Why Study Cognitive Deficits in Schizophrenia?

For much of the 20th century schizophrenia was considered a profound mystery and psychodynamic theories of its origin predominated. Over the past several decades, major advances in neuroscience have drastically changed the way schizophrenia is viewed, have deepened our understanding and have led to better treatments. Most importantly, it is now abundantly clear that schizophrenia is a brain disorder with strong genetic contributions. It is characterized by "positive" psychotic symptoms such as hallucinations and delusions, and "negative" symptoms such as amotivation, social withdrawal and apathy. Positive symptoms, the most dramatic manifestations, were, until relatively recently, the primary focus of drug development. But even after the florid psychotic symptoms are effectively managed with antipsychotic drugs, debilitating cognitive deficits persist. Consequently, cognitive deficits are the strongest predictor of functional outcome and only ~20% of individuals with schizophrenia are able to work. Since schizophrenia strikes in late adolescence/early adulthood and affects ~1% of the population worldwide, this has staggering economic and psychosocial costs. Because there is a dearth of effective treatments, ameliorating cognitive deficits has become a priority of the schizophrenia research community. A better understanding of the pathophysiology of cognitive deficits is needed to guide these efforts.

Since its initial conceptualization as "dementia praecox," cognitive dysfunction has been recognized as integral to schizophrenia. Rather than being an epiphenomenon of psychosis, cognitive deficits reflect the pathophysiology that gives rise to schizophrenia. They are more closely related to predisposing genes and are better predictors of social function and outcome than are the symptoms that define schizophrenia. Increasingly, the goal of schizophrenia research is to understand the neural and genetic mechanisms of cognitive deficits. In addition to being able to target their mechanisms for treatment, there are other compelling reasons to understand cognitive deficits: (1) Because cognitive deficits predate the onset of illness, they may identify individuals at high risk for developing schizophrenia and enable early intervention; (2) Their presence in some healthy relatives of individuals with schizophrenia suggests that they are markers of genetic vulnerability that can guide the search for susceptibility genes; (3) Schizophrenia is a heterogeneous illness, and identifying core cognitive deficits and their genetic mechanisms may lead to more valid subtyping, which has important implications for research, treatment and prognosis. In summary, understanding cognitive deficits, along with relatively preserved abilities in schizophrenia, will implicate underlying neural circuitry, guide the search for neuropathology, lead us to susceptibility genes, mechanisms and molecular targets for treatment and thereby provide clues to etiology (or etiologies), which will contribute to a theoretical understanding of this enigmatic disorder.

Article Overview

The literature documents impairments in a wide range of neurocognitive functions in schizophrenia. In fact, most meta-analytic studies of cognition in schizophrenia demonstrate that no domain tested is spared. The aim of this article is not to
provide an exhaustive list of cognitive deficits, rather it is to highlight a subset that seem most central to schizophrenia and that hold the most promise for shedding light on its pathophysiology. One criterion for identifying core deficits is whether they are present in increased rates in healthy relatives of patients with schizophrenia. This would suggest that they are markers of genetic vulnerability to illness or "cognitive endophenotypes." The "endophenotype" concept in psychiatry is discussed in section Cognitive "Endophenotypes". Meta-analytic studies of relatives show the strongest effect sizes for impairments on tasks with high executive function demands such as set-switching, inhibition, and working memory (section Executive Function Deficits). Disturbances of memory, thought, and language are described in sections Memory and Thought, Language and Semantic Memory Disturbances. Section Challenges and Potential Confounds in the Study of Cognition outlines some of the challenges to identifying specific cognitive deficits. And section Are There Fundamental Deficits That Give Rise to Widespread Cognitive Dysfunction? considers whether there are more elementary deficits that can parsimoniously account for the range of cognitive dysfunction. Finally, the advent of sophisticated neuroimaging techniques and the revolution in genetics hold tremendous promise for illuminating the neural bases of cognitive deficits in schizophrenia (section Promising Advances Relevant to the Study of Cognition).

