What Are the Functional Consequences of Neurocognitive Deficits in Schizophrenia?

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Objective: *It has been well established that schizophrenic patients have neurocognitive deficits, but it is not known how these deficits influence the daily lives of patients. The goal of this review was to determine which, if any, neurocognitive deficits restrict the functioning of schizophrenic patients in the outside world.* *Method:* *The author reviewed studies that have evaluated neurocognitive measures as predictors and correlates of functional outcome for schizophrenic patients. The review included 1) studies that have prospectively evaluated specific aspects of neurocognition and community (e.g., social and vocational) functioning (six studies), 2) all known studies of neurocognitive correlates of social problem solving (five studies), and 3) all known studies of the neurocognitive correlates and predictors of psychosocial skill acquisition (six studies).* *Results:* *Despite wide variation among studies in the selection of neurocognitive measures, some consistencies emerged. The most consistent finding was that verbal memory was associated with all types of functional outcome. Vigilance was related to social problem solving and skill acquisition. Card sorting predicted community functioning but not social problem solving. Negative symptoms were associated with social problem solving but not skill acquisition. Notably, psychotic symptoms were not significantly associated with outcome measures in any of the studies reviewed.* *Conclusions:* *Verbal memory and vigilance appear to be necessary for adequate functional outcome. Deficiencies in these areas may prevent patients from attaining optimal adaptation and hence act as "neurocognitive rate-limiting factors." On the basis of this review of the literature, a series of hypotheses are offered for follow-up studies.*

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There is no question that schizophrenic patients suffer from neurocognitive deficits. Neurocognitive research in schizophrenia has typically emphasized basic questions about the range and nature of neurocognitive deficits associated with the disorder. Hence, after nearly a century's worth of effort to characterize these deficits, we know remarkably little about their functional consequences.

Schizophrenic patients show deficits across a large number of neurocognitive domains. It is possible, although unlikely, that all of these neurocognitive deficits restrict the functioning of the patient. Some studies (reviewed by Heaton and Pendleton [1]) have been hampered by rather global measures of neurocognitive functioning, such as IQ, which lead to equally global conclusions (e.g., smarter patients function better than duller patients). The challenge for studies in this area is to move beyond a general level of investigation to evaluating whether *specific* neurocognitive processes are linked to specific functional outcomes. In the review described in this paper I attempted to identify the neurocognitive deficits that restrict patients' ability to retain, acquire, or relearn skills that are needed for real-world functioning. In essence, I looked for neurocognitive "rate-limiting factors" (2).

Recent critiques of cognitive remediation in schizophrenia have emphasized the need for studies of neurocognitive rate-limiting factors to determine which cognitive deficits, among many, should be selected for remediation. For example, Hogarty and Flesher stated, "Thus, before one embarks on the remediation of cognitive deficits, it would help to know a bit more how a specific deficit or pattern of deficits systematically relates to schizophrenic disability" (3, p. 53). In a similar vein, Bellack wrote, "In any case, little is known about precisely which information-processing deficits compromise social behavior in schizophrenia or the amount of variance accounted for

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TABLE 1. Literature on Relation Between Neurocognitive Measures and Functional Outcome for Schizophrenic Patients

