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The schizophrenia research community, including government, industry, and academia, has made development of procognitive treatment strategies a priority. Much current research is directed at dividing broad impairments in cognition into more delineated components that might correspond to relatively specific neural systems and serve as targets for intervention. Sometimes overlooked in this ambitious agenda is the substantial neuropsychological literature that signals a more broadly generalized dysfunction in higher order cognitive functions in this illness. In this article, we argue that a generalized cognitive deficit is at the core of the disorder, is not a methodological artifact, and deserves more focused consideration from cognitive specialists in the field. Further, we weigh evidence that this broad deficit may have systemic biological underpinnings, at the level of the central nervous system (CNS) and more generally.

Key words: schizophrenia/cognition/neuropsychology/general cognitive deficit/gray matter/white matter/energy metabolism/inflammation

Introduction

With the field focused on development of procognitive treatment strategies, the debate about how best to characterize the cognitive performance deficits shown by individuals with schizophrenia has renewed currency. Do these deficits represent a single, generalized deficit, a number of discrete cognitive domain–specific deficits, or some combination of generalized and specific effects? In this article, we argue that a generalized cognitive deficit is at the core of the disorder and deserves more focused consideration from cognitive specialists in the field. Further, we weigh evidence that this broad deficit may have systemic biological underpinnings, at the level of the central nervous system (CNS) and more generally.

Cognitive Performance in Schizophrenia

Background

Drawing on evidence from other illnesses that performance on certain tests may be specifically affected by deterioration in specific brain regions, much schizophrenia research has focused on “localizing” neuropsychological tests. Among people with schizophrenia, however, performance is impaired across tests that are sensitive to localized impairments in frontal, temporal, hippocampal, parietal, striatal, and cerebellar functions. Indeed, cognitive performance deficits in schizophrenia have been identified in almost every measurable cognitive ability domain, from basic sensory and perceptual functions (including olfaction, vision, and audition) through preconscious information processing (eg, mismatch negativity) and early attention (eg, P300) to higher order cognition, including selective and sustained attention, working memory, episodic memory in verbal and nonverbal domains, processing speed, and problem solving. These impairments are present in patients in every clinical state and at every time period of the illness. Deficits emerge from studies using widely varying assessment techniques, including simple checklist measures, clinical neuropsychological tests, and elegant experimental paradigms. Cognitive performance deficits are seen in high-risk groups prior to the onset of psychotic illness. Deficits are broadly evident and well established at first episode and remain fairly stable through middle age.
In nonacute patients, the deficits are largely independent of symptomatology and are only modestly affected by current pharmacological treatments that improve other aspects of the illness. More so than other dimensions of the schizophrenia syndrome, cognitive deficits are associated with levels of day-to-day functioning in the community. There is evidence of exacerbation of deficits in later life, perhaps due to the duration of initially untreated psychosis. However, there is essentially no evidence of changes in the profile of cognitive impairments even in cases where cognitive impairments worsen over time, and the structure of cognitive impairments appears stable across treatment-related improvements in clinical state. Finally, a similar range of cognitive deficits is reported, in milder form, in the close relatives of people with schizophrenia.

“Generalized” Cognition in Schizophrenia

The history of study of cognitive impairments in schizophrenia has long been influenced by hypotheses regarding regional brain dysfunction, but the specificity of the findings is actually quite limited. A growing literature indicates that the latent structure of cognitive performance in schizophrenia is more unitary than was assumed previously. Perhaps the strongest evidence of this comes from the recent analysis of baseline cognitive performance data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. CATIE used an “all-comers” approach to recruit 1493 typical schizophrenia patients from 57 participating institutions representative of the real-world settings where these patients receive treatment. The test battery included 10 cognitive tests with multiple dependent measures representing traditional neuropsychological domains of processing speed, reasoning, verbal memory, working memory, and vigilance, with an additional test representing social cognition. More than 1300 participants completed at least 8 tests of the 11 cognitive tests, and 1005 participants completed all 11. A variety of statistical analyses showed that individual test scores and domain composites were significantly intercorrelated and that domain composites were highly correlated with a global composite score. Exploratory principal components analysis yielded a single significant component accounting for 45.2% of the overall variance in test scores. (See also Green et al.) Using confirmatory factor analyses, we examined several plausible models of the dimensional structure of cognitive impairments. A hierarchical, unifactorial model, with the 5 domain scores loading on a common hierarchical factor, provided the best fit to the observed data.

