A Review of Longitudinal Studies of Cognitive Functions in Schizophrenia Patients

by Bjørn Rishovd Rund

Abstract

Even though the idea that schizophrenia is a neurobehavioral syndrome has become a mainstream position, there is no consensus on the precise nature of the cognitive and neuropsychological impairment. Research on cognitive dysfunctions in schizophrenia has been directed toward discriminating stable dysfunctions (traits) from symptom-linked (state) deficits. A longitudinal study design is the only one that can provide answers to the question of the stability of psychological functions. This article reviews 15 studies with a follow-up of at least a year. The main conclusion drawn from these studies is that after the onset of schizophrenia, cognitive deficits are relatively stable over long periods. No support for a decline in cognitive functions is found. Thus, schizophrenia does not appear to be a degenerative process, but rather a static encephalopathy. Whether or not the cognitive deficits found in schizophrenia can be remediated is still an open question that needs to be examined.

Key words: Cognitive dysfunction, stability, longitudinal studies.

***Schizophrenia Bulletin*, 24(3):425–435, 1998.**

The view of schizophrenia as a neurobehavioral syndrome with a neurodevelopmental origin is now widely accepted (Kremen et al. 1994; Murray 1994). Ample evidence of cognitive and neuropsychological deficits in patients with schizophrenia supports this view. A certain movement from laboratory studies of particular cognitive processes, such as attention, toward comprehensive neuropsychological evaluations has taken place during the past decade.

However, there is no agreement as to the precise nature of the cognitive/neuropsychological impairment (Nuechterlein and Dawson 1984; Rund and Landrø 1990). The reason is related to several factors. One is that so far we have not clarified whether patients with schizophrenia demonstrate only certain areas of dysfunction or show a more generalized deficit. Establishment of a selective deficit requires demonstration of specific dysfunction against the expected background of global impairment. To demonstrate which cognitive functions represent a differential deficit (specific dysfunction) in subjects with schizophrenia, the experimental and control tasks must be equated on psychometric variables, such as difficulty, variability, and reliability on test items (the so-called discriminating power). Such matching of tasks has been neglected to a great extent in the field (Miller et al. 1995). One of the few tasks that has been matched on discriminating power is the Digit Span test constructed by Oltmanns and Neale (1975). In this test, two sets of neutral and distractor Digit Span tests were carefully matched for psychometric properties affecting discriminating power. For the most part, this task has shown a differential deficit on distractibility in patients with schizophrenia when compared with normals (Oltmanns and Neale 1975; Oltmanns 1978; Oltmanns et al. 1978; Rund 1983, 1989).

Chapman and Chapman (1989) have also recommended two alternative strategies: use of standardized residual scores or titration of accuracy by manipulating test conditions. By using the first approach, Saykin et al. (1991) demonstrated a selective deficit in memory and learning as compared with other cognitive areas in a sample of 36 unmedicated patients with schizophrenia.

Another factor that has made it difficult to get a definite answer to the question of the precise nature of the cognitive deficit in patients with schizophrenia is the diagnostic specificity of a dysfunction. Very few, if any, cognitive/neuropsychological deficits have proven to be a specific characteristic of schizophrenia. Typically, a certain deficit has been found first in a sample of patients with schizophrenia. Then, some time later, it has been found in

Reprint requests should be sent to Dr. B.R. Rund, Institute of Psychology, University of Oslo, P.O. Box 1094, Blindern N-0317 Oslo, Norway.

other psychiatric groups as well, for instance, in affectively disturbed patients (Rund 1993).

There is also great variety within the diagnostic group called "schizophrenia." Most often only some patients with schizophrenia manifest a dysfunction, and researchers are fortunate if these constitute a definable subgroup of patients.

During the past two decades, much research in this area has been focused on discriminating cognitive deficits that are "stable vulnerability factors" from "episode indicators" (Nuechterlein and Dawson 1984; Rund et al. 1997). Deficits that fall into the category of vulnerability markers are stable characteristics that consistently deviate from normal levels, even during remission without florid symptoms. They should also be detectable in vulnerable persons who are not symptomatic. "Episode indicators," however, are associated with certain features of schizophrenic symptomatology. They deviate from normal levels during symptomatic episodes but return to normal levels during symptom-free periods. "Episode indicators" seems to have been used as a term synonymous with "state-dependent components" (Saccuzzo and Braff 1986). "Vulnerability" or "trait factor" suggests structural abnormalities. "State" suggests that cognitive deficits vary because of underlying neurochemical or neurophysiological disturbances.

It is also worth noting that few research reports specify the phase of the illness in which patients are examined or tested. Typically, the symptoms of schizophrenia wax and wane. The illness fluctuates between stages of florid symptoms and periods of (partial) remission. Most often the subject sample is described as "chronic," or "first-episode schizophrenia," and so on. It is most likely that these samples consist of a heterogeneous group of patients with respect to symptom severity and stages of the illness. However, the samples may be relatively homogeneous in terms of such variables as length of illness and hospitalization.

A follow-through longitudinal study is the only design that can answer questions about the stability of a psychological function. It is also the best suited to discriminate vulnerability factors from symptom-linked factors. Cross-sectional comparisons of patient groups in different stages of the illness or at different ages are likely to be confounded by sampling biases that create differences. These differences are not due to intraindividual processes (Strauss 1978). Thus, longitudinal studies are essential to determine whether cognitive and neuropsychological abnormalities in schizophrenia reflect traits, clinical states, or a combination of the two (Nuechterlein et al. 1992). For this reason, only studies with a longitudinal design are considered in the present review. Given the importance attached to the question of discriminating vulnerability from symptom-linked factors, it is astonishing that so few longitudinal studies have been done in this area.

