Section 1 Characteristics of cognitive impairment in schizophrenia

Chapter 1

Cognition as a central illness feature in schizophrenia

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Introduction

Schizophrenia is a loose and heterogeneous syndrome defined by implausible and peculiar beliefs and sensory experiences, social withdrawal, restricted or inappropriate emotional expression, and disorganized behavior. These positive and negative symptoms were described clearly and comprehensively in Kraepelin's (1896, 1919) seminal accounts of dementia praecox. It is perhaps less well appreciated that a range of cognitive deficits were also considered characteristic of the illness (Table 1.1). Indeed, another pioneer, Bleuler (1943, 1950), argued that impairments in "associative" thinking were "fundamental" abnormalities in schizophrenia whereas delusions and hallucinations were only "accessory" symptoms. Nevertheless, for several decades psychotic symptoms were used to define the disorder and impairments in basic cognitive processes were neglected, excluded, or viewed as peripheral treatment artifacts (Randolph et al., 1993). Over the last 20 years this situation has changed and cognition has re-emerged as a core domain of schizophrenia research and intervention initiatives. Yet determining the meaning and significance of cognitive performance and impairment in the disorder remains both a challenge and an opportunity. Is an understanding of cognition essential to advance schizophrenia science and treatment or is it a secondary problem, an interesting sideline that addresses a correlate, but not a determinant of the disorder? This chapter considers evidence from both perspectives and argues for a critical appraisal of the role of cognition in psychotic illness.

Early research on cognition in schizophrenia

The psychiatric pioneers of schizophrenia research considered a variety of cognitive problems in their clinical case descriptions, but these efforts were limited by the questionable validity of interviews and subjective data and observations as well as by sampling biases. For example, dementia praecox was regarded initially as a deteriorative disorder associated with poor outcome in the majority of cases (Kraepelin, 1919). Yet this poor prognosis probably reflected, in part, the nature of psychiatric caseloads in the early twentieth century. Patients with favorable outcomes were omitted or not followed and study samples were seldom representative of the patient population (Riecher-Rössler & Rössler, 1998).

Another limitation was the estimation of cognitive profiles on the basis of clinical experience and observation alone. Thus Bleuler (1943) maintained that patients with schizophrenia had preserved or even superior memory for events and personal material

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Table 1.1.

Kraepelin's (1919) psychic symptoms of dementia praecox	
1. Perception	19. Impulsive actions
2. Attention	20. Catatonic excitement
3. Hallucinations	21. Stereotyped attitudes, movement
4. Orientation	22. Mannerisms
5. Consciousness	23. Parabulia (illogical actions)
6. Memory	24. Negativism
7. Retention (pseudomemories)	25. Personality
8. Train of thought	26. Practical efficiency
9. Association	27. Movements of expression
10. Stereotypy (repetitive ideas)	28. Incoherence
11. Paralogia, evasion	29. Stereotypy (sentence repetitions)
12. Constraint of thought	30. Negativism (mutism, evasion)
13. Mental efficiency	31. Derailments in word-finding
14. Judgment	32. Paraphasia
15. Delusions	33. Neologisms
16. Emotional dullness	34. Akataphasia (peculiar language)
17. Weakening of volitional impulse	35. Syntax
18. Automatic obedience	36. Derailments in train of thought

and were forgetful only on occasion due to "disorganization." This conclusion was based on responses to questions posed during clinical interviews. Bleuler typically assessed autobiographical memory through the process of obtaining a patient's life history. In contrast, "memory for experiences during the examination" was assessed by asking for an account of what had been discussed at the beginning of the interview. Although the importance of cooperation and comprehension of instruction was recognized, there was no standard stimulus material or objective scoring, no validity checks, no normative comparison, and little reference to or appreciation of findings from memory research. Not surprisingly, therefore, Bleuler's assertion about preserved memory has been contradicted by subsequent documentation of relatively severe memory problems in schizophrenia, including episodic and autobiographical deficits (Aleman et al., 1999; Berna et al., 2011; Heinrichs & Zakzanis, 1998). Interview and self-report data continue to yield poor or marginal validity in the estimation of cognitive ability (Johnson et al., 2011; Ventura et al., 2010). However, impairment is demonstrated readily and reliably through application of a variety of psychometric and experimental tasks that are informed by cognitive and neuropsychological research. These tasks measure performance objectively in terms of accuracy, error rates, and completion times as well as in deviations from general population norms. The transition from observation and interview to measurement and performance was an