Other recent work indicates that the CATIE findings are representative of the schizophrenia literature more broadly. This hierarchical structure is exactly what we found in investigations of “within-groups” cognitive structure in matched samples of schizophrenia patients and healthy controls. And our meta-analysis of cross-domain correlations, showed a similar, intercorrelated structure of schizophrenia cognitive data across many studies.

Such findings are by no means specific to schizophrenia but, rather, echo an extensive literature addressing nonclinical samples. Numerous studies of healthy research participants indicate that diverse cognitive measures are correlated positively and to at least a moderate degree. It is generally held that this network of correlations is characterized by a hierarchical factor structure in which individual measures load on broad cognitive ability factors, such as verbal comprehension or working memory, which in turn load on a higher order latent factor representing general cognitive ability or “g.”

In other work, we also considered the structure of the “between-groups” deficit in schizophrenia cognitive performance relative to control performance. Two separate structural equation modeling analyses showed that more than 60% of the between-groups deficit in cognitive performance was mediated through a common cognitive ability factor—representing, in essence, a “deficit g.” Both analyses found disproportionate effects of diagnosis on certain cognitive domains. But these effects were small in magnitude and were confined to selected cognitive domains. It seems to follow from the findings regarding unitary cognitive structure in schizophrenia, both within schizophrenia samples and between schizophrenia and control groups, that much of what is measured by traditional neuropsychological assessment reflects broad cognitive ability rather than genuine domain-specific performance. This conclusion raises important questions about the validity of domain-specific interpretations of neuropsychological test findings from numerous areas of research, including clinical trials and studies of schizophrenia genetics.

Reservations About Generalized Cognition

Although we emphasize the generalized performance deficit in this article, it is clear that cognitive deficits in schizophrenia are not monolithic. Investigators sometimes have failed to find deficits where they were predicted (eg, in certain facets of early attention). More commonly, various investigations have shown relatively preserved abilities in areas of word reading and other language skills, recognition memory, simple motor skills, and other performance domains. Indeed, because word reading performance is relatively stable even in the face of illness, it has been used to reference the magnitude of neuropsychological impairment in other areas. At the more impaired end of the deficit spectrum, a vast literature has attempted to identify areas of “differential deficit” in schizophrenia, which might reflect abnormalities in discrete brain systems, although the results have been quite inconsistent. In sum, across the range of higher order cognitive functions, variation in average performance deficits across ability areas among those with schizophrenia is considerably smaller than the overall average deficit relative to normal...
performance. Large meta-analyses suggest that a distribution of mean cognitive performance in schizophrenia shifted approximately 1 SD to the left relative to controls across numerous domains and measures, with most individual measure effects falling within one-third SD above or below that level.\(^7\,8\,37\)

A large factor-analytic literature also bears on the debate about generalized cognitive performance in schizophrenia. Obtained factors differ somewhat among studies, depending on the batteries used. Nevertheless, almost all studies have found that cognitive performance in schizophrenia, as measured by traditional neuropsychological tests, is characterized by multiple factors.\(^38\) This literature provided a foundation for the recent designation of “separable” ability domains in schizophrenia that might serve as targets for new cognition-enhancing agents with the potential specifically to benefit (or worsen) performance in these ability areas.\(^38\) However, “separable” does not mean “independent,” even in the opinion of the proponents of this approach. Historically, the bulk of factor analyses in the schizophrenia literature have been conducted with orthogonal rotations, which constrain resulting factors to be independent.\(^21\) When factor analyses use oblique rotations or confirmatory methods that leave the factors free to associate, the cross-domain correlations are invariably substantial.\(^18\,20\,39\,40\) Some in the field have argued that these factors, and the separate groups of traditional neuropsychological variables used to measure them, are sufficiently independent of one another to tap discrete neural systems or molecular targets.\(^38\,41\) Others, highlighting the interactive and multidimensional nature of most neuropsychological tests and the observed intercorrelations among cognitive domains and measures, have questioned the directness of factor connections to discrete neural substrates.\(^21\,35\,42\)