Functional Area and Study	Subjects	Follow-Up	N[a]	Power[b]	Predictor/Correlative Measures[c]
Community outcome					
Buchanan et al. (6), 1994	Patients with treatment-resistant schizophrenia	1 year	29	0.36	Wechsler Memory Scale—Revised, verbal fluency, Block Design, visuospatial measures, Wisconsin Card Sorting Test, Trail Making Test, Stroop test
Goldman et al. (7), 1993	Schizophrenic patients	1 year	19	0.24	*Neurocognitive:* Block Design, Trail Making Test, Vocab, Selective Reminding, Digit Span; *symptom:* psychotic symptoms (BPRS), negative symptoms (SANS)
Jaeger and Douglas (8), 1992	Patients with first-episode schizophrenia	≤18 months	19	0.24	Wisconsin Card Sorting Test
Johnstone et al. (9), 1990	Patients with first-episode schizophrenia	2 years	137	0.95	*Neurocognitive:* Peabody Picture Vocabulary Test, Digit Symbol Substitution Test; *symptom:* behavioral ratings
Lysaker et al. (10), 1995	Patients with schizophrenia or schizoaffective disorder	3 weeks	89	0.82	Wisconsin Card Sorting Test
Wykes et al. (11), 1990	Schizophrenic patients	3 years	28	0.35	*Neurocognitive:* complex reaction time; *symptom:* psychotic and negative items (PSE)
Social problem solving					
Bellack et al. (12), 1994	Schizophrenic inpatients	—[e]	27	0.34	*Neurocognitive:* verbal IQ, Wechsler Memory Scale—Revised; *symptom:* psychotic symptoms (BPRS), negative symptoms (SANS)
Bowen et al. (13), 1994	Schizophrenic inpatients	—[e]	30	0.37	Continuous Performance Test, Span of Apprehension, Digit Span Distractibility Test
Corrigan et al. (14), 1994	Schizophrenic inpatients	—[e]	26	0.33	*Neurocognitive:* Continuous Performance Test, Span of Apprehension, Rey Auditory List Learning Test, Digit Span Distractibility Test, Wisconsin Card Sorting Test; *symptom:* psychotic and negative symptoms (BPRS)
Penn et al. (15), 1993	Dutch schizophrenic inpatients	—[e]	31	0.38	COGLAB[f]
Penn et al. (16), 1995	Inpatients with schizophrenia or schizoaffective disorder	—[e]	38	0.46	COGLAB[f]
Skill acquisition					
Bowen et al. (13), 1994	Schizophrenic inpatients	—[e]	30	0.37	Continuous Performance Test, Span of Apprehension, Digit Span Distractibility Test
Corrigan et al. (17), 1994	Schizophrenic inpatients	—[e]	30	0.37	*Neurocognitive:* Continuous Performance Test, Span of Apprehension, Rey Auditory List Learning Test, Digit Span Distractibility Test, Wisconsin Card Sorting Test; *symptom:* psychotic and negative symptoms (BPRS)
Kern et al. (18), 1992	Psychotic inpatients (mainly schizophrenic)	8 months	16	0.21	Continuous Performance Test, Digit Span Distractibility Test, Rey Auditory List Learning Test, Wisconsin Card Sorting Test, Peabody Picture Vocabulary Test, Rey Figure, Pin Test, backward masking
Lysaker et al. (19), 1995	Inpatients and outpatients with schizophrenia or schizoaffective disorder	13 weeks	53	0.60	*Neurocognitive:* Wisconsin Card Sorting Test, Proverbs; *symptom:* psychotic and negative symptoms (Positive and Negative Syndrome Scale)
Mueser et al. (20), 1991	Inpatients and outpatients with schizophrenia or schizoaffective disorder	2 and 6 weeks	30	0.37	*Neurocognitive:* Wechsler Memory Scale; *symptom:* psychotic and negative symptoms (BPRS)
Weaver and Brooks (21), 1964	Schizophrenic inpatients and outpatients	2 years	248	0.99	*Neurocognitive:* psychomotor tests (including reaction time, dexterity, motor learning)

[a]Subjects in the analyses relevant to the current review.
[b]Statistical power for a medium effect size of r=0.30 with an alpha value of 0.05, two-tailed.
[c]References are as follows: Wechsler Memory Scale—Revised (22), Block Design (23), Digit Span (23), Digit Symbol Substitution Test (23), Vocab (23), Verbal IQ (23), Wisconsin Card Sorting Test (24), Trail Making Test (25), Stroop test (26), Selective Reminding (27), Brief Psychiatric Rating Scale (BPRS) (28), Scale for the Assessment of Negative Symptoms (SANS) (29), Peabody Picture Vocabulary Test (30), Present State Examination (PSE) (31), Continuous Performance Test (32), Span of Apprehension (33), Digit Span Distractibility Test (34), Rey Auditory List Learning Test (35), COGLAB (36), Rey Figure (37), Pin Test (38), backward masking (39), Proverbs (40), Positive and Negative Syndrome Scale (41), Wechsler Memory Scale (42).

by cognitive deficits" (4, p. 44). "In light of this confusing picture, it is not clear which cognitive process or processes should be targeted for rehabilitation" (4, p. 45). The dilemma is that generalization studies of cognitive remediation require an a priori selection of neurocognitive domains for intervention efforts. Clearly, without basic

