

NEUROCOGNITIVE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA: AN OVERVIEW

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Increasingly, neurocognitive paradigms are used to study patients with schizophrenia. With such paradigms, the cognitive abnormalities in schizophrenia are characterized by means of experimental and clinical tests. These techniques have indicated that some types of cognitive impairment are not only reliably present in schizophrenia, but are also central and enduring features of the disease. This chapter, a revision of the one published in 1995, focuses on certain recent advances in characterizing the precise nature of cognitive impairments in schizophrenia, on understanding the implications of these for treatment given the course and relationship to outcome of these variables, and on novel applications of neurocognitive approaches to the genetics of schizophrenia.

Cognitive abnormalities were noted by early investigators of schizophrenia. In the original clinical descriptions of schizophrenia made by Kraepelin (64), he commented, "Mental efficiency is always diminished to a considerable degree. The patients are distracted, inattentive . . . they cannot keep the thought in mind." Some years later, Shakow (95) began a series of studies in which he examined abnormalities in patients' reaction time in response to different types of readiness information and imperative stimuli. Hunt and Cofer (54) noted the intellectual quotient (IQ) of schizophrenic patients to be lower than that of normal controls. However, the increasing influence of psychodynamic theory tended to minimize the significance of the cognitive deficits of schizophrenia. It was thought that the deficits displayed on formal psychologic testing were secondary to impaired motivation or cooperation, gross breakdowns in reality testing, or disordered thought processes.

This view changed rapidly with the advent of *in vivo* techniques of brain imaging. First, it became evident that the lateral cerebral ventricles of patients with schizophrenia are larger than those of controls on computed tomography (96). Second, functional brain imaging suggested that the frontal lobe blood flow or metabolism of schizophrenic patients is decreased. Moreover, it was shown that one type of cognitive impairment, poor performance on the Wisconsin Card Sorting Test (WCST), is directly linked to impaired activation of the prefrontal cortex in regional cerebral blood flow (106). It was within this context that a series of studies in which broad neuropsychological test batteries were used demonstrated that patients with chronic schizophrenia could not be reliably discriminated from heterogeneous brain-damaged populations (69). These findings led to a reinterpretation of the original neuropsychological studies; it was increasingly realized that patients with schizophrenia perform in the range typically found in brain-damaged populations because schizophrenia involves structural and functional abnormalities of the brain that are, in some sense, primary, and compromise to a differential degree frontal lobe and temporal lobe function. From this perspective, schizophrenia is viewed as a disease of cortex in which information processing dysfunction is an obligatory concomitant.

We examine certain crucial, conceptually driven issues that derive from this view: What is the course of global cognitive impairment in schizophrenia? What is the character of neurocognitive impairments in schizophrenia? What is the relevance of traits like neurocognitive impairment to linkage or association studies in which the goal is to discover susceptibility genes relevant to the etiology of schizophrenia? We conclude this chapter by noting that neurocognitive impairments may be of prognostic significance in schizophrenia because of the importance of such functions in providing orientation to and encoding relevant environmental information, remembering new information, propitiously

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retrieving old information, and working on line with old and new information to make responses or decisions. In this account, cognitive impairments in schizophrenia can be considered target symptoms that must be corrected.

COURSE

Several contrasting views of the course of cognitive function in schizophrenia are extant. One view suggests that cognitive deficits become progressively worse throughout the long duration of the illness. After an insidious onset, patients' intellectual functions become weaker and social skills become coarser (73). A second view suggests that cognitive deficits, once they arise, remain relatively stable; this view is thus consistent with the notion of a static encephalopathy.

It is clear that once the clinical manifestations of the illness become overt, a sharp decline in cognitive ability takes place in many patients. In longitudinal studies spanning the premorbid and morbid periods, Schwartzman and Douglas (92) found a significant decrement in the performance of schizophrenic patients tested on an army intelligence examination (standard deviation of nearly 0.5), whereas the score of controls improved. (The patients were similar to controls in the premorbid period.) In the study of Weickert et al. (105), about 50% of a large series of treatment-refractory patients exhibited a large decline in IQ (> 10 points) from estimated premorbid levels, although a minority of patients had marked cognitive limitations from early on (see ref. 89). This is not to say that subtle premorbid deficits do not exist in the majority of patients. Recent population-based studies have demonstrated attenuations in intelligence measures in schizophrenic patients-to-be (13,16), in addition to delays in the attainment of some early developmental milestones (58).

Studies of patients during their first episode of schizophrenia substantiate the view that marked cognitive abnormalities are present at the very onset of the illness. In several studies (8,36), the neuropsychological profile of first-episode schizophrenic patients was remarkably similar to that of patients with chronic schizophrenia and did not show a decline at 1- to 2-year follow-up. Both groups of patients performed poorly on a wide range of tests, including tests assessing memory, executive functioning, and attentional abilities.

