

Stability and Course of Neuropsychological Deficits in Schizophrenia

Robert K. Heaton, PhD; Julie Akiko Gladsjo, PhD; Barton W. Palmer, PhD; Julia Kuck, PhD; Thomas D. Marcotte, PhD; Dilip V. Jeste, MD

Background: Neuropsychological deficits in schizophrenia appear to predate clinical symptoms of the disease and become more pronounced at illness onset, but controversy exists about whether and when further neuropsychological progression may occur.

Objective: To identify and characterize any subset of patients who evidenced progressive neuropsychological impairment, we compared the longitudinal stability of neuropsychological functioning in schizophrenic outpatients and normal comparison subjects.

Methods: One hundred forty-two schizophrenic outpatients and 206 normal comparison subjects were given annually scheduled comprehensive neuropsychological evaluations during an average of 3 years (range, 6 months to 10 years). Clinically and demographically defined subgroups were compared, and test-retest norms were used to identify individual patients who showed unusual worsening over time.

Results: The schizophrenic group was neuropsychologically more impaired than the normal comparison subjects but showed comparable test-retest reliability and comparable neuropsychological stability over both short (mean, 1.6 years) and long (mean, 5 years) follow-up periods. No significant differences in neuropsychological change were found between schizophrenic subgroups defined by current age, age at onset of illness, baseline level of neuropsychological impairment, improvement or worsening of clinical symptoms, and occurrence of incident tardive dyskinesia. Norms for change also failed to show neuropsychological progression in individuals with schizophrenia.

Conclusions: Neuropsychological impairment in ambulatory persons with schizophrenia appears to remain stable, regardless of baseline characteristics and changes in clinical state. Our results may not be generalizable to the minority of institutionalized poor-outcome patients.

Arch Gen Psychiatry. 2001;58:24-32

THERE IS a high prevalence of neuropsychological impairment in persons with schizophrenia, ranging from mild deficits to frank dementia.¹⁻⁵ Consistent with a neurodevelopmental view, some such deficits appear to predate clinical symptoms and exacerbate with typical illness onset during late adolescence or early adulthood.⁶⁻⁸

There remains considerable controversy about whether there is further progression of neuropsychological deficits after the onset of the illness.⁹ With a few notable exceptions,¹⁰⁻¹² cross-sectional studies generally have not found evidence of increased neuropsychological deficits in association with duration of illness or (relative to age-matched controls) in older than in younger patients with schizophrenia.^{2,13-17} Definitive answers to questions regarding possible pro-

gression of neuropsychological deficits in schizophrenia must come from longitudinal studies. The available studies, however, provide conflicting results and have a variety of methodologic limitations (eg, small or nonrepresentative samples, no controls, brief follow-ups, and/or limited neuropsychological testing).^{2,18-36}

Both neurodevelopmental and neurodegenerative views of neuropsychological deficits in schizophrenia seemingly remain viable.¹⁰ While progression of deficit after illness onset clearly is not universal, or even typical of the disorder, a subset of persons with schizophrenia may evidence cognitive deterioration over time. The size and nature of that subgroup are unclear, but the existing studies suggest that potentially relevant issues include subject age, duration of illness, level of initial neuropsychological impairment, improvement or deteriora-

From the Department of Psychiatry, University of California, San Diego (Drs Heaton, Gladsjo, Palmer, Kuck, Marcotte, and Jeste, and the Veterans Affairs San Diego Healthcare System, San Diego, Calif (Dr Jeste).

SUBJECTS AND METHODS

SUBJECTS

Subjects included 142 outpatients with schizophrenia and 206 NCs, who had completed at least 2 comprehensive neuropsychological evaluations. Each patient and NC was a participant in 1 of 3 university-based clinical research centers, and most have contributed baseline neuropsychological data to previously published reports.³⁷⁻⁴⁰ Diagnostic procedures for subjects in both groups included the Structured Clinical Interview for the *DSM-III-R* or *DSM-IV*.^{41,42} Subjects were also screened by a physician using a physical examination and a structured medical history questionnaire; those with current or past medical conditions likely to affect central nervous system functioning (such as significant head injuries, seizure disorder, or acute medical conditions), as well as those meeting *DSM-III-R*⁴³ or *DSM-IV*⁴⁴ criteria for current alcohol or substance abuse or dependence, were excluded. All subjects provided written informed consent before participation in the research.

NEUROPSYCHOLOGICAL EXAMINATIONS

The patients and NCs were assessed with an annually scheduled comprehensive neuropsychological test battery (in actuality, the mean test-retest interval between the first 2 of these evaluations was 16.6 months [SD, 8.6 months; range, 6-81 months]). Eighty-nine schizophrenic patients and 119 NCs completed at least 1 additional neuropsychological follow-up evaluation. The total number of evaluations ranged from 2 to 10 (mean, 3.38; SD, 1.57; median, 3.00). The interval between the first and last neuropsychological evaluations ranged from 6 to 125 months and was not significantly different for the schizophrenic patients vs NCs (mean and SD, 37.0 and 22.3 months vs 37.1 and 25.7 months, respectively; $t_{346}=0.05$, $P=.96$).

Except where otherwise indicated, each of the neuropsychological measures was part of the expanded Halstead-Reitan battery, and details of administration and scoring were as described by Reitan and Wolfson⁴⁵ and Heaton and colleagues.^{46,47} The individual measures were grouped into 7 ability areas based on the neuropsychological constructs that they are putatively designed to measure. The verbal ability area included the Aphasia Screening Test, Boston Naming Test, and the Controlled Oral Word Association Test.^{48,49} Scores on the latter test were unavailable for a few subjects, so the Thurstone (written) Word Fluency task was substituted for 2 subjects at the baseline evaluation and

5 subjects at the first follow-up. The psychomotor ability area included the block design, object assembly, and digit symbol subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R)⁵⁰ and the Trail Making Test Part A (total time), Tactual Performance Test (total time), and Digit Vigilance Test (time). The abstraction and cognitive flexibility ability area included the Category Test (errors), Trail Making Test Part B (total time), and Wisconsin Card Sorting Test⁵¹ (perseverative responses). The attention ability area included the digit span and arithmetic subtests from the WAIS-R,⁵⁰ the Rhythm Test, Speech Sounds Perception Test, and Digit Vigilance (errors). The learning and delayed recall ability areas included those scores from the Figure and Story Memory Tests, and the California Verbal Learning Test.⁵² The motor skills ability area included the right- and left-hand scores on Finger Tapping, Grooved Pegboard, and Hand Dynamometer.

