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Nonsocial and social cognition in schizophrenia: current evidence and future directions

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Cognitive impairment in schizophrenia involves a broad array of nonsocial and social cognitive domains. It is a core feature of the illness, and one with substantial implications for treatment and prognosis. Our understanding of the causes, consequences and interventions for cognitive impairment in schizophrenia has grown substantially in recent years. Here we review a range of topics, including: a) the types of nonsocial cognitive, social cognitive, and perceptual deficits in schizophrenia; b) how deficits in schizophrenia are similar or different from those in other disorders; c) cognitive impairments in the prodromal period and over the lifespan in schizophrenia; d) neuroimaging of the neural substrates of nonsocial and social cognition, and e) relationships of nonsocial and social cognition to functional outcome. The paper also reviews the considerable efforts that have been directed to improve cognitive impairments in schizophrenia through novel psychopharmacology, cognitive remediation, social cognitive training, and alternative approaches. In the final section, we consider areas that are emerging and have the potential to provide future insights, including the interface of motivation and cognition, the influence of childhood adversity, metacognition, the role of neuroinflammation, computational modelling, the application of remote digital technology, and novel methods to evaluate brain network organization. The study of cognitive impairment has provided a way to approach, examine and comprehend a wide range of features of schizophrenia, and it may ultimately affect how we define and diagnose this complex disorder.

Key words: Schizophrenia, cognition, social cognition, cognitive neuroscience, social neuroscience, functional outcome, cognitive enhancement, cognitive remediation, metacognition, computational modelling, childhood adversity, brain network organization

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The study of cognition has substantial implications for understanding neural systems, treatment and prognosis in schizophrenia. It has been a major research focus for a long time. How long? That depends.

It can be argued that cognition has been a focus for schizophrenia research over 100 years, since the insightful observations of Bleuler, Kraepelin and early phenomenologists[1-3]. It can also be said that it has been a focus since the infusion of experimental psychology into schizophrenia studies following World War II[4-6]. Or, it has been a major focus since cognitive neuroscience and the associated neuroimaging methods opened up non-invasive ways to examine brain functioning in schizophrenia[7-9]. Or when its relevance for daily functioning was realized and documented[10-12]. Or when it started to become a focus of pharmacological and cognitive remediation treatments[13-16]. Or, perhaps, the focus is finally emerging now with the development of a wealth of novel concepts and methods.

This paper considers two branches of cognition: nonsocial and social. Nonsocial cognition includes the more commonly considered mental abilities, such as attention/vigilance, working memory, learning and memory, speed of processing, and reasoning and problem solving[17,18]. It can also include auditory and visual perceptual processes[18,19]. Social cognition refers to psychological processes involved with the perception, encoding, storage, retrieval and regulation of information about other people and ourselves[20-23].

We first summarize knowledge about some aspects of cognition in schizophrenia that are longstanding and well-established. We then provide a status report on the relevant cognitive domains, the neural substrates of cognition, the connections to community integration, and the variety of treatment approaches designed to improve cognition in schizophrenia. In the last section, we present a selection of topics that have emerged only in recent years.

NATURE OF NONSOCIAL AND SOCIAL COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Cognitive domains relevant to schizophrenia research

Research on cognition encompasses a broad range of processes involved in perceiving, processing and generating responses to stimuli in the physical and social environment to achieve goals and function adaptively during the course of daily life.

It is now very clear that schizophrenia is associated with wide ranging cognitive impairments. As summarized in Table 1, the breadth of impairment spans from basic perceptual processes to complex nonsocial and social cognitive processes. The table also provides examples of daily life functioning tasks that are associated with each of these processes. Here we summarize the types of cognitive and perceptual deficits that are typically assessed with performance-based cognitive tasks used in schizophrenia research.

Nonsocial cognition

Schizophrenia research has predominantly focused on nonsocial cognition (also referred to as neurocognition). Scores of studies document that nonsocial cognitive impairments are pervasive, substantial and fundamental illness features. Impairments are seen across a range of domains, assessed through computerized or pencil-and-paper tasks, most

Table 1 Relevant perceptual, nonsocial cognitive, and social cognitive domains in schizophrenia

Domain	Description of process	Real-world example
Perception		
Visual	Using the visual system to perceive and interpret what is seen in the surrounding environment	Identifying structural visual features in faces or objects
Auditory	Using the auditory system to perceive and interpret what is heard in the surrounding environment	Distinguishing between the tone or pitch of voices
Nonsocial cognition		
Speed of processing	Responding quickly and accurately when performing relatively simple perceptual, motor or cognitive tasks	Being able to rapidly add up a set of numbers or count out change
Verbal learning and memory	Ability to acquire, store and retrieve verbal information for more than a few minutes	Remembering a list of items to purchase at the supermarket, or remembering what you read hours ago
Visuospatial learning and memory	Ability to acquire, store and retrieve information about objects and spatial locations for more than a few minutes	Remembering where you placed something in a closet
Working memory	Ability to hold and manipulate information "online" in a temporary store	Retaining and dialing a phone number you were just told
Attention/Vigilance	Ability to respond to targets, and not respond to non-targets, over a period of time	Focusing attention while receiving instructions or reading a book
Reasoning and problem solving	Ability to apply and shift strategies effectively to find optimal solutions to problems	Figuring out how to get to an important appointment when your car breaks down
Social cognition		
Emotion processing	Ability to effectively identify emotions (e.g., facial expression) in others and to manage one's own emotions	Being able to identify from your boss' face whether he/she is angry at you
Social perception	Ability to identify social roles, rules and context from non-verbal cues including body language, prosody and social schema knowledge	Figuring out the relationship between two people based on a brief sample of conversation
Attributional bias/style	The way in which individuals explain the causes and make sense of social events or interactions	Jumping to the conclusion that you are in danger when you feel fearful
Mentalizing	Ability to represent the mental states of others and make inferences about their intentions and beliefs	Being able to take another person's perspective during a conversation

commonly including speed of processing, verbal learning and memory, visuospatial learning and memory, working memory, attention/vigilance, and reasoning and problem solving[24].