Cognitive "Endophenotypes"

Schizophrenia arises from a poorly understood and complex interaction of multiple genetic, environmental and epigenetic risk factors. Identifying genes that predispose to schizophrenia can lead to early identification of individuals at risk, foster a better understanding of schizophrenia at a molecular level, improve pharmacotherapy and guide the development of preventive interventions. Since only a small portion of individuals who have genes that predispose to schizophrenia will become ill, we cannot rely on the presence of symptoms alone to identify individuals who carry susceptibility genes. Because cognitive deficits are associated with illness within families, and are present at a higher rate among family members than in the general population, they can be used to identify individuals who lack any overt symptoms of illness, but who carry susceptibility genes. These cognitive deficits can be considered "endophenotypes" or markers of genetic vulnerability to illness. The endophenotype concept was first presented in relation to psychiatric disorders by Gottesman and Shields in 1972. Endophenotypes are manifestations of pathology that may not be obvious without specialized testing and that are thought to be more closely related to the genes that predispose to illness than are symptoms. Because endophenotypes fill gaps in the causal chain between genes and more distal, complex disease manifestations such as symptoms, they may provide clues to etiology. The characteristics of useful endophenotypes are listed in Fig. 1. Candidate cognitive endophenotypes include deficits in executive functions such as working memory and inhibition. Abnormalities in several psychophysiological measures have also been proposed as candidate endophenotypes. These include smooth pursuit eye tracking, the P300 event-related potential, and indices of sensorimotor gating such as backward masking, prepulse inhibition of the startle blink, and gating of the auditory P50 event-related potential component. These abnormalities in early information processing are mentioned here because they might have ramifications for cognitive processing down the line, although such links are still more theoretical than established.

Figure 1 A schematic model of the frequency (left) and characteristics (right) of a cognitive endophenotype (e.g., inefficient working memory, formal thought disorder, antisaccade errors). It is most frequent in schizophrenia, then in schizophrenia spectrum disorders, then in unaffected family members, and then in the general population. It is presumed to reflect the influence of a susceptibility gene or genes. Endophenotypes are a subset of biological markers that can be distinguished by meeting the criteria listed that suggests that they are genetic in origin (as opposed to primarily environmental, epigenetic, or multifactorial). The right side of the figure is adapted from Gould, T.D., Gottesman, I.I., 2005. Psychiatric endophenotypes and the development of valid animal models. Genes Brain Behav., 1–7 with permission from I. Gottesman who owns the Copyright.
Executive Function Deficits

Executive functions are a diverse set of cognitive abilities that allow flexible rather than reflexive responses to events. They are necessary for coordinating thought and action in the pursuit of goals. These goals may be immediate, such as finding food, but they are often remote, higher order goals such as earning an academic degree. Executive functions include switching flexibly from one task to another, inhibiting prepotent, but contextually inappropriate response tendencies, problem-solving and planning. The prefrontal cortex plays a pivotal role in mediating executive function on the basis of studies of monkey neurophysiology, frontal lesion patients, and human neuroimaging. Neuroimaging studies consistently implicate prefrontal neural circuitry in the executive function deficits of schizophrenia.

In schizophrenia, executive function deficits are reflected in behavior that is stimulus-bound rather than guided by context, perseverative, and stereotyped. The seminal studies that first established a direct link between deficient executive function and abnormal prefrontal activity employed the Wisconsin Card Sort Test (WCST) (Fig. 2). The WCST is a complex, multidimensional task that is highly sensitive to dysfunction of prefrontal neural circuitry. Successful performance requires sustained attention, concept formation, response monitoring, task-switching and working memory. This complexity does not allow it to isolate the specific cognitive deficits underlying the poor performance and differential brain activation seen in schizophrenia. More recent neuroimaging studies have employed tasks that constrain demands to identify specific executive processes that are intact or impaired.

Inhibition is the ability to suppress automatic or prepotent responses (e.g., looking toward a suddenly appearing object). Individuals with schizophrenia consistently show increased errors and frequently also show increased latencies for correct responses on tasks requiring inhibition such as the Stroop interference paradigm, the go, no-go task, and the antisaccade task (Fig. 3). In real life, deficits in inhibition might translate into behavior that is impulsive and stimulus-bound.