We also had data from baseline and at least 1 retest evaluation with an even more comprehensive neuropsychological evaluation on a subsample of patients and NCs, permitting calculation of the WAIS-R Verbal, Performance, and Full-Scale IQs⁵⁰ for 81 patients and 86 NCs, and the Halstead-Reitan battery Average Impairment Rating⁵³ for 74 patients and 82 NCs.

Neuropsychological test raw scores were converted to standardized scaled scores (mean and SD, 10 and 3, respectively, in normal subjects) and age-, education-, and sex-corrected T-scores (mean and SD, 50 and 10, respectively, in normal subjects), by means of previously published normative data.^{46-48,51,54} We then calculated the mean scaled scores and T-scores within each ability area, and a composite global scaled score and T-score.

PSYCHIATRIC AND MOTOR SYMPTOM RATINGS

Longitudinal ratings of psychiatric symptoms were also obtained for a subset ($n=116$) of the schizophrenic patients, as well as a smaller subset of NCs ($n=86$ to 88). Psychiatric symptom rating scales included the Brief Psychiatric Rating Scale⁵⁵ and the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively).⁵⁶ Tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale.⁵⁷

STATISTICAL METHODS AND ANALYSES

The test-retest reliability of neuropsychological measures and symptom rating scales was assessed in terms of

Continued on next page

tion in clinical status, and emergence of neuroleptic-induced dyskinesia.^{2,29-31}

The current study addressed these issues by longitudinally observing sizable samples of ambulatory schizophrenic patients and normal comparison subjects (NCs) with a comprehensive battery of neuropsychological tests. These groups were compared with respect to test-retest correlations and neuropsychological stability over shorter vs longer follow-up periods. Also compared were schizophrenic subgroups defined on the basis of demographic and clinical variables, as well as initial level of neuropsychological functioning. Finally, data from NCs were

used to define normal test-retest variability; these definitions were then applied to the results of the schizophrenic subjects, in an attempt to identify and characterize any subgroup of individuals who demonstrated unusual decreases in neuropsychological functioning over time.

RESULTS

BASELINE CHARACTERISTICS

As shown in **Table 1**, there were small but statistically significant group differences in age, education, and test-

McGraw and Wong's⁵⁸ intraclass correlation coefficients for degree of consistency between measurements at the baseline and 1-year follow-up evaluations. The magnitudes of the intraclass correlation coefficients for the neuropsychological and symptom rating scale scores of patients and NCs were compared by means of Fisher *r*-to-*z* transformations for intraclass correlation coefficients.⁵⁸ The neuropsychological scaled scores, rather than T-scores, were used for these analyses, since the latter would underestimate the stability of neuropsychological performance by removing variance related to the stable traits of education and sex.

To examine the effects of length of follow-up on neuropsychological stability, patients and NCs were divided into diagnosis-by-length of follow-up groups, wherein "short" follow-up was defined as less than 36 months and "long" follow-up was defined as 36 months or longer. This yielded 121 NCs and 75 schizophrenic patients with short follow-up (mean, 19.5 months; SD, 6.8 months) and 85 NCs and 67 schizophrenic patients with long follow-up (mean, 59.7 months; SD, 19.6 months).

In addition to the primary subject groupings described above, we were interested in examining the possible influence of substantial differences in current age, age at onset of illness, duration of illness, and symptom changes on the stability of neuropsychological performance among the schizophrenic patients. Hence, we conducted a series of analyses in which we dichotomized the schizophrenic patients in terms of these characteristics. The definition of the symptom change groups and the resulting samples are described later. The other groupings included 22 elderly patients (age at study entry, ≥ 65 years; mean, 69.2 years; SD, 3.3 years) vs 120 younger patients (age at study entry, < 65 years; mean, 43.7 years; SD, 13.7 years); 24 patients with late-onset schizophrenia (aged ≥ 45 years at onset of prodromal symptoms; mean, 55.0 years; SD, 5.6 years) vs 118 with earlier onset (onset at age < 45 years; mean, 22.7 years; SD, 7.3 years); and 30 patients with a duration of illness less than 5 years (mean, 2.0 years; SD, 1.4 years) vs 105 subjects with a duration of illness of 5 years or more (mean, 23.6 years; SD, 12.5 years). We also dichotomized patients in terms of sex and initial level of neuropsychological functioning (low [global neuropsychological T-score, ≤ 39] vs high [global neuropsychological T-score, > 45]) and anticholinergic use (receiving vs not receiving anticholinergic medication).

Repeated-measures analysis of variance (ANOVA) was used to examine effects of diagnosis (schizophrenic patients vs NCs) and length of follow-up (as noted above,

short vs long) on changes in neuropsychological performance. These analyses were conducted on T-scores (to correct for changes attributable to the effects of normal aging during long-term follow-up) for the entire neuropsychological battery (global neuropsychological T-score) as well as for each of the specific neuropsychological ability areas. We also used repeated-measures ANOVA to examine the various pairs of schizophrenic subgroups on changes in global neuropsychological performance and the 7 ability domains.

To assess the relationship between clinical change and neuropsychological functioning, patients were categorized into 3 groups based on change in clinical symptom scores from baseline to follow-up. Patients whose clinical symptom score (either SAPS or SANS total score) fell in the lower 25% of the distribution were considered to have a "low" level of symptoms, those in the middle 50% were labeled "middle," and those in the upper 25% of the distribution were categorized as "high." To meet criteria for a clinically significant change in symptoms, a subject had to move at least 1 category from baseline to follow-up, and by at least 3 points. Separate analyses were conducted for the SAPS- and SANS-defined change groups.