In the present review, relevant reports were identified by a literature survey using the keywords "schizophrenia," "cognition," "neuropsychology," and "longitudinal." In addition, some outstanding researchers in this area were asked to add to the identified list relevant studies that were not included.

Seen from the perspective of the course of a chronic disease like schizophrenia, a followup period of a few weeks tells us little about the stability of psychological function. Thus, this review considers only studies with a minimum 1-year followup period. A few studies of cognitive dysfunction with a shorter followup period, included in the initial literature survey, have been omitted.

Why is it important to obtain more exact knowledge about cognitive dysfunction in patients with schizophrenia over time? The answer is twofold:

1. Knowledge about the natural course of cognitive deficits will help clarify the etiology of schizophrenia. An important question in this connection is whether schizophrenia is a dementing disorder or a static encephalopathy. A dementing disorder can be related to a neurodegenerative process. After an insidious onset, the patient's symptoms become even more disabling and cognitive functions and social skills more impaired (Goldberg et al. 1993). A static encephalopathy is generated by a neurodevelopmental process or arrest. If this is the case, cognitive deficits will be relatively stable. With the onset of clinical symptoms, the patient's cognition declines and he or she becomes disabled. Patients can remain in this stable but impaired condition for many years (Goldberg et al. 1993).
2. Treatment and possibilities for cognitive remediation depend on the natural course of the cognitive deficit. Enduring cognitive deficits can be responsible for patients' failure to rehabilitate cognitively and even socially. Treatment evaluation is more complicated against a background of progressive dementia.

The Review

Diagnoses, tasks, and main findings are summarized in table 1 for the 15 studies reviewed.

The Moran et al. (1960) study was the first one reporting longitudinal data in the area of cognition. They examined 55 patients with chronic paranoid schizophrenia with an extended battery of word meaning measures. Thirty patients were followed up with the same test battery 6 years later. The authors found that overall performance was "remarkably stable" over the 6-year period but that there was a slight decline in performance on defini-

Table 1. Longitudinal studies of cognitive and neuropsychological functions in patients with schizophrenia

Study	Subjects	Tasks	Followup (years)	Results
Moran et al. (1960)	30 schizophrenia	Word meaning	6	High stability
Smith (1964)	24 schizophrenia	IQ test	8.4	High stability on higher mental functions A certain loss in shifting capacity (Weigl)
Klonoff et al. (1970)	66 schizophrenia	WAIS	8	Significant improvement
Flekkøy (1975)	72 schizophrenia	Word association	16.6 mean	Moderate stability, tendency toward improvement
Nuechterlein (1985)	14 schizophrenia	CPT, DS–CPT	1	High stability on perceptual sensitivity DS–CPT Moderate stability on conventional CPT
Rund (1989)	20 normal 14 schizophrenia	Short-term memory Distractibility (Digit Span)	4	High stability
Bilder et al. (1991)	28 schizophrenia	Neuropsychological test battery (4 measures)	1	High stability in neuropsychological deficit Improvement on most functional domains Decline on attentional span
Sweeney et al. (1991)	39 schizophrenia	Neuropsychological test battery (7 measures)	1	High stability on memory, verbal fluency, verbal learning/recall, visual memories Improvement on verbal recognition memory, orientation, psychomotor skills
Nuechterlein et al. (1992)	17 normal 17 (13) schizophrenia	CPT, SPAN	1	High stability on attention measures Low stability on memory for contextual cuing
Hoff et al. (1992)	17 schizophreniform	Neuropsychological test battery (7 measures)	2	Improvement on complex attention, concentration, motor speed, conceptual problem solving High stability on language, verbal and spatial memory
Rund et al. (1993)	14 normal 8 nonschizophrenia 22 schizophrenia	Backward-masking	2	High stability
Nopoulos et al. (1994)	35 schizophrenia	Neuropsychological test battery (5 measures)	1 (17 patients) 2 (18 patients)	High stability Improvement on complex attention and set-response-shift
Harvey et al. (1995)	224 schizophrenia geriatric	MMSE	1	High stability
Rund and Landrø (1995)	22 schizophrenia 8 affective 14 normal	RT, Vigilance (CPT, SPAN), Short-term memory, Long-term memory	1	Moderate stability, some improvement

Table 1. Longitudinal studies of cognitive and neuropsychological functions in patient with schizophrenia—*Continued*

Study	Subjects	Tasks	Followup (years)	Results
Rund et al. (1997)	14 normal 15 schizophrenia	Cognitive test battery (4 measures)	1–2	High stability on backward-masking and long-term memory Moderate stability on cognitive shift Improvement on short-term memory

Note.—IQ = Intelligence quotient; WAIS = Wechsler Adult Intelligence Scale (Wechsler 1958); CPT = Continuous Performance Test (Rosvold et al. 1956); DS-CPT = degraded stimulus Continuous Performance Test (Nuechterlein 1983); SPAN = Span of Apprehension Test (Asarnow et al. 1991); RT = reaction time; MMSE = Mini-Mental State Exam (Folstein et al. 1975).

tions. This decline was assumed to be associated with normal aging rather than with increased schizophrenic pathology or length of institutionalization. A methodological strength in this study was that the patients were probably not medicated (Moran et al. 1952).

Smith (1964) tested 11 younger patients with schizophrenia with a hebephrenic-catatonic symptom complex, and tested 13 older patients with paranoid schizophrenia on higher mental functions (intelligence quotient [IQ]) and shifting capacity as a specific effect of frontal lobe lesions. The patients were retested 8.4 years later. The most striking finding here was the remarkable stability of test scores on measures of intelligence. A certain loss in shifting capacity was observed in 10 patients from the first to the second assessment. This study was hampered by several methodological shortcomings, however. Among them was the lack of a control group to decide whether the cognitive functions examined represented a deficit in the patients with schizophrenia, as is the case with many of the studies reviewed in this article.