Task-switching refers to switching flexibly from one set of rules to another in response to changing contingencies. Task-switching requires processes that are not necessary when simply repeating the same task and generally incurs costs in the form of increased response latency and errors. Clinical observations of perseveration—the contextually inappropriate and unintentional repetition of responses—and impaired performance of neuropsychological tests such as the WCST have lead to the presumption of task-switching deficits in schizophrenia. Using tasks that isolate cognitive processes, however, several groups have reported that task-switching is normal. For example, while performing random sequences of prosaccades and antisaccades (Fig. 3) patients showed normal task-switching costs. But unlike healthy individuals, their errors tend to be in the same direction of the prior saccade. This suggests an abnormally strong influence of the prior response. Thus, instead of reflecting a problem with switching rules, perseveration may reflect an unwanted repetition of responses. Such dissociations suggest that there are selective impairments of executive function in schizophrenia that can help to pinpoint dysfunction in specific neural circuitry.

Working memory refers to actively holding information "on-line" in the mind's eye and manipulating it in the service of guiding behavior. It is a temporary store whose contents are continually updated, and scanned in response to immediate information processing demands. Daily activities, from mentally rehearsing a phone number to considering alternative perspectives and outcomes, depend on it. In schizophrenia, there is abundant evidence of both behavioral impairment and anomalous patterns of brain activity.
during working memory performance. What is less clear is whether particular subcomponents of working memory are differentially affected. Working memory is comprised of distinct stages (encoding, maintaining and manipulating information, and then selecting the appropriate response) and operates on different domains of information (e.g., spatial, verbal, and object features). These stages and domains are associated with overlapping but distinct patterns of neural activity. Regardless of which subcomponents of working memory are disrupted in schizophrenia, impoverished internalized representations may lead to behavior that is unduly driven by external stimuli.

**Error processing (response monitoring):** Learning from errors is fundamental to adaptive human behavior. It requires detecting errors, evaluating what went wrong and adjusting behavior accordingly. These dynamic adjustments are at the heart of behavioral flexibility and accumulating evidence suggests that deficient error processing contributes to maladaptively rigid and repetitive behavior in schizophrenia.

Error processing relies on neural circuitry involving the anterior cingulate cortex, which is functionally and structurally abnormal in schizophrenia. Following error commission, patients with schizophrenia show blunted neural markers of errors: both functional MRI activation of the anterior cingulate cortex and the error-related negativity (ERN). The ERN is an event-related potential that peaks ~100 ms following an error. It is thought to reflect error detection and error-based reinforcement learning (the strengthening or weakening of stimulus-response mappings based on behavioral outcomes). A blunted ERN, similar to that observed in schizophrenia, has been observed in healthy siblings of individuals with schizophrenia, in never-medicated children with putative antecedents to schizophrenia and in antipsychotic naïve patients at high clinical risk for psychosis. These studies suggest that blunted error processing is not simply a byproduct of antipsychotic drugs but instead may be an endophenotype of schizophrenia. In spite of these abnormalities, post-error slowing (the slowing of responses in trials that follow errors) and error positivity (Pe), an event-related potential associated with both error awareness and post-error slowing, are often found to be intact. Such dissociations have been observed within single studies and suggest that error detection and evaluation have different neural mediation than remedial performance adjustments, and are differentially impaired in schizophrenia. Impairments in evaluating and learning from errors may contribute to generalized performance impairments and to perseveration, a classic behavioral abnormality in schizophrenia.