Speed of processing refers to the ability to perform cognitive operations, typically involving relatively simple perceptual and motor tasks, quickly and efficiently. Verbal learning and memory refers to the initial encoding and subsequent recall and recognition of words and other abstractions (e.g., stories, word pairs) involving language. Visuospatial learning and memory similarly involves the initial encoding and subsequent recall and recognition of non-verbal information such as color, shape, movement and location. Working memory involves temporarily holding, or holding and manipulating, information online, typically over a relatively brief period (e.g., several seconds); it can be assessed with either verbal or visual stimuli. Attention/vigilance refers to sustained concentration over prolonged periods of time, which is required to direct and focus cognitive activity on specific stimuli. Finally, reasoning and problem solving refers to a set of cognitive processes involved in logical and strategic thinking, generating and initiating plans, and behavioral monitoring to flexibly solve problems and attain goals. These domains are rather broad, and specific subprocesses within them, such as cognitive control within reasoning and problem solving, are often the focus of particular studies in schizophrenia.

All of these domains, when assessed reliably, reveal notable differences between schizophrenia and healthy comparison groups. Across domains, people with schizophrenia typically show impairments ranging between 0.75 and 1.5 standard deviations from healthy samples[25,26]. In the context of pervasive impairment on these types of tasks, particularly marked deficits are often found for the domains of long-term memory and speed of processing.

Several converging lines of evidence support the conceptualization of nonsocial cognitive impairments as core features of the illness[27-29]. Nonsocial cognitive impairments are largely independent of positive psychotic symptoms, cannot be explained by antipsychotic medications or their side effects, are present at comparable levels at the time of illness onset, are relatively stable over time until late life, and are detectable at attenuated levels in unaffected biological relatives of patients and in prodromal samples (i.e., samples considered to be at high risk for psychosis). The evidence that nonsocial cognitive impairments reflect a primary deficit associated

with vulnerability to schizophrenia is thus strong and compelling.

Social cognition

Interest in social cognition as it relates to schizophrenia is a more recent development, and research in this area has grown dramatically over the past 10-15 years. Social cognition is a very broad area that encompasses the mental operations needed to perceive, interpret and process information for adaptive social interactions. The most commonly studied aspects of social cognition in schizophrenia include emotion processing and mentalizing. A considerably smaller number of studies have examined the areas of social perception and attributional bias.

Emotion processing refers broadly to perceiving and using (e.g., regulating) emotions adaptively, with facial emotion perception/identification being the most frequently studied aspect in this area. Mentalizing refers to the ability to infer the intentions, dispositions, emotions and beliefs of others, including whether they are being sincere, sarcastic or deceptive. Over 50 studies consistently document large impairments in emotional perception/processing (d=0.89) and mentalizing (d=0.96)[30] in people with schizophrenia.

Social perception assesses an individual's ability to identify social roles, social rules, and social contexts from non-verbal cues (e.g., voice intonation, body language, proxemics). A small number of studies indicate a large impairment in this area (n=12; d=1.04)[30] in people with schizophrenia.

Attributional bias refers to how different individuals typically infer the causes of particular positive and negative events, such as having an increased tendency to attribute hostile intentions to others in ambiguous social situations. Unlike the other social cognitive areas, results across the smaller number of studies of attributional bias are mixed as to whether those with schizophrenia do or do not show significant differences from healthy individuals[30,31].

Similar to nonsocial cognition, there is growing evidence that emotion processing, mentalizing, and social perception impairments are core features of schizophrenia that are present at a comparable level in recent-onset patients, not secondary to positive symptoms or medication effects, relatively stable over the course of illness, and detectable at attenuated levels in unaffected biological relatives of patients and in prodromal or other high-risk samples[32,33].

Perceptual impairment in schizophrenia

Perception can be considered the initial step in cognition. One can regard cognition as a cascade of processing events beginning with early perception and leading in steps to higher mental processes. If the perception information is degraded, the subsequent steps will be affected. Although less studied than higher-level nonsocial cognitive abilities (such as memory, problem solving, and attention), people with schizophrenia also experience a range of perceptual deficits, including problems in processing auditory and visual stimuli[19,34]. Many experimental paradigms have been used to explore early visual and auditory processing impairment in schizophrenia. Here we briefly describe one from each sensory modality.

The visual masking paradigm is one way to probe early visual processing with excellent temporal precision[35]. In this paradigm, a visual target is followed or preceded by a "mask" that can either completely overlap or surround the target. When the mask follows the target, it is called backward masking; when the mask precedes the target, it is called forward masking. Data from numerous laboratories consistently show impairment in schizophrenia during backward masking compared to healthy controls[36-38]. Visual perceptual impairments assessed with visual masking paradigms in schizophrenia are related to both social and nonsocial cognition[39,40], consistent with a cascade model of cognition.

Auditory information processing deficits have been consistently identified in patients with chronic, recent-onset, and unmedicated schizophrenia, and in individuals at high clinical risk for developing psychosis (i.e., prodromal)[34,41-43]. One commonly used early auditory assessment index is mismatch negativity (MMN), which is an event-related potential elicited in response to infrequent, deviant tones interspersed in the repeated presentation of a standard tone[44]. MMN is thought to reflect automatic, preattentive information processing, as it can be elicited without directing attention to stimuli[44]. It tends to correlate with measures of nonsocial cognition[41,45], social cognition[46], and functional outcome[47,48].

Cognitive impairment in schizophrenia vs. other disorders

Considerable work has been conducted to compare the magnitude and pattern of cognitive impairment of schizophrenia to other disorders. In terms of comparisons with neurological disorders, schizophrenia patients showed a distinctly different pattern of cognitive impairments from those with dementia – for example, memory retention (i.e., holding on to information that is already learned, as opposed to how long it took to learn the material in the first place) is markedly impaired in Alzheimer's disease, but intact in schizophrenia[49,50]. The distinctive patterns of cognitive impairment between schizophrenia and dementia indicate that different underlying mechanisms are at work.