Perhaps the most reliable evidence in the schizophrenia literature supports a limited number of disproportionate effects of illness, rather than “differential” or “separate” effects. Across numerous cognitive test studies, investigators have observed small but significant, disproportionate effects on verbal episodic memory and processing speed tasks.\(^7\,8\) Measures of processing speed, particularly digit symbol coding from the Wechsler Adult Intelligence Scale, may be the most impaired element of performance. In the CATIE trial, digit symbol was the best predictor of global performance, accounting for as much as 60% of the variance in total scores derived from larger cognitive assessment batteries.\(^18\) It is unclear whether these disproportionate effects are the result of the measurement properties of different instruments.\(^43\,44\)

That is, we may just measure processing speed and verbal memory more reliably than other capacities, or these measures may be simultaneously sensitive to a greater number of somewhat differentially impaired abilities. However, even assuming these are true effects, it is increasingly clear that this profile of somewhat preserved performances and somewhat disproportionate deficits comes against a backdrop of broadly generalized impairment, with most complex cognitive operations impaired to a quite similar degree.\(^22\,37\)

Schizophrenia researchers have raised a number of questions about the generalized cognitive performance deficit. One long-standing critique attributes the deficit to global, noncognitive, and possible nonspecific factors such as reduced motivation, demoralization, and the effects of institutionalization. (See Harvey and Sharma\(^45\) (pp12–13) for a discussion.) It has also been suggested that antipsychotic medications might cause a general dulling of cognitive performance. However, reviews have documented modest beneficial effects of both conventional and atypical medications overall.\(^46\,47\) Even if these findings reflect practice effects,\(^48\) it seems reasonable to believe that these medications are fairly neutral cognitively.

In recent years, another prominent critique has been that the generalized deficit reflects the multifactorial character of the neuropsychological measures used to assess cognitive function, more so than the actual structure of cognition.\(^42\,49\,50\) This critique is difficult to answer directly. Although the first generation of differential deficit research seems inconclusive, new efforts are under way to adapt behavioral measurement techniques from cognitive neuroscience,\(^51\,52\) and this work may enable researchers to more reliably link specific cognitive operations with specific genetic and neural targets.\(^53\,55\) However, we might then learn that these newer measures are correlated among themselves, or with traditional neuropsychological performance. And even if the new measures are substantially independent of one another,\(^56\,57\) that finding would not necessarily mean that the more generalized findings with traditional neuropsychological measures are somehow spurious or misleading.

That these traditional measures are multifactorial may be a disadvantage from a mechanism-discovery standpoint, but an advantage from other perspectives. More so than highly refined experimental paradigms, the traditional tests index integrated, interactive assemblies of cognitive operations—in other words, cognition at a “systems” level. This is an essential level of understanding for any complex disorder, in some ways less reductionistic and more “ecologically valid” than the level of disaggregated cognitive operations. It is this more global level of cognitive performance that has demonstrated relevance to disability and functional status\(^58\,59\) and it is questionable whether narrowly circumscribed deficit areas can be considered viable treatment targets until they can be shown to relate to functional disability.

**Systemic Accounts of Generalized Cognitive Impairment in Schizophrenia?**

It is more and more difficult to dismiss as artifact the generalized character of cognitive impairment in schizophrenia...
and the generalized nature of performance deficits in patients relative to control groups. As we have reviewed, broadly targeted investigations have typically found broadly generalized cognitive impairment, with considerable variance shared in common across performance domains. While not challenging the importance of targeted cognitive investigations, it may be that the field can also progress by taking a more systemic perspective on cognitive impairment in schizophrenia. Taking the generalized cognitive ability findings at face value, what neurobiological and pathophysiological hypotheses might account for them? Of course, one possibility is that a relatively specific lesion (eg, in dopamine-mediated frontal-striatal loops) could create an information-processing bottleneck (eg, poor response selection and programming) that in turn causes extensive problems with performance on neuropsychological and other measures. A variation on this idea is that performance on different cognitive measures is similarly impaired in schizophrenia because the measures tap into an overlapping set of distinctly impaired, “regionally specific” capacities. By this reasoning, a measure showing disproportionate impairment, like digit symbol coding, does so because it simultaneously assesses a larger set of these discrete deficits than other measures. Arguments of these sorts were easier to make in 20 years ago. Now, they must contend with waves of additional evidence—first, the findings supporting generalized cognitive impairment and, second, findings of widespread and intermingled brain abnormalities that could play a central role in broad cognitive performance deficits.