Klonoff et al. (1970) also followed the intellectual functioning of a group of 66 chronic patients with schizophrenia over a period of 8 years, using the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1958). The data indicated a significant improvement in IQ on the WAIS during this time period. Verbal IQ tended to be more stable than performance IQ. (For a review of studies on IQ changes over the course of schizophrenia, see Aylward et al. 1984.)

Flekkøy's (1975) examination is remarkable in the sense that it has a much longer followup period than any of the other studies. The mean test-retest interval was 16.6 years, with a range from 15 to 19 years. Seventy-two patients with schizophrenia were assessed with a word association test consisting of 50 common nouns. Their responses were examined in relation to an associative norm. The patients with schizophrenia showed a significant normalization of performance with respect to associative commonality, idiosyncratic responses, and response latency during the followup period. However, a methodological problem with this study was that only 36 percent of the patients received psychotropic drugs at the time of the first testing, whereas 93 percent received such medication at the time of retesting. Thus, the normalization of associative responses could be attributed chiefly to the effects of psychotropic drugs as well as improved psychiatric treatment.

Nuechterlein (1985) examined 21 patients with chronic schizophrenia longitudinally with a traditional and degraded stimulus Continuous Performance Test (DS-CPT; Nuechterlein 1983). Also, 14 patients were examined 1 year after the initial testing. Nuechterlein found that the test-retest correlations for overall perceptual sensitivity in the DS-CPT were fairly high. However, parallel correlations for the conventional CPT (Rosvold et al. 1956) were substantially lower, which indicated relatively little performance stability on this version.

Rund (1989) twice assessed 14 patients with schizophrenia, 8 nonpsychotic psychiatric controls, and 20 normals on recall performance and distractibility, with an interval of 4 years. The method was a Digit Span test with neutral and distractor condition strings. The two conditions were matched for difficulty level and reliability to avoid the problem associated with different discriminating power (Chapman and Chapman 1973, 1978; see also the introduction). Results showed that patients with schizophrenia, primarily nonparanoid patients, were inferior to normals with respect to short-term recall both times. No significant differences were found as to the influence of distraction when patients with schizophrenia were compared with the two control groups. An analysis of variance (ANOVA) revealed no main effect of time, which implies a relatively stable pattern of performance in both patients with schizophrenia and controls on recall performance as well as on distractibility over time. A certain decline in distractibility performance was observed in the patients with paranoid schizophrenia from time 1 to time 2, however. Methodological weaknesses in this study were the small sample of patients and the uncertainty associated

with changes in neuroleptic medication from the first to the second testing.

Bilder et al. (1991) reported findings from a prospective longitudinal study of 28 first-episode patients with schizophrenia on a broad battery of neuropsychological tests (motor, attentional, executive, and language functions). Patients were assessed before initial treatment and after 1 year. A generally high stability of neuropsychological deficits was found. Further, an overall improvement in most neuropsychological functional domains (tests of motor functions, learning, and memory) and an overall decline on tests of attention span were reported.

Sweeney et al. (1991) evaluated the longitudinal stability of neuropsychological deficits in 39 patients with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients were first tested with a comprehensive battery of neuropsychological tests assessing seven functions: motor speed, psychomotor speed and attention, visual-spatial skills, verbal fluency, verbal memory, visual memory, and flexibility of cognitive set. They were tested after achieving sufficient clinical recovery to warrant discharge and again 1 year after the first assessment during a nonacute period. Significant improvement from the first to the second assessment was observed on Trail Making Task A and B (Adjutant General's Office 1944), WAIS–R Digit Symbol (Wechsler 1981), Judgment of Line Orientation (Benton 1983), recognition memory on the Rey Auditory Verbal Learning Test (Rey 1964), the Wisconsin Card Sorting Test (WCST; Heaton 1981), Finger Tapping (Rey 1964), and perseverative error on the WCST. These improvements were unrelated to treatment history. Regardless of whether patients were first-episode cases or had experienced previous episodes of psychosis, similar levels of improvement were observed. No changes were evident on the Digit Span test, Block Design, verbal fluency, verbal learning/recall, or immediate or delayed visual memory. No significant deterioration in functioning over the 1-year followup period was evident on any test. Sweeney et al. (1991) concluded that considerable improvement in neuropsychological functioning can occur in patients with schizophrenia over the months following an acute episode. The authors suggest that improvement during the followup period could result in part from a gradual physiological recovery of brain function after a psychotic episode. This study had the following methodological shortcomings: Schizophreniform and schizoaffective patients were included; a comparison group was not used to control for practice effects; there was a relatively short followup period; and antipsychotic doses were reduced during the followup period.

Nuechterlein et al. (1992) reported some preliminary results from a longitudinal study of patients with schizophrenia. These patients were tested 1 month after a standardized medication level was achieved and 1 year from this initial assessment. In the 1992 report, data were analyzed for 17 pairs of patients and normal controls on two information processing tasks: the DS–CPT and a forced-choice Span of Apprehension Test (SPAN; Asarnow et al. 1991). Analyses suggested that both discrimination of ambiguous perceptual information presented in rapid succession (DS–CPT) and the ability to apprehend simultaneous information (SPAN) remained impaired in a relatively stable way during the early course of schizophrenia. This was indicated even with all symptoms going into remission. Nuechterlein et al. (1992) understand this finding as consistent with the hypothesis that subtle information-processing anomalies are genetically transmitted components of vulnerability to schizophrenia. In contrast to these two measures, the performance of patients with schizophrenia on a memory-load CPT (3–7 CPT) varied significantly in patients across psychotic and remitted states. This finding suggests that increased disturbances in use of active memory for contextual cuing accompany and possibly contribute to psychotic symptoms.