We also examined significant decreases in global neuropsychological T-scores of individual subjects, by means of the reliable change index method with adjustments for practice effect.^{59,60} This approach involves constructing prediction intervals around each subject's expected follow-up score. The predicted follow-up score is the subject's baseline score, adjusted for practice effects among cognitively stable individuals (as determined from the mean change observed among the NCs). The boundary values of the prediction interval around the predicted follow-up score are determined by the normal variability of baseline to follow-up changes (SE of the difference) determined from the NC group. Specifically, 90% prediction intervals were built around these predicted follow-up scores by multiplying the SD of the difference among NCs by 1.64. Subjects whose observed follow-up scores were below the lower limits of the 90% prediction interval (ie, the bottom 5% of normal controls) were considered to have shown significant declines in neuropsychological functioning. These procedures were conducted twice: once to evaluate changes from baseline to first retest among all patients and NCs, and then again in terms of changes from the first to last neuropsychological assessment among subjects with long follow-ups.

Two-tailed tests were used for all analyses. To help avoid type I errors associated with multiple comparisons, significance was defined as $P < .01$.

retest interval. There were no significant differences in sex or ethnicity. As expected, the patients had substantially greater global neuropsychological impairment and more severe clinical symptoms than the NCs.

There were some differences between subjects with and without WAIS-R IQ scores and Average Impairment Rating scores, which primarily reflected different demographic recruiting emphases and slight differences in neuropsychological protocols among the 3 research centers from which the present sample was drawn. Schizophrenic patients who had WAIS-R IQ scores were different from those without only in age

(mean, 41.4 years [SD, 16.6 years] vs 55.9 years [SD, 9.5 years], respectively; $t_{131,65} = 6.55$; $P < .001$). Relative to NCs without WAIS-R IQ scores, those with WAIS-R IQ scores were younger (mean age, 45.4 years [SD, 16.8 years] vs 56.2 years [SD, 21.1 years], respectively; $t_{201,65} = 4.09$; $P < .001$); completed slightly more education (mean education, 14.8 years [SD, 2.4 years] vs 13.7 years [SD, 2.9 years], respectively; $t_{200,73} = 3.12$; $P = .002$); had higher baseline neuropsychological performance (mean global neuropsychological T-score, 50.8 [SD, 4.0] vs 48.6 [SD, 4.9], respectively; $t_{204} = 3.46$, $P = .001$); and were more likely to be male

Table 1. Baseline Characteristics of Normal Comparison Subjects and Patients With Schizophrenia*

	Normal Comparison Subjects (n = 206)	Patients With Schizophrenia (n = 142)	t or χ^2	df	P
Age, y	51.7 (20.1)	47.6 (15.7)	2.12	340.63	.04
Education, y	14.2 (2.8)	12.8 (2.3)	4.85	332.70	<.001
Sex, % M	64.1	69.7	1.20	1	.23
Ethnicity, % white	81.6	79.6	0.21	1	.65
Retest interval, mo	15.6 (5.3)	18.1 (11.7)	2.35	181.10	.02
Total No. of neuropsychological evaluations	3.4 (1.7)	3.3 (1.4)	1.04	338.09	.30
Global neuropsychological T-score	49.5 (4.7)	41.9 (6.5)	12.00	239.57	<.001
BPRS	22.2 (3.7)	33.8 (10.2)	12.13	180.75	<.001
SAPS	1.0 (1.4)	5.8 (3.8)	13.45	181.56	<.001
SANS	1.3 (1.7)	8.6 (5.1)	15.37	171.78	<.001
Age at onset of schizophrenia, y	NA	28.2 (14.0)	NA	NA	NA
Duration of illness	NA	18.8 (14.3)	NA	NA	NA
Paranoid subtype, %	NA	45.8	NA	NA	NA
Median CPZE, mg	NA	313 (n = 101)	NA	NA	NA
Median BZE, mg	NA	4 (n = 49)	NA	NA	NA

*Values represent means (with SD) or proportions for all variables other than medication dosages; these are presented as medians for the subgroups taking the respective types of medication. Significance of differences was assessed with independent t tests for variables involving means and with Pearson χ^2 for those involving proportions. The mean daily dose of antipsychotic medication was 993.1 (SD, 1742.3; range, 29.0-12 250.0) mg CPZE. The mean daily anticholinergic dose was 9.4 (SD, 28.1; range, 0.5-200.0) mg BZE. Twenty-five patients were taking an atypical antipsychotic medication at some point in their participation in this longitudinal study (11 risperidone, 9 clozapine, 2 olanzapine, and 3 ramoxipride). Repeated-measures analysis of variance showed no significant differences in the stability of neuropsychological performance between these patients and the other patients. BPRS indicates Brief Psychiatric Rating Scale; SAPS and SANS, Scales for the Assessment of Positive and Negative Symptoms, respectively; CPZE, daily chlorpromazine equivalent⁶¹; BZE, daily benztropine equivalent⁶²; and NA, not applicable.

(76.7% vs 55.0%; $\chi^2_{1,N=206}=10.29$; $P=.002$) and white (94.2% vs 72.5%; $\chi^2_{1,N=206}=15.66$; $P<.001$). There were no significant differences between the 2 subgroups of NCs in the interval between the baseline to first-retest neuropsychological evaluation. More important, the same patterns of neuropsychological test-retest change were present for schizophrenic patients and NCs with vs without the Halstead-Reitan battery Average Impairment Rating score.

One concern about participant attrition in a longitudinal study is that nonrandom factors may influence who remains in the study, resulting in nonrepresentative (biased) samples. We used Mann-Whitney tests to compare the baseline characteristics of subjects who completed at least 1 follow-up evaluation with patients who dropped out after completing the baseline assessment. Demographic characteristics (except for age), baseline clinical symptoms and cognitive performance (including IQ), and global neuropsychological functioning did not differ between the groups. Patients who dropped out were, however, older than those with follow-up visits (mean ages, 57 and 48 years, respectively; Mann-Whitney $P<.001$).