**CNS Hypotheses**

Prominent CNS findings in schizophrenia that might account for generalized cognitive dysfunction include (1) extensive reductions in gray matter and neuronal arborization, (2) diminished myelin density and fiber coherence in major white matter tracts; (3) poor signal integration at the level of the neuron and the neural network, and (4) abnormalities associated with the brain’s main excitatory and inhibitory neurotransmitters, glutamate and γ-aminobutyric acid (GABA). These findings are reviewed briefly below, followed by a discussion of more global systemic hypotheses.

**Gray Matter.** Ample literature documents decreased gray matter volumes in schizophrenia, generally and in numerous more narrowly defined regions of interest. Importantly, related findings in healthy schizophrenia relatives and at-risk groups are emerging, as well. Most evidence suggests a neurodevelopmental origin for these reductions, although some evidence of progressive volume loss over time has been presented. There is evidence that the gray matter reductions are not attributable to a reduction in the number of cells per se, as much as to reduced neuronal arborization and connectivity in distal dendritic processes. The suggestion of reduced synaptic connectivity, in turn, has been supported by a number of cognitive models of schizophrenia, including “cognitive dysmetria” and the “disconnection hypothesis.” The connection of reduced gray matter to broad cognitive performance in schizophrenia is increasingly well established, with evidence reported of numerous associations to association cortices and other regions.

**White Matter.** White matter abnormalities have been proposed as another explanation of functional connection failures in schizophrenia. However, it is only over the past decade or so that new imaging technologies have facilitated studies of the organization and integrity of white matter in this illness. Though inconsistent, studies using diffusion tensor imaging techniques have found various abnormalities, including decreased coherence and density in major fiber tracts. Recent studies extended these findings to recent onset patients and unaffected relatives. Substantial attention has also focused on myelin integrity. Alteration in numbers, distribution, structural integrity, and genetics of oligodendrocytes has been reported in the prefrontal cortex in schizophrenia. Hypotheses regarding reduced fiber tract coherence and myelin integrity have obvious intuitive appeal in a disease characterized by slowed processing and diffuse cognitive dysfunction. Findings connecting these white matter abnormalities to cognitive performance are also emerging. Interestingly, the association of white matter function with glutamate and acetylcholine neurotransmission provides possible links across categories of neurobiological models.

**Neural Network Integration.** Evidence is mounting that brain regions communicate by recognizing the concurrence of neural activity across neurons, neural assemblies, and neural networks and that schizophrenia is characterized by reduced communication and coordination. In general, the literature suggests that oscillatory responses in the beta and gamma bands are involved in integrating distributed neural activity to perform a variety of integrative cognitive functions. Research now implicates irregularities in these frequency bands as mechanisms of cognitive dysfunction in schizophrenia. Other work provides evidence that the signaling problems across these frequency bands are associated with increased response variability (“noise”) resulting from slow and variable phase resetting in pyramidal neurons after exposure to new stimuli. This abnormality was observed in patients and their relatives and was associated with cognitive performance. These investigators emphasized the likely association of these findings with dopamine D1 and D2 receptor–mediated optimization of signal-to-noise ratios in cortical microcircuits, which contributes broadly to the stability of cortical representations of internal and
external stimuli. Others tie these network integration abnormalities to GABA neurotransmission (see below).

Glutamate and GABA. Hypotheses concerning the brain’s main excitatory and inhibitory neurotransmitters, glutamate and GABA, are converging in the schizophrenia literature. One prominent example focuses on disturbances in N-methyl-D-aspartate (NMDA) receptor–mediated glutamate neurotransmission. NMDA receptors are ubiquitous in the neocortex and play a critical role in experience-dependent plasticity and the fast integration of information from multiple pathways. Slowed and inefficient processing across a wide range of cognitive operations could be a manifestation of dysfunction in such a fundamental neurotransmission system. Networks of GABA neurons give rise to oscillations in the gamma frequency band, discussed above, and allow synchronization of pyramidal cells in multiple cortical regions, providing a direct link to associated broad cognitive deficits. Drawing these lines of research together, the activity of GABA neurons is regulated, in part, by glutamatergic inputs and therefore likely reflects the influence of irregular NMDA receptor action.

