocial intervention, such as cognitive remediation therapy (CRT), has shown more encouraging and positive results for treating cognitive impairments in schizophrenia. Moreover, meta-analyses demonstrate that CRT may improve cognition in individuals with chronic schizophrenia or schizoaffective disorders (e.g., McGurk et al., 2007; Wykes et al., 2011; Grynszpan et al., 2011). Some evidence of CRT efficacy for enhancing cognition has also been demonstrated in first episode psychosis and in early phases of psychosis in patients, as well as in clinical high-risk individuals (e.g., Rauchensteiner et al., 2011; Hooker et al., 2014). While the observed effect ranges from mild to moderate, this intervention is one of the more promising among existing treatments. Additional research is, nonetheless, needed to understand the underlying mechanisms responsible for the observed effects and to improve the efficacy of such treatment, especially in the early phases of illness.

Additionally, many studies have shown a positive impact of CRT in schizophrenia, not only on cognition, but also on related brain structures (e.g., Eack et al., 2010; Penadés et al., 2013; Ramsay et al., 2017) and functions (e.g., Ramsay and MacDonald III, 2015; Wei et al., 2016). Thus, it has been proposed that cognitive changes observed following CRT are associated with brain plasticity in patients. Some recent studies have even investigated the level of cortical resource available in patients before CRT as a predictor of treatment response. These studies have observed that patients with more cortical reserve at baseline are those who show the greatest improvement in cognition following CRT intervention (Guimond et al., 2018; Keshavan et al., 2011).

More research linking brain plasticity and cognitive improvement following CRT is, nonetheless, needed, as these studies could pave the way to novel intervention combining approaches that harness brain plasticity (i.e., potential drug agent, brain stimulation, or physical exercises) with CRT to enhance the efficacy of treating cognitive impairments in schizophrenia (e.g., Best and Bowie, 2017; Keshavan et al.,

2014). Considering that brain plasticity is probably more preserved in the early stages of the illness, this observation highlights the importance of early CRT. Furthermore, and as reviewed above, cognitive impairments are observed before the development of a first psychosis episode in individuals who are at clinical and genetic high-risk for developing schizophrenia. Hence, CRT could provide potential benefit as a preventive intervention for psychosis and could potentially prevent further cognitive decline in high-risk populations.

8. Discussion

The aim of this review was to provide an account of the evidence demonstrating neural correlates of cognitive dysfunction across the schizophrenia epoch, using the integrative framework of RDoC cognitive domains. Although many unanswered questions persist with regard to cognition and the developmental trajectory of schizophrenia, a number of assertions emerge from the literature. More specifically, the data suggest that neurocognition is broadly impaired in schizophrenia, as well as in first-episode and high-risk groups. However, some domains demonstrate impairment across all phases of the illness (e.g., working memory, attention, cognitive control), whereas other domains seem to be impared in the early phases (e.g. verbal fluency and auditory perception). Domains that seem to show impairment in chronic phases of the illness include visual perception, selective attention, and item-specific episodic memory. Finally, neurocognitive impairment across each phase of illness is associated with differences in brain function and/or structure. Taken together, these data may shed light on the etiology of cognitive deficits in schizophrenia and could help to guide the development of novel targets for treatment.

8.1. Summary of the main observations

The main findings from this review are summarized in Tables 1 and 2, with associated brain regions illustrated in Fig. 1. Many cognitive impairments and associated brain abnormalities are observed in the chronic phases of schizophrenia and most seem to also be present, with varying levels of severity, before illness onset. Nonetheless, the brain networks underlying these impairments are expansive and overlap between cognitive domains. Moreover, it is well recognized that schizophrenia is a complex disorder and thus it is difficult to assert that a single mechanism could explain the diverse array of cognitive impairments associated with the illness.

However, it is possible that a common core mechanism may underlie a subset of cognitive deficits. For example, it has been suggested that a common denominator to many cognitive deficits may be the impaired function of the DLPFC and its connectivity with other brain regions that are implicated in goal representations that enable cognitive control (Barch and Ceaser, 2012). This would suggest that some cognitive deficits outlined in this review could be mediated, at least partially, by deficits in cognitive control. Furthermore, evidence suggests that there may be subtypes of psychosis characterized by either predominantly "top-down" abnormalities (i.e., cognitive control) or bottom-up impairments (i.e., attention and sensorimotor reactivity) (e.g., Clementz et al., 2016). However, this remains to be confirmed and investigated further in future studies.