Hoff et al. (1992) administered a large battery of neuropsychological tests consisting of seven summary scales (language, executive, verbal memory, spatial memory, concentration/speed, sensory/perceptual, and global) to 56 schizophreniform patients and 57 normal controls. Patients were tested within several weeks of hospitalization. Seventeen of the patients were followed up after 2 years. The main findings were that several neuropsychological summary scales revealed in the schizophreniform patients as compared with normals a diffuse pattern of cognitive impairment that appeared to improve over time. Improvement was primarily found in tasks involving complex attention, concentration, motor speed, and higher order conceptual problem solving. Hoff et al. (1992) assume that the cognitive improvement resulted from improvement in clinical state.

Rund et al. (1993) also investigated the stability of information processing tasks involving the earliest phases of visual processing: a backward-masking test. Twenty-two patients with schizophrenia, 8 nonschizophrenia patients, and 14 normal controls were tested three times, with an interval of 1 year between each session. There were significant differences between patients with schizophrenia and normal controls, and the masking performance proved to be stable across the three test sessions.

In another publication, Rund and Landrø (1995) reported the longitudinal data on a simple reaction time task, a vigilance task, a short-term memory task, and a long-term memory task from the same subject sample. Results showed that normals performed better than patients with schizophrenia and affectively disturbed patients on almost all of these tests. The groups' perform-

ance changed to some extent over time on most of the measures, but the changes were not significantly different for different groups. In general, subjects' performance improved from the first to the second testing, but the improved results might in some cases reflect a learning effect, as with the vigilance (SPAN) and the memory tasks. Methodological shortcomings in this study were the small group sizes and the fact that patients were for the most part medicated at the first testing (though only a few of them were medicated at the second and third testing).

Nopoulos et al. (1994) evaluated the stability of cognitive functioning early in the course of schizophrenia by testing 35 patients with schizophrenia with nine neuropsychological tests: CPT, Finger Tapping, Trail Making Task B, Controlled Oral Word Test, Logical Memory Test, Rey Auditory Verbal Learning Test, Paired Associated, Benton Visual Retention Test (Benton 1983), and Stroop Color-Word Test (Golden 1978). Five neuropsychological measures were derived from this battery of tests: psychomotor speed and attention, verbal fluency, verbal memory, visual reconstruction memory, and shift response set. Sixty-eight controls were also assessed with the same battery of tests, but with no followup testing. Seventeen of the patients initially tested were tested again after 1 year; the other 18 patients were retested after 2 years. The results indicated that performance on most measures was stable over time. A small subset of functions improved: complex attention (Trail Making Test B) and set-response-shift (Stroop). Nopoulos et al. (1994) concluded on the basis of these findings, that the neuropsychological functions of motor speed, verbal and nonverbal memory, and verbal learning are traits of the illness. Complex attention and executive functions are state dependent. However, the results indicated that these functions were related to changes in symptom severity and not to changes in medication doses.

Harvey et al. (1995) examined 224 geriatric inpatients with schizophrenia for changes in cognitive functioning over a 1-year followup period. Forty-five of them were also assessed over a 2-year period. The assessment method used was the Mini-Mental State Examination (MMSE; Folstein et al. 1975). This is a 22-item examination that assesses various cognitive skills including orientation, short-term memory, and language and praxis skills. However, it is a rating scale, not a neuropsychological or cognitive test. The MMSE scores did not change over a 1- or 2-year followup period, and the test-retest reliability of the scale was extremely good at both retest intervals. These results are interpreted as support for the viewpoint that cognitive changes in these patients are very slow—more consistent with a neurodevelopmental process than a neurodegenerative one.

A different research approach was used by Rund et al. (1997) in a longitudinal study of 15 patients with schizophrenia and 14 normal controls. The purpose of this study was to classify cognitive dysfunctions in patients with schizophrenia according to a trait/state model. The sample of patients was therefore examined on four different cognitive functions (10 scores) in two distinctly different phases: an acute psychotic state and partial remission. Six of the 10 measures examined could be classified as cognitive deficits in patients with schizophrenia. Since backward-masking scores and long-term memory scores proved to be fairly stable in patients with schizophrenia, they were classified as trait-dependent components. A short-term memory score was the only one on which the patients' performance significantly improved from the acute to the remission phase. Therefore, this measure was classified as an episode-linked factor. The other cognitive deficits found could be characterized as intermediate factors: They are more prominent in the acute psychotic state but do not completely disappear during remission states.

Discussion and Conclusions

Most of the studies reviewed have methodological shortcomings and confounding variables that have to be considered before general conclusions can be drawn: The first general problem in research on schizophrenia is the reliability and validity of diagnoses. There is considerable evidence to suggest imperfect overlap in diagnoses by the early and late diagnostic systems; for instance, *DSM–II, DSM–III,* and *DSM–IV* (American Psychiatric Association 1968, 1980, 1994). Accordingly, there are criterion validity differences between the early and later studies assessed. An indication that this is not a big problem is the fact that the findings with respect to stability in cognitive deficits seem to point in the same direction in the early and later studies.