General System Hypotheses

Each of the CNS systems noted above is present throughout the brain, with the potential for broad impact on cognitive operations. However, other findings and hypotheses provide the basis for an even wider “general systems” perspective on cognitive dysfunction in schizophrenia. Areas of interest include lipid metabolism, oxidative stress, energy metabolism, and inflammatory processes associated with vascular functioning. Especially intriguing are the growing number of findings suggesting possible genetic underpinnings for general systems hypotheses. Such systems not only are essential for brain cell development and integrity but also impact processes throughout the body. Further, they are complexly interactive. If such abnormalities are supported through further research, they might encourage an enlarged conception of schizophrenia as a general somatic disorder, rather than only a brain disease. The work associating these systems with cognition in schizophrenia is highly speculative. However, in light of recent empirical findings separately linking type 2 diabetes and chronic inflammation to impaired cognitive performance in schizophrenia, we examine aspects of energy metabolism and inflammation in hopes of opening a discussion of the possibility and potential importance of such broad systemic influences on cognitive performance in schizophrenia.

Insulin Resistance. Metabolism of glucose accounts for most brain energy needs and cognitive performance is sensitive to acute changes in blood glucose levels. Across clinical and nonclinical groups, acute glucose administration improves episodic memory and other cognitive capacities. This acute glucose benefit has been demonstrated in schizophrenia patients without diabetes or related clinical conditions. In light of these findings of glucose facilitation, the fact that chronic hyperglycemia and type 2 diabetes are associated with cognitive impairments requires further explanation. The phenomenon of insulin resistance is a likely part of the explanation. Insulin regulates the uptake, oxidation, and storage of glucose in insulin-sensitive tissues, such as adipose tissue, liver, and skeletal muscle. Insulin also plays important roles in the CNS. It modulates glucose utilization in a regionally selective way, in particular in the medial temporal lobe and prefrontal cortex. It influences levels of cognition-relevant neurotransmitters, especially acetylcholine. Insulin also influences neuronal physiology, particularly NMDA glutamate receptor–mediated long-term potentiation (LTP), consistent with a role in memory processes. As with glucose, acute insulin administration has been shown to facilitate memory and other cognitive performance in experimental paradigms.

In individuals experiencing ongoing insulin resistance, however, the ordinary functions of insulin are subverted. Insulin resistance is characterized by a self-reinforcing cycle of persistent high levels of insulin in peripheral tissue and a reduced sensitivity of the tissue to insulin’s essential metabolic functions, such as mediating glucose uptake into muscle. Over time, insulin resistance also downregulates insulin transport across the blood-brain barrier into the brain, ultimately leaving the brain in an insulin-depleted and functionally hypoglycemic state. Insulin resistance may be present years before the loss of glycemic control characteristic of diabetes. Even after control for confounders such as body mass and cardiovascular disease, insulin resistance and hyperinsulinemia have been shown to be associated broadly with cognitive function. Insulin dysregulation also has been proposed as a possible mechanism in neurodegenerative diseases known to impair cognition. Thus, it is quite clear that insulin dysregulation has central as well as peripheral effects and that these effects are associated with changes in brain structure and in the development of cognitive impairment.

Chronic Inflammation. Recent studies indicate that low-grade inflammation in peripheral tissue might have a central role in the pathogenesis of insulin resistance and type 2 diabetes. Proinflammatory cytokines (eg, interleukin 6 or IL-6) and closely associated acute-phase reactants (eg, C-reactive protein or CRP) are increased during insulin resistance. Importantly, the insulin resistance/inflammation association is potentiated by obesity and lifestyle factors. Proinflammatory cytokines, similarly to insulin, cross the blood-brain barrier and have regionally specific direct effects on brain function. IL-6, in particular, also like insulin, primarily modulates action in medial temporal and
prefrontal regions \(^{137}\) and impairs LTP and cognitive behavior in animal models. \(^{138}\) Further, numerous human and animal studies link insulin resistance and inflammation, on the one hand, with vascular dysregulation and cardiovascular disease, on the other. \(^{124,156}\) Other studies have linked inflammation and cognitive performance in healthy middle-aged individuals \(^{137}\) and well-functioning elderly. \(^{139}\) Recent evidence also documents a 3-way association between inflammation, the insulin resistance syndrome, and cognitive impairment, with vascular effects as a primary mediating hypothesis. \(^{140}\)