A number of cross-sectional studies searched for evidence of decline during the chronic phases of the illness. Davidson et al. (14) reported a decline of two to three points per decade in a global measure of cognitive functioning, the Mini-Mental State Examination, across the range of 25 to 95 years. (To place this in perspective, the decline in patients with Alzheimer disease is 1.5 points per year.) Consistent with these results, Harvey et al. (49) recently found that elderly patients in this cohort display a marked decline on a clinical global rating of functioning. However, when pa-

tients were followed longitudinally on a variety of cognitive measures for 1- to 2-year periods, little change was evident. As Harvey noted, the changes were not continuous, nor did they occur in the sample as a whole. It is possible the effects observed were secondary to the interaction between compromised cognitive reserve in schizophrenia and normal aging; it is also possible that high doses of neuroleptics and long-term institutionalization had a significant effect on daily living skills and some cognitive functions.

In contradistinction to these findings, Goldstein and Zubin (41) found no differences in performance on the complex cognitive tasks of the Halstead Reitan Battery between large samples of younger and older patients with chronic schizophrenia. Heaton et al. (51) demonstrated that a large sample of older schizophrenic outpatients did not manifest deterioration in performance above and beyond that of normal aging. Hyde et al. (55) used a cross-sectional approach in which successive cohorts of schizophrenic patients were assessed. The study design allowed comparison over an extremely wide range of duration of illness (patients ranged in age from 18 to 70 years). In addition, each cohort was matched on a measure of premorbid intellectual ability, and patients with confounding neurologic or systemic diseases were excluded. No significant differences between age cohorts were noted on tests known to be sensitive to progressive dementias: the Mini-Mental State Examination, Dementia Rating Scale, verbal list learning, and semantic fluency. Thus, over five decades of illness, no progression was noted. A synthesis of these results suggests that in the modal patient, a sharp decline in cognitive ability, including general intellectual efficiency, occurs around the time of the onset of clinical symptoms (\pm 3 to 5 years), which is followed by an arrest in deterioration and a long period of impaired but stable cognitive function.

This view of the natural history of schizophrenia is consistent with a neurodevelopmental perspective (107) in that a prenatal lesion remains silent for years before manifesting itself in overt symptomatology and cognitive impairment. Contrary to some interpretations, Kraepelin (64) held to this account, stating, "As a rule, if no essential improvement intervenes in at most two or three years after the appearance of the more striking morbid phenomena, a state of weak mindedness will be developed which usually changes slowly and insignificantly." At the very least, the set of findings suggests that cognitive impairment in schizophrenia is an enduring feature of the disorder.

COGNITIVE IMPAIRMENTS

It is possible that nearly every cognitive function of a schizophrenic patient is impaired, and to an equivalent degree (1, 2). However, we examine three functions in detail because (a) evidence has been found of differential impairments,

especially in the cognitive domains related to frontal system executive and attentional systems and medial temporal memory systems; (b) these measures are important in regard to outcome (see below); (c) ongoing and systematic experimental work indicates that these cognitive functions can be mapped onto neural systems in a principled manner in normal and schizophrenic persons (30); and (d) such measures are useful in intermediate phenotyping.

Attention

Early descriptions of the clinical phenomenology of schizophrenia emphasized impairment of volitional attention. This clinical observation has been amply supported by many years of experimental study with the use of a wide variety of tasks. Recent models have sharpened the lines between selective attention, shifting attention, and biasing for and encoding relevant target information. We investigate some of these functions by examining three tasks: the Continuous Performance Test (CPT), the Covert Visual Orienting test, and the Stroop Test.

The classic test of selective attention is the Stroop color–word task, in which a word (e.g., red) can be printed in incongruent colors (e.g., green). Depending on instructions, the task is either to name the actual word or name the ink color in which the word is written. The attentional task requires the subject to focus selectively on one dimension of the stimulus and ignore or inhibit contextually inappropriate response tendencies. Normal subjects are slowed when they have to name a color of ink that is incongruent with the word because they have to inhibit their overlearned tendency of reading the word (see ref. 68 for review). Schizophrenic patients may have differential problems on this task in reaction time or accuracy, a finding that has been taken to suggest that they have disproportionate difficulty in inhibiting overlearned tendencies (of reading the word), and may be susceptible to failure in conditions of cognitive conflict more generally, because they are unable to use the contextual information appropriately (e.g., by focusing) (22, 83).

Another type of task requires covert shifts of attentional resources in response to task instructions or cues, but this time in anticipation of a target in a particular location. It was pioneered by Posner and Dehaene (84). In this paradigm, participants view a central fixation point flanked by two small squares, within which a target is to appear. Participants are to respond as quickly as possible to the target. The reliability with which a preceding cue predicts the location of the target is manipulated and thus provides a measure of two components of selective attention: *engagement* (the benefit of a valid cue as evidenced by a fast response) and *disengagement* (the cost of focusing on an invalid cue followed by orientation and response to the actual location of the target). Although qualitative problems have been reported in patients in this domain (e.g., hemifield-dependent RT effects or a disproportionately slow response to invalid

cues), several other studies have not found differences beyond general slowing (35).

A test of “sustained” attention, the CPT, has been used to demonstrate consistently that patients with schizophrenia “miss” targets (77). This task involves monitoring a random series of numbers or letters that are represented continuously, often at a rate of approximately one per second. Participants are asked to detect a target event by pressing a response button and to avoid responding to foils or distracting stimuli.