A second confounding variable in most of the studies reviewed is the effect of drugs—neuroleptics as well as anticholinergic drugs. Neuroleptic treatment seems to improve some cognitive functions and to have a deteriorating effect on others (Spohn and Strauss 1989; Rund et al. 1996, 1997). Antipsychotic drugs might also have different effects in the short and long run. Anticholineric drugs have been shown to impair some cognitive functions, such as verbal recall, independently of any autochthonous process of deterioration (Spohn and Strauss 1989). Further, attention and information processing impairment is related to tardive dyskinesia, particularly in patients with long-term neuroleptic treatment (Waddington and Youssef 1986; Spohn and Coyne 1993). In the longitudinal studies reviewed, in which a great number of cognitive and neuropsychological functions have been assessed and the doses of neuroleptic and anti-

cholinergic medication might have changed dramatically or been discontinued, it is a complex task to evaluate how the findings are affected by medication.

A third serious methodological problem in longitudinal studies is the dropout of patients between the first test and retest times. Most of the studies reviewed are hampered by a certain dropout. This limitation is serious because those patients who could not be contacted or were unable to participate may have experienced a different course from that of patients who were retested; that is, they may have had a cognitive decline. In a sense, there may have been ascertainment bias toward those individuals without cognitive decline.

A fourth methodological question that should be mentioned concerns the practice or learning effects in test-retest studies. Ideally, a comparison group of normal controls screened for personal or family history of psychopathology should be included to control for practice effects. However, with the long intervals between test sessions in the studies reviewed (at least 12 months), any carryover that occurs is probably minimal. This assumption is also supported by the normal control group data from our latest longitudinal study (Rund et al. 1993, 1997).

Although there are several methodological limitations that make it difficult to draw firm conclusions from the studies reviewed, some clear trends that create a basis for some tentative conclusions appear. The main conclusion is that cognitive deficits are relatively stable over long periods after the onset of schizophrenia. If any change occurs, it is most often an improvement in performance following remission after an acute psychotic episode. In several of the studies (Sweeney et al. 1991; Hoff et al. 1992; Nopoulos et al. 1994) some neuropsychological functions were found to improve in first-episode patients during the first stage of the illness when they were recovering from the acute episode.

The relatively high stability of cognitive deficits in patients with schizophrenia is also supported by cross-sectional studies (e.g., Hyde et al. 1994; Strandberg et al. 1994). However, these are not included in this review for methodological reasons.

The most stable deficits seem to include verbal skills (word meaning, word association, verbal fluency, etc.), memory (long- and short-term, spatial and visual), and preattentional information processing (backward-masking).

Less stability has been found in the following cognitive functions: complex attention and concentration, set-response-shift (WCST), and attentional span. Bilder et al. (1991) found a significant decline in attentional span over a 1-year period.

The present review of stability of cognitive dysfunctions gives no support for hypothesizing a degenerative process in schizophrenia once positive symptoms appear and the disorder manifests (Goldberg et al. 1993; Harvey et al. 1995; McGlashan and Johannessen 1996). Schizophrenia seems to be a static encephalopathy rather than a progressive dementia (Hyde et al. 1994).

There is ample empirical evidence that the performance of patients with schizophrenia is impaired on a wide range of cognitive and neuropsychological tests, representing a generalized cognitive decline. There is also evidence for specific cognitive and neuropsychological deficits that may occur over and above this general impairment involving memory, attention, and ability to switch attentional set (frontal lobe functions).

It is the hypothesis of this review that this general cognitive decline occurs gradually, often during adolescence. Specific impairments found in patients with schizophrenia are triggered to a greater extent by the onset of the illness. An alternative view is that individuals with schizophrenia simply fail to develop the same cognitive capacities as normal individuals, that is, they never reach a peak of performance from which to decline (Murray et al. 1992). Crow et al. (1989) have suggested that this entails a lack of left hemisphere growth.

The pattern of deficit in patients with schizophrenia shows a wide degree of individual variation. Although the present evidence does not allow the description of a more distinct association between clinical symptoms and neuropsychological deficits (Elliott and Sahakian 1995), there seems to be empirical evidence to assume that patients with the most negative symptoms show the clearest cognitive impairment. Some patients with schizophrenia, perhaps as many as 30 percent, do not manifest any deviance in cognitive or neuropsychological functioning.

The high stability of cognitive deficits found in these longitudinal studies probably masks the fact that a few functions are episode linked and thus fluctuate with the symptoms. Short-term memory may be such an episode indicator (see Rund et al. 1997). Most cognitive deficits can be characterized as intermediate factors, that is, they are more prominent in acute psychotic states but do not completely disappear during remission. A few cognitive deficits are stable over time and can be classified as trait-dependent components. However, none of them seem to indicate a decline over time beyond what can be expected from normal aging. Thus, as concluded above, there is no indication of a degenerative process in schizophrenia.

A kind of "moderating" factor that has to be taken into consideration in this connection is that in most longitudinal studies the baseline assessment is done shortly after remission or when patients are in partial remission from an acute episode of illness. Thus, if the followup testing is done in a state of relatively stable functioning, patients can have both state and trait-like abnormalities at baseline, but only trait-related deficits at followup.

Recovery of function from acute episodes of illness might show improved function, while a mild deteriorating condition might worsen function to a net "no change" effect. To the degree that learning effects might be assumed, the result would be an improvement in function, in effect masking deteriorative changes.

Another factor that contributes to the conclusion that the stability of cognitive functions is indicative is the limitation of group data that can conceal a mild deterioration over the course of the illness. It is plausible that a subset of perhaps 10 to 20 percent of cases do show a mild deterioration in the course of illness, but this subgroup is not identified in group analyses.