In sum, evidence is accumulating that insulin resistance and inflammation form an interactive complex that helps to account for cognitive impairment in diabetes and perhaps in cases of metabolic dysregulation before diabetes diagnostic thresholds are met. The effects of insulin resistance may be more direct, affecting aspects of energy metabolism in the brain and undermining other insulin-mediated processes. The effects of inflammation may be secondary to cytokine-induced reductions in the reactivity of CNS microvasculature in the shorter term and to permanent microvascular damage induced by chronic inflammation over the longer term. Obesity and lifestyle factors (especially exercise and smoking) are likely to play an important potentiating role in this complex of effects.

*The Schizophrenia Evidence.* Irregularities of energy metabolism might contribute to cognitive dysfunction in schizophrenia in different ways, \(^{141}\) but hypotheses focused on insulin resistance and inflammation and their interaction are attractive for several reasons. The prevalence of diabetes in schizophrenia is 2–4 times higher than the general population rate. \(^{142}\) Additionally, more than 40% of schizophrenia patients meet criteria for the metabolic or “insulin resistance” syndrome, which strongly predicts diabetes and cardiovascular disease. \(^{143,144}\) Evidence is growing that schizophrenia is associated with metabolic disturbance, even at first episode, prior to treatment. \(^{145,146}\) This very early onset might suggest that effects of these changes could be related to cognitive impairments seen prior to the onset of the illness, such as during premorbid and prodromal periods. The onset of diabetes occurs at significantly younger ages in schizophrenia than in comparison groups, with the sharpest disparity among individuals aged less than 49 years. \(^{147,148}\) Also, in roughly one-quarter of cases, the illness emerges without significant weight gain. \(^{133,148}\) Evidence is accumulating that widely used second-generation antipsychotic (SGA) medications worsen problems of metabolic dysregulation and disease. \(^{133,148,149}\) Early evidence that SGAs improved cognitive performance has been called into question, \(^{19,150}\) accentuating concerns about metabolic effects without the concurrent procognitive benefits that were previously expected.

With this background in mind, we hypothesized that schizophrenia patients with diabetes might show exacerbated cognitive impairment compared with matched schizophrenia patients without diagnosed metabolic disease. \(^{125}\) Results indicated that the schizophrenia/diabetes group was globally impaired relative to the “schizophrenia only” group (effect size [ES] = 0.26), with disproportionate effects in the domains of processing speed and visual/spatial ability (ES = 0.40). Additionally, these impairments were associated with diabetes severity markers (hemoglobin A1C, age of diabetes diagnosis, and diabetes duration). Given significant cognitive impairment in metabolically normal schizophrenia, we do not suggest that metabolic dysregulation is causal for cognitive impairment. Rather, it may be the case for some subset of patients that metabolic compromise provides a partial explanation of cognitive dysfunction and helps to account for its generalized character. In the schizophrenia genetics literature, it has become routine to refer to “multiple genes of small effect.” This may serve as one useful metaphor for conceptualizing generalized cognition: it is doubtless biologically complex, with many contributing and interacting factors.

The biological substrate of the diabetes exacerbation effect is unclear. However, insulin resistance could be one contributing mechanism of cognitive impairment. Specific insulin abnormalities have been reported in schizophrenia (eg, a decrease in insulin receptor [IR]–mediated signal transduction\(^{115}\)). In general, insulin irregularities emerge earlier than glycemic dyscontrol\(^{113}\) and are associated with cognition in nonpsychiatric groups independently of diabetes, glucose, body mass index, and other confounds, \(^{134}\) even in middle-aged subjects. \(^{135}\) Further, recent schizophrenia studies have documented increased insulin resistance (ie, homeostatic model assessment) with certain antipsychotic treatments even in the absence of changes in blood glucose levels. \(^{152–154}\)