TEST-RETEST RELIABILITY

The test-retest reliability coefficients (intraclass correlation coefficients) of neuropsychological and psychiatric rating scale scores for NCs and patients were highly significant within each group (**Table 2**). With the exception of Performance IQ (where the test-retest reliability was higher in the schizophrenic group), the magnitudes of the test-retest correlations for the patients were not significantly different from those observed among the NCs.

MAGNITUDE OF PRACTICE EFFECTS: BASELINE TO FIRST AND LAST REPEATED ASSESSMENT

There were no significant differences between schizophrenic patients and NCs with respect to practice effects (T-score at first follow-up visit minus T-score at baseline visit) for the WAIS-R IQs, neuropsychological summary scores, or neuropsychological ability area scores (**Table 3**).

The **Figure** depicts the changes in global neuropsychological T-scores from baseline to last follow-up, for subgroups with short vs long follow-up periods. Regardless of length of follow-up, the test-retest changes for schizophrenic patients and NCs were essentially parallel lines. Repeated-measures ANOVAs confirmed this finding, not only for the global neuropsychological score but also for all neuropsychological ability areas. There were highly significant group effects ($P<.001$), and sometimes significant time effects (reflecting modest improvement because of practice), but no significant diagnostic group \times time interactions.

ADDITIONAL SCHIZOPHRENIC SUBGROUP COMPARISONS

To further examine the change in cognitive functioning over time, we compared longitudinal global neuropsychological performance changes in subgroups of schizophrenic subjects defined on the bases of demographic and clinical variables (as listed and defined above). These ANOVAs disclosed no significant group effects. As shown in **Table 4**, with 1 exception there also were no significant group \times time interactions, indicating that the characteristics defining the various groups were not related

Table 2. Test-Retest Reliability of Neuropsychological and Psychiatric Symptom Rating Scale Scores for Normal Comparison Subjects vs Patients With Schizophrenia*

	Normal Comparison Subjects, ICC (C,1)	Patients With Schizophrenia, ICC (C,1)	z	P
Summary scores				
Global neuropsychological scaled score	0.94 (n = 206)	0.93 (n = 141)	0.52	.61
Average impairment rating raw score	0.88 (n = 82)	0.86 (n = 74)	0.42	.67
WAIS-R				
Verbal IQ	0.86 (n = 86)	0.91 (n = 81)	1.31	.19
Performance IQ	0.72 (n = 86)	0.88 (n = 81)	2.97	.003
Full-Scale IQ	0.85 (n = 86)	0.92 (n = 81)	2.19	.03
Specific neuropsychological ability area scaled scores				
Verbal	0.82 (n = 183)	0.86 (n = 139)	1.33	.18
Psychomotor	0.92 (n = 167)	0.88 (n = 139)	2.14	.03
Abstraction/cognitive-flexibility	0.86 (n = 201)	0.81 (n = 135)	1.22	.22
Attention	0.80 (n = 184)	0.81 (n = 133)	0.41	.68
Learning	0.83 (n = 204)	0.81 (n = 140)	0.64	.52
Delayed recall	0.63 (n = 206)	0.72 (n = 140)	1.45	.15
Motor	0.80 (n = 199)	0.85 (n = 133)	1.57	.12
Psychiatric symptom scales				
BPRS	0.48 (n = 88)	0.45 (n = 116)	0.27	.79
SAPS	0.42 (n = 86)	0.57 (n = 116)	1.37	.17
SANS	0.52 (n = 87)	0.56 (n = 116)	0.41	.68

*Test-retest reliability values are intraclass correlation coefficients for degree of consistency between measurements (ICC [C,1]).⁵⁸ The z and P values reflect the comparison of ICC magnitude among normal comparison subjects vs patients with schizophrenia. WAIS-R indicates Wechsler Adult Intelligence Scale-Revised; BPRS, Brief Psychiatric Rating Scale; and SAPS and SANS, Scales for the Assessment of Positive and Negative Symptoms, respectively.

Table 3. Change in Neuropsychological T-Scores (First Retest Minus Baseline T-Score) for Normal Comparison Subjects vs Patients With Schizophrenia*

	Normal Comparison Subjects	Patients With Schizophrenia	t	df	P
Summary score changes					
Global neuropsychological T-score	1.3 (2.4) (n = 206)	1.6 (3.2) (n = 142)	1.30	251.84	.20
Average impairment rating T-score	1.6 (9.2) (n = 82)	3.9 (7.9) (n = 74)	0.94	154.00	.35
WAIS-R					
Verbal IQ T-score	0.9 (4.8) (n = 86)	1.3 (5.6) (n = 81)	0.44	165.00	.66
Performance IQ T-score	3.3 (6.9) (n = 86)	1.9 (5.7) (n = 81)	1.46	165.00	.15
Full-Scale IQ T-score	2.2 (5.1) (n = 86)	1.6 (4.8) (n = 81)	0.73	165.00	.47
Neuropsychological ability area T-score changes					
Verbal	1.5 (5.6) (n = 183)	0.9 (5.4) (n = 140)	0.99	321.00	.32
Psychomotor	1.2 (4.3) (n = 167)	1.6 (4.7) (n = 140)	0.87	305.00	.38
Abstraction/cognitive-flexibility	3.0 (7.3) (n = 201)	4.5 (7.3) (n = 136)	1.87	335.00	.06
Attention	0.7 (4.6) (n = 184)	1.1 (5.0) (n = 134)	0.69	316.00	.49
Learning	1.4 (5.9) (n = 205)	2.8 (6.9) (n = 141)	1.94	269.47	.05
Delayed recall	1.5 (6.7) (n = 206)	1.7 (7.4) (n = 140)	0.23	344.00	.82
Motor	1.0 (5.0) (n = 199)	0.6 (5.7) (n = 135)	0.78	332.00	.44

*Values reflect the mean (and SD) of the difference scores between each subject's score at the first follow-up assessment, and that at baseline. Therefore, positive values reflect improved test performance. WAIS-R indicates Wechsler Adult Intelligence Scale-Revised.

to changes in neuropsychological performance over time. The 1 significant interaction reflected the fact that the schizophrenic subgroup with short duration of illness (mean, 2 years at baseline) had a slightly larger neuropsychological improvement than the subgroup with long duration (mean, 24 years at baseline). The smaller "improvement" (practice effect) shown by the long-duration group was the same as that of the NCs (both means, 1.3 T-score points).