Outcome Measures[d]	Major Findings
Level of functioning, Quality of Life Scale	Secondary verbal memory, visual memory, and verbal fluency predicted Quality of Life Scale score; visual memory predicted level of functioning
Strauss-Carpenter Scale	Secondary verbal memory predicted community functioning; symptoms did not predict outcome
Social Adjustment Scale	Perseveration predicted social adjustment
Occupational functioning	Neurocognitive measures and psychotic behaviors did not predict outcome, but ratings of social withdrawal (negative symptoms) did
Occupational functioning, Work Personality Profile	Card sorting predicted task orientation and social skills at work
Independent living	Complex reaction time predicted degree of independent living; symptoms did not
Social Problem Solving Assessment Battery	Verbal IQ, secondary memory, and negative symptoms correlated with some outcome measures; immediate memory and psychotic symptoms did not
Assessment of Problem Solving Skill	Vigilance correlated with overall problem solving; immediate verbal memory and early visual processing did not
Social Cue Recognition Test	Immediate verbal memory, secondary verbal memory, early visual processing, and negative symptoms correlated with social cue recognition summary score; vigilance, card sorting, and psychotic symptoms did not
Means-Ends Problem-Solving Procedure, Alternative Solution Generation Test	Generally negative results
Role playing	Vigilance and reaction time correlated with role playing
Single-session skill acquisition	Vigilance, early visual processing, and immediate verbal memory correlated with total skill acquisition
Single-session skill acquisition	Immediate and secondary verbal memory and vigilance correlated with overall skill acquisition; card sorting, early visual processing, and symptoms did not
Pre- and posttraining tests and on-task behaviors during training	Secondary verbal memory correlated with baseline test; immediate and secondary verbal memory correlated with on-task behaviors; vigilance correlated with change score
Work-related social skills, Work Personality Profile	Card sorting and proverb interpretation predicted improvement in social skills; symptoms did not
Change scores from skills training program	Immediate and secondary verbal memory and visual memory predicted skills acquisition; symptoms did not
Rehabilitation potential	Psychomotor speed predicted patients selected for rehabilitation programs

[d]References for the outcome measures are as follows: Level of functioning (43), Quality of Life Scale (44), Strauss-Carpenter Scale (45), Social Adjustment Scale (46), Work Personality Profile (47), Social Problem Solving Assessment Battery (48), Assessment of Problem-Solving Skill (49), Social Cue Recognition Test (50), Means-Ends Problem-Solving Procedure (51), Alternative Solution Generation Test (52).
[e]Cross-sectional.
[f]Includes vigilance, card sorting, masking, and reaction time.

knowledge of which specific neurocognitive deficits are linked to real-world functioning, such cognitive remediation efforts are destined to remain unfocused.

If left unchecked, the jargon in this area will soon render it impenetrable to the reader. Consequently, I have tried to narrow both the scope and the terminology of the current review. The terms "cognition," "information processing," and "neuropsychology" all carry slightly different nuances of meaning but are often used interchangeably. I will use the term "neurocognitive" to apply broadly to all three of these areas. This term clearly indicates an awareness that the capacities are rooted in neural structures. However, for the purposes of this review we do not need to make assumptions about which particular neural system underlies performance in this population (5), nor will we make any assumptions about etiology of the deficits.

In regard to the outcome measures, functional outcome is the result of competence in a large number of constituent social and instrumental role tasks. For outpatients, these skills can be summarized in terms of relatively global indices of community (mainly social and occupational) functioning. For inpatients, the functional outcome measures in this review will be the somewhat more specific indices of social problem solving and skill acquisition.

The review is not intended to be comprehensive. It will not include a rich and complex literature of psychophysiological predictors of outcome in schizophrenia. Nor will it include symptom-related outcome measures, such as time to symptom remission, rehospitalization rate, and eventual clinical state. It is entirely possible that the neurocognitive predictors of these clinical outcome variables are different from those of functional measures. Finally, the review will be limited to schizophrenia, even though several of the

TABLE 2. Results From Studies of Relation Between Neurocognitive Measures and Community Outcome for Schizophrenic Patients

Predictor/Correlate and Study	p[a]	Number of Correlations or Variables
Probable associations (replicated findings)		
Secondary verbal memory		
Buchanan et al. (6)	0.04	>20 correlations
Goldman et al. (7)	0.05	5 variables (multiple regression)
Card sorting/executive functions		
Jaeger and Douglas (8)	0.01	Unspecified
Lysaker et al. (10)	0.05	4 or 5 variables (in each of 5 multiple regression analyses)
Buchanan et al. (6)	n.s.	
Possible associations (nonreplicated findings)		
Complex reaction time		
Wykes et al. (11)	0.01	8 variables (discriminant function analysis)
Visual memory		
Buchanan et al. (6)	0.03	>20 correlations
Verbal fluency		
Buchanan et al. (6)	0.04	>20 correlations
Negative symptoms		
Johnstone et al. (9)	0.01	>20 correlations
Goldman et al. (7)	n.s.	
Wykes et al. (11)	n.s.	
Negative findings		
Trail making		
Buchanan et al. (6)	n.s.	
Goldman et al. (7)	n.s.	
Block design		
Buchanan et al. (6)	n.s.	
Goldman et al. (7)	n.s.	
Vocabulary		
Goldman et al. (7)	n.s.	
Johnstone et al. (9)	n.s.	
Psychotic symptoms		
Goldman et al. (7)	n.s.	
Johnstone et al. (9)	n.s.	
Wykes et al. (11)	n.s.	