The findings outlined above, with respect to a degenerative process in most patients with schizophrenia, can be related to a neurodevelopmental arrest at the neurobiological level. There is some empirical evidence to support the hypothesis that connections between subcortical areas, including the limbic system and the frontal cortex, may be impaired in schizophrenia (Robbins 1990; Elliott and Sahakian 1995). This hypothesis is compatible with Weinberger's proposal of a developmental framework for such impairments. It has been found that anatomical and functional characteristics of prefrontal connectivity with limbic structures of the temporal lobe appear in adolescence and develop through early adulthood (Breslin and Weinberger 1990). The peak age of onset for schizophrenia is at this developmental stage. Saugstad (1989) has argued that schizophrenia is a disorder occurring in extremely late maturers. She claims that in individuals with an extremely late and prolonged pubertal period, a greater than optimal attenuation of synaptic density may have occurred.

A neurodevelopmental arrest can account for the generalized cognitive impairment in schizophrenia, which is also stable over time and can be classified as a trait component. This is primarily frontal lobe dysfunction. The symptom-linked cognitive deficits that accompany the onset of an acute psychotic episode are thought to be mediated by an additional abnormality in dopaminergic transmission (Meltzer 1991). The abnormalities in dopamine activity could be due to the effects of stress or could be secondary results of frontostriatal dysfunction (Elliott and Sahakian 1995).

What implications for treatment and rehabilitation can be drawn from these conclusions? The natural course of schizophrenia does not imply a decline in cognitive abilities. The observation of not only stability but sometimes even improvement in neuropsychological functions should be grounds for clinical optimism, provided relapses are prevented.

Whether or not cognitive deficits can be modified is still an open question. A few attempts to remediate specific cognitive functions have been successful to some extent: Examples are span of apprehension (Kern et al. 1995) and a decrease in the frequency of perseverative errors on the WCST (Bellack et al. 1990; Summerfelt et al. 1991; Green et al. 1992). It is less clear whether these gains can be maintained over time and generalized to other areas of functioning (Green et al. 1992).

References

The Adjutant General's Office, War Department. *Army Individual Test Battery: Manual of Directions and Scoring.* Washington, DC: The Office, 1944.

American Psychiatric Association. *DSM–II: Diagnostic and Statistical Manual of Mental Disorders.* 2nd ed. Washington, DC: The Association, 1968.

American Psychiatric Association. *DSM–III: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington, DC: The Association, 1980.

American Psychiatric Association. *DSM–IV: Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: The Association, 1994.

Asarnow, R.F.; Granholm, E.; and Sherman, T. Span of apprehension in schizophrenia. In: Steinhauer, S.R.; Gruzelier, J.H.; and Zubin, J., eds. *Handbook of Schizophrenia: Neuropsychology, Psychophysiology, and Information Processing.* Vol. 5. Amsterdam, The Netherlands: Elsevier Science Publishers, 1991. pp. 335–370.

Aylward, E.; Walker, E.; and Bettes, B. Intelligence in schizophrenia: Meta-analysis of the research. *Schizophrenia Bulletin,* 10(3):430–459, 1984.

Bellack, A.S.; Mueser, K.T.; Morrison, R.L.; Tierny, A.; and Podell, K. Remediation of cognitive deficits in schizophrenia. *American Journal of Psychiatry*, 147:1650–1655, 1990.

Benton, A.L.; Hamsher, K.; Varney, N.R.; and Spreen, O. *Contributions to Neuropsychological Assessment.* New York, NY: Oxford University Press, 1983.

Bilder, R.M.; Kipschultz-Broch, L.; Reiter, G.; Mayerhoff, D.; Loebel, A.; Degreef, G.; Ashtari, M.; and Lieberman, J.A. Neuropsychological studies of first episode schizophrenia. *Schizophrenia Research,* 4:381–397, 1991.

Breslin, N.A., and Weinberger, D.R. Schizophrenia and the normal functional development of the prefrontal cortex. *Developments in Psychopathology,* 2:409–424, 1990.

Chapman, L.J., and Chapman, J.P. *Disordered Thought in Schizophrenia.* New York, NY: Appleton-Century-Crofts, 1973.

Chapman, L.J., and Chapman, J.P. The measurement of differential deficit. *Journal of Psychiatric Research,* 14:303–311, 1978.

Chapman, L.J., and Chapman, J.P. Strategies for resolving the heterogeneity of schizophrenics and their relatives using cognitive measures. *Journal of Abnormal Psychology,* 98:357–366, 1989.

Crow, T.; Colter, N.; Frith, C.D.; Johnstone, E.C.; and Owens, D.G.C. Developmental arrest of cerebral asymmetries in early onset schizophrenia. *Psychiatry Research,* 29:247–253, 1989.

Elliott, R., and Sahakian, B.J. The neuropsychology of schizophrenia: Relations with clinical and neurobiological dimensions. *Psychological Medicine,* 25:581–594, 1995.

Flekkøy, K. Changes of associative performance in hospitalized schizophrenics: A 16-year follow-up. *Acta Psychiatrica Scandinavica,* 52:330–335, 1975.

Folstein, M.F.; Folstein, S.E.; and McHugh, P.R. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research,* 12:189–198, 1975.

Goldberg, T.E.; Hyde, T.M.; Kleinman, J.E.; and Weinberger, D.R. Course of schizophrenia: Neuropsychological evidence for a static encephalopathy. *Schizophrenia Bulletin,* 19(4):797–804, 1993.

Golden, C.J. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Chicago, IL: Stoelting Company, 1978.

Green, M.F.; Satz, P.; Ganzell, S.; and Vaclav, J.F. Wisconsin Card Sorting Test performance in schizophrenia: Remediation of a stubborn deficit. *American Journal of Psychiatry,* 149:62–67, 1992.

Harvey, P.D.; White, L.; Parrella, M.; Putnam, K.M.; Kincaid, M.M.; Powchik, P.; Mohs, R.C.; and Davidson, M. The longitudinal stability of cognitive impairment in schizophrenia. Mini-Mental State scores at one- and two-year follow-ups in geriatric in-patients. *British Journal of Psychiatry,* 166:630–633, 1995.