In an important study of the CPT, Servan-Schreiber et al. (94) showed that when the delay interval between the cue and the stimulus to which a response is to be made was increased to 5 seconds, patients were disproportionately inaccurate in their responding. It is possible that the use of rather long delays changes the basic nature to one of delayed response. Thus, in a recent study, Elvevaag et al. (26) were unable to replicate these findings of delay-induced impairment. Indeed, of the numerous errors made by the patients with schizophrenia, disproportionately more were omission errors at short delay intervals and low target probabilities, a finding taken to suggest a specific problem in rapidly encoding and acting on the imperative stimulus (i.e., constructing a representation of the stimuli to be attended to) under certain unengaging situations (i.e., when few responses are required) or in biasing perceptual representations for target recognition, presumably by an executive system. Based on work on a very different paradigm involving short-term memory in the auditory system, Javitt et al. (56) also proposed that precision or efficacy of encoding is impaired in schizophrenic patients.

Memory

Memory impairment is often the most striking feature of neurocognitive impairment in schizophrenia. Newer work has sought to determine if patients with schizophrenia have qualitative abnormalities in specific stages of mnemonic processing. Toward this end, Elvevaag and colleagues conducted an encoding study in which subjects had to state whether the letter *a* was present in a word (shallow level) or make a decision as to whether the word represented a living thing or not (deep level). Much previous work has demonstrated that words are recalled better when they are encoded deeply. Preliminary results indicated that although patients’ performance was worse than that of controls, they showed the same benefit of deep encoding (B. Elvevaag and T. E. Goldberg, 2001, *unpublished observations*). Although Kareken et al. (60) noted that failures in strategy-driven semantic encoding on this task contributed to impaired performance, their measures were indirect. Elvevaag and colleagues (24) also examined schizophrenic patients’ susceptibility to “false recognition.” They found that patients not only did patients make fewer false-positive errors by incorrectly recognizing semantic lures when poor general mem-

ory (e.g., impaired recall or recognition) was covaried, but they also again were not differentially impaired (24). Consistent with this finding, another study found that susceptibility to interference effects in patients with schizophrenia in so-called AB-ABr paradigms (in which an initial list of paired associates is presented, followed by representation after the items have been “shuffled”) is not a differential problem, but rather one that is confounded by general memory problems (B. Elvevaag and T. E. Goldberg, *unpublished observations*). Together, these findings demonstrate that patients with schizophrenia respond in a systematic and lawful manner to a variety of manipulations that target specific mnemonic encoding and orthogonalization (e.g., resistance to interference) processes. Thus, patients may have subtle impairments in different mnemonic processing stations that additively or interactively produce effects of large magnitude.

Moreover, the memory problem in schizophrenia does not appear to be one of binding (the ability to learn associations between various items and distinguish those items from other items that may be similar). This has implications for those who premise aberrant consciousness based on so-called binding abnormalities (12).

Working Memory

Patients with schizophrenia often seem unable to maintain some form of volitional control over the maintenance and manipulation of even basic information. They appear to have difficulty in formulating plans, initiating them, and flexibly changing a strategy once it is no longer effective; they also have difficulty in using feedback efficiently. Moreover, patients sometimes have problems when interrupted; they appear to forget what they were doing after only short periods of interference. One construct that attempts to capture these types of processing failures is working memory, which can involve not only the storage of information over brief delays, but the simultaneous storage and processing of information in a capacity-limited store or computational workspace. These types of behavior have been investigated in various laboratory-based neurocognitive tasks, including the Brown–Peterson test, digit span, WCST, Intradimensional/Extradimensional Set Shifting Test, and various delayed-response tasks.

Patients with schizophrenia have difficulty on the Brown–Peterson test, in which words have to be remembered over short delays during which covert rehearsal is prevented, presumably because of a compromised executive component. Patients are differentially sensitive to longer delays and larger memory sets (38a). However, patients perform abnormally even on basic short-term verbal working memory tasks, including digit span (100)

Several investigators demonstrated that schizophrenic patients exhibit deficits on the WCST, which demands set shifting, response to feedback, and abstraction (28). Patients

seem to have difficulty abstracting concepts, and they also make perseverate responses to incorrect responses. Shallice et al. (95a) stressed the consistency of executive deficits in their detailed analyses of single cases, as most patients in their series displayed difficulties in generating rules for the WCST or solving puzzles of the Tower of Hanoi type.