Using the SAPS to categorize clinical change status resulted in 11 patients being classified as worse, 27 as better, and 78 as stable. With the use of repeated-measures ANOVAs, no significant group × time interactions were

found for the neuropsychological global score or for scores on any of the 7 ability areas (Table 4). Categorization of schizophrenic patients on the basis of SANS scores yielded 19 subjects identified as significantly worse, 80 subjects as stable, and 17 subjects as better. The results of repeated-measures ANOVAs for the neuropsychological global score were similar to those with the SAPS change groups, ie, no significant group × time interactions.

We also compared patients with initial high vs low global neuropsychological performance (global neuropsychological T-score ≥45 vs ≤39, respectively), and those with vs without tardive dyskinesia as defined by the Schooler and Kane criteria⁶³ and those used by Wad-

dington.⁶⁴ Again, the groups did not differ significantly with respect to the change in the global neuropsychological score or the 7 neuropsychological ability domain scores (Table 4).

SUBJECTS WITH UNUSUAL DECREASES IN GLOBAL NEUROPSYCHOLOGICAL T-SCORES

The modified Reliable Change Index method, described above, was used to identify and compare the percentages of individual NCs and schizophrenic patients who evidenced unusual neuropsychological worsening from baseline to first retest. With the use of the 90% prediction interval, 10 NCs were so identified (about 5% of the total sample); the latter proportion did not differ significantly from the 5.6% of patients with schizophrenia who evidenced unusual worsening ($\chi^2_{1,N=348}=0.10$; $P=.75$).

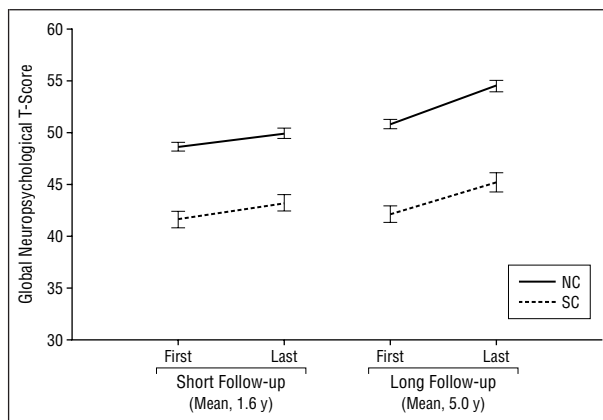
The above procedures were also used to evaluate baseline to final follow-up scores of the 85 individual NCs and 67 patients with schizophrenia with follow-up intervals of 36 months or longer (mean, 59.7 months; SD, 68 months). Again, the proportion of patients below the 90% prediction interval was not significantly different from that of the NCs (7.5% vs 4.7%, respectively; $\chi^2_{1,N=152}=0.51$; $P=.48$).

COMMENT

To our knowledge, this is the first longitudinal study to compare comprehensive neuropsychological test results of large samples of NCs and patients with schizophrenia during a multiyear follow-up period. After comparing the two groups with respect to test-retest reliabilities, we attempted to determine whether the schizophrenic patients, or even a subset of that group, evidenced progressive neuropsychological decline.

Consistent with previous reports,^{22,65} presence of psychosis did not appear to affect the reliability of neuropsychological test performance. Across the entire neuropsychological battery, reliability estimates were quite high, and were at least as high for the schizophrenic group as for the NCs. This was true even though clinical symptoms were relatively variable over time (Table 2), and even though the test-retest intervals were longer than those in most previous reliability studies with NCs.^{50,66} These stability results support the view that neuropsychological deficits in schizophrenia are stable traitlike dimensions of the disorder, rather than reflecting state-related features.

Acceptable test-retest reliability does not rule out the possibility that neuropsychological deficits may be progressive in at least some patients with schizophrenia. Our results, however, provided no evidence of a deteriorating neuropsychological course in the total schizophrenic group, or in subgroups defined on the basis of age, sex, early vs late or recent vs remote onset of illness, baseline level of neuropsychological impairment, or length of follow-up. In each analysis, the schizophrenic groups showed slight improvements that were comparable with those evidenced by the NCs, and these likely represented practice effects. Even rather extreme



Changes in overall neuropsychological performance by diagnostic group and duration of follow-up. Short follow-up indicates less than 36 months; long follow-up, 36 months or longer; NC, normal comparison group; and SC, schizophrenic patient group. In the short-follow-up groups, sample sizes were 121 for NC and 75 for SC; in the long-follow-up groups, they were 85 for NC and 67 for SC. Vertical lines depict SEMs.

clinical changes did not appear to influence the subjects' neuropsychological performance.

Longitudinal research in institutional settings has shown evidence of neuropsychological decline in some low-functioning, chronically hospitalized patients with schizophrenia.²⁹⁻³¹ Even in those studies, however, such worsening was observed only in small subsets of the groups being followed up. In the absence of longitudinal data from a neurologically stable comparison group, it is unclear whether these observed neuropsychological changes represent true neuropsychological decline, as in a neurodegenerative disorder, or whether they represent the tail of the distribution of test-retest fluctuations in neurologically stable (albeit very low-functioning) persons. It might be argued that the types of change observed in these patients (eg, change in the rated level of dementia) are too gross to be considered "normal fluctuation" and are pathognomonic of a progressive disorder. During approximately a 4-year follow-up interval, however, Ivnik and colleagues⁶⁷ found remarkable test-retest differences in neuropsychological performances of some elderly subjects who did not have any neuromedical disorder likely to affect cognition, eg, on neuropsychological factor scores with IQ-type scaling, test-retest differences of 20 or more points were not unusual. Therefore, the outer range of possible fluctuation in performance of neurologically stable persons cannot be assumed and should be established by means of an appropriate comparison group.