Given the known association of insulin resistance with inflammation, immune system response could be another contributor to generalized cognitive dysfunction in some individuals with schizophrenia. Numerous studies have documented immune system activation and increases in proinflammatory cytokines in schizophrenia, \(^{120,155,156}\) as well as changes with antipsychotic therapy. \(^{155,157}\) Most importantly for present purposes, Dickerson et al\(^{122}\) recently completed the first analysis of the relationship between CRP and cognitive performance in large, community-based sample of schizophrenia patients. They found elevated CRP significantly associated with worse global cognitive performance (ES = 0.30). In another recent study, adjunctive anti-inflammatory medication was associated with a trend toward improvement of cognition in patients. \(^{158}\) These findings suggest that, even independently of insulin resistance and diabetes, schizophrenia may be characterized by unusual vulnerability to inflammatory processes and that this inflammation is related to cognitive performance. Indeed, Hanson and Gottesman\(^{119}\) have elaborated a broad
theory of schizophrenia etiology and course founded on inflammation susceptibility and resulting vascular compromise.

As a hypothesis for further research, we propose that insulin resistance interacting with inflammatory processes may be associated with some of the variance in broad cognitive functioning in schizophrenia. Medication, obesity, and lifestyle are likely to amplify these effects, creating a special risk for poor cognitive outcomes. Figure 1 depicts this possible complex of influences and outcomes.

Implications of Systemic Hypotheses for Treatment

Importantly, systemic illness conceptualizations of cognitive deficits in schizophrenia also open new avenues for intervention research. Since the discovery of chlorpromazine and the development of additional antipsychotic medications, there has been a focus on specific transmitter-based interventions in schizophrenia, especially on antipsychotic blockade of the dopamine D2 receptor. This focus was paralleled by the development of serotonin receptor inhibitor treatments for depression, cholinesterase inhibitor treatments for Alzheimer’s disease, and stimulant treatments affecting dopamine and norepinephrine neurotransmission for attention deficit hyperactivity disorder. To date, most research on cognition-enhancing medications for schizophrenia has also followed this path—focusing on cholinesterase inhibitors, norepinephrine agents, glutamatergic agents, dopaminergic agents, selective serotonin reuptake inhibitors—with mixed and minimal results to date.

Yet, some of the somatic dimensions described earlier, such as inflammation and irregularities of energy metabolism, may be far more tractable from an intervention standpoint than either broad cognition or the full schizophrenia syndrome. Certainly, inflammation and diabetes are modifiable through education, lifestyle changes, and treatment. Further research could address whether early treatment with thiazolidinediones (to improve insulin sensitivity), sulfonylureas (to increase insulin production), salsalates (to reduce inflammation), or statins (to improve lipid profile and moderate inflammation) shows benefits for cognitive performance and whether any change is related to improvements in relevant biomarkers and indices of functional status. Impaired sleep is associated both with metabolic irregularity and schizophrenia. Behavioral, mechanical, and pharmacologic interventions to improve sleep and sleep architecture might similarly spill over into improved cognitive performance. Effects of diet and exercise programs on metabolic, inflammatory, and cognitive outcomes also merit investigation.

Conclusions

Our reading of the literature indicates that there is a substantial general component to the cognitive performance deficit in schizophrenia that is more strongly connected than other markers to functional outcome in the community. Despite a long history, efforts to disaggregate this generalized impairment have had only mixed success. Although currently available clinical neuropsychological measures are not optimal for a detailed assessment of all aspects of the cognitive impairment in schizophrenia, it does not appear that psychometric limitations of traditional tests can explain away the general deficit. At the same time, emerging evidence suggests an account of the broad deficit based on plausible, systemic biological factors.
factors, either originating in the CNS (eg, gray and white matter abnormalities) or more generally influencing CNS functions (eg, energy metabolism and inflammation). This argument complements rather than replaces explanations of schizophrenia cognitive deficits based on more precisely defined cognitive and neural abnormalities in the illness—but it strongly suggests that the search for causes of and treatments for cognitive impairments should include attention to general and systemic factors.

Funding
VA Rehabilitation Research and Development Service (to D.D.); National Institute of Mental Health (MH63116, MH78775 to P.D.H.).

Acknowledgments
Dr Dickinson has no financial disclosures or conflicts of interest. In the past year, Dr Harvey served as a consultant for Pfizer, Ortho-McNeil, Neurogen, Dainippon Sumitomo America, Merck, and Wyeth. He received research support from Bristol Myers Squibb and Johnson and Johnson. He was on the speaker’s bureau for Eli Lilly.

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