Strong evidence indicates that the WCST may involve the working memory system. For instance, Sullivan et al. (101) found that WCST perseveration is strongly associated with other tests that are thought to require working memory, including self-ordered pointing (in which a subject monitors his or her own series of responses). Gold et al. (34) found the WCST to be highly correlated with a letter–number span task that involves information maintenance and manipulation over short delays. Statistical differences between normal and schizophrenic subjects on the WCST were eliminated when letter-number span performance was covaried, which suggests that both tasks are performed in a similar multimodal or all-purpose cognitive workspace

Much recent work has focused on a task requiring both intradimensional and extradimensional set shifting, in effect a componential version of the WCST. In intradimensional shifts, subjects are required to change their response set to an alternative design within a category (e.g., a new exemplar of a line design) while an irrelevant dimension (e.g., shape) introduced earlier continues to be ignored. In a later stage, an extradimensional shift is demanded as new exemplars are introduced, but subjects are now required to respond to the previously irrelevant dimension (e.g., shapes rather than lines). Subjects make decisions based on feedback after each trial. Patients with chronic schizophrenia display markedly impaired attentional set shifting on the intradimensional/extradimensional task. They demonstrated a significantly higher rate of attrition at the intradimensional shift stage in comparison with patients with frontal lobe lesions, and they were similarly impaired in comparison with patients with frontal lobe lesions at the extradimensional shift stage (79). Patients with chronic disease also showed impairments in regard to Tower tasks, spatial memory span, and spatial working memory tasks. Thus, patients with schizophrenia showed an overall deficit in executive function, often greater than that observed in patients with frontal lobe lesions (80).

Several studies have indicated that an impairment of working memory is present in schizophrenia, even in patients who are relatively intellectually intact. For instance, Pantelis et al. (79) found that although patients with a high IQ performed better than patients with low IQ on the intradimensional/extradimensional task, their performance was still remarkably abnormal, especially in the extradimensional shifts. Elliot et al. (21) were able to confirm these results, even in patients with preserved intellectual function (i.e., IQs > 100). Weickert et al. (105) used a different methodology to reach similar conclusions. They found that nearly all patients—irrespective of whether they exhibited

developmentally compromised intellectual function, normal premorbid intellectual function that declined significantly (the modal subgroup in this study), or preserved intellectual function (i.e., both current and putative premorbid IQ was normal)—displayed deficits in comparison with a normal control group on the WCST measure of perseveration. These results indicate that working memory may represent a core deficit in schizophrenia.

Another set of studies also argues for a deficit in working memory's "visual scratchpad." They are particularly important because failure on this class of delayed response tasks is often taken to be the signature of abnormalities in dorsolateral prefrontal cortex, an area uniquely positioned and designed to exert control over a wide variety of information processing. Using an ocular motor-delayed response paradigm developed by Goldman-Rakic (40) for use in primates, Park et al. (82) found that patients with schizophrenia have grave difficulties maintaining information for location over a brief delay in which they have to perform an interference task. Fleming et al. (29) replicated the findings of this study by using short-term memory for visual patterns. Because patients in these studies also were impaired on control tasks that did not have delays, encoding problems may have contributed to overall level of performance.

NEUROCOGNITION AS AN INTERMEDIATE PHENOTYPE

Although schizophrenia is a heritable condition, linkage studies in which diagnosis is used as a phenotype have been disappointing, as few significant or replicable chromosomal loci have been identified (20). Using psychiatric diagnosis as the major phenotype may be a major confound. One possible reason is that people may not inherit schizophrenia *per se*, but rather a variety of information-processing deficits from which schizophrenia emerges. In other words, although impairment in any given cognitive process may exact only a small cost in social and vocational functioning, a constellation of impairments may be disabling and result in the emergence of psychosis. Thus, understanding the genetic architecture of individual processes may well be critical for understanding the genetics of "schizophrenia." This account is consistent with a polygenic model of schizophrenia, which implies that the genetic complexity of schizophrenia qua schizophrenia can be reduced by determining affected status based on neurobiological or neurocognitive dimensions; the genetic architecture of these dimensions is simpler than that of schizophrenia but segregates both illness and family risk for illness. This approach involves identifying abnormalities that (a) are quantitative, stable, and enduring; (b) have a pathophysiology that involves neural systems implicated in the disorder; and (c) have a clear effect on outcome. Certain cognitive functions may meet these criteria.

A spate of work has examined early stimulus processing

and cognition in relatives of patients with schizophrenia. This so-called high-risk approach has several strengths; for example, abnormalities cannot be attributed to florid psychopathology, cooperation, and medication. It can also be used to identify cognitive processes that may serve as intermediate phenotypes. Several recent studies, in addition to many older ones (65), have produced strong evidence that relatives of patients have subtle impairments in select cognitive functions. In a study of Cannon et al. (6), siblings showed deficit profiles intermediate between those of patients and controls in verbal memory, abstraction, attention, and language. Faraone et al. (27) examined neurocognitive performance in 35 relatives (sibs and children) and 72 normal controls and found deficits in abstraction, attention, and verbal memory in relatives. Classification analysis was highly significant. Studies with other paradigms, including backward masking, delayed response, and verbal working memory, also revealed differences between sibling and controls (10,46,82). In an important study, Cassens et al. (7) showed that a variety of tasks demanding frontal lobe processing, including complex verbal working memory, semantic encoding, and source monitoring, are not only heritable but are impaired in a stepwise genetically-at-risk fashion in the monozygotic and dizygotic co-twins of schizophrenic persons.