**Figure 3** An example antisaccade paradigm. The cross-hair represents the point of regard. A trial begins with a visual cue instructing either a prosaccade or an antisaccade (in this case an orange circle for prosaccades and a blue X for antisaccades). Following the disappearance of the cue, participants maintain fixation on the center until a stimulus appears over one of the two peripheral dots, the side randomly determined. Participants are instructed to look toward the suddenly appearing stimulus on prosaccade trials. For antisaccade trials, they are instructed to look in the opposite direction. After stimulus offset, fixation returns to the center as participants await the beginning of the next trial. While prosaccades are a relatively automatic response, antisaccades require executive control. To perform an antisaccade correctly one must suppress the prepotent response of looking toward a suddenly appearing stimulus (i.e., prosaccade) and generate the novel behavior of looking in the opposite direction. Outcome measurements include directional accuracy of the saccadic eye movement and latency to initiate the saccade. Individuals with schizophrenia generally perform normally on prosaccade trials, but show increased errors (failures of inhibition), and depending on task parameters, may also show increased latency for correct responses on antisaccade trials.
Memory

Clinical observation suggests that individuals with schizophrenia have problems with memory. But memory is a broad term that encompasses the myriad ways that experience leaves durable traces in the brain. Declarative memory, particularly for verbal materials, has been a focus of research and is found to be deficient. Declarative memory includes both episodic memory (memory for events) and semantic memory (memory for facts) and can be divided into stages that engage distinct neural circuits: acquiring and organizing new information (encoding), retaining it (storage), and retrieving it when necessary. Encoding and retrieval are both active processes that are vulnerable to disruptions of attention and depend on prefrontal networks. The storage of new declarative information, in contrast, is not under voluntary control and is critically dependent on hippocampal mediation. There is ample evidence of deficient encoding and retrieval in schizophrenia, but in spite of reports of structural and functional hippocampal abnormalities, there is scant evidence for accelerated loss of information from memory storage.

A burgeoning literature highlights the importance of deficient sleep-dependent memory consolidation among the memory deficits of schizophrenia. After encoding, memories are not just passively stored, rather they undergo active “consolidation” processes that stabilize, enhance, integrate and reorganize memory traces in the brain. These processes operate outside of conscious awareness over an indeterminate period of time, hours, days or even years. A wealth of evidence suggests an evolutionarily conserved function for sleep in memory consolidation. In particular, animal studies suggest that sleep spindles, a defining thalamocortical oscillation of non-rapid eye movement Stage 2 sleep, are a key facilitator of the synaptic plasticity involved in memory. In humans, sleep spindles correlate with the sleep-dependent consolidation of both declarative and procedural (“how to” or skill) memory. Individuals with schizophrenia, including antipsychotic naïve patients, have reduced sleep spindle activity that common in some studies, is associated with impaired sleep-dependent consolidation of declarative and procedural memory. Using a well-validated probe of sleep-dependent motor procedural memory, the finger-tapping motor sequence task (MST, Fig. 4), several studies have demonstrated that, unlike healthy individuals, patients with schizophrenia fail to show overnight enhancement of performance despite intact initial learning. Schizophrenia patients also show reduced sleep-dependent consolidation of a mirror tracing procedural motor memory task despite intact initial learning, and impaired consolidation of declarative memory after a night of sleep, tested with a picture recognition task, that correlated with reduced sleep spindle activity.

Sleep spindle activity is highly heritable and spindle deficits that are associated with cognitive impairments are also seen in healthy first-degree relatives of schizophrenia patients. Recent large-scale genome-wide association studies have identified schizophrenia risk genes that may contribute to spindle deficits and illuminate their mechanisms and thereby provide molecular targets for treatment.

Figure 4  Finger tapping Motor Sequence Task (MST). (A) The MST requires participants to repeatedly type a 5-digit sequence (e.g., 4-1-3-2-4) on a keyboard with the left hand, “as quickly and accurately as possible” for 12 30 s trials separated by 30 s rest periods. Participants train before sleep and test on and additional 12 trials after sleep. The primary outcome measure is overnight improvement calculated as the percent increase in correctly typed sequences from the last three training trials to the first three test trials. (B) Sleep-dependent MST performance. Left: At training, SZ patients (red triangles) and healthy controls (blue squares) show a similar time course of improvement, although SZ patients are slower overall (see y-axis on right). Right: Following a night of sleep, only the healthy controls show sleep-dependent improvement. Data from Manoach, D.S., Cain, M.S., Vangel, M.G., Khurana, A., Goff, D.C., Stickgold, R., 2004. A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. Biol. Psychiatry 56, 951–956.
Thought, Language and Semantic Memory Disturbances