[a]Uncorrected for number of analyses conducted.

studies included psychiatric comparison groups. Despite considerable interest in all of these omitted areas, the hope is that trends can be extracted more easily if the scope of the review is limited.

LITERATURE REVIEW

The results of the review are listed in table 1. The table is divided into three sections according to type of outcome measure. The first section includes studies of community (e.g., social and occupational) functioning, which used fairly global indices of outcome (6–11). The review moves from general to more specific outcome measures, and the next section of the table includes laboratory studies that assessed social problem solving, a critical component of social functioning (12–16). In the last group of studies, we approach functioning from a rehabilitation perspective and consider studies that have examined patients' ability to acquire psychosocial skills needed for community functioning from their psychosocial rehabilitation programs (13, 17–21).

Results for each section were divided into three types of findings. *Probable associations* are relationships that were significant in at least two separate studies. *Possible associations* are significant relationships that were not replicated, either because of a failure to replicate or because no other study used a similar measure. *Negative findings* indicate a failure to find a relationship in at least two different studies and the lack of a significant relationship in any other study.

Community Outcome

The initial step in the review was selection of prospective studies that assessed specific aspects of neurocognition at baseline and then subsequently assessed community functioning at follow-up (top section of table 1). This selection procedure omitted a number of informative cross-sectional studies (53, 54) and one prospective study in which neurocognitive assessment was done only at follow-up (55).

The results of these studies are summarized in table 2. Despite considerable variability in the selection of measures, there are two replicated findings: secondary verbal memory and card sorting both emerged as predictors of community functioning. There is a critical distinction between immediate (or primary) verbal memory and secondary verbal memory. Immediate memory is equivalent to a short-term store and is assessed with measures such as the Digit Span. This type of memory is not usually affected in amnesic patients. Secondary memory is memory for lists of words or stories, and it is often assessed after a time delay. This type of memory is dysfunctional in amnesia. Card sorting in table 2 refers to performance on the Wisconsin Card Sorting Test, which is considered a measure of executive functioning, concept formation, or cognitive flexibility. The most consistent negative finding, from three studies, is the failure to a show relationship between psychotic symptoms and community outcome.

It is difficult to arrive at unclouded conclusions from this group of studies because of wide differences in the selection of neurocognitive and outcome measures. This inconsistency in methods arises largely because of the exploratory nature of these studies and absence of hypotheses that could have guided test selection. This problem will be revisited later.

Social Problem Solving

Community functioning is a rather global and multifaceted concept. More specific, laboratory-based investigations of skills that are needed for community functioning have tended to emphasize psychosocial functioning, such as the ability to solve social problems (56). Standardized assessments of social problem solving usually involve videotaped vignettes in which the subject is shown an interpersonal situation. Depending on the specific test,

the subject may be asked to recognize features that are present in a social interaction, identify a social problem, generate solutions for the problem, engage in role playing to demonstrate the solution to the problem, or any combination of these activities. The studies that have examined the relationship between neurocognitive performance and social problem solving in schizophrenia are listed in the middle section of table 1.

The results across these studies are summarized and represented in table 3. In some of these studies the social problem solving measure yielded a wide array of dependent measures. If summary scores were available, I used them as the basis of the review.

As in the previous group of studies, some commonalities emerged despite substantial variability in selection of measures that obscures our view. Secondary verbal memory is again a replicated finding. The distinction between immediate and secondary memory is useful in this cluster. Immediate verbal memory correlated with social problem solving in one study but not in two others, and this correlation is listed as a possible association. Vigilance is also a replicated finding, although two other studies failed to support this association. Vigilance is measured by a continuous performance test in which the subject is instructed to press a button in response to a specified target (a letter or number). The ability to discriminate targets from nontargets (signal from noise) is usually the primary measure. Negative symptoms were correlated with social problem solving in two studies.

This set of studies may be more informative in terms of what they failed to show. Card sorting tests were administered in three studies but were not associated with any of the outcome measures. Psychotic symptoms failed to correlate with social problem solving in the two studies that assessed them.