essential precondition for an accurate understanding of cognition in schizophrenia. Yet, by itself, this methodological advance did not ensure that cognitive studies were considered central to schizophrenia science.

The first systematic research application of objective methods to cognition in schizophrenia was developed by Shakow (1962, 1963). This ground-breaking research was concerned primarily with preparatory intervals and reaction time performance and the concept of "set." Set involves the ability to respond adaptively and appropriately to a stimulus situation. Schizophrenia patients found it difficult to "maintain" set and tended to respond to parts and irrelevant aspects of the situation. The concept of set maintenance lives on in measures like the Wisconsin Card Sorting Test and has also been integrated into the study of attention (Cautin, 2008; Mirsky et al., 1992). Unfortunately, the research approach and findings developed by Shakow remained peripheral to the understanding of psychotic illness for many years. More recently, his legacy and the application of methods grounded in experimental psychology to schizophrenia have gained new strength and impact through the development of cognitive neuroscience.

Nevertheless, it is largely through a parallel development, the introduction and use of neuropsychological test batteries designed for clinical assessment of large numbers of schizophrenia patients and comparison subjects, that evidence of cognitive impairment has become overwhelming. By the 1970s it was apparent that the Halstead–Reitan and Luria–Nebraska test batteries were able to discriminate heterogeneous neurological patients from healthy controls (Kane et al., 1985). Hit rates and group discrimination were often greater than 90% (Golden, 1981). However, the scores of neurological and schizophrenia patients overlapped and discrimination was lower or difficult to replicate (Heaton et al., 1978). Initially this score overlap was interpreted as evidence of instrument invalidity or alternately as evidence for the existence of a subset of schizophrenia patients with both "brain damage" and psychosis. Distinguishing between schizophrenia and brain damage was regarded as a difficult diagnostic challenge for clinical neuropsychologists. Then with the rapid expansion and extension of neuroscience theory and methods to psychiatry, views shifted and cognitive impairment in psychotic disorders increasingly "made sense" and came to be expected. Impairment could be understood as a reflection of underlying disturbances in neural systems that mediated the disorder (Flor-Henry, 1990). Hence the inclusion of neuropsychological measures in schizophrenia research became relatively routine during the 1990s. In tandem with these developments and a burgeoning literature, the first meta-analyses became feasible, quantifying results from hundreds of studies and thousands of patients and healthy comparison subjects (Aleman et al., 1999; Heinrichs & Zakzanis, 1998). Thus cognitive impairment, initially viewed as essential to schizophrenia, only to be relegated to the periphery by mid-twentieth century research and clinical lore, has returned as a "core" feature of the disorder and a key target of treatment efforts. Consider the evidence in support of this rediscovered importance.

Criteria for judging the importance of cognition in schizophrenia

There are at least four ways in which cognition may represent a primary and essential feature of schizophrenia and related psychotic illnesses. First, the illness may express itself pervasively and reliably in cognitive performance in the same way that, say, parkinsonism expresses itself in resting tremor or Alzheimer's disease expresses itself in rapid forgetting.