Table 1
Behavioral findings for cognitive differences across schizophrenia developmental phases (+ impaired; − no impairment).

RDOC cognitive domain	Chronic	First-episode	High-risk
Visual perception	+	−	−
Auditory perception	+	+	+ clinical high risk − genetic high risk
Attention	+	− selective + sustained	+
Working memory	+	+	+
Declarative memory	+	+	+ verbal fluency − broader semantic memory
Cognitive control	+	+	+

Disentangling the specific effects of each cognitive domain on the individual's general functioning and clinical outcome is also quite challenging. Nonetheless, decline in cognition and abnormalities in associated brain regions may be specific to the risk for developing schizophrenia, with some cognitive domains being more predictive of conversion than others, such as working memory, verbal learning, semantic memory (i.e., verbal fluency), auditory perception as measured by MMN, and prefrontal cognitive function associated with cognitive control. Further research in this area may help us to identify key targets for early intervention.

8.2. Limitations

Finally, the findings of this selective review should be interpreted in the context of limitations in the current literature. For example, it can be difficult to generalize across studies where there is a large variability in the selection of case and control samples. Furthermore, there is also considerable individual variability in terms of cognitive profiles in patients with schizophrenia (e.g., Gilbert et al., 2014; Joyce and Roiser, 2007), and most neuroimaging studies do not take this variability into consideration within study designs and data analyses. For example, while the majority of schizophrenia patients show evidence of declarative verbal memory decline from higher premorbid ability level, subgroups of patients show a preserved and normal profile of verbal declarative memory performance (Heinrichs et al., 2017). This further highlights the challenge of heterogeneity in cognitive deficits profiles that is inherent in schizophrenia.

Furthermore, heterogeneity in methodologies across studies should be considered when interpreting findings. For example, different psychometric evaluations may be used to assess the same cognitive functions and some cognitive domains are lacking corresponding evidence from imaging modalities. Future research should define as precisely as possible these cognitive processes and investigate their association with all brain structures and networks that might be involved in the cognitive process. The advent of advanced imaging analysis techniques, the harmonization of cognitive and imaging data, and the application of multi-modal designs, will tremendously impact advances in our understanding of brain structural and functional abnormalities underlying cognitive deficits in schizophrenia.

8.3. Future directions

Developmental changes in gray matter and white matter should also be taken into account when characterizing the brain networks underlying different phases of schizophrenia. For example, gray matter volume peaks during childhood and decreases thereafter, whereas total white matter volume increases through young adulthood (e.g., Groeschel et al., 2010). There are also gender differences in brain structure and function (e.g., Goldstein et al., 2002, 2005). Thus gender needs to be investigated as an important biological variable and this has not been given the importance that it deserves. This focus might also help to reduce the heterogeneity of schizophrenia. Further, as well as developmental changes, the role of genotypes on cognition in schizophrenia should also be considered (e.g., Ho et al., 2006). For example, examining the overlap in the genetic architecture of schizophrenia and cognitive functions, may help us to understand better the relationship between cognition and schizophrenia (Smeland and Andreassen, 2018).

While there has been great progress in understanding the brain mechanisms underlying cognitive deficits present in schizophrenia, the neurobiology of these impairments is an area that needs further investigation. Moreover, while Positron emission topography (PET) studies are beyond the scope of this review, they have, over the last

Table 2
Neuroimaging correlates of cognitive abnormalities across developmental phases of schizophrenia.