TABLE 3. Results From Studies of Relation Between Neurocognitive Measures and Social Problem Solving for Schizophrenic Patients

Correlate and Study	p[a]	Number of Correlations[b]
Probable associations (replicated findings)		
Secondary verbal memory		
Bellack et al. (12)	0.02	16
Corrigan et al. (14)	0.001	9 (summary score)
Vigilance		
Bowen et al. (13)	0.01	4 (overall score)
Penn et al. (16)	0.01	6 (global score)
Corrigan et al. (14)	n.s.	
Penn et al. (15)	n.s.	
Negative symptoms		
Bellack et al. (12)	0.02	>20
Corrigan et al. (14)	0.01	2
Possible associations (nonreplicated findings)		
Immediate verbal memory		
Corrigan et al. (14)	0.05	9 (summary score)
Bellack et al. (12)	n.s.	
Bowen et al. (13)	n.s.	
Early visual processing		
Corrigan et al. (14)	0.001	9 (summary score)
Bowen et al. (13)	n.s.	
Reaction time		
Penn et al. (16)	0.05	6 (global score)
Penn et al. (15)	n.s.	
Verbal IQ		
Bellack et al. (12)	0.005	16
Negative findings		
Card sorting/executive functions		
Corrigan et al. (14)	n.s.	
Penn et al. (15)	n.s.	
Penn et al. (16)	n.s.	
Backward masking		
Penn et al. (15)	n.s.	
Penn et al. (16)	n.s.	
Psychotic symptoms		
Bellack et al. (12)	n.s.	
Corrigan et al. (14)	n.s.	

[a]Uncorrected for number of analyses conducted.
[b]Summary scores, if available, were used as a basis for this column. Whenever possible, the numbers of analyses were estimated separately for neurocognitive measures and symptom ratings.

Social Skill Acquisition

One key determinant of instrumental role functioning of patients in the community is the ability to acquire or relearn psychosocial skills. Rehabilitation programs provide instruction in medication management, conversation, leisure, resolution of interpersonal problems, and vocational skills. Through didactic exchanges and role-playing exercises, these training programs involve both informational and behavioral components of skill learning. Skill acquisition can be reliably assessed by pre- and posttraining tests and by role-playing exercises that are scored by trained raters. The series of studies shown in the bottom section of table 1 addressed the question of which neurocognitive abilities are required for patients to acquire or relearn social skills.

The results of studies of skill acquisition are shown in table 4. The selection of measures was more consistent in this group of studies, and the findings cohere in several respects. Immediate and secondary verbal memory were both consistently associated with skill acquisition. Likewise, vigilance was consistently associated with skill acquisition. Notably, not one study failed to find an association with verbal memory or vigilance. Neither psychotic nor negative symptoms showed any significant relationship with skill acquisition. From these studies it appears that verbal memory and vigilance are critical prerequisite capacities for skill acquisition in psychosocial rehabilitation programs but that symptoms are not related.

CONCLUSIONS AND FUTURE DIRECTIONS

General Conclusions

Despite a longstanding curiosity about the functional consequences of neurocognitive deficits in schizophrenia, empirical studies with specific predictor and outcome variables have been lacking until recently. Five years ago this literature review would have been impossible because there was essentially no literature to re-

TABLE 4. Results From Studies of Relation Between Neurocognitive Measures and Skill Acquisition for Schizophrenic Patients

Predictor/Correlate and Study	p[a]	Number of Correlations or Variables[b]
Probable associations (replicated findings)		
Secondary verbal memory		
Corrigan et al. (17)	0.001	6 correlations (overall score)
Kern et al. (18)	0.01	>20 correlations
Mueser et al. (20)	0.05	12 correlations
Vigilance		
Bowen et al. (13)	0.01	4 correlations (total score)
Corrigan et al. (17)	0.05	6 correlations (overall score)
Kern et al. (18)	0.05	>20 correlations
Immediate verbal memory		
Bowen et al. (13)	0.01	4 correlations (total score)
Corrigan et al. (17)	0.01	6 correlations (overall score)
Kern et al. (18)	0.01	>20 correlations
Mueser et al. (20)	0.05	12 correlations
Possible associations (nonreplicated findings)		
Early visual processing		
Bowen et al. (13)	0.01	4 correlations (total score)
Corrigan et al. (17)	n.s.	
Card sorting/executive function		
Lysaker et al. (19)	—[c]	6 variables (multiple regression)
Corrigan et al. (17)	n.s.	
Proverb interpretation		
Lysaker et al. (19)	—[c]	6 variables (multiple regression)
Psychomotor speed		
Weaver and Brooks (21)	—[c]	>20 correlations
Negative findings		
Psychotic symptoms		
Corrigan et al. (17)	n.s.	
Lysaker et al. (19)	n.s.	
Mueser et al. (20)	n.s.	
Negative symptoms		
Corrigan et al. (17)	n.s.	
Lysaker et al. (19)	n.s.	
Mueser et al. (20)	n.s.	