The mean global neuropsychological score for our patient group was 1.62 SDs below that of NCs (Table 1), consistent with the range of effect sizes in a recent meta-analytic review of studies comparing controls and schizophrenic patients.⁵ Although severely demented patients were not represented in our sample, our "low-functioning" subgroup (n=45; Table 4) was very significantly impaired (ie, more than 3 SDs below NCs on the global neuropsychological T-score).

Limitations of this study include absence of chronically institutionalized patients, and therefore its results may not be generalizable to that minority of patients (but

Table 4. Repeated-Measures Analyses of Variance of Schizophrenia Subgroups on Global Neuropsychological Functioning

Groups	Mean (SD)		df	Group × Time F
	Baseline Global Neuropsychological T-Score	Follow-up Global Neuropsychological T-Score		
Age, y				
<65 (n = 120)	41.9 (6.6)	43.8 (7.1)	1,140	3.28
≥65 (n = 22)	41.5 (5.9)	42.1 (5.5)		
Sex				
Male (n = 99)	42.2 (6.4)	43.6 (6.5)	1,140	2.17
Female (n = 43)	41.1 (6.7)	43.4 (7.7)		
Age at onset of schizophrenia, y				
<45 (n = 118)	41.5 (6.5)	43.3 (6.9)	1,140	1.30
≥45 (n = 24)	43.4 (6.3)	44.4 (7.0)		
Duration of illness, y				
<5 (n = 30)	43.6 (6.5)	46.6 (7.0)	1,133	6.75*
≥5 (n = 105)	41.4 (6.5)	42.7 (6.7)		
Initial global neuropsychological T-score†				
Low (≤39) (n = 45)	34.2 (3.4)	36.7 (5.2)	1,94	3.88
High (>45) (n = 51)	48.5 (2.7)	49.9 (3.6)		
Change in positive symptoms				
Better (n = 27)	42.7 (6.8)	44.0 (7.5)	1,36	0.03
Worse (n = 11)	45.1 (5.2)	46.6 (6.6)		
Change in negative symptoms				
Better (n = 17)	41.7 (6.9)	43.3 (7.3)	1,34	0.29
Worse (n = 19)	42.1 (5.3)	44.2 (5.8)		
Schooler and Kane tardive dyskinesia criteria				
No tardive dyskinesia (n = 41)	42.0 (6.7)	42.5 (6.9)	1,52	1.03
Incident tardive dyskinesia (n = 13)	40.8 (8.3)	42.4 (8.4)		
Waddington orofacial tardive dyskinesia criteria				
No tardive dyskinesia (n = 20)	43.0 (6.9)	43.4 (6.7)	1,31	0.53
Incident tardive dyskinesia (n = 13)	39.8 (6.0)	39.1 (6.6)		

*P = .01.

†Because the single score distributions did not meet the repeated-measures analysis of variance requirements for normality and equal variances, the dependent variable in this analysis was the global score Δ.

most contemporary schizophrenic patients are not institutionalized).⁶⁸⁻⁷⁰ Also, there was limited representation of elderly subjects, and subjects who evidenced substantial clinical change or incident tardive dyskinesias during follow-up (Table 4). Although relatively few of our patients were tested initially very early in the course of their illness, 2 recent studies of first-break schizophrenia showed no significant cognitive decline during the first several years of illness.^{35,36} Moreover, despite the limited power associated with some of the subgroup analyses in the current study, the data summarized in Table 4 show that these various subject characteristics were associated with clinically trivial effect sizes for changes in cognitive performance.

Considered together, the results of available longitudinal studies strongly suggest that the large majority of people with schizophrenia do not experience progressive neuropsychological decline after the initial onset of their illness. We found no evidence of such decline, even in our ambulatory patients with long follow-up, who were observed for an average of 5 years. It remains possible that a subset of patients with very poor outcome (not represented in our study) do experience progressive neuropsychological decline. Future research with this population should attempt to document such decline by ruling out nonsignificant fluctuations in performance as evidence of progressive impairment. This might be done by

using neuropsychological norms for change developed with a similarly impaired but neurologically stable comparison group, and determining whether any unusual neuropsychological worsening in the schizophrenic patients remains stable or progresses further during a subsequent follow-up period. If future research should conclusively establish progressive neuropsychological decline in a subset of schizophrenic patients, questions arise as to why only a minority are so affected. Is this another example of the heterogeneous manifestations of a common disease,⁷¹⁻⁷⁴ or are other factors involved, such as treatment history⁷⁵ or comorbid neuromedical conditions (eg, age-related neurodegenerative changes, possibly in combination with schizophrenia-related low “cognitive reserve”)?⁷⁶ There is a need for larger, collaborative studies using the same methods with patients in different treatment settings.

Accepted for publication July 20, 2000.

This study was supported in part by grants MH43695, MH45131, MH49671, MH19934, MH01452, and MH45294 from the National Institute of Mental Health, Bethesda, Md; State of California (Sacramento) Department of Mental Health grant DMH 89-7000; and the Department of Veterans Affairs, Washington, DC.

Preliminary versions of this work were presented in part at the Mt Sinai Conference on the Role of Cognitive Dysfunc-

tion in Schizophrenia, New York, NY, April 6, 1996; the annual meeting of the International Neuropsychological Society, Chicago, Ill, February 16, 1996; and the annual meeting of the American Association of Geriatric Psychiatry, San Diego, Calif, March 10, 1998.

We thank Lou Ann McAdams, PhD, for her comments on an earlier draft of this article.

Reprints: Robert K. Heaton, PhD, Department of Psychiatry, University of California, San Diego, 140 Arbor Dr, San Diego, CA 92103 (e-mail: rheaton@ucsd.edu).