It follows that cognitive abnormalities and traits should occur at extremely high rates in patients with the diagnosis. Second, an essential and primary illness feature is one that is intrinsic and not peripheral to the disorder. Impaired cognitive performance should not be reducible to secondary or iatrogenic influences that reflect treatments, prolonged illness burden, hospitalization, or associated stresses and state influences. In other words, cognitive impairments should be inherent in the disease process and not by-products of receiving a diagnosis. Third, insofar as the symptoms of schizophrenia result from underlying defects in cognitive operations and their neural substrates, it should be possible to index these operations and therefore predict symptom occurrence and severity. If this holds true, the clinical illness cannot be understood without reference to cognition. Fourth, it stands to reason that cognitive processes are essential for adaptive transactions with the environment and impairment limits these transactions, giving rise to inadequate life skills, dependency, unemployment, and other aspects of low functional status. Thus cognitive performance should be a powerful predictor of functionality in schizophrenia patients. Understanding functional outcome in the disorder should require cognitive theory and data. Moreover, cognition may be more than a predictor and correlate of functionality; it may be a causal determinant. If this is the case, then changing a patient's cognitive status should lead to changes in functional status and improvements in outcome that would not otherwise be possible. Successful functionally oriented treatment may require the enhancement of cognitive performance.

Do all patients with schizophrenia have cognitive impairment?

Meta-analytic quantification of cognitive data in schizophrenia patients and nonpsychiatric subjects shows unequivocally that very large standardized differences in group means exist across a variety of tests and constructs (Aleman et al., 1999; Forbes et al., 2009; Heinrichs & Zakzanis, 1998; Johnson-Selfridge & Zalewski, 2001; Mesholam-Gately et al., 2009). The magnitude of these differences reliably approaches 1.5 pooled standard deviation units for processing speed and aspects of sensory, verbal, and working memory and averages 1.0 standard deviation unit across tests of attention, executive function, language, motor and spatial abilities, as well as general intelligence. More refined syntheses indicate that measures of processing speed may be the single most sensitive cognitive indicator of schizophrenia, but the broadly based nature of the impairment has continued to receive support (Dickinson et al., 2007). An interpretive reference point for these averaged group differences is provided by Cohen's (1988) idealized distribution overlap percentages. Thus a standardized mean difference of 1.5 corresponds to an estimated overlap between schizophrenia and control distributions of less than 30%, and even 1.0 separates a large majority (65%) of patients and healthy people.

For a comparative perspective, consider the selection of standardized schizophrenia–healthy control group differences presented in Table 1.2 in relation to findings in other areas of the brain and behavior. The magnitude of differences in cognition equal or exceed effect sizes (ES) for moderate–severe traumatic brain injury and composite cognition measures (ES=0.92±0.17; Schretlen & Shapiro, 2003), right cerebral hemisphere stroke effects and nonverbal memory (ES=1.20±0.40; Gillespie et al., 2006), preclinical and subsequent Alzheimer's disease and memory scores (ES=1.06±0.21; Schmand et al., 2010), and attention deficit hyperactivity disorder and executive function (ES=0.54±0.03; Willcutt et al., 2005). In addition, Table 1.2 shows that within the schizophrenia literature,

Table 1.2. Selected meta-analytical findings and abnormalities in schizophrenia patients

Finding: Effect size	Distribution	Separation (%)[1]
1. Neurological soft signs (sensory and motor)[2]	1.59±0.21	73
2. Impaired coding (processing speed)[3]	1.57±0.09	72
3. Reduced letter–number span (working memory)[4]	1.36±0.14	67
4. Reduced semantic word fluency[5]	1.34±0.22	67
5. Backward visual masking[6]	1.27±0.24	64
6. Impaired learning of word lists[3]	1.25±0.20	64
7. Impaired general intellectual ability[3]	1.19±0.29	63
8. Impaired executive ability (WCST)[3]	1.00±0.19	55
9. P50 sensory gating ratio[7]	0.93±0.35	52
10. Maintenance gain in eye tracking[8]	0.87±0.12	50
11. Reduced P300 amplitude[9]	0.85±0.20	50
12. Increased dopamine receptors (PET)[6]	0.70±0.54	43
13. Reduced hippocampal volume (MRI)[10]	0.55±0.19	36
14. Hypofrontality during activation (PET)[10]	0.37±0.08	25