The pattern of cognitive impairments in schizophrenia has also been compared with other psychiatric disorders, such as bipolar disorder. One meta-analysis[51] found that schizophrenia patients were impaired, compared with healthy controls, on premorbid nonsocial cognitive function with an effect size of approximately 1.30, whereas bipolar patients showed an effect size of 0.6. A similar pattern was also found in a meta-analysis on first-episode patients with bipolar disorder or schizophrenia[52]. Schizophrenia patients also showed impairment on multiple social cognitive domains compared to both controls (effect sizes 0.88-1.04)[30] and patients with bipolar disorder (effect sizes 0.39-0.57)[53]. Notably, patients

with mood disorders who have a history of psychosis appear to show impairments that are comparable to those of schizophrenia patients on some cognitive domains (e.g., attention, working memory), but not others (i.e., speed of processing)[54]. Thus, schizophrenia patients show greater impairment compared to patients with bipolar disorder on both nonsocial and social cognition.

Recently, a few studies have compared social cognitive impairments in schizophrenia to those in autism, yielding mixed findings. Specifically, some studies found comparable impairments between individuals with schizophrenia and adults with autism on facial affect recognition and mentalizing[55,56]. However, others reported that schizophrenia patients showed poorer performance on an auditory affect recognition task, but better performance on a mentalizing task, compared to adults with autism[57,58]. Given a paucity of comparisons on nonsocial cognition, it remains to be determined whether these two disorders show distinct patterns of impairment across social and nonsocial domains.

Cognitive impairment across phases of illness and across lifespan

A large literature has examined cognitive impairment across phases of schizophrenia. Several meta-analyses showed cognitive impairments among individuals who are at clinical high risk for psychosis[33,59], who experience their first episode of psychosis[60], or who have chronic schizophrenia[61]. Among individuals at clinical high risk for psychosis, those who later developed psychosis did not differ from those who did not on several domains of nonsocial cognition[62].

These findings raise at least two intriguing questions. The first is whether cognitive impairments change over the course of illness (e.g., decline or improve as clinical symptoms change). Longitudinal studies with patients who recently experienced psychotic episodes showed that performance on cognitive tasks remained stable over time. For example, levels of nonsocial cognitive impairment at the onset of psychotic symptoms were similar to those at 2-year or 10-year follow-up assessment[63]. Similarly, performance of first-episode schizophrenia patients on social cognitive tasks was stable over five years[64]. However, some studies suggest that older schizophrenia patients (e.g., over 65 years old) show worsening nonsocial cognitive performance[65,66].

The second question is whether cognitive impairments are present even before clinical manifestations start emerging (i.e., in the premorbid period). Findings from population-based studies largely support premorbid deficits in nonsocial cognition in schizophrenia. For example, individuals who later developed schizophrenia showed impaired cognition even before age 10[67,68]. Subjects who later developed schizophrenia also showed increasing deficits in cognition over time, especially during adolescence[69,70]. It remains to be determined whether individuals who develop schizophrenia also show premorbid deficits in social cognition.

FUNCTIONAL NEUROIMAGING AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

During the past two decades, a remarkable amount of work has been done to characterize the neural bases of cognitive impairment in schizophrenia, using diverse neuroimaging and electrophysiological methods.

We briefly focus here on findings from studies using functional magnetic resonance imaging (fMRI), as this is the primary method used to explore regional specificity and neural circuits related to cognitive impairment in schizophrenia. Rather than trying to summarize the very extensive available literature, we describe the types of approaches that have been used.

Regional activation patterns and cognitive impairment

Earlier work using fMRI focused on regional activation associated with a specific cognitive function. Overall, this line of work demonstrated that schizophrenia patients show abnormal fMRI activations in key regions compared to healthy controls during cognitive tasks.

If we use working memory as an example, schizophrenia patients showed less fMRI activation in the dorsolateral prefrontal cortex and posterior parietal cortex[71-73], although the exact pattern of fMRI activations in these regions may vary based on task characteristics[74,75]. During long-term memory tasks, schizophrenia patients showed reduced fMRI activation in the medial temporal regions, including hippocampus, and dorsolateral and ventrolateral prefrontal cortex[76,77]. During a visual perception task, schizophrenia patients showed reduced fMRI activation in the lateral occipital complex[78,79].

In addition to these findings of reduced activation during cognitive tasks, there are sometimes reports of hyperactivation in schizophrenia. When hyperactivation is observed in brain regions that are normally activated for that specific cognitive function (e.g., hyperactivation in the dorsolateral prefrontal cortex during working memory[80,81]), they are often attributed to inefficient recruitment of neural resources. In contrast, studies that have found hyperactivation in regions different from those typically involved in a given cognitive task[82] are viewed as evidence of compensatory processes in schizophrenia.

Fewer studies have examined the neural bases of social cognitive impairment in schizophrenia, but emerging evidence indicates aberrant neural activations in this domain as well. For example, meta-analytic reviews of fMRI studies on facial affect recognition[83,84] have showed hypofunction in key social brain regions, including amygdala and fusiform gyrus, and hyperactivation in brain regions that are not typically associated with facial affect recognition, such as parietal lobule and superior temporal sulcus.

Similarly, aberrant neural activation has been observed during mentalizing[85]. Schizophrenia patients showed hypoactivation in several areas related to mentalizing, including medial prefrontal cortex, posterior temporoparietal junction and ventromedial prefrontal cortex, as well

as hyperactivation in the dorsal section of temporoparietal junction.

Less work has been done on an integrative social cognitive process such as empathy (i.e., sharing, understanding and responding to the emotional experiences of another person)[86-88]. During cognitive empathy (same as mentalizing) tasks, schizophrenia patients showed reduced fMRI activation in several key regions, including medial prefrontal cortex and precuneus[89,90], whereas normal neural activation was observed during tasks of affective empathy (also called affect sharing)[91,92].