Imaging modality	Chronic	First-episode	High-risk
Perception			
EEG	Abnormal P100 and MNN	Auditory: No MMN reduction to pitch-deviants but small reduction to duration-deviants. Visual: No robust differences detected in first-episode	Auditory: MMN impairments in individuals at clinical high-risk for psychosis. Visual: No evidence of differences in visual P300 No clear evidence of auditory or visual deficits in genetic high-risk
Functional MRI	Impaired visual perceptual organization associated with disruption of early visual cortex, inferior temporal and parietal regions, ventrolateral and orbitofrontal cortex		
Attention			
EEG	Abnormal auditory and visual P300	Reduced visual P300 amplitude and increased latency P300, with P300 showing progressive amplitude reduction over the course of the illness	Auditory P300 amplitude is reduced in genetic high-risk groups Auditory P300 abnormalities observed in individuals who convert to psychosis compared to those who don't convert
Structural MRI		Gray matter density of the left thalamic nucleus, left angular, and supramarginal gyrus, and left inferior frontal and postcentral gyri correlates with performance on attention tasks.	
Functional MRI	Abnormal activation of attentional network, including the dorsolateral prefrontal cortex (DLPFC), the insula, the anterior cingulate gyrus (ACG), the amygdala, hippocampus, ventral striatum, thalamus and cerebellum Findings vary depending on type of attention elicited		
Diffusion MRI	Fractional anisotropy of the uncinate associated with performance in attention and spatial memory		
Working memory			
Structural MRI	Deficits associated with lower cortical thickness and hippocampal volume	Deficits associated with reduced cerebellar volume Reduced anterior cingulate volume in females	Deficits associated with reduced hippocampal volume
Functional MRI	Reduced activation in DLPFC. Hyper-activation of this region also observed Increased activity in anterior cingulate. Abnormal temporal, parietal, prefrontal connectivity.	Hypofrontality Impaired fronto-parietal effective connectivity Compensatory prefrontal responses in dorsolateral and ventrolateral PFC	Differences in parietal and temporal networks subserving visuospatial working memory in prodromal period Disturbances in PFC activation in genetic high-risk.
Diffusion MRI	FA of superior longitudinal fasciculus correlates with performance in verbal working memory task		
Declarative memory			
EEG	Abnormal N400 semantic priming effect under explicit conditions	Inconsistent N400 findings	Inconsistent N400 findings.
Structural MRI	Deficits associated with structural abnormalities in medial temporal cortex and prefrontal cortex.	Verbal memory performance related to hippocampal volume.	Verbal memory related to cortical thickness in temporal lobes.
Functional MRI	Deficits associated with functional abnormalities in medial temporal cortex and prefrontal cortex	Abnormal activation in medial temporal cortex and prefrontal cortex during episodic encoding and recollection.	Abnormal brain activity in hippocampus and fronto-medial-temporal regions during episodic encoding
Diffusion MRI	Increased radial diffusivity in fornix associated with episodic memory encoding Episodic memory encoding correlates with white matter volume in orbiofrontal cortex Memory retrieval associated with white matter volume in posterior parietal cortex		
Cognitive Control			
Structural MRI	Deficits associated with structural and functional abnormalities in medial temporal cortex and prefrontal cortex	Deficits associated with differences in anterior cingulate morphology	
Functional MRI	Elevated fronto-parietal network connectivity	Reduced activation of DLPFC and fronto-parietal network	Reduced activation of anterior cingulate, inferior frontal gyrus, middle frontal gyrus. Reduced activation in ventral and dorsal striatum. Reduced DLPFC activation in converters v non-converters Increased activity in right dorsal and ventral PFC, left parietal cortex, as well as significantly decreased activity in the left DLPFC for relatives
Diffusion MRI	Lower FA in ALIC, thalamus, and CC.		

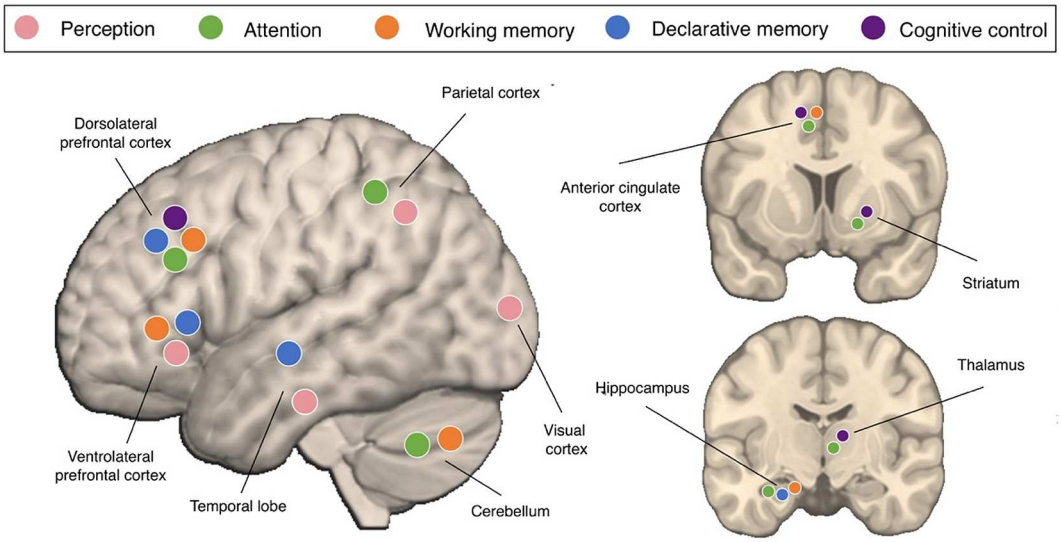

Fig. 1. Schematic representation of the main brain regions implicated in abnormal cognitive functioning present across all developmental phases of schizophrenia.