However, simply examining group differences does not directly address issues of familiarity/heritability. A newer approach uses computations of relative risk (RR) (88) in necessarily large samples of controls, sibling, and index cases. One type of RR is based on comparisons of concordance rates for impairment on a given trait within sibships with the rate of impairment in the general population. The statistic indicates whether a given quantitative trait is familial and by inference heritable. It is important for predicting the strength of genetic effects on a given phenotype.

In an earlier study in which Goldberg et al. (39) examined monozygotic twins discordant for schizophrenia, they found subtle attenuations of performance in otherwise-well co-twins when they were compared with normal twins on neurocognitive measures indexing working memory, speed of information processing, and episodic memory. The concordance for these traits was thus higher than the concordance for illness. Based on these results, Egan and colleagues (19a) have used a variety of paradigms to assess specific cognitive functions in a sample of schizophrenic index cases, their well siblings, and healthy controls. Specific tests were selected because they reliably measure impairments in schizophrenic patients, are stable, and, in many cases, are known to be heritable. These criteria are obviously of key importance in determining if a person is impaired because of genetic or environmental factors, or simply because of measurement error.

They first assessed RR of the CPT, given that prior work from other groups had suggested that this type of test might be sensitive to certain cognitive impairments in relatives of

patients (19). In the study of Chen et al. (9), who reported an extremely high RR in a Chinese cohort when degraded and nondegraded versions of a CPT were used, seemingly minor features of the methodology, including a sample in which siblings and parents with attendant age differences and a low educational level were combined and psychotic relatives were included, might have led to artifactual inflation of risk computations. Egan et al. (19a) examined 147 patients with schizophrenia, 193 of their siblings, and 47 controls. They did not include parents, and the educational of the groups was high and equivalent in siblings and controls (above grade 13). The IQ of index cases was 94, for their siblings it was 107, and for controls it was 108. The percentage of siblings carrying the schizophrenic spectrum diagnosis was relatively low—under 5%. In a version of the CPT that had flanking distracters, they found that 50% of patients, 24% of siblings, and 18% of controls performed one standard deviation below the control mean when d' was used as a dependent measure. The RR for this phenotype was 2.1. This finding suggested that the cognitive demands that this test imposes are under genetic control, the alleles that control this type of information process may be overrepresented in some families of schizophrenic patients, and that this finding is not redundant with diagnosis. However, it was not clear whether CPT impairment is a disease-modifying variable or a susceptibility trait, given that the sibling group as a whole did not differ from controls. In contrast, examination with a test of continuous working memory (the so-called n -back task, which demands rapid encoding of stimuli, temporal coding, interference by a restricted set of stimuli, and maintenance) revealed that at “2-back” the RR was above 7.5 and that the sibling group as a whole was significantly impaired in comparison with normal controls, which suggests that the genetic structure that underlies impaired performance may also confer liability (37).

Impairments in several other domains of cognition have also been examined. To assess the suitability of cognitive function for use as a phenotype in genetic studies, Egan et al. estimated RR (19a) in the aforementioned cohort of siblings. They hypothesized that the RR of cognitive dysfunction would be moderate and that different subgroups of families would demonstrate different patterns of impairment. A set of instruments measuring these constructs included IQ, set shifting and working memory, memory, speed, and fluency. RR was estimated by using cutoff scores of one and two standard deviations below the control mean. Patients performed markedly worse than controls on all tests except a measure of premorbid intelligence. The entire sibling group showed impaired performance on the WCST, letter fluency, and Trails B. Siblings of patients with impaired performance also showed deficits on the CVLT, Wechsler Memory Scale-Revised (WMS-R), and Trails A. When one standard deviation was used as the cutoff, the RR of siblings was elevated on the Trails B (RR, 3.8). Trends

($p = .01$ to $.05$) toward an increased RR were also seen with the California Verbal Learning Test (CVLT), WCST, letter fluency, memory for stories, and Wide Range Achievement Test (WRAT) (RR, 1.7 to 2.8). When two standard deviations was used as the cutoff, the RRs were generally higher, ranging from 4.3 to more than 13. Correlations between tests of different cognitive functions were weak, which suggests they measure relatively independent processes; factor analysis confirmed this. Multiple regression analysis also demonstrated that impairment on one test did not predict impairment on another test in the sibling group. Thus, cognitive dysfunction along several dimensions is familial and probably genetic. The use of cognitive phenotypes may reduce clinical and genetic heterogeneity and improve the power of genetic studies of schizophrenia.

NEUROCOGNITIVE DEFICITS AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

By any standard, schizophrenia is a remarkably disabling illness. Among young adults in developed countries, it ranks near the top of causes of disability in both men and women (75). There is now increasing support for the idea that key aspects of disability, such as reductions in social competence and the capacity for independent living and vocational success, are the result of neurocognitive compromise.

Although the neurocognitive deficits of schizophrenia have been long recognized, their functional consequences have only recently been appreciated. Throughout most of the twentieth century, studies of the neurocognition of schizophrenia focused rather narrowly on attempts to define and characterize the deficits. However, initial forays to study the implications of these deficits for daily living suggested that neurocognitive deficits may be critical for functional outcome (50). Starting in the early 1990s, a large number of studies examined the associations between rather specific neurocognitive measures and functional outcome in schizophrenia. This being said, individual studies were underpowered with small sample sizes and were mainly atheoretic. To make inferences even more difficult, there was little overlap in either the neurocognitive or the functional outcome measures. Nonetheless, some conclusions from this literature can be drawn.