In addition to abnormalities in the content of thought (e.g., delusions and hallucinations), schizophrenia is characterized by disturbances in the form of thought. Formal thought disorder refers to impairments in the organization and control of thoughts as expressed through language. It ranges in severity and type, from disturbances of logical concept formation to peculiar word usage. Although viewed as a symptom, formal thought disorder has cognitive origins and milder manifestations have been documented in healthy relatives suggesting that it may be an endophenotype. Whether formal thought disorder reflects a primary thought or language disturbance has been debated since it was first described by Bleuler as, "loosening of associations." Although not specific to schizophrenia—it is seen in other psychotic disorders and even healthy individuals show instances of thought slippage—qualitatively, the flavor of formal thought disorder in schizophrenia is unique. It is frequently characterized by confusion, instability, and unusual word and phrase usage in contrast to, for example, the loosely combined ideas and jocularity often seen in mania. At its most extreme, language is incoherent. Milder manifestations include vagueness (language that lacks specific information) or its opposite, overly specific and excessively qualified speech (e.g., a four-legged pig).

Even patients without overtly thought disordered language may show abnormalities of language production and comprehension at the levels of individual words (in terms of how semantic relationships between words are stored and retrieved from memory), sentences (how the meaning of individual words are combined within a syntactic structure to build up sentence meaning), and discourse (how sentences are combined to construct a higher order meaning). Studies examining the organization and retrieval of individual words from semantic memory suggest that there is no loss of lexical or semantic knowledge in schizophrenia, but that the storage and/or access to words is less organized than in healthy individuals. At the sentence level, patients have difficulty in the “on-line” use of semantic context to constrain their expectations of what will follow in the sentence and this impairs comprehension. The difficulty in building up context may arise from deficits in combining semantic with syntactic information. At the discourse level, patients are impaired in generating bridging inferences across sentences (links that connect the meaning of one sentence to another) leading to reduced higher-level coherence of discourse and comprehension.

Challenges and Potential Confounds in the Study of Cognition

Characterizing deficient vs. preserved cognitive abilities has proved an elusive goal in schizophrenia, and the literature is replete with ambiguous or contradictory results. Several factors contribute to this difficulty.

Heterogeneity: Schizophrenia is a heterogeneous disorder without a clear etiology or pathognomic signs. In most cognitive studies only a subset of patients shows deficits on any given measure, and the particular subset showing a deficit varies from measure to measure. Thus, compared to demographically-matched healthy individuals, patients with schizophrenia show a greater range of values on outcome measurements ranging from simple reaction time to neuroimaging measurements. The effects of course variables (e.g., first episode vs. chronic, acute exacerbation vs. partially remitted state); medication type, duration and dosage; severity of illness and the interaction of illness with factors that normally contribute to individual differences (e.g., gender, age, intelligence) also contribute to measurement heterogeneity. Thus, depending on the composition of the sample a particular cognitive deficit may or may not be detectable.

Paradoxically, in spite of this heterogeneity, schizophrenia has defied meaningful subdivision. Most subtyping schemes are based on phenomenology rather than biology, lack temporal stability and fail to provide an adequate account of the variability in neuroanatomic abnormalities, cognitive dysfunction, outcome, response to medications and other signs of schizophrenia. The failure of phenomenology to map onto specific biological substrates suggests that it may not be the most valid organizing principle for illness heterogeneity. Identifying core cognitive deficits that can be mapped onto specific neural substrates may lead to more meaningful subtyping.