REFERENCES

1. Heaton RK, Crowley TJ. Effects of psychiatric disorders and their somatic treatments on neuropsychological test results. In: Filskov SB, Ball TJ, eds. *Handbook of Clinical Neuropsychology*. New York, NY: Wiley-Interscience; 1981:481-525.
2. Heaton RK, Drexler M. Clinical neuropsychological findings in schizophrenia and aging. In: Miller NE, Cohen GD, eds. *Schizophrenia & Aging*. New York, NY: Guilford Press; 1987:145-161.
3. Seidman L. Schizophrenia and brain dysfunction: an integration of recent neurodiagnostic findings. *Psychol Bull*. 1983;94:195-238.
4. Levin S, Yurgelun-Todd D, Craft S. Contributions of clinical neuropsychology to the study of schizophrenia. *J Abnorm Psychol*. 1989;98:341-356.
5. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12:426-445.
6. Green MF. *Schizophrenia From a Neurocognitive Perspective: Probing the Impenetrable Darkness*. Boston, Mass: Allyn & Bacon; 1998.
7. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1983;17:319-334.
8. Murray RM. Neurodevelopmental schizophrenia: the rediscovery of dementia praecox. *Br J Psychiatry*. 1994;25:6-12.
9. Lieberman JA. Is schizophrenia a neurodegenerative disorder? a clinical and neurobiological perspective. *Biol Psychiatry*. 1999;46:729-739.
10. Davidson M, Haroutunian V. Cognitive impairment in geriatric schizophrenic patients. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Raven Press Ltd; 1995:1447-1549.
11. Bilder RM, Turkel E, Lipschutz-Broch L, Lieberman JA. Antipsychotic medication effects on neuropsychological functions. *Psychopharmacol Bull*. 1992;28:353-366.
12. O'Donnell BF, Faux SF, McCarley RW, Kimble MO, Salisbury DF, Nestor PG, Kininis R, Jolesz FA, Shenton ME. Increased rate of P300 latency prolongation with age in schizophrenia. *Arch Gen Psychiatry*. 1995;52:544-549.
13. Hyde TM, Nawroz S, Goldberg TE, Bigelow LB, Strong D, Weinberger DR, Kleinman JE. Is there cognitive decline in schizophrenia? a cross-sectional study. *Br J Psychiatry*. 1994;164:494-500.
14. Goldberg TE, Greenberg RD, Griffin SJ, Gold JM, Kleinman JE, Pickar D, Schulz SC, Weinberger DR. The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *Br J Psychiatry*. 1993;162:43-48.
15. Goldberg TE, Torrey EF, Berman KF, Weinberger DR. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. *Psychiatry Res Neuroimaging*. 1994;55:51-61.
16. Goldstein G, Zubin J. Neuropsychological differences between young and old schizophrenics with and without associated neurological dysfunction. *Schizophr Res*. 1990;3:117-126.
17. Eyster-Zorrilla LT, Heaton RK, McAdams LA, Zisook S, Jeste DV. Cross-sectional study of older outpatients with schizophrenia and healthy comparison subjects: no differences in age-related cognitive decline. *Am J Psychiatry*. 2000;157:1324-1326.
18. Moran LJ, Gorham DR, Holtzman WH. Vocabulary knowledge and usage of schizophrenic subjects: a six-year follow-up. *J Abnorm Soc Psychol*. 1962;61:246-254.
19. Ginnette LE, Moran LJ. Stability of vocabulary performance by schizophrenics. *J Consult Psychol*. 1964;28:178-179.
20. Smith A. Mental deterioration in chronic schizophrenics. *J Nerv Ment Dis*. 1964;139:479-487.
21. Hamlin RM. The stability of intellectual function in chronic schizophrenia. *J Nerv Ment Dis*. 1969;149:497-503.
22. Klonoff H, Fibiger CH, Hutton GH. Neuropsychological patterns in chronic schizophrenia. *J Nerv Ment Dis*. 1970;150:291-300.
23. Martin PJ, Friedmeyer MH, Sterne AL, Brittain HM. IQ deficit in schizophrenia: a test of competing theories. *J Clin Psychol*. 1977;33:667-672.
24. Hamilton V. IQ changes in chronic schizophrenia. *Br J Psychiatry*. 1963;109:642-648.
25. Foulds GA, Dixon P, McClelland M, McClelland WJ. The nature of intellectual deficit in schizophrenia, part II: a cross-sectional study of paranoid, catatonic, hebephrenic and simple schizophrenics. *Br J Soc Clin Psychol*. 1962;1:141-149.
26. Schwartzman AE, Douglas VI. Intellectual loss in schizophrenia, part II. *Can J Psychol*. 1962;16:161-168.
27. Haywood HC, Moelis I. Effects of symptoms change on intellectual function in schizophrenia. *J Abnorm Soc Psychol*. 1963;67:76-78.
28. Abrams S, Nathanson IA. Intellectual deficit in schizophrenia: stable or progressive? *Dis Nerv Syst*. 1966;27:115-117.
29. Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, Davidson M, Davis KL. Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. *Biol Psychiatry*. 1999;45:32-40.
30. Waddington J, Youssef HA. Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychol Med*. 1996;26:681-688.
31. Waddington JL, Youssef HA, Kinsella A. Cognitive dysfunction in schizophrenia followed up over 5 years, and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychol Med*. 1990;20:835-842.
32. Harvey PD, Lombardi J, Kincaid MM, Parrella M, White L, Powchik P, Davidson M. Cognitive functioning in chronically hospitalized schizophrenic patients: age-related changes and age disorientation as a predictor of impairment. *Schizophr Res*. 1995;17:15-24.
33. Nopoulos P, Flashman L, Flaum M, Arndt S, Andreasen N. Stability of cognitive functioning early in the course of schizophrenia. *Schizophr Res*. 1994;14:29-37.
34. De Lisi LE, Tew W, Xiew S, Hoff AL, Sakuma M, Kushner M, Lee G, Shedlack K, Smith AM, Grimson R. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry*. 1995;38:349-360.
35. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *Am J Psychiatry*. 1999;156:1336-1341.
36. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *Am J Psychiatry*. 1999;156:1342-1348.
37. Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test Results. *Arch Gen Psychiatry*. 1991;48:891-898.
38. Heaton R, Paulsen J, McAdams LA, Kuck J, Zisook S, Braff D, Harris MJ, Jeste DV. Neuropsychological deficits in schizophrenia: relationship to age, chronicity, and dementia. *Arch Gen Psychiatry*. 1994;51:469-476.
39. Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, Wolfson T, Velin R, Marcotte TD, Hesselink JR, Jernigan TL, Chandler J, Wallace M, Abramson I, and the HNRC Group. The HNRC 500: neuropsychology of HIV infection at different disease stages. *J Int Neuropsychol Soc*. 1995;1:231-251.
40. Jeste DV, Harris MJ, Krull A, Kuck J, McAdams LA, Heaton R. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *Am J Psychiatry*. 1995;152:722-730.
41. Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-III-R: Patient Version*. New York: Biometric Research Dept, New York State Psychiatric Institute; 1986.
42. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorder: Patient Edition*. New York: Biometrics Research Dept, New York State Psychiatric Institute; 1995.
43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
44. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
45. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. 2nd ed. Tucson, Ariz: Neuropsychology Press; 1993.
46. Heaton RK. *Comprehensive Norms for an Expanded Halstead-Reitan Battery: A Supplement for the Wechsler Adult Intelligence Scale-Revised*. Odessa, Fla: Psychological Assessment Resources Inc; 1992.
47. Heaton RK, Grant I, Matthews CG. *Comprehensive Norms for Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications*. Odessa, Fla: Psychological Assessment Resources Inc; 1991.
48. Gladsjo AJ, Schuman C, Evans J, Peavy G, Miller S, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*. 1999;6:147-178.
49. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration*