The literature generally supports the conclusion that neurocognitive deficits are related to functional outcome in schizophrenia (42,45), including skill acquisition in psychosocial rehabilitation programs, laboratory assessments of social problem-solving ability or analogue measures of instrumental skills, and broader aspects of behavior in community outcome and activities of daily living.

Indeed, using intrapair differences in twins concordant for schizophrenia, Goldberg et al. (38) observed that vir-

tually all the variance on the Global Assessment Scale could be accounted for by differences in the performance of four neuropsychological variables: IQ, memory for stories, fluency, and card sorting. In this design, the experience of illness, institutionalization, medication, psychotic symptomatology, and, of course, genome is shared. Although in one sense the design “stacks the deck” because of its

TABLE 48.1. NEUROCOGNITIVE CONSTRUCTS EXAMINED IN STUDIES OF FUNCTIONAL OUTCOME

Secondary memory	<i>Secondary</i> (also called <i>episodic</i> or <i>strategic</i>) <i>memory</i> refers to the ability to acquire and store information over a period of time that lasts for at least several minutes. Typically, this type of memory is assessed with a list of words or passages of text. The amount of information in the words or passages exceeds the immediate memory span.
Working or immediate memory	<i>Immediate memory</i> refers to the ability to maintain a limited amount of information for a brief time (usually a few seconds). Immediate memory is considered to be a component of working memory. Most of the studies of neurocognition and functional outcome have used passive tasks instead of more typical working memory tasks that require the information to be both maintained and manipulated.
Attention/vigilance	Sometimes called <i>sustained attention</i> , this ability involves maintaining a readiness to respond to a particular target stimulus and inhibiting responses to nontargets over a period of time. It requires one to distinguish signal (targets) from noise (nontargets), an ability known as <i>sensitivity</i> . It is typically measured with a CPT in which a series of briefly presented stimuli appear on a computer screen; subjects are asked to respond only to selected targets.
Executive functioning/ card sorting	<i>Executive functioning</i> refers to volition, planning, purposive action, and self-monitoring of behavior. Problem solving tests such as the WCST are frequently used to assess executive functioning. These tests assess the subject's ability to attain, maintain, and shift cognitive set.

CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test.

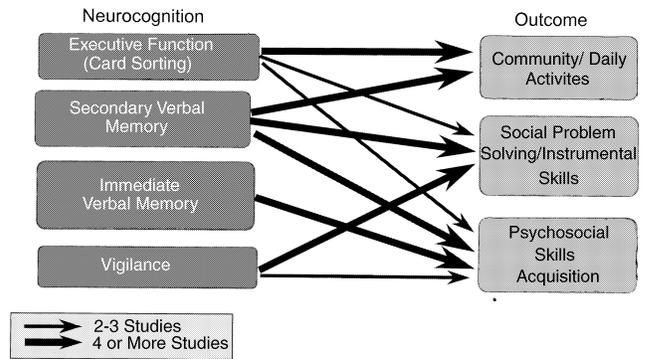


FIGURE 48.1. Neurocognitive constructs and functional outcome. Two levels of replication are represented. A heavy arrow indicates that at least four studies found a significant relationship between the neurocognitive construct and the outcome domain; a thin arrow indicates that significant relationships were uncovered in two or three studies.

artificiality, it does illustrate the importance of neurocognition in predicting level of functioning. This is not to say that symptoms do not have an impact on social and vocational outcome; they do, at least in the short term. What is important to note is that cognitive impairment may also contribute in a unique manner to outcome. These results suggest that patients’ deficits in learning new information, rapidly completing tasks, purposefully recalling old information, and generating novel plans or hypotheses may have an impact on their capacity to perform a job efficiently, take part in social transactions, and make decisions.

It is not clear which neurocognitive measures are the most useful predictors and correlates of functional outcome. Despite this lack of consensus, studies on the relationships between neurocognition and functional outcome have frequently included assessments for one or more of the neurocognitive constructs listed in Table 48.1.

This literature includes a substantial number of replicated findings (Fig. 48.1). A tally of replications by themselves is not entirely useful because they do not indicate how many times an association was sought, nor the strength of the relationships. Metaanalysis is more useful for examining the strengths of associations across studies. Table 48.2 shows the results of metaanalyses of four key neurocognitive constructs collapsed across the three outcome domains. In this type of analysis, the combined sample sizes are large and the relationships between neurocognition and functional outcome are highly significant. The metaanalyses demonstrate that these four neurocognitive constructs are significantly related to functional outcome and that the effect sizes for these relationships are generally in the medium range.

Most of the studies in this area have used rather specific measures of neurocognition, and it is the results of these

TABLE 48.2. METAANALYSES: NEUROCOGNITIVE PREDICTION OF FUNCTIONAL OUTCOME

Domain	Total Sample Size	Pooled Estimated r^a	Effect Size	p Value
Secondary verbal memory	727	.29	Medium	<.0001
Immediate verbal memory	188	.40	Medium–Large	<.0001
Executive functions (card sorting)	1002	.23	Small–Medium	<.0001
Attention/vigilance	682	.20	Small–Medium	<.0001

^aEstimates weighted by sample size.