Functional connectivity and cognitive impairment

Researchers are increasingly examining the connections between regions and neural networks that subserve cognitive processes[80]. During working memory tasks, schizophrenia patients showed several forms of reduced connectivity compared with controls: between prefrontal cortex and parietal cortex[93,94], between thalamus and the frontoparietal regions[95], and between prefrontal cortex and basal ganglia[96]. Also, during episodic memory tasks, schizophrenia patients showed reduced connectivity between hippocampus and frontal regions[97,98].

Similarly, studies on social cognitive impairment suggested that the associated neural circuits are disrupted. For example, compared to controls, schizophrenia patients showed reduced functional connectivity involving the limbic structures (including amygdala) during facial affect processing[99,100]. During a mentalizing task, schizophrenia patients showed reduced connectivity between temporoparietal junction and temporal lobe regions (including hippocampus and middle temporal gyrus) compared to controls[101].

While connectivity studies are informative regarding the ways and degree to which regions interact, the field is now moving to more sophisticated studies of network organization and graph theory methods that can examine how large sets of nodes communicate (see below the section on "Brain network organization").

IMPLICATIONS OF COGNITIVE IMPAIRMENT FOR COMMUNITY INTEGRATION

The introduction of antipsychotic medications in the 1950s was a game changer in schizophrenia treatment and outcome[102], but its impact was more narrow than first anticipated. Medications reduced psychotic symptoms in the majority of people with schizophrenia, and it was expected that such improvement would be accompanied by enhanced community integration. That did not happen. Unfortunately, the introduction of antipsychotics had little impact on functional outcomes[103,104]. It took some time to appreciate the key difference between remission (i.e., symptom reduction) and recovery (i.e., full participation in social, work, and independent activities), which depends on other factors, including cognition.

There is a very substantial literature on the relation between cognitive impairment and functional outcome in schizophrenia. For example, a PubMed search with the terms "schizophrenia", "cognition" and "functioning" yields over 200 published articles on this topic each year from 2011 to 2017.

Nonsocial cognition and functional outcome

All of the earlier reviews focused on nonsocial cognition[10-12,105]. The reviews demonstrated that cognitive impairment has reliable relationships to functional outcomes in schizophrenia. These outcomes included community-based functioning (e.g., work success, independent living) or ability to acquire skills in rehabilitation programs for inpatient samples. The consistency of the relationships was impressive, but the strengths of the associations were typically in the medium range (e.g., r=0.3) when considering individual cognitive domains. The relationships were generally stronger (r=0.5 or greater) when multiple cognitive domains were combined into composite scores[11].

This association between nonsocial cognition and outcome has been replicated in many countries, in different languages, with different types of cognitive assessments, and in different patient groups. Further, it has been found across different phases of illness, including the prodromal phase[106] and the first episode[107]. The relationships are present in prospective as well as in cross-sectional studies, indicating that cognitive impairment is a legitimate predictor of later community functioning. For example, several studies have found significant associations with outcome as long as 2-4 years after baseline assessment[108-111].

Social cognition and functional outcome

Following the established connections between nonsocial cognition and functional outcome in schizophrenia, the question turned to the associations between social cognition and outcomes. It soon became apparent that these latter associations were at least as large, and often larger, than those observed for nonsocial cognition[112,113].

Medium to large associations between social cognitive domains and community functioning were reported, with mentalizing showing the strongest relationship in a meta-analysis[113]. This meta-analysis reported that social cognition explained roughly 16% of the variance in community functioning, while nonsocial cognition accounted for about 6%.

The association between social cognition and functioning has been found to hold up over time. For example, significant associations between baseline social cognition and community functioning can be seen one year[107] and even five years[64] later.

Pathways from nonsocial and social cognition to functioning

The current question is no longer *whether* but *how* cognition is related to functional outcome. Considering the highly complex nature of community functioning in schizophrenia or any other condition, it is clear that many of the observed relationships between cognition

and community integration involve mediating variables. The identification of such key mediators is very important, because it can suggest specific therapeutic targets. If we identified a key mediator of functional outcome, this would become a rational target for intervention, especially because it would be considered to be closer (i.e., more proximal) to the eventual outcome of interest.

An initial series of studies evaluated whether aspects of social cognition (e.g., emotion perception and social perception) act as mediators between nonsocial cognitive processes and functional daily outcomes – demonstrated by significantly reducing or eliminating the direct relationship between nonsocial cognition and outcome. The results were consistent: in these models, social cognition acts as a mediator for functional outcome[39,114,115], with approximately 25% of the variance in functional outcome being explained by such mediation models[115].

These models are limited in the amount of explanation they can provide. Multistep models with several intervening variables can be more informative about the pathway(s) to functional outcome in schizophrenia. However, these latter models require more sophisticated analyses, such as structural equation modelling, and are difficult to test unless one has a sufficient number of variables, a large sample size, and a reasonable theory as to how the variables are expected to interact.

Beyond social cognition, additional intervening variables between nonsocial cognition and functional outcome include defeatist beliefs (i.e., an individual holds generalized negative beliefs about his/her ability to successfully perform tasks[116,117]) and motivational factors[118,119]. A study from our group using structural equation modelling found support for a single pathway from early visual perception (measured with visual backward masking) to functional outcome through social cognition, defeatist beliefs, and motivational negative symptoms[120]. The results indicated that cognition and motivation can be represented on a single pathway.

A more complex pattern of relationships emerged from a large multisite US study that examined the pathways from early auditory processing (including MMN and other early event-related potentials) to functional outcome[121]. Unlike the previous modelling study, this investigation did not include measures of social cognition or defeatist beliefs. The final model showed an indirect pathway from cognition through negative symptoms as well as a separate pathway from motivational/experiential negative symptoms to functioning. That is, a single pathway from cognition to motivation to functioning did not fully explain the data, perhaps because defeatist beliefs were not included in the model.

A third example comes from a large Italian multisite study that found multiple indirect pathways between nonsocial cognition and functioning. Social cognition and negative symptoms were important, but so were other factors such as internalized stigma, resilience, and engagement with services[122].

Overall, these complex modelling studies are extremely valuable in suggesting and testing mechanisms by which perception and cognition can lead to functioning through a series of intervening variables. However, the key question as to whether cognitive variables and motivational variables form single versus multiple pathways remains unresolved.