[a]Uncorrected for number of analyses conducted.
[b]Summary scores, if available, were used as a basis for this column. Whenever possible, the numbers of analyses were estimated separately for neurocognitive measures and symptom ratings.
[c]Unspecified.

view. All except one of the data-based studies in this review were published in the 1990s.

Even with obvious differences in methods, limited statistical power, and huge variability in the selection of measures, some general conclusions are warranted. First, secondary verbal memory turned out to be a remarkably strong predictor or correlate of outcome. Not one of the seven studies that included measures of secondary verbal memory failed to show an association, regardless of the functional outcome measure. Immediate verbal memory was also associated with skill acquisition, but it was only inconsistently related to social problem solving. The relationships between verbal memory and skill learning have a certain face validity; they make sense when we consider the nature of the tasks. For successful skill acquisition, the participants need to encode and recall material presented by their instructors and through videotapes. In addition to rehabilitation, verbal encoding and mediation of daily activities are likely to be necessary for adequate instrumental role functioning in the community.

Another noteworthy finding was that vigilance was consistently associated with acquisition of social skills, and it was associated with social problem solving in two out of four studies. Vigilance is an attentional process. Attentional problems have long been considered a central feature of schizophrenia. Both Kraepelin (57) and Bleuler (58) considered attentional deficits to be characteristic of the disorder. Vigilance encompasses two different types of attentional processes (59). Vigilance level is the ability to discriminate signal (target) from noise (nontarget) stimuli across an entire vigilance period. For the purposes of the current review, "vigilance" refers to vigilance level. "Vigilance decrement" refers to the drop in vigilance level over the course of the test. Although this process is more closely related to the notion of sustained attention, it is used less often in the schizophrenia literature and was not part of the current review.

The relationships between vigilance and both skill acquisition and social problem solving also have a certain face validity. Perhaps patients who are better able to distinguish signal from noise in a computerized test are also better able to separate relevant from irrelevant information in the flow of continually changing social situations. We would naturally like to know whether this ability is related to community functioning. Unfortunately, none of the studies of community functioning evaluated vigilance.

Card sorting was consistently related to community outcome, inconsistently related to skill acquisition, and not related to social problem solving. The Wisconsin Card Sorting Test, which was used in most of these studies, is considered a measure of executive functions, such as concept formation and cognitive flexibility. Possibly these abilities are more related to community functioning than they are to laboratory assessments of problem solving. Before we jump to this conclusion, it may be worthwhile to consider that two of the three studies with positive findings for card sorting had statistical powers of 0.60 or greater, whereas none of the studies with negative findings had a power greater than 0.50.

Although we cannot rule out the possibility of a global deficit, it seems unlikely that a single generalized deficit could account for difficulties in both neurocognitive and functional domains. In the pattern of correlations there is no indication that patients who performed poorly on some measures tended do so on all. Most of the neurocognitive measures had adequate ranges and variance, so the failure of some neurocognitive measures to correlate significantly with outcome measures cannot be easily explained by statistical artifacts.

Negative symptoms showed consistent associations with social problem solving, inconsistent relationships with community functioning, and no relationships with skill acquisition. It is surprising that the relationships, especially the association with community functioning, were not stronger. Several of the measures of negative symptoms (e.g., the Scale for the Assessment of Negative Symptoms) include measures of social contacts and persistence at school and work. These areas of overlap between ratings of negative symptoms and functional outcome would be expected to artificially inflate the strength of the relationships. If this overlap were eliminated, for example by using a narrow definition of negative symptoms, we would expect the relationship between negative symptoms and functional outcome to be even weaker.

The most consistent, and perhaps most surprising, negative finding from this review was that psychotic symptoms were not significantly associated with functional outcome measures in any of the eight studies that evaluated them. This negative finding may not fit with clinical impressions, but it fits well with previous research on predictors of occupational functioning. This literature has generally shown psychotic symptoms to be poor predictors of future work performance in the chronically mentally ill (60, 61). After reviewing the literature, Anthony and Jansen concluded, "There appear to be no symptoms or symptom patterns that are routinely related to individual work performance" (61, p. 539). In contrast to this general conclusion, Breier et al. (55) more recently reported that psychotic symptoms rated during optimal neuroleptic treatment were significant predictors of future social and work functioning.