Heaton, R.K. *Wisconsin Card Sorting Test Manual.* Odessa, FL: Psychological Assessment Resources, 1981.

Hoff, A.L.; Riordan, H.; O'Donnell, D.; Stritzke, P.; Neale, C.; Boccio, A.; Anand, A.K.; and DeLisi, L.E. Anomalous lateral sulcus asymmetry and cognitive function in first-episode schizophrenia. *Schizophrenia Bulletin,* 18(2):257–272, 1992.

Hyde, T.M.; Nawroz, S.; Goldberg, T.E.; Bigelow, L.B.; Strong, D.; Ostrem, J.L.; Weinberger, D.R.; and Kleinman, J.E. Is there cognitive decline in schizophrenia? A cross-sectional study. *British Journal of Psychiatry,* 164:494–500, 1994.

Kern, R.S.; Green, M.F.; and Goldstein, M.J. Modification of performance on the Span of Apprehension, a putative marker of vulnerability to schizophrenia. *Journal of Abnormal Psychology,* 104:385–389, 1995.

Klonoff, H.; Fibiger, C.H.; and Hutton, G.H. Neuropsychological patterns in chronic schizophrenia. *Journal of Nervous and Mental Disease,* 150:291–300, 1970.

Kremen, W.S.; Seidman, L.J.; Pepple, J.R.; Lyons, M.J.; Tsuang, M.T.; and Faraone, S.V. Neuropsychological risk indicators for schizophrenia: A review of family studies. *Schizophrenia Bulletin,* 20(1):103–119, 1994.

McGlashan, T.H., and Johannessen, J.O. Early detection and intervention with schizophrenia: Rationale. *Schizophrenia Bulletin,* 22(2):201–222, 1996.

Meltzer, H.Y. The neurobiology of schizophrenia. *Current Opinion in Psychiatry,* 4:90–95, 1991.

Miller, M.B.; Chapman, J.P.; Chapman, L.J.; and Collins, J. Task difficulty and cognitive deficits in schizophrenia. *Journal of Abnormal Psychology,* 104:251–258, 1995.

Moran, L.J.; Gorham, D.R.; and Holtzman, W.H. Vocabulary knowledge and usage of schizophrenic subjects: A six-year follow-up. *Journal of Abnormal and Social Psychology,* 61:246–254, 1960.

Moran, L.J.; Moran, F.A.; and Blake, R.R. An investigation of the vocabulary performance of schizophrenics: II. Conceptual level of definitions. *Journal of Genetic Psychology,* 80:107–231, 1952.

Murray, R.M. Neurodevelopmental schizophrenia: The rediscovery of dementia praecox. *British Journal of Psychiatry,* 165(Suppl.):6–12, 1994.

Murray, R.M.; O'Callaghan, E.; Castle, D.J.; and Lewis, S.W. A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin,* 18(2):319–332, 1992.

Nopoulos, P.; Flashman, L.; Flaum, M.; Arndt, S.; and Andreasen, N. Stability of cognitive functioning early in the course of schizophrenia. *Schizophrenia Research,* 14:29–37, 1994.

Nuechterlein, K.H. Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *Journal of Abnormal Psychology,* 92:4–28, 1983.

Nuechterlein, K.H. Converging evidence for vigilance deficit as a vulnerability indicator for schizophrenic disorders. In: Alpert, M., ed. *Changes and Constancies.* New York, NY: Guilford Press, 1985. pp. 175–198.

Nuechterlein, K.H., and Dawson, M.E. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophrenia Bulletin,* 10(2):160–203, 1984.

Nuechterlein, K.H.; Dawson, M.E.; Gitlin, M.; Ventura, J.; Goldstein, M.J.; Snyder, K.S.; Yee, C.M.; and Mintz, J. Developmental processes in schizophrenic disorders: Longitudinal studies of vulnerability and stress. *Schizophrenia Bulletin,* 18(3):387–426, 1992.

Oltmanns, T.F. Selective attention in schizophrenic and manic psychoses: The effect of distraction on information processing. *Journal of Abnormal Psychology,* 87:212–225, 1978.

Oltmanns, T.F., and Neale, J.M. Schizophrenic performance when distractors are present. Attentional deficit or differential task difficulty? *Journal of Abnormal Psychology,* 84:205–209, 1975.

Oltmanns, T.F.; Ohayon, J.; and Neale, J.M. The effect of anti-psychotic medication and diagnostic criteria on distractibility in schizophrenia. *Journal of Psychiatric Research,* 14(1–4):81–91, 1978.

Rey, A. *L'Examen Clinique en Psychologie.* Paris, France: Presses Universitaires de France, 1964.

Robbins, T.W. The case of frontostriatal dysfunction in schizophrenia. *Schizophrenia Bulletin,* 16(3):391–402, 1990.

Rosvold, H.E.; Mirsky, A.F.; Sarason, I.; Bransome, E.D., Jr.; and Beck, L.H. A continuous performance test of brain damage. *Journal of Consulting Psychology,* 20:343–350, 1956.

Rund, B.R. The effect of distraction on focal attention in paranoid and non-paranoid schizophrenic patients compared to normals and non-psychotic psychiatric patients. *Journal of Psychiatric Research,* 17:241–250, 1983.

Rund, B.R. Distractability and recall capability in schizophrenics. A 4 year longitudinal study of stability in cognitive performance. *Schizophrenia Research,* 2(3):265–275, 1989.

Rund, B.R. Backward-masking performance in chronic and nonchronic schizophrenics, affectively disturbed patients, and normal control subjects. *Journal of Abnormal Psychology,* 102(1):74–81, 1993.