INTERVENTIONS FOR COGNITIVE IMPAIRMENTS

Over the past decade, there has been a great deal of excitement about developing new treatments that target nonsocial and social cognitive impairments as a means to improving functional outcomes in schizophrenia.

For nonsocial cognition, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative by the US National Institute of Mental Health (NIMH) spawned major efforts to discover new pharmacological approaches. There was also an extensive body of research on cognitive remediation interventions. Overall, the results have been mixed.

Social cognition has been a more recent topic of treatment development research. Efforts have predominantly focused on psychosocial training approaches, which are encouraging, with only a few studies considering pharmacological strategies.

Beyond these main treatment approaches, we also consider emerging evidence that alternative interventions, such as physical exercise and neurostimulation, may prove useful as adjuncts for enhancing cognition.

Nonsocial cognition

Pharmacological approaches

A wide range of candidate mechanisms involving diverse neurotransmitter systems have been proposed for pharmacological enhancement of nonsocial cognition[123]. The majority of studies have focused on glutamatergic and cholinergic agents, with fewer targeting other neurotransmitters, such as serotonin, dopamine, GABA and noradrenaline.

Despite considerable efforts across dozens of studies, these agents have not been consistently successful in improving cognition and functioning. Overall, a recent meta-analysis[124] reported that across all available studies (n=93) there was a significant, though quite small (Hedges' g=0.10), effect for overall cognition, with no significant effects for any cognitive subdomain.

For particular neurotransmitter systems, the literature is characterized by a lack of replication, and only a few agents have shown any evidence of positive benefits. The strongest findings were for agents acting predominantly on the glutamatergic system (overall cognition: g=0.19, n=29; working memory: g=0.13, n=20). Sub-analyses of particular glutamatergic agents indicated a significant small-to-medium benefit for AMPA receptor agonists on working memory (g=0.28; n=5) and a non-significant trend for memantine/amantadine on overall cognition (g=0.34; n=6). There were very few findings for other neurotransmitter systems: cholinesterase inhibitors showed a small yet significant effect on working memory

(g=0.26; n=6), and dopaminergic agents showed a non-significant effect on the domain of reasoning (g=0.34; n=4).

Despite several positive phase II studies showing cognition enhancement, these findings have not been replicated in larger phase III studies. Thus, the field is still struggling to find pharmacological interventions for cognitive enhancement in schizophrenia that show efficacy in multisite trials.

Cognitive remediation

Compared to pharmacological approaches, psychosocial interventions for cognitive remediation have produced more encouraging findings. A wide range of cognitive remediation approaches have used computerized or non-computerized (paper-and-pencil) training exercises with titrated increases in difficulty as participants progress through what is typically several months of fairly intensive treatment.

Cognitive remediation interventions can be classified along two broad dimensions: therapeutic target and therapeutic modality[125]. The therapeutic target can range from basic perceptual skills using a "bottom-up" approach (training on lower-level sensory processing to impact neuroplastic processes which are thought to generalize to higher-level cognitive and functional outcomes) to higher-level cognitive skills using a "top-down" approach (assuming that improvements will generalize to lower level and community functioning). The therapeutic modality can range from self-directed administration of cognitive training exercises with minimal therapist involvement to integrated cognitive training exercises with additional strategy monitoring, bridging, or other psychosocial treatments.

A meta-analysis of 40 studies demonstrated that, regardless of treatment target or modality, cognitive remediation shows significant, moderate gains in terms of near-transfer to untrained cognitive tests (d=0.45 for global cognition)[126]. Further, these gains were durable at follow-up assessments following active treatment (d=0.43). Notably, beyond cognitive task improvement, there is emerging evidence that cognitive remediation is also associated with significant structural (both grey and white matter) and functional (particularly in prefrontal and thalamic regions) brain changes[127].

Importantly, however, treatment modality is a key mediator of generalization to improvements in community functioning. Specifically, the effect of cognitive remediation is moderate when combined with adjunctive psychiatric rehabilitation (d=0.60), but only small and marginally significant when cognitive training is provided alone (d=0.19-0.29)[128]. Thus, while cognitive remediation generally yields moderate gains on cognitive task performance, it may be necessary to administer additional interventions (e.g., vocational rehabilitation, strategic bridging, or skills training) in order to achieve meaningful real-world functional benefits.

Emerging approaches

There is clearly ample room for improvement in the treatment of nonsocial impairment in schizophrenia. Efforts to develop new medications have been disappointing so far. Although there has been more progress for integrated cognitive remediation approaches at the group level, there is substantial individual variability in treatment response and many patients exhibit little benefit. One possible path forward is to examine whether the impact of integrated cognitive remediation is boosted when combined with pharmacological therapies. This is an active area of investigation, though preliminary findings have been mixed[129].

Another possibility that has opened up in recent years involves the use of novel non-pharmacological augmentation approaches intended to promote neuroplasticity, such as physical exercise and neurostimulation. A recent meta-analysis has shown that physical exercise can improve cognition in schizophrenia compared to non-aerobic control activities[130]. These encouraging findings have led to a few small pilot studies which found that the combination of cognitive remediation plus aerobic exercise leads to differential improvement for some aspects of cognition and functioning[131]. Similarly, based on findings that transcranial direct current stimulation (tDCS) may improve selected aspects of cognition in schizophrenia, a few small pilot studies have reported differential benefits of brief cognitive remediation plus tDCS (versus sham) interventions on trained cognitive tasks[131,132].

Social cognition

Training approaches

Over the past decade, there has been considerable progress in the development of psychosocial treatments for social cognition in schizophrenia. Initial proof-of-concept trials demonstrated that brief "targeted" interventions focusing on a single social cognitive domain (e.g., affect perception) led to significant task improvements[133,134]. Given the complex, multifaceted nature of social interactions and the wide range of social functioning difficulties seen in schizophrenia, the field has shifted toward "comprehensive treatments" that address multiple, rather than single, social cognitive domains. These are typically interactive, group-based treatments that incorporate a range of visual, auditory, video stimuli depicting social stimuli, though other formats, such as individual computerized interventions, have also been developed[135].