Psychotic symptoms may predict functioning under certain circumstances. First, while psychotic symptoms do not seem to be informative *within* a group of schizophrenic patients, it is possible that psychotic symptoms would be informative in a group with mixed psychiatric diagnoses, which would have more variability both in symptoms and in outcome. Second, not all psychotic symptoms are equally disruptive to functional outcome. Some especially intrusive behaviors, e.g., psychotic assaultiveness (62), would be incompatible with community adaptation and may turn out to be stronger predictors than psychotic symptoms in general. Third, within occupational functioning, not all jobs would be equally affected. We might predict that jobs with minimal demands for interpersonal interactions would be less affected by ongoing psychotic symptoms. These caveats, however, do not challenge a central conclusion from this review: that certain neurocognitive measures are more strongly associated with functional outcome than are psychotic symptoms.

Psychotic symptoms may be a better predictor of clinical outcome measures, such as rates of relapse and rehospitalization. The degree of independence of the clinical and functional domains has not been entirely settled, but these domains appear to be at least partially separate. In their influential studies, Strauss and Carpenter (45, 63) described occupational functioning, social relations, symptoms, and hospitalization as "semi-independent" processes, each with its own separate predictors. This formulation was clearly supported by a recent study (64) that showed certain psychophysiological indices correlated with better social outcome but poorer clinical outcome.

Strauss and Carpenter found that previous occupational functioning and social functioning were each the best predictor of the respective outcome function. Other studies have shown that premorbid functioning predicts functional outcomes following onset of illness (65, 66). Although significant, the correlations in these studies (r=0.36–0.44 [63], r=0.26–0.39 [65], r=0.35–0.49 [66]) were generally smaller than the significant correlations in the current review. One obvious explanation for the associations between previous and later functioning is that it is easier to reestablish previously learned social and vocational skills than it is to learn them from scratch. However, there is a less obvious reason to expect an association between past and future functioning: both are likely to be mediated by neurocognitive abilities and many of these abilities are known to be highly stable over time. Not only are some neurocognitive deficits stable during the course of illness, it is highly likely that certain deficits are present long before the onset of symptoms. For example, vigilance deficits are found in children who are considered to be at high risk for developing schizophrenia because their mothers have schizophrenia (67, 68). Neurocognitive deficits in the premorbid period should have the same associations with premorbid functioning (probably in attenuated form because of reduced range of outcomes) as were found in this review. The stability of these neurocognitive deficits would partially account for correlations between premorbid and later functioning. After the onset of illness, other neurocognitive deficits that are associated with the presence of illness will emerge. This process of acquiring additional neurocognitive liability with the onset of illness could help explain the functional decline that is characteristic of schizophrenia.

In this review I sought to determine whether certain neurocognitive abilities act as rate-limiting factors and restrict the functioning of patients. While this goal is reasonable, the effects are unlikely to be strictly unidirectional. Patients' activities certainly influence the development of neurocognitive abilities. As mentioned earlier, some neurocognitive deficits begin before the onset of illness and restrict the patient's initial level of functioning. However, patients who can adapt to the challenges of job tasks or the demands of social interactions probably will experience strengthening of their neurocognitive abilities. In this view, the neurocognitive abilities are considered primary but still modifiable by environmental factors.

Applications for Studies of Neurocognitive Rate-Limiting Factors

If we assume that some of the patterns noted in this review will be replicated, what are the practical applications of these studies of neurocognitive rate-limiting factors? One potential application would be the plan-

ning of services or training for patients. Let us say that we have two inpatients who are comparable in most respects except that one has poor and the other has adequate vigilance. The patient with good vigilance would probably benefit from skills training programs as they are currently designed, whereas the other patient may need a form of skills training that is slower paced, is offered in shorter segments, or includes more redundancy. Likewise, a patient with relatively poor verbal memory who is about to enter a community placement may need additional mental health support services to achieve and maintain optimal social and work outcome. In these examples, the focus is on predicting the individual's need for support.