Note: the table shows average effect sizes (standardized mean differences) from schizophrenia patient–healthy control group comparisons, 95% confidence intervals, and estimated joint distribution separation (non-overlap). WCST, Wisconsin card sorting test; PET, positron emission tomography; MRI, magnetic resonance imaging.
[1] Cohen, 1988
[2] Chan et al., 2010
[3] Dickinson et al., 2007
[4] Forbes et al., 2009
[5] Doughty & Done, 2009
[6] Heinrichs, 2001
[7] Chang et al., 2011
[8] O'Driscoll & Callahan, 2008
[9] Bramon et al., 2004
[10] Davidson & Heinrichs, 2003

effect magnitudes for cognitive impairment are larger than effects reported for regional frontal and temporal lobe brain volumes and reduced prefrontal lobe activation in the illness and also exceed effects reported for dopamine receptor densities. Moreover, confidence intervals for averaged cognitive effects consistently exclude 0 (zero) and compare favorably with or exceed margins of error found with neurobiological data (Heinrichs, 2001). This stability reflects the highly reproducible nature of group differences in cognitive performance. Overall, the strength and stability of the evidence supports assertions that the psychotic disease process expresses itself very frequently in cognitive aspects of brain function (Heinrichs, 2005).

Nonetheless, despite this wealth of robust evidence, it may be a mistake to conclude that cognitive impairment truly is pervasive and inevitable across the patient population. Meta-analytic quantification implies that 70%–75% of schizophrenia patients perform below general population values on many standard cognitive tasks. Therefore, a significant

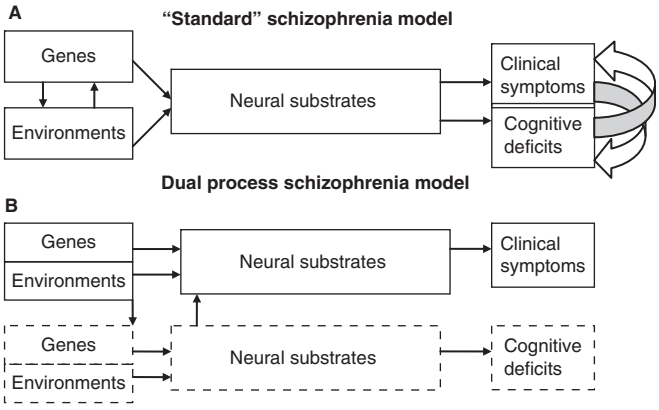

Figure 1.1. Diagram illustrating the distinction between "standard" disease models assuming common neural substrates and pathologies for both psychotic symptoms and cognitive deficits and dual process models that posit independent or weakly correlated psychotic and cognitive substrates in schizophrenia.

minority, 20%–25%, must overlap with healthy people on many ability indicators. A much smaller but potentially important minority may even perform above the healthy mean on these tasks.

The existence of cognitively exceptional schizophrenia patients, or those with task performance at or above normal control values, challenges prevailing assumptions of obligatory deficit and may have major consequences and value for understanding the illness. In particular, preserved and proficient cognitive ability occurring in the presence of a psychotic process implies a dissociation and duality of pathophysiologies underpinning the schizophrenia syndrome. "Standard" models of schizophrenia (see Figure 1.1A) assume that cognitive impairments are inherently tied to the disease process, perhaps preceding the expression of psychosis and persisting with symptom remission, but reflecting the same underlying matrix of neural substrates and genetic and environmental variables. In contrast, a dual process model (Figure 1.1B) holds that cognitive performance deficits index a disturbed system that is partly to completely dissociable from the process underpinning psychotic symptoms. Indeed, from this alternate perspective, cognitive impairment is a secondary process that occurs frequently and in combination with the primary (psychotic) disease process, but remains biologically and behaviorally distinct and not reducible to the psychotic process.