The results to date provide several reasons for optimism. A recent meta-analysis of 16 studies[136], conducted in diverse cultural settings, reported medium-to-large improvements in the two most commonly assessed domains: facial affect identification (d=0.84 in 12 studies) and mentalizing (d=0.70 in 13 studies). Effect sizes were also large for a smaller number of studies assessing social perception (d=1.29 in four studies) and small-to-medium for attributional bias (d=0.30-0.52 in seven studies).

Notably, treatment-related gains in social cognition are not accompanied by

improvements in nonsocial cognition[136], suggesting that social cognitive changes are independent of changes in nonsocial cognition. Consistent with this notion, nonsocial cognitive remediation alone does not result in significant social cognitive improvements[128]. Beyond improvements in social cognitive task performance, preliminary evidence also indicates that social cognitive interventions produce detectable structural and functional brain changes[137].

While these findings are quite encouraging, this is a relatively young area of research, and several factors should be considered[138]. First, most studies included small samples (<20), methodological quality varied considerably, and the durability of treatment effects is largely unknown. Second, there is currently no consensus in the field about an optimal set of social cognition outcome measures for clinical trials. Third, the generalizability of treatment benefits to meaningful improvements in daily life functioning has not yet been consistently demonstrated.

Thus, several open questions remain. For example, it is unclear which type of social cognitive treatment (e.g., group-based vs. individualized computer-based) is optimal, or whether treatment formats can be better matched to the personal characteristics of participants.

Emerging approaches

The few efforts to develop pharmacological approaches to social cognition in schizophrenia have focused on oxytocin. Building on extensive basic and clinical evidence that this neuropeptide enhances the salience of social information[139-141], a number of studies have examined the impact of intranasal oxytocin, using single or repeated administration strategies, on social cognitive tasks. Results have been mixed. A recent meta-analysis of 12 studies that randomized participants to oxytocin vs. placebo found no overall effect for social cognitive measures, although there was some suggestion (from a very small number of studies) of a significant (albeit small, d=0.20) effect for higher level (e.g., mentalizing) but not lower level social cognitive tasks[142].

Two studies evaluated oxytocin augmentation during the course of social cognitive training programs, using very different strategies, and yielded mixed findings. Our group administered oxytocin (vs. placebo) only prior to each training session, and found differential improvement in one aspect of empathy (how well someone can track momentary changes in mood in another person, referred to as empathic accuracy)[143], whereas the other study used twice-daily chronic dosing throughout treatment and found no social cognitive benefits[144].

Aside from oxytocin, studies have started to examine the possibility of improving social cognition in schizophrenia through physical exercise and neurostimulation with tDCS. Only a few studies have examined the effects of exercise, providing early encouraging results (g=0.71, based on three studies)[131]. An initial study by our team found that a single session of tDCS (vs. sham), administered over the prefrontal cortex, significantly improved facial identification task performance, though not other social cognitive domains[145]. However, a subsequent tDCS study using two stimulation sessions over the prefrontal cortex did not show any social cognitive benefits[146].

To summarize, oxytocin and tDCS appear to be safe, well-tolerated potential adjuncts to psychosocial interventions, though it remains to be determined how they can be optimally administered (e.g., which dosing to use[147]) to boost social cognitive training effects.

RECENT DEVELOPMENTS AND FUTURE DIRECTIONS FOR RESEARCH ON COGNITION IN SCHIZOPHRENIA

In this section we look to what lies on the horizon for research into cognition in schizophrenia. The topics are, by necessity, selective, and we could have chosen others. In the first part, we discuss lines of research that are growing and already have a reasonably large data base to support them. In the second, we discuss areas that are just getting off the ground, but have potential to substantially change our understanding of cognition in schizophrenia.

Recent areas of growing interest

The interface of motivation with cognition

There has been considerable research interest in how cognitive processes interface with disturbances in motivation and emotion in schizophrenia. Translational research based on developments in affective neuroscience has focused on how disturbances in reward-related information processing relate to diminished engagement in goal-directed behavior. Much of this work builds on the consistent finding that immediate hedonic responses to rewarding or pleasurable stimuli are largely intact in schizophrenia[148-150], indicating that motivational disturbances do not simply reflect a diminished capacity to experience pleasure. Instead, people with schizophrenia seem to have difficulty using reward-related information to adaptively guide future behavior. This has led schizophrenia researchers to develop and test multicomponent models of the computational processes through which reward-related information is translated into productive goal-directed activity[151,152].

Individuals with schizophrenia show impairments in several reward processing subcomponents that involve applying cognitive operations to rewarding stimuli. These include disturbances in long-term memory for rewarding/pleasurable experiences[153,154], reward learning and prediction error processing[155-157], the representation and maintenance of reward value within working memory[158], decision making concerning effort costs associated with obtaining rewards[159], and anticipation/prospection for future rewards[160,161]. Impairments in these areas are often, though not always, related to clinical ratings of motivational negative symptoms (e.g., anhedonia, asociality).

Along these lines, recent research has identified disturbances at the interface of

emotion and cognitive control processes. For example, in contrast to healthy individuals, reward incentives fail to enhance performance and associated neural activation (particularly of dorsolateral prefrontal cortex) during cognitive control tasks in schizophrenia[162-164], which has been described as impaired "motivated cognitive control". This failure to energize cognitive control processes required to formulate and execute goal-directed action plans has also been linked to motivational negative symptoms.

The impact of cognitive control disturbances also extends to processing negative emotional stimuli in schizophrenia. For example, people with schizophrenia show a diminished ability to downregulate their responses to unpleasant stimuli using effortful emotional regulation strategies such as cognitive reappraisal or directed attention[165-167]. Relatedly, they demonstrate an impaired ability to appropriately modulate or filter out negative distractor stimuli during tasks involving cognitive control (e.g., working memory, attention)[168,169]. Again, these control disturbances have often, but not always, been linked to negative symptoms or poor functioning.