decades, provided important new insights into the neurobiology of cognitive impairments in schizophrenia. For example, PET studies have suggested that hypofrontality in schizophrenia is a possible explanation for lower cognition and memory performance in patients (e.g., Molina et al., 2009). These studies have also highlighted the role of glucose metabolism and lower cerebral blood flow in fronto-temporal regions and verbal learning performance (e.g., Hazlett et al., 2000; Ragland et al., 2001). PET studies have also played an important role in our understanding of the dopaminergic system and cognitive difficulties schizophrenia. For instance, dopamine deficiency within the dorsolateral prefrontal cortex in schizophrenia has been linked to abnormal activation in this region during tasks requiring working memory and cognitive control (e.g., Goldman-Rakic et al., 2004; Slifstein et al., 2015; Rao et al. 2018). Furthermore, a few PET studies have examined the role of the serotonin system and neuroinflammation in cognitive deficits in first-episode individuals and in high-risk populations, but further studies are needed before clear conclusions can be drawn (e.g., Fusar-Poli et al., 2010b; Hafizi et al., 2016).

Cognitive performance in older patients with schizophrenia has also not been specifically addressed in this review. However, there are conflicting findings in the literature, with some studies suggesting that the rate of cognitive decline in schizophrenia is similar to the rate observed in healthy controls (Irani et al., 2011), while other studies have observed greater age associated decline in cognition in schizophrenia compared to healthy controls (Loewenstein et al., 2012). A cross-sectional and longitudinal meta-analysis, nonetheless, concluded that cognitive impairments in older individuals with schizophrenia are similar to impairments observed across the life span (Irani et al., 2011). However, the authors acknowledge that age-associated cognitive decline on more complex tests of information processing have been observed, and concluded that these changes may be a function of both the course of the illness and the demands of the cognitive test. Finally, these investigators highlight a subgroup of “poor outcome” or institutionalised patients who may also be underrepresented in the meta-analysis. Although this meta-analysis found no indication of significant medication effects, the authors caution that this may be a result of lack of reporting medication effects in the literature. They also point out that first-generation antipsychotic medications prescribed to older patients may contribute to cognitive deficits. Finally, cognition remains a strong predictor of functional outcome across the lifespan in schizophrenia, suggesting that therapies to improve cognitive impairments associated with schizophrenia may also improve functional outcome, independent of age (Kalache et al., 2015).

Finally, the current review is a selective and focused review on RDoc domains of attention, perception, working memory, declarative memory, and cognitive control. Further reviews should also include additional domains such as language and social cognition, as both are impaired in schizophrenia and both have been a major focus of research (e.g., Green et al., 2015; Hinzen and Rosselló, 2015; Kuperberg, 2010; Penn et al., 2007; Pinkham et al., 2003).

9. Conclusion

The literature highlighted in this selective review includes findings in schizophrenia in the cognitive domains of attention, perception, working memory, declarative memory, and cognitive control, which are impaired across developmental phases of the illness. Evidence suggests that these deficits are associated with differences in measures of brain structure and/or function. The identification of brain networks associated with cognitive deficits across the developmental phases in schizophrenia may aid in the development of targets for pharmacological and psychosocial treatments, as well as for targeted interventions before illness onset. Moreover, it is important to understand further the subgroup of individuals who are at clinical and genetic high-risk for developing schizophrenia but who do not convert to the illness. This subgroup may provide important information regarding the underlying mechanisms of protective factors for schizophrenia and may lead to novel developments for early intervention. Finally, while evidence is limited regarding the reversibility of impairments using pharmacological interventions, cognitive remediation has yielded some promising results (e.g., Keshavan et al., 2014; Wykes et al., 2011). It is for this reason that experts in the field now predict that cognitive interventions may play a more significant role in the neuropsychology of schizophrenia in the coming years (e.g., Seidman and Mirsky, 2017).

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