Evidence of relative performance normality in a small portion of patients has been reported occasionally since standard neuropsychological test batteries were first applied to schizophrenia in the 1970s (Golden et al., 1982; Silverstein & Zerwic, 1985). Yet interest in these patients as a potentially valuable resource for understanding psychotic illness has developed slowly and only in the last decade. True neurocognitive normality in the disorder, not to mention giftedness or exceptionality, is a controversial idea and requires careful validation. There are striking case examples of the co-occurrence of psychosis and intellectual or artistic brilliance, but these may be exceptions that prove the rule (see Figure 1.2). It is a challenge to determine the breadth, validity, and possible limits of exceptionality in the patient population in part because of the large number and diversity of measures used in neuropsychological research. The neuropsychological literature on schizophrenia comprises hundreds of studies, thousands of patients and comparison participants, and dozens of tasks and experimental paradigms indexing aspects of intelligence and reasoning, memory and

Figure 1.2. Illustration demonstrates the co-existence of psychosis and highly developed artistic and constructional skill in the work of Franz Xaver Messerschmidt (1735–1783). Messerschmidt was a Bavarian sculptor who developed schizophrenia and continued to produce technically accomplished pieces, but strongly influenced by delusions and hallucinations (Heinrichs, 2003). The sculpture shown was given the title *The Yawner* not by the artist, but by later observers and critics. (Reproduced with permission of the Museum of Fine Arts, Budapest, 2012.)

learning, language, attention, and executive and spatial ability. The most frequently used measures include standardized tests like the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008), Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), and Wechsler Memory Scale (WMS) (Pearson Education, 2008), but there are also batteries of composite and specially constructed measures including the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Nuechterlein et al., 2008) combination of tasks selected specifically for schizophrenia. Moreover, there is no single definition of normality or exceptionality in psychometric terms.

One frequently used definition of normality involves average-level performance as determined by published general population norms on a selection of standard ability measures. Norm-referenced approaches are sometimes augmented or alternated with expert ratings of individual patient test profiles. The validity of normality definitions is then evaluated by comparing putatively normal patient and healthy groups directly on a battery of tasks. However, average or even above-average scores on a subset of ability measures do not guarantee equivalent levels of performance across all possible neurocognitive tests. Thus Palmer et al. (1997) used a combination of expert ratings and normative criteria to identify 27.5% of their sample of schizophrenia patients as neuropsychologically normal. This subgroup was statistically indistinguishable from a healthy control group on a

comprehensive test battery except for a mild deficiency on learning tasks. An even smaller subgroup comprising 11% of the patients also performed normally in learning. Several later investigations supported a 20%–30% overall prevalence of performance normality in schizophrenia (Allen et al., 2003; Holtahusen et al., 2002; Kremen et al., 2000; Weickert et al., 2000). Nevertheless, direct comparison of putatively normal patient and healthy control groups has often found differences in specific abilities including abstraction and executive cognition (Allen et al., 2003; Kremen et al., 2000; Weickert et al., 2000), attention (Kremen et al., 2000; Weickert et al., 2000), and motor skill (Allen et al., 2003; Holtausen et al., 2002; Kremen et al., 2001). Moreover, average-range performance on norms-based summary indices like IQ may mask abnormal ability patterns in patient groups. For example, Wilk et al. (2005) studied schizophrenia patients matched to healthy people with average IQs and found that subtest profiles differed, with patients showing relative deficiencies on memory and processing speed tasks and relative superiority in verbal comprehension and nonverbal reasoning. This study is also notable because it reported data on 13 patients and 13 controls with IQs in the "high-average" range. Group differences in cognitive performance were observed even in these higher functioning patients. Accordingly, patients may score in a norms-defined "average range" on a battery of measures or on a composite score like IQ, but still demonstrate abnormalities or deficiencies on specific tasks when compared directly with a healthy control group.