A second, and more ambitious, application involves cognitive remediation efforts. The term "cognitive remediation," as it is used in psychopathology, actually applies to three types of designs: studies of rate-limiting factors, feasibility studies, and generalization studies (2). All of the studies in the current review can be considered studies of neurocognitive rate-limiting factors in that they examined the correlations between neurocognitive variables and outcome measures that are believed to be relevant to functioning in the real world. Feasibility studies are designed to determine whether performance deficits can be modified under any conditions. These studies typically use experimental probes to determine whether a certain type of intervention modifies performance on a specific neurocognitive measure, such as the Wisconsin Card Sorting Test (69–71) or the Span of Apprehension (72). In generalization studies, the intervention is directed at one level (ranging from basic cognition to complex social functioning), but the effects of the intervention are assessed in another domain (e.g., clinical). For example, the work of Brenner and colleagues (73) is representative of this type of design, in which interventions directed at neurocognitive abilities are expected to have therapeutic value.

The generalizability of cognitive remediation in schizophrenia is a matter of some debate. The current review will not help to resolve this debate, but it may allow for more informed and meaningful tests of generalizability. Studies of generalization require an a priori selection of neurocognitive processes that receive the intervention. In addition, they require a decision about the relevant outcome variable. How does one decide which of the many neurocognitive deficits shown by schizophrenic patients should be targeted or which outcome measures should be selected in generalization studies? Studies of rate-limiting factors, such as those in the current review, should guide these decisions. An adequate test of generalizability should build on a clearly demonstrated association between the neurocognitive ability that receives the intervention and the outcome. Otherwise, it is simply not a fair test.

Where Do We Go From Here?

As a group, the studies in the current review lacked two essential elements: power and hypotheses. With a median power of only 0.37, most of the studies were substantially underpowered. A glance at table 1 shows that only three studies had acceptable powers, i.e., 0.80 or greater. We have to assume that many more correlations would have been revealed if the studies had been better powered.

The second major problem stems from a lack of hypotheses. The absence of guiding hypotheses means that different laboratories selected widely different measures, making it more difficult to draw general conclusions. The lack of hypotheses means that most of the analyses were conducted in a post hoc fashion. Post hoc analyses capitalize on chance, so some of the significant associations in this review were probably accidental. It is not surprising that these initial forays into a new research area were underpowered and overanalyzed. It is surprising that, despite these sources of error, some findings were remarkably consistent across studies.

It is difficult to overstate the importance of hypotheses for an area as methodologically diverse as this. From the review we are now in a position to generate, at least tentatively, some testable hypotheses so that the next phase of investigations will be convergent instead of divergent.

1. One obvious hypothesis is that the same measures that predict skill acquisition (verbal memory and vigilance) will also predict community functioning. The results for secondary verbal memory tentatively support this hypothesis, but vigilance has not yet been evaluated as a predictor of community functioning. We ideally would want to predict social functioning independently from occupational functioning, but there are not sufficient data to support differential predictions at this time.

2. From this review we can generate hypotheses to guide studies of generalization. Specifically, we hypothesize that generalization effects of cognitive remediation, if they can be found, are most likely to be seen when the interventions are directed at neurocognitive abilities that have documented associations with the relevant functional outcome.

3. Although fairly specific neurocognitive variables have been used, the functional outcomes in these studies have not been as well differentiated. Exploratory studies should investigate whether neurocognitive measures offer differential prediction among the domains of functional outcome. We might hypothesize that verbal memory and language processing skills may be more closely related to social functioning, which involves verbal mediation. In contrast, jobs that have relatively little interpersonal demands may rely more on visual or motor skills.

4. The results for negative symptoms are inconsistent so far. We might expect negative symptoms or the deficit form of schizophrenia to emerge as a predictor for selected outcome measures. For example, negative symptoms may have a greater impact on activities with large interpersonal demands (e.g., establishing social networks).

5. In terms of service delivery, we can hypothesize that patients who perform poorly on measures of neurocognitive rate-limiting factors, such as verbal

memory and vigilance, will have more intensive utilization of services than those who perform well. Follow-up studies could examine the specificity of the type of service needs associated with a particular deficit.

6. One type of learning that was not evaluated in any of the studies in this review was procedural learning (e.g., learning of motor skills). A reasonable hypothesis to be tested in future studies is that procedural learning is associated with work functioning, particularly when the job involves motor sequencing demands.

For nearly a century, neurocognitive research in schizophrenia has "looked inward" to identify and characterize the deficits that are central to the disorder. The studies in this review represent an attempt to "look outward" to better understand how the deficits affect individuals in their daily lives. We are, of course, some distance away from our goal of knowing which specific neurocognitive capacities affect particular types of outcome. However, the initial hypothesis-generating phase seems to be nearing completion, and it may be time to move on to the hypothesis-testing phases.

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