Rund, B.R., and Landrø, N.I. Information processing: A new model for understanding cognitive disturbances in psychiatric patients. *Acta Psychiatrica Scandinavica,* 81:305–316, 1990.

Rund, B.R., and Landrø, N.I. Memory in schizophrenia and affective disorders. *Scandinavian Journal of Psychology,* 36:37–46, 1995.

Rund, B.R.; Landrø, N.I.; and Ørbeck, A.L. Stability in backward masking performance in schizophrenics, affectively disturbed patients, and normal subjects. *Journal of Nervous and Mental Disease,* 181:233–237, 1993.

Rund, B.R.; Landrø, N.I.; and Ørbeck, A.L. Stability in cognitive dysfunctions in schizophrenic patients. *Psychiatry Research,* 69(2–3):131–141, 1997.

Rund, B.R.; Øie, M.; and Sundet, K. Backward-masking deficit in adolescents with schizophrenic disorders or attention deficit hyperactivity disorder. *American Journal of Psychiatry,* 153(9):1154–1158, 1996.

Saccuzzo, D., and Braff, D.L. Information-processing abnormalities: Trait- and state-dependent components. *Schizophrenia Bulletin,* 12(3):447–459, 1986.

Saugstad, L. Social class, marriage, and fertility in schizophrenia. *Schizophrenia Bulletin,* 15(1):9–43, 1989.

Saykin, A.J.; Gur, R.C.; Gur, R.E.; Mozley, P.D.; Mozley, L.H.; Resnick, S.M.; Kester, D.B.; and Stafiniak, P. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Archives of General Psychiatry,* 48:618–624, 1991.

Smith, A. Mental deterioration in chronic schizophrenia. *Journal of Nervous and Mental Disease,* 139:479–487, 1964.

Spohn, H.E., and Coyne, L. The effect of attention/information processing impairment of tardive dyskinesia and neuroleptics in chronic schizophrenics. *Brain and Cognition,* 23:28–39, 1993.

Spohn, H.E., and Strauss, M.E. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *Journal of Abnormal Psychology,* 98:367–380, 1989.

Strandburg, R.J.; Marsh, J.T.; Brown, W.S.; Asarnow, R.F.; and Guthrie, D. Information-processing deficits across childhood- and adult-onset schizophrenia. *Schizophrenia Bulletin,* 20(4):685–695, 1994.

Strauss, M.E. The differential and experimental paradigms in the study of cognition in schizophrenia. *Journal of Psychiatric Research,* 14:316–320, 1978.

Summerfelt, A.T.; Alphs, L.S.; Funderburk, F.B.; and Strauss, M.E. Impaired Wisconsin Card Sort performance may reflect motivational deficits. *Archives of General Psychiatry,* 48(3):282–283, 1991.

Sweeney, J.A.; Haas, G.L.; Keilp, J.G.; and Long, M. Evaluation of the stability of neuropsychological functioning after acute episodes of schizophrenia: One-year followup study. *Psychiatry Research,* 38:63–76, 1991.

Waddington, J.L., and Youssef, H.A. An unusual cluster of tardive dyskinesia in schizophrenia: Association with cognitive dysfunction and negative symptoms. *American Journal of Psychiatry,* 143:1162–1165, 1986.

Wechsler, D. *The Measurement of Adult Intelligence.* 4th ed. Baltimore, MD: Williams & Wilkins Company, 1958.

Wechsler, D. *Wechsler Adult Intelligence Scale–Revised Manual.* New York, NY: The Psychological Corporation, 1981.

Acknowledgments

The author thanks four anonymous *Schizophrenia Bulletin* reviewers for their valuable critiques. Some of their comments have been included in the final version of this article.

The Author

Bjørn Rishovd Rund, Ph.D., M.H.A., is Professor of Psychology at the Institute of Psychology, University of Oslo, Oslo, Norway.

Recent Books

Blum, K., and Noble, E.P., eds. *Handbook of Psychiatric Genetics.* Boca Raton, FL: CRC Press, 1997.

Breier, A., ed. *The New Pharmacotherapy of Schizophrenia.* Washington, DC: American Psychiatric Press, 1996. 224 pp.

Halligan, P.W., and Marshall, J.C., eds. *Method in Madness.* East Sussex, United Kingdom: Psychology Press, 1996. 310 pp.

Hedaya, R.J. *Understanding Biological Psychiatry.* New York, NY: W.W. Norton & Company, 1996. 320 pp.

Mednick, S.A., and Hollister, J.M., eds. *Neural Development and Schizophrenia: Theory and Research.* New York, NY: Plenum Press, 1995. 262 pp.

Minkoff, K., and Pollack, D., eds. *Managed Mental Health Care in the Public Sector: A Survival Manual.* Amsterdam, The Netherlands: Harwood Academic Publishers, 1997. 336 pp.

Oliver, J.; Huxley, P.; Bridges, K.; and Mohamad, H., eds. *Quality of Life and Mental Health Services.* New York, NY: Routledge, 1996. 310 pp.

Sims, A. *Symptoms of the Mind.* Philadelphia, PA: W.B. Saunders & Company, 1995. 430 pp.

Smulevich, A.B. *Slowly Progressive Schizophrenia and the Boundary Conditions.* Moscow, Russia: Moscow University Press, 1996. 208 pp.

Tansella, M., ed. *Making Rational Mental Health Services.* Rome, Italy: Il Pensiero Scientifico Editore, 1997. 245 pp.

Wasow, M. *The Skipping Stone: Ripple Effects of Mental Illness on the Family.* Palo Alto, CA: Science and Behavior Books, 1995. 232 pp.