From Green MF, Kern RS, Braff DL, et al. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophr Bull* 2000; 26:119–136, with permission.

studies that are reflected in Fig. 48.1 and Table 48.2. Although effect sizes for the individual constructs are mainly in the medium range, they can become quite large when global or composite measures of neurocognition are used instead of individual measures (48,104). Such composite measures indicate that neurocognition can explain between 20% and 60% of the variance in outcome.

How do these relationships compare with those for clinical symptoms? In general, psychotic symptoms (hallucinations and delusions) fare rather poorly as predictors and correlates of functional outcome (43). Negative symptoms are more highly correlated with functional outcome, but across studies, the relationships are neither stronger nor more consistent than those for neurocognitive deficits (17, 48,104). Little is known about disorganized symptoms, which often constitute a separate syndromal dimension that includes formal thought disorder, although recent studies suggest that this type of symptom may be related to functional outcome (76,86).

The relative contributions of symptoms and neurocognition to functional outcome have only rarely been tested with appropriate statistical analyses, including multiple regression (48,71). These studies do, however, support the idea that the neurocognitive contributions to outcome are stronger than those of symptoms. In one study (104), sophisticated path analyses were used to test the associations among positive symptoms, negative symptoms, cognition, and activities of daily living in two separate samples of schizophrenic patients. A global measure of cognition had strong relationships with activities of daily living (48% and 42% of the variance in the activities of daily activities for the two samples). Various causal models were tested in which certain pathways were omitted. The pathway from cognitive impairment to functional outcome was necessary in the model; the fit was poor when it was omitted. To the extent that symptoms were correlated with functional outcome, the relationships seem to be indirect. In other

words, although negative symptoms covary to at least a modest extent with neurocognition (17,104) and their relationship to function appears to be mediated through this overlap, *in toto* the results suggest that cognitive impairment, rather than symptoms, most strongly influences functional outcome.

Just as the neurocognitive deficits in schizophrenia are not fully specific to schizophrenia, the correlations with functional outcome are unlikely to be specific to schizophrenia. Based on the role of neurocognitive deficits in other disorders, one would not expect them to be. The functional consequences of neurocognitive deficits have been observed in a variety of neurologic conditions, including head injury, Alzheimer disease, multiple sclerosis, Parkinson disease, and AIDS encephalopathy (51,87,103). In fact, neurocognitive deficits have been associated with activities of daily living even in a nonclinical sample of elderly persons (74).

The work so far has been aimed at determining *whether* neurocognition is related to functional outcome. At this time, it can be concluded that it is related, and the effect sizes are generally medium for individual constructs and generally large for composite measures. However, rather little is known about *how* neurocognition is related to functional outcome. It is likely that some cognitive domains have direct, causal relationships, although others may be related to functional outcome through mediators, such as social cognition or the application of knowledge and reasoning to problem solving.

EFFECTS OF MEDICATIONS ON NEUROCOGNITIVE DEFICITS

One of the most surprising aspects of conventional antipsychotic medications is that although they usually have a profound impact on psychotic symptoms, their effects on neu-

rocognitive deficits tend to be negligible (7,11,98). Occasionally, treatment with conventional antipsychotic medications has led to improvement in basic perceptual or attentional processes (3,98). However, it can be concluded that changes in neurocognition, if they occur, are small compared with the changes in psychotic symptoms. In terms of disability, this presents a rather unfortunate mismatch in which the domain of illness most affected by conventional medications is not the domain most closely linked to functional outcome.

Conventional antipsychotic medications probably do not directly impair neurocognitive abilities, but they can do so indirectly when they involve the simultaneous administration of anticholinergic medications. Anticholinergic medications given for extrapyramidal side effects compromise certain neurocognitive abilities. Although the range of effects of anticholinergic medications is not well characterized, they may disrupt aspects of secondary verbal memory that rely on rehearsal strategies (18). Other aspects of memory, including immediate or working memory, appear to be less affected (4,38), and the effects on other neurocognitive abilities, such as visual processing, are relatively unknown.

The situation with newer atypical antipsychotic agents appears to be more promising. Initial interest in the neurocognitive effects of new antipsychotic medications was stimulated by a series of (mainly open-label) studies of clozapine (4,38,47,53,67). The results of these studies were surprising in two respects: First, in most of the studies, clozapine treatment resulted in improvement in verbal fluency (i.e., the ability to generate words that begin with a certain letter or belong to a certain semantic category) and possibly psychomotor speed. Second, the initiation of clozapine treatment in some studies appeared to have at least short-term detrimental effects on visual memory and possibly verbal working memory (38,47,53).