Overall, there is growing evidence of widespread disintegration between cognitive and motivational/emotional processes in schizophrenia, which appears to have important clinical and functional implications.

Childhood adversity and cognition

Childhood adversity – such as physical and/or emotional neglect/abuse, poverty, malnutrition, traumatic experience – can have long-lasting negative consequences. It affects the development of the brain, such that individuals show both structural[170,171] and functional[172] cerebral abnormalities during adulthood. Because childhood adversity is also associated with increased risk for developing severe mental illnesses, including schizophrenia[173,174], it has been suggested that it could contribute to features of this disorder, including cognitive impairment.

Several studies examined the effect of childhood adversity on cognition in schizophrenia, primarily focusing on nonsocial cognition, and the findings have been mixed. A recent meta-analysis found a small effect of childhood adversity on cognition in schizophrenia, and this was significantly smaller than that seen in controls[175]. However, this meta-analysis examined only studies of nonsocial cognition, and did not explore whether different types of adversity or the timing of adversity (e.g., neglect vs. trauma, early vs. late childhood) has differential effects on cognition in schizophrenia. Notably, findings from recent studies suggest that social cognitive impairment is more related to neglect than other types of adversity[176,177].

Further, the mechanism through which childhood adversity may influence cognition in schizophrenia (e.g., neuroinflammation, neural changes), or any factors that may modulate this mechanism (e.g., gender, genetic or epigenetic processes), remain largely unknown[178-180].

Metacognition

Metacognition has received notable interest in both clinical and treatment development research on schizophrenia. Since the term was first used in the context of psychosis in the 1980s, to describe thoughts about one's own thoughts in a model of psychotic symptom formation[181,182], the definitions of metacognition have varied considerably, with some being quite broad. As an example of a broad definition, Lysaker and colleagues[183,184] propose that metacognition refers to a range of activities ranging from discrete (i.e., creating an idea about a specific thought or emotion) to highly synthetic (i.e., forming separate thoughts into complex representations of oneself and others). From this perspective, metacognition allows people to "access a sense of themselves (and of others) which is multifaceted and multidimensional, while also allowing for that sense of self and others to change responsively and adaptively as contexts change"[183].

Dozens of studies now document impairments in metacognition in individuals with, or at risk for, schizophrenia using discrete (based primarily on self-report questionnaires) or expansive (based primarily on clinical ratings of narratives) definitions[183,185,186]. Further, indexes of metacognitive impairment show associations with a wide array of clinical features, including positive, negative and disorganized symptoms, social and nonsocial cognition, motivation, self-agency, insight, and functional outcomes[183,185,187,188].

The varying definitions of metacognition make it challenging to provide an integrative summary of findings in this area. For example, the more expansive definitions of metacognition appear to have considerable overlap with other areas considered in the present paper, including aspects of social cognition (e.g., mentalizing, empathy) and nonsocial cognition (e.g., cognitive control, performance monitoring). While it can be argued that these are separable constructs[189,190], the extent of overlap among them is debatable.

Similarly, there are currently at least four different psychotherapies for schizophrenia that all include the term "metacognition" in their titles[191], as well as metacognitively-oriented cognitive remediation and social skills training[192,193]. Yet, these programs look rather different. Indeed, this has led to a debate in the schizophrenia literature about what constitutes a "true" metacognitive treatment[184,194,195]. Hence, fundamental questions remain about the scope and boundaries of this construct, and how it can be most productively distinguished from other areas of schizophrenia research.

Nascent areas with potential impact

Neuroinflammation and cognition

Accumulating evidence indicates the presence of an abnormal immune system in schizophrenia. For example, epidemiological studies have reported an association between maternal infection during pregnancy and increased risk for schizophrenia[196,197]. Also, a meta-analysis showed an association between schizophrenia and autoimmune disorders[198]. Recent evidence from genetic studies

indicates that schizophrenia-related loci include several genes involved in the immune system[199]. Patients appear to show elevated levels of peripheral inflammation markers[200] and increased activation of the central immune system[201].

Only a few studies so far have examined the associations between inflammation and cognitive impairment in schizophrenia. Most have focused on peripheral markers of inflammation, and the results have been mixed. For example, patients with elevated levels of peripheral inflammation markers showed poorer cognitive performance than patients with lower levels of inflammation[202]. A study of first-episode psychotic patients found that higher levels of inflammation were associated with greater cognitive impairment[203], whereas another study found the opposite pattern[204].

The associations between inflammation and cognition may differ across subgroups of patients. For instance, inflammation was associated with cognitive impairment only in patients who did not use illicit substances or alcohol[205], or only when patients were experiencing acute psychotic symptoms[206].

Thus, while a limited number of studies generally support the notion that inflammation is related to cognitive impairment in schizophrenia, the nature and strength of this association is still unclear.

Computational modelling of cognitive processes

Computational psychiatry is an emerging field that employs interdisciplinary tools from computational neuroscience, including machine learning algorithms, to address complex problems such as the classification of subgroups and characterization of cognitive impairment[207-209].

Computational psychiatry includes both data-driven and theory-driven approaches. Data-driven approaches have not been directed at probing cognitive impairment in schizophrenia as yet. Theory-driven approaches employ mathematical models to understand at a deep level cognitive impairments in schizophrenia. For example, one biophysically-based model focused on cortical microcircuits and working memory impairment in schizophrenia[210,211], suggesting that disturbed excitatory-inhibition balance due to disrupted glutamatergic signaling could explain working memory deficits. Another model suggested that reduced GABAergic activity in the visual cortex and disturbed connection between lateral geniculate nucleus and visual cortex contribute to visual perceptual abnormalities in schizophrenia[212]. Yet another approach focused on processes derived from a specific neural computing process (i.e., reinforcement learning) to explore latent processes that could contribute to impaired performance of patients during reinforcement learning tasks[156,213]. Finally, predictive coding (i.e., based on Bayesian inferences) is a neurocomputational process that may help to explain perceptual abnormalities of schizophrenia patients (e.g., MMN, motion perception)[214,215].