Variability: In addition to showing a wide range of performance across individuals, there is more variable cognitive performance within individuals, both within a single session (i.e., from trial to trial) and over separate sessions (i.e., test-retest) compared to demographically-matched healthy individuals. For example, while performing a working memory task, patients with schizophrenia show greater variability of response time within a single session and reduced test-retest reliability of brain activation across sessions. Even the demonstration of hand preference on simple tasks is less stable over two sessions. Increased variability and unreliability of performance are among the most consistent findings in schizophrenia research. Although frequently viewed as a measurement confound, it may be more productive to regard variability as intrinsic to schizophrenia and having a neurological basis that requires explanation. This is supported by findings that frontal lobe damage in humans leads to increased variability of cognitive performance.

Amotivation: Amotivation is a core negative symptom of schizophrenia that makes it difficult to determine whether poor performance reflects a true deficit or that the subject was unwilling or unable to exert the effort necessary for optimal performance. Because tasks differ in the amount of effort required, amotivation may be more detrimental to the performance of some tasks than to others.

Medications: Antipsychotic medications have thus far targeted symptoms rather than cognition, and there is a vast, and often contradictory literature on whether conventional antipsychotics impair cognition and whether atypical agents might improve it. Adjunctive anticholinergic drugs may also be detrimental to memory and other cognitive abilities.

Generalized deficit: Meta-analytic studies demonstrate widespread cognitive dysfunction suggesting that schizophrenia is characterized by a global blunting of performance. In addition to potential impairments attributable to amotivation and medication,
patients may appear to have a generalized cognitive deficit because schizophrenia interferes with education and occupational attainment and many cognitive measurements are sensitive to these factors. In addition, acute psychosis and associated disruptions of attention may prevent optimal engagement in cognitive testing. For these reasons, simply demonstrating that patients perform worse on a particular task is not terribly revealing.

To some extent, the concept of a “generalized deficit” is a straw man. Existing data in patients do not support such a simplistic explanation. And a generalized deficit cannot account for the findings of highly selective cognitive deficits in unaffected relatives. Sorting out cognitive deficits that reflect the pathology of schizophrenia from those that are epiphenomena of having and being treated for a severe, chronic mental illness is an ongoing challenge. Strategies for identifying specific deficits in schizophrenia include demonstrating a pattern of both proficient and deficient performance across tasks that are matched for discriminating power, and finding tasks on which a cognitive abnormality is actually advantageous to performance. Successful employment of this superiority strategy is illustrated by a series of numerosity studies in which the intact perceptual organizational ability of controls interfered with the rapid counting of elements (i.e., perceptual gestalts had to be broken for elements to be counted). Because patients failed to form gestalts, they were faster at counting.

**Are There Fundamental Deficits That Give Rise to Widespread Cognitive Disturbance?**

The seeming generality of neurocognitive deficits in schizophrenia leaves one searching for a parsimonious explanation—are there more basic problems that can organize and account for the diverse deficits seen? Some investigators have hypothesized that many cognitive deficits stem from deficient working memory that leads to a failure to guide behavior on the basis of internalized representations such as schemata and ideas. Deficits earlier in the information processing pipeline, such as in sensorimotor gating, have been proposed to account for higher order difficulties in inhibiting thoughts, speech and action. While a theoretical case can be made for a number of integrative explanations, empirical evidence of links between elementary and higher order deficits is lacking.

**Attention:** A wide range of cognitive deficits in schizophrenia could be viewed as failures of the effective deployment and control of attention. The term attention refers to a broad array of cognitive functions that enable the individual to select relevant aspects of either the internal or external milieu (i.e., thoughts or environmental stimuli) for further processing, while keeping others at bay. Particularly during the acute phases of schizophrenia, patients describe difficulties filtering the continuous barrage of stimuli present at every moment and focusing on what is relevant. For example, they may have difficulty selectively attending to the voice of the person addressing them rather than to noise from the refrigerator. Inattention, however, cannot account for findings of deficits when attention is controlled or for information processing deficits on measurements that minimize its contribution such as the auditory mismatch negativity (MMN). MMN is an event-related brain potential that is sensitive to stimulus deviation from a repetitive pattern, and that is reduced in chronic schizophrenia. It can be elicited in healthy individuals regardless of whether they are paying attention to the sequence.