An additional criterion for normality used by some researchers requires equivalence between current and estimated premorbid levels of performance. The logic underlying this criterion is that intellectual performance in the average population range may reflect deterioration from even higher or above-average ability prior to illness. Oral reading tests are used to provide estimates of premorbid intellectual ability insofar as visual word recognition seems to resist diffuse and multifocal neurological processes (Nuechterlein et al., 2004; Strauss et al., 2006). Weickert et al. (2000) found no difference in the Wide Range Achievement Test (WRAT) reading scores between healthy controls and intellectually "preserved" schizophrenia patients. In contrast, and consistent with a "deterioration" hypothesis, Kremen et al. (2000) reported significantly higher reading scores in neuropsychologically normal patients relative to healthy controls. The premorbid level-of-performance issue remains both infrequently researched and unresolved. In addition, the validity of the idea that a true period of premorbidity exists in a disorder that already expresses itself neurodevelopmentally in childhood and adolescence is questionable.

In a recent study of patients and healthy people with superior verbal ability, our group (Heinrichs et al., 2008) used vocabulary scaled scores $\geq$14 (90th percentile) from the WAIS-III as the criterion for exceptionality. The use of individual rather than composite ability scores like IQ as exceptionality markers has advantages that include efficiency and validity, while also preventing the kind of performance masking described by Wilk et al. (2005). Vocabulary scores are believed to reflect longstanding cognitive traits and are excellent estimators of general ability. Nonetheless, superior range vocabulary scores do not guarantee this level of performance across all tasks. It is noteworthy that verbally exceptional patients in this study scored within average-high-average rather than superior ranges in terms of nonverbal reasoning, working memory, processing speed, verbal learning, word generation, and response inhibition. However, the same pattern of high verbal relative to other abilities was seen in healthy people, and we found no statistically significant group differences across these tasks. Therefore, a pronounced relative strength in verbal skill, with more average or high-average performance in other abilities, is probably a normal pattern

in the general population. This study also found no evidence of current versus estimated premorbid functioning discrepancies based on reading scores. The lack of such a discrepancy argues strongly against the idea that verbally superior patients were functioning at even higher levels prior to illness and subsequently declined into the superior range. Nevertheless, the battery of measures used was relatively brief and lacked data for two of the eight separable ability factors identified for schizophrenia (Nuechterlein et al., 2004). These unrepresented abilities include visual learning and memory, and social cognition. Thus the possibility remains that verbally exceptional patients are impaired relative to exceptional controls on these missing ability factors.

It seems reasonable to conclude that cognitive impairment reliably occurs at very high rates in schizophrenia, typically approaching 75% of the patient population, which equals or exceeds the prevalence of impairment in many neurological disorders. However, the existence of even relatively small proportions of neuropsychologically normal or gifted patients makes it hard to answer with an unequivocal "yes" to the question of whether impairment is universal in the illness. To be sure, apparently normal patients may have subtle deficits relative to healthy comparison groups even when test scores are within norm-referenced limits and conventionally defined "average" ranges. Yet until the possibility of preserved cognition in schizophrenia is resolved, impairment should be regarded as probable and highly prevalent, but not obligatory in the illness.

Cognitive impairment in schizophrenia: essence or artifact?

Averaged patient–control group differences in cognitive impairment may be relatively large, but do these differences express the underlying disease process or are they products of powerful medications, years of chronic stress and social disadvantage, and poor motivation? Perhaps surprisingly, meta-analyses and longitudinal studies show that antipsychotic medications have a mildly beneficial rather than adverse effect on cognition in chronic patients (Harvey & Keefe, 2001; Keefe et al., 2007; Mishara & Goldberg, 2004; Thornton et al., 2006). A recent clinical trial comparing first- and second-generation medications in first-episode patients found that all treatments yielded standardized mean differences ranging from ES=0.33 to ES=0.56 relative to baseline at six-month follow-up on a composite cognition measure (Davidson et al., 2009). Moreover, there is evidence that these findings hold up cross-culturally, at least in terms of patients assessed relatively early in their illness (Guo et al., 2011). It is unclear to what extent practice effects may contribute to these improvements in performance, but some recent data suggest this contribution is fairly small (Keefe et al., 2011).