Hence, computational psychiatry is an emerging field that may provide valuable insights into the underlying mechanisms of cognitive impairments in schizophrenia.

Cognition and remote digital technology

There is now considerable interest in conducting cognitive assessments remotely on mobile devices. However, the benefits of this type of assessment are unclear. It has not been established that frequent, very brief, cognitive assessments of uncertain reliability are more valuable than fewer, longer assessments with demonstrated reliability. Further, there are benefits to having a tester in the room with a participant to monitor focus and effort of the testing session, something that is not possible with remote assessment. On the other hand, there would be advantages if participants can take tests from their home computers (as opposed to their smartphones), because the testing parameters and visual display could approximate those that occur in a testing lab. This arrangement would save the participant from coming into the lab, but would still not provide an ability to monitor the degree of engagement with the tests.

It is important to keep in mind the difference between two forms of digital data collection: active and passive. This distinction was not relevant until the arrival of smartphones. Active data collection is anything that involves intentional responses on the part of the participant, such as filling out an ecological momentary assessment survey of what they are doing or how they are feeling. Passive data collection, on the other hand, does not require actions from participants. These include using the global positioning system (GPS) functions to estimate the number of locations or the amount of distance traveled by participants[216,217]. The ability to collect passive data, for long periods of time and with no effort on the part of the subjects, opens up a new world of information derived from big data[218]. It is possible that cognitively relevant indices can be obtained from passive data, but this remains to be demonstrated.

Brain network organization

As mentioned above, studies of isolated brain regions have shifted to a focus on connectivity, which fits with one of the most influential theories of the pathophysiology of schizophrenia, that of neural disconnection[219,220]. According to this theory, several features of schizophrenia, including problems in social functioning, arise from an underlying problem in neural connectivity.

Until recently, the field had limited tools to examine connectivity with functional neuroimaging, and most of the work was to examine connections between pairs of regions. One key development has been the change from traditional (i.e., seed-based) connectivity approaches to graph-based methods for examining brain network organization[221]. Graph theory provides powerful quantitative tools for network analyses of brain connectivity and organization. It can characterize network structure by identifying local contributions of individual nodes and connections, as well as the network's global capacity to integrate information[222].

Graph theory studies of schizophrenia have so far produced mixed results[223,224], perhaps because some studies use resting state and others task-based imaging data. Nonetheless, these approaches have tremendous potential for understanding psychiatric conditions. It is likely that schizophrenia, as well as other major mental illness, are associated with specific and characteristic disturbances of network connectivity[225].

CONCLUSIONS

Breakthroughs, incremental steps, and a disappointment

If we look at the developments over the past 5-10 years, it is our impression that most of the advances have been incremental – steps toward a better understanding of the nature and implications of cognition in schizophrenia. Some of these steps were made possible by advances in related areas of science, such as neuroimaging, social neuroscience, big data methods, or neuropharmacology. Also, many of the advances reflected recent empirical maturity, in which meta-analyses were employed to detect signals by combining a large number of studies, or multisite consortia were formed to recruit a large number of subjects with detailed assessments and phenotyping.

Aside from an inevitable march forward with incremental steps, some areas related to cognition in schizophrenia seemed to take large leaps in recent years. An admittedly subjective list of such examples would include the dramatic advances in neuroimaging methods such as connectivity and network analysis methods, the highly informative modelling of the pathway(s) from brain processes to community integration and daily functioning, and the rapid inclusion of methods and concepts from social and affective neurosciences.

In contrast to these areas of impressive impact, we note one area of disappointment. We still do not have powerful methods for cognitive enhancement in schizophrenia. The developments in non-pharmacological methods are impressive, but do not reliably generalize to functionally meaningful improvements. In terms of new medications, substantial enthusiasm in early phase studies has not been born out in larger, and more dispersed, phase III studies. Meaningful cognitive enhancement in schizophrenia appears to be close, but remains elusive.

Implications for subgrouping and the diagnosis of schizophrenia

The US NIMH initiated the Research Domain Criteria (RDoC) project, which provocatively asks whether specific psychiatric diagnoses, such as schizophrenia, will fit with our rapidly growing knowledge from neuroscience[226,227]. As a result of this emphasis, many studies and some multisite consortia are currently recruiting participants across various psychotic disorders, not schizophrenia alone, to address key scientific questions. For example, the Bipolar and Schizophrenia Network for Intermediate Phenotypes Consortium has proposed cognitive-based biotypes that can be compared in terms of their external validity with existing diagnostic classifications[228,229]. Similarly, the Consortium on the Genetics of Endophenotypes in Schizophrenia has closely examined the genetic influences on a wide range of cognitive endophenotypes for schizophrenia, thereby providing a way to identify genetic subgroups of patients or to parse the genetic architecture of the disorder[230,231].

Perhaps a better understanding of brain-based cognitive, emotional and motivational domains will lead to a reorganization of diagnostic groupings. If so, schizophrenia might cease to exist as a separate disorder and could be lumped together with other types of psychosis, or split into biologically validated subtypes. While we can speculate on such long-range possibilities, the fact remains that schizophrenia will not disappear as a diagnosis any time soon. As long as schizophrenia is a diagnosis, a key question will be whether cognitive impairment should be part of the diagnosis. That outcome very nearly happened in the DSM-5, in which cognition was one of several dimensions that was initially slated for inclusion. Very late in the revision process, it was moved from the main body of the manual to Section III, meaning that it requires additional study before being implemented.

The situation is different with the ICD-11 diagnostic guidelines, in which the level of cognitive impairment is listed as a qualifier for schizophrenia[232], meaning that it will be rated after coding the diagnosis, along with other key features of illness, such as positive, negative and depressive symptoms. Cognition was considered to be an appropriate qualifier because it is related to the prognosis and management of the illness. The rationale for inclusion is that knowing something about the level of cognition will help clinicians and families to anticipate the patients' degree of problems and success in work, school, social functioning, or rehabilitation.

This development marks the first time that clinicians throughout the world will be asked to notice, evaluate and record the cognitive status of schizophrenia patients as part of routine diagnosis.

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