**Deficient automation:** In healthy individuals, practice and sleep can increase the speed of performance and reduce the variability of responses and error rate, reflecting a shift from effortful to more automatic processing, and a corresponding shift in the brain networks that support performance. Tasks, or components of tasks, that have become automated proceed efficiently with reduced demands on attention. If schizophrenia were characterized by deficient automation, increased attention would be required for task components that should have been automated and consequently fewer processing resources would be available for other, higher-order task demands. The interaction between automatic and effortful processes is what allows a limited capacity brain to carry out complex cognitive tasks. Although there are only a few studies of automation per se in schizophrenia, deficient automation provides a plausible account for increased variability and impairments of performance across a range of tasks.

**Context Processing:** As illustrated in section Executive Function Deficits, the balance between past and present influences on behavior is upset in schizophrenia. Patients have trouble learning from error feedback suggesting that the influence of previous experience is too weak. On the other hand, they also show perseveration of responses from trial-to-trial, indicating that the influence of the recent past is too strong and/or the influence of the current contingency is too weak. These difficulties in appropriately using information from both the past and present to optimize behavior can be said to reflect deficient context processing. A number of executive functions are subsumed under the term “context processing” (e.g., working memory since a representation of context has to be held “on-line”). Computational models have shown that a deficit in a single context processing module can mimic patient performance on a variety of cognitive tasks.

**Promising Advances Relevant to the Study of Cognition**

**Neuroimaging:** Neuroimaging findings continue to form the crux of many theoretical conceptualizations of schizophrenia and continued technical advances hold promise for understanding its pathophysiology. The search for the neural basis of cognitive dysfunction in schizophrenia has evolved from key brain regions (e.g., prefrontal cortex or hippocampus) to also considering the integrity of neural circuits and the timing and spectral characteristics of brain activity across different regions. Advances in functional magnetic resonance imaging (fMRI) are providing ever higher spatial resolution. In combination with methods that provide high temporal resolution such as magnetoencephalography (MEG) and electroencephalography (EEG), it is possible to examine the
neural correlates of cognitive processes at each stage of performance and pinpoint exactly where and when they go awry. Complementary structural MRI can reveal anatomical correlates of abnormal activation and cognitive performance.

Since performance of even simple cognitive tasks is the product of coordinated activity in distributed networks, it is important to assess the structural and functional connectivity of the brain. New generations of scanners have been specifically designed for "connectomics" imaging and offer considerable advantages in terms of the signal to noise of Diffusion-Weighted Imaging (DWI) and the ability to resolve fiber crossings. This is a considerable value in modeling fiber tracts in the brain and assessing their integrity. Recent evidence suggests that white matter tract integrity contributes to individual differences in cognitive processing in health, and an emerging literature in schizophrenia links regionally reduced white matter integrity to cognitive dysfunction.

Although brain communication depends on the anatomical connections mapped by DWI, communication need not mechanically follow the most direct or obvious path and a full picture of brain connectivity requires more than a static wiring diagram. Functional connectivity MRI (fcMRI) during resting state extends our understanding of brain connectivity. This technique examines correlations in activity across brain regions and reveals highly organized patterns of coherent activity in a set of networks with different functional affiliations. fcMRI has proven to be a powerful method for evaluating network dysfunction in schizophrenia. By impairing communication in local circuitry and between connected brain regions, abnormal connectivity may contribute to cognitive dysfunction in schizophrenia.

There are a number of important caveats to psychiatric neuroimaging. Neuroimaging techniques are highly sensitive to physiological artifacts such as subject motion, which may differ as a function of group membership. Other potential confounding factors that may vary systematically by group include psychotropic drug use, smoking and body mass index. Importantly, differences in task performance or even the mental states of participants during resting scans, may also confound the interpretation of group differences in brain activity. Investigators need to consider these caveats when designing studies and look for a convergence of performance or even the mental states of participants during resting scans, may also confound the interpretation of group differences in cognitive dysfunction in schizophrenia.