Against this evidence of mild–moderate cognitive benefits for antipsychotic medication there are occasional findings of adverse effects. For example, coding and symbol substitution tasks that require processing speed but also manual dexterity and fine control are highly sensitive to schizophrenia (Dickinson et al., 2007). However, a recent meta-analytic report suggests that a substantial proportion of this effect may be due to adverse motor effects of a chlorpromazine-equivalent medication dose (Knowles et al., 2010). The report found that studies reporting data from highly medicated patients yielded significantly larger impairments in processing speed than studies on less medicated patients. In contrast, other aspects of cognitive performance did not vary with medication dose across studies. One conjecture that may account for such findings involves interference with basal ganglia motor systems due to dopamine receptor blockade. Presumably these dopamine-containing

systems contribute to the motor and learning components of processing speed tasks and cannot function normally in the presence of this blockade. Yet a small number of studies suggest that antipsychotic medication may affect task performance even in the absence of a motor task component. For example, there are data indicating that different aspects of nondeclarative memory are reduced as a function of whether schizophrenia patients are treated with first- or second-generation medications (Beninger, 2006; Beninger et al., 2003). In addition, spatial working memory deficits have been reported in first-episode patients treated with risperidone (Reilly et al., 2007). At the same time, it is noteworthy that secondary medications used to treat or reduce the side effects of therapeutic drugs may have negative effects on cognition. McDermid Vaz & Heinrichs (2002) found that memory-impaired patients were more likely to be receiving anticholinergic medication relative to unimpaired patients. Recent evidence confirms this association and suggests that anticholinergic drugs reduce the effectiveness of cognitive training (Vinogradov et al., 2009). Moreover, discontinuing anticholinergic drugs can lead to cognitive improvements (Drimer et al., 2004). Taken together, reports in the literature suggest that antipsychotic drugs may yield mild performance-enhancing benefits for many cognitive tasks, but also some adverse effects. These adverse effects are especially indicated in relation to adjunct anticholinergic medication. However, there is no compelling evidence that the breadth and magnitude of cognitive impairment in schizophrenia is attributable to the use of these medications.

Apart from medication, many patients with schizophrenia endure years of chronic illness, social disadvantage, and recurrent hospitalization. There is evidence that stress has physiological and structural effects, and impairs cognitive operations associated with the prefrontal cortex (Hains et al., 2009). Perhaps enduring a socially stigmatized chronic illness rather than the intrinsic schizophrenic disease process itself gives rise to lowered cognitive performance. Against this, it is important to note that cognitive deficits are present in patients with first-episode psychosis (Mesholam-Gately et al., 2009), as well as in attenuated form during the prodrome prior to symptom onset (Seidman et al., 2010) and in adolescents with elevated genetic risk for the illness (Fusar-Poli et al., 2007; Lewandoski et al., 2011). In addition, deficits found in first-episode patients are broadly based but somewhat larger in processing speed and verbal memory, thereby underscoring similarities with data obtained from more chronic samples. Bozikas and Andreou (2011) report that cognitive impairment was stable for up to 10 years in first-episode patients, with possible deterioration noted only in some aspects of verbal memory. Moreover, cross-sectional studies comparing first-episode and chronic psychosis patients provide further evidence that cognitive impairment occurs early and persists rather than developing slowly over the course of illness and treatment (Mesholam-Gately et al., 2009; Sponheim et al., 2010). In light of such findings it is difficult to maintain that the experience of becoming a chronic psychiatric patient rather than the underlying condition is the primary influence on cognitive performance in schizophrenia.

Do cognitive deficits produce the psychopathology of schizophrenia?

Cognitive impairment may be prevalent and largely intrinsic to schizophrenia, but can cognitive theory and data account for delusions, hallucinations, disorganized speech and behavior, withdrawal, and restricted emotion? The interface between cognition and psychosis is a longstanding puzzle that stems in part from the search for neuropsychological correlates of symptom states during the 1990s. Numerous investigations showed that