- tion, Norms and Commentary. 2nd ed. New York, NY: Oxford University Press; 1998.
50. Wechsler D. *WAIS-R Manual: Wechsler Adult Intelligence Scale-Revised*. New York, NY: Psychological Corp; 1981.
 51. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. *Wisconsin Card Sorting Test Manual: Revised and Expanded*. Odessa, Fla: Psychological Assessment Resources Inc; 1993.
 52. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test (CVLT) Manual*. San Antonio, Tex: Psychological Corp; 1987.
 53. Russell EW, Neuringer C, Goldstein G. *Assessment of Brain Damage*. New York, NY: John Wiley & Sons Inc; 1970.
 54. Norman M, Evans J, Miller S, Heaton R. Demographically corrected norms for the California Verbal Learning Test. *J Clin Exp Neuropsychol*. 2000;22:80-94.
 55. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962; 10:799-812.
 56. Andreasen NC, Olsen S. Negative vs positive schizophrenia: definition and validation. *Arch Gen Psychiatry*. 1982;39:789-794.
 57. National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). *Early Clin Drug Eval Unit Intercom*. 1975;4:3-6.
 58. McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychol Methods*. 1996;1:30-46.
 59. Jacobsen NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59:12-19.
 60. Temkin NR, Heaton RK, Grant I, Dikmen SS. Detecting significant change in neuropsychological test performance: a comparison of four models. *J Int Neuropsychol Soc*. 1999;5:357-369.
 61. Jeste DV, Wyatt RJ. *Understanding and Treating Tardive Dyskinesia*. New York, NY: Guilford Press Inc; 1982.
 62. de Leon J, Canuso C, White AO, Simpson GM. A pilot effort to determine benzotropine equivalents of anticholinergic medications. *Hosp Community Psychiatry*. 1994;45:606-607.
 63. Schooler N, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry*. 1982;39:486-487.
 64. Waddington JL. Tardive dyskinesia in schizophrenia and other disorders: associations with aging, cognitive dysfunction and structural brain pathology in relation to neuroleptic exposure. *Hum Psychopharmacol*. 1987;2:11-22.
 65. Harvey PD, White L, Parrella M, Putnam KM, Kincaid MM, Powchik P, Mohs RC, 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. *Br J Psychiatry*. 1995;166:630-633.
 66. Wechsler D. *Wechsler Adult Intelligence Scale, 3rd Edition: Administration and Scoring Manual*. San Antonio, Tex: Psychological Corp; 1997.
 67. Ivnik RJ, Smith GE, Malec JF, Petersen RC, Tangalos JF. Long-term stability and intercorrelations of cognitive abilities in older persons. *Psychol Assess*. 1995; 7:155-161.
 68. Cohen CI, Cohen GD, Blank K, Gaitz C, Katz IR, Leuchter A, Maletta G, Meyers B, Sakauye K, Shamoian C. Schizophrenia and older adults, an overview: directions for research and policy. *Am J Geriatr Psychiatry*. 2000;8:19-28.
 69. Jeste DV, Alexopoulos GS, Bartels SJ, Cummings JL, Gallo JJ, Gottlieb GL, Halpain MC, Palmer BW, Patterson TL, Reynolds CF III, Lebowitz BD. Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next two decades. *Arch Gen Psychiatry*. 1999;56:848-853.
 70. Palmer BW, Simjee McClure F, Jeste DV. Schizophrenia in late-life: findings challenge traditional concepts. *Harvard Rev Psychiatry*. In press.
 71. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry*. 1999;56:781-787.
 72. Buchanan RW, Strauss ME, Kirkpatrick B, Holstein C, Breier A, Carpenter WT. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. *Arch Gen Psychiatry*. 1994;51:804-811.
 73. Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, Zisook S, Jeste DV. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*. 1997;11:437-446.
 74. Palmer BW, Heaton SC, Jeste DV. Older patients with schizophrenia: challenges in the coming decades. *Psychiatr Serv*. 1999;50:1178-1183.
 75. Wyatt RJ, Henter ID. The effects of early and sustained intervention on the long-term morbidity of schizophrenia. *J Psychiatr Res*. 1998;32:169-177.
 76. Dwork AJ, Susser ES, Keilp JG, Waniek C, Lieu D, Kaufman M, Zemishlany Z, Prohovnik I. Senile degeneration and cognitive impairment in chronic schizophrenia. *Am J Psychiatry*. 1998;155:1536-1543.