A large number of studies are emerging for recently approved antipsychotic medications: risperidone, olanzapine, and quetiapine (31,85,90,99). These studies (again, mostly open-label) have generally shown that they have benefits for neurocognition in comparison with conventional antipsychotic medications. Indications of short-term detrimental effects, similar to those seen in some clozapine studies, have so far not been reported for the other newer antipsychotic medications. A rather comprehensive review (72) and a meta-analysis (61) of the existing literature have both provided a basis for optimism about the beneficial neurocognitive effects of newer medications. The meta-analysis of Keefe et al. (61) showed significant effects for the new generation of medications in comparison with conventional agents across a range of neurocognitive areas, including attention, executive functions, and verbal fluency.

The emerging optimism in this area should be tempered by the fact that the lion's share of the studies have been "open-label," with the associated risks of experimental bias

that can accompany such studies. In many of these studies, a single group was assessed at baseline while on a conventional medication and then assessed again after being switched to an atypical medication. Inferences from these types of studies are necessarily tentative because no control is made for repeated testings and possible practice effects. A small number of parallel group blinded studies are emerging for clozapine (4,108), risperidone (44,62), and olanzapine (85). These studies offer more convincing support for the proposal that new medications convey neurocognitive benefits in comparison with conventional medications.

Even more than clinical trial studies of symptom reduction, studies of neurocognitive effects raise questions about alternative explanations for treatment effects. For the most part, studies have not been designed or analyzed in a way that allows one to rule out indirect effects. For example, if a newer antipsychotic medication has a better clinical effect than a conventional medication, it may improve neurocognition as an indirect benefit of greater symptom reduction. This explanation, although plausible, seems unlikely. Several studies have noted that changes in neurocognition appear to be independent of any changes in symptoms (38, 44,47,67,62). An alternative explanation is that the neurocognitive benefits of newer medications are mediated by a reduced need for anticholinergic medications. Although this may turn out to be true in some instances, the differential use of anticholinergic medications did not explain the effects of risperidone on immediate and secondary verbal memory in one project (44,92). The beneficial effects of newer medications on neurocognition may be mediated by lower rates of extrapyramidal symptoms. It is not known whether such effects will be seen in comparisons with very low doses of conventional medications, when side effects are minimal. Moreover, although a number of mechanisms have been proposed (5-hydroxytryptamine subtype 2A antagonism, indirect glutamate release, dopamine D4 antagonism), all are problematic, and simple reduction of D2 blockade or transient D2 blockade remains a viable explanation of "atypicality" (59). Thus, it is possible that the administration of conventional neuroleptics in inappropriately high doses resulted in a lack of improvement, although dose-reduction studies do not support this explanation (93,97). The pharmacologic basis for cognitive enhancement remains obscure. In any event, a single neurotransmitter effect seems unlikely to account for the effects, which probably involve a constellation of actions at serotonergic, adrenergic, cholinergic, and dopaminergic receptors (72). However, it is important to recognize that such actions probably are initiators of changes that ultimately effect gene expression for major excitatory and inhibitory transmitters and their receptors and neuroplasticity.

Although these alternative explanations require serious consideration, it remains possible that the neurocognitive effects of the new generation of antipsychotic medications

are a direct result of the medications themselves (rather than indirect effects of a reduction of clinical symptoms or anticholinergic medications). If so, the effects are serendipitous. These medications were not developed or initially evaluated with neurocognition in mind. The possible role of adjunctive pharmacology specifically for neurocognitive deficits is now receiving serious consideration.

A key challenge for directing studies of adjunctive nosotropic medications in schizophrenia is deciding which neurotransmitter systems are most critical in the pathophysiology of neurocognitive deficits in schizophrenia. One that has been implicated is the glutamate system (78). Based on the cognitive and behavioral effects of antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor, such as phencyclidine and ketamine, it has been suggested that schizophrenia may involve hypofunction of this receptor (66,70). Because the NMDA receptor is modulated by glycine, glycinergic agents can provide a useful means for manipulating glutamate function. Glycine itself has been utilized by Javitt et al. (56) with some effect on negative symptoms. The administration of D-cycloserine, a partial glycine agonist, resulted in a benefit in choice reaction time when it was utilized in conjunction with conventional antipsychotic medications (32), but not when added to clozapine (33). A full glycine agonist, D-serine, demonstrated some success in improving WCST performance (102). If these studies of adjunctive agents result in reliable improvement in neurocognition in schizophrenia, it may become routine for schizophrenic patients to receive a medication for each of the major domains of illness, clinical symptoms and neurocognitive deficits.

CONCLUSIONS

In the lay imagination, schizophrenic patients experience problems in living because they are divided against themselves, out of touch with reality, and disorganized. The view of scientists, once not altogether different, has changed. Not only have the symptoms been defined and codified, but the neurobiological underpinnings of the disorder have begun to be described. Emerging also is a view in which cognitive impairments may be a relatively central feature of the disorder. Cognitive impairments are involved in the genetic etiology of schizophrenia. They seem enduring in that they are present for much of the clinical history and are associated with outcome. Cognitive impairments also may have a relatively well-delineated profile in which executive, memory, and attentional deficits are prominent. This account carries with it implications for treatment, in that cognitive impairments should be considered target symptoms in the same way as hallucinations, delusions, and anergia.

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