Cognitive deficits in schizophrenia are likely to have arisen recently (and might even be de novo in the proband) and are less subject than common variants to natural selection. This is a considerable value in modeling heredity in psychiatric traits. Recognizing this, connectomics and offer considerable advantages in terms of the signal to noise of Diffusion-Weighted Imaging (DWI) and the ability to resolve fiber crossings. This is a considerable value in modeling fiber tracts in the brain and assessing their integrity. Recent evidence suggests that white matter tract integrity contributes to individual differences in cognitive processing in health, and an emerging literature in schizophrenia links regionally reduced white matter integrity to cognitive dysfunction.

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Genetics: A promising avenue of research, made possible by advances in genetics, links variability in cognitive function and associated brain activity to genetic variation. The goal of this approach is to identify susceptibility genes and potential mechanisms that contribute to the development of schizophrenia. For example, in an early groundbreaking neuroimaging genetics study, Egan and et al. (2001) reported that a common functional polymorphism in the catechol-O-methyltransferase (COMT) gene, which reduces the amount of dopamine available in the synapses of the prefrontal cortex and is slightly more common in individuals with schizophrenia than their unaffected family members, was associated with both poorer performance of the WCST and increased prefrontal cortical activation during working memory performance in both patients with schizophrenia and healthy control participants. This suggests that prefrontal cortical function is influenced by genes that increase susceptibility to schizophrenia. Increased prefrontal activation is thought to reflect "inefficient" function (i.e., increased resources are necessary to support a given level of performance). Several groups have shown that prefrontal inefficiency is also present in unaffected siblings of schizophrenia patients. The siblings showed greater activation than controls even though their task performance did not differ. These findings suggest that physiological indices derived from neuroimaging, because they more directly reflect the effects of genes (e.g., increased metabolism of dopamine), may prove more sensitive endophenotypes than behavioral ones.

Failures to find increased frequencies of the high risk COMT polymorphism in schizophrenia in some studies (e.g., of Asian populations), are not surprising given the number of factors that contribute to variability in association studies, and point to the need for caution in generalizing such findings. In addition, particular polymorphisms only account for a small portion of the variance in cognitive performance and regional activation, as would be expected for complex, multi-locus traits. A gene such as COMT interacts with other genetic and environmental factors to either diminish or exacerbate its effect on brain function, and investigations of the effects of gene/gene and gene/environment interactions on cognition are underway.

To understand genetic contributions to cognitive deficits in schizophrenia, it will be important to conduct well-powered genetic studies. Like most human traits, cognitive abilities have complex genetic architectures, with allelic variants in many genes combining to influence expression. A major challenge deciphering the genetic architecture of cognitive deficits in schizophrenia is that it is expensive and time-consuming to assess cognition and conduct genetic characterization in large samples. This has motivated international collaborations to pool data across sites. Alleles identified with statistical confidence can then help to establish the broader gene networks that underlie variation in phenotypic expression. Genome-wide association study (GWAS) data can also be used to estimate genetic correlations between pairs of traits or disorders: the extent to which genetic influences on one trait are shared by a second trait. For example, if a specific cognitive deficit is an endophenotype of schizophrenia, one would expect a significant degree of shared genetic influences (as genes that influence the cognitive deficit will indirectly influence schizophrenia risk). Contrasting the genetic association profiles across cognitive deficits, their neural correlates and schizophrenia may illuminate causal relations between these traits. It is now also feasible to sequence the entire exome or genome in large numbers of individuals—an approach that can identify rare variants that may have larger effects on cognition than common allelic variation, since rare variants are likely to have arisen recently (and might even be de novo in the proband) and are less subject than common variants to natural selection.

Cross-disciplinary research in humans and animals will be necessary to forge empirical links in causal chains from risk genes to proteins and cellular functions, through to endophenotypes, cognitive impairments, symptoms and diagnosis. This approach has the potential to advance the mechanistic understanding, treatment and prevention of schizophrenia.
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Further Reading

Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70 (10), 1107–1112.

Relevant Website