Early treatment-induced improvement of negative symptoms predicts cognitive functioning in treatment-naive first episode schizophrenia: a 2-year followup

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Early Treatment-Induced Improvement of Negative Symptoms Predicts Cognitive Functioning in Treatment-Naïve First Episode Schizophrenia: A 2-Year Followup

by Daniel Schuepbach, S. Kristian Hill, Richard D. Sanders, Daniel Hell, Matcheri S. Keshavan, and John A. Sweeney

Abstract

Studying neuroleptic-naïve first episode schizophrenia is a strategy for investigating clinical and neuropsychological abnormalities at a very early phase of the disease without confounding influences of illness duration and medication effects. We examined the clinical and neuropsychological time course over 2 years in 32 neuroleptic-naïve first episode patients (20 males, 12 females) and 21 healthy individuals with similar sociodemographic characteristics. Early treatment-induced reduction of negative symptoms predicted superior cognitive performance throughout followup in the domains of verbal fluency, attention, and nonverbal learning and memory. There were no associations between psychotic or disorganized symptoms and cognitive variables. These findings suggest an important relationship between treatment efficacy of antipsychotic medication and the longer term course of cognitive deficits in schizophrenia.

Keywords: Schizophrenia, followup, verbal memory, learning, neuropsychology.


Schizophrenia is a severe mental illness that has interested clinicians and researchers for more than a century (Bleuler 1911; Kraepelin 1919), and disturbances of thinking were recognized very early as one of the disease’s core features. Cognitive deficits have been described in schizophrenia in general (for review, see Heinrichs and Zakzanis 1998; Rund and Borg 1999), and more recently as occurring in first episode schizophrenia close to the time of illness onset (Sweeney et al. 1991; Bilder et al. 1992; Hoff et al. 1992; Saykin et al. 1994; Censits et al. 1997; Mohamed et al. 1999; Bilder et al. 2000). These deficits involve multiple areas of functioning, such as complex language functions, verbal learning and memory, attention, executive functions, visual memory, and motor speed. Censits et al. (1997) and Hoff et al. (1999) demonstrated a stable pattern of cognitive dysfunction over time periods from 1 to 4 years, and associations between symptoms and cognitive performance. Censits et al. (1997) showed broad-based correlations between negative symptom severity and impairments in cognition. These associations were evident for domains of attention, language, abstraction, verbal memory, and spatial memory, and spatial and sensory abilities. In large studies on first episode schizophrenia, the Hillside group published several important reports addressing clinical and neuropsychological measures at followup (Lieberman et al. 1992; Robinson et al. 1999). Robinson et al. (1999) evaluated a considerable number of predictors of treatment response in this patient group and found that, apart from sociodemographic and premorbid factors, measures of attention predicted treatment response. Another group found an association between treatment response and negative symptoms in first episode schizophrenia (Scottish Schizophrenia Research Group 1987). Finally, Bilder et al. (2000) investigated a large sample of first episode patients in a cross-sectional design and found only small-to-medium effect sizes when estimating relationships between clinical and neuropsychological measures. Of interest, these authors observed smaller associations between those variables at study entry than they did between those variables close to the time of neuropsychological assessment, when patients were clinically stable. Mainly negative symptoms had an inverse association with memory, attention, and global neuropsychological performance.

Hoff et al. (1999) used a multiple-time-point design to characterize first episode schizophrenia from a clinical, neuropsychological, and neuroradiological perspective, yielding valuable information regarding possible change of those parameters over time. Cognitive deficits were evi-
dent at initial hospitalization, with little change during the observation period.

In recent years there has been great interest in the prediction of functional outcome in schizophrenia. Green et al. (2000) and Green and Nuechterlein (1999) emphasized the role of cognitive deficits (e.g., verbal memory) for functional outcome, suggesting a closer linkage to fundamental aspects of the illness rather than its immediate symptomatic expression. In a recently published study from our group with neuroleptic-naive schizophrenia patients (Schuepbach et al. 2002), early treatment-induced reduction in negative symptoms was associated with enhanced cognitive functions after 1 month of treatment, especially in the domains of verbal fluency and attention.

Based on these results, we were particularly interested in addressing the following predictions: (1) that early treatment-induced reduction in negative symptoms is associated with long-term cognitive outcome in first episode schizophrenia, thus extending our findings on this association in the period immediately following treatment initiation; and (2) that because there is ample evidence that cognitive functioning is a core feature of schizophrenia, early cognitive performance change is associated with long-term symptom severity.

Methods

Subjects. Thirty-two neuroleptic-naive first episode psychotic subjects were recruited who were initially diagnosed with schizophrenia or schizoaffective disorder and later confirmed as having schizophrenia ($n = 30$) or schizoaffective disorder ($n = 2$) according to DSM-IV (APA 1994). Patient reports of prior treatment history were confirmed by family members and treating physicians. The diagnoses were based on the Structured Clinical Interview for DSM-III-R or DSM-IV disorders (SCID; Spitzer et al. 1987, 1994) and all other available information, which was reviewed at a consensus diagnosis meeting by senior investigators and clinical staff. Patients interviewed with the SCID for DSM-III-R had their responses reviewed to verify that they met DSM-IV diagnostic criteria for disorders of interest.

The focus of this report was on symptom and cognitive performance change in patients with schizophrenia. However, to estimate how neuropsychological performance (baseline/followup) differed between patients and healthy subjects, a comparison group was included in this study. Data presentation was restricted for the following reasons: (1) to show an overall estimate of performance difference at baseline assessment; (2) to demonstrate, on a descriptive basis, the time course of selected cognitive functions as compared with patients; and (3) to provide information on consistency of neuropsychological tests in healthy subjects, a relevant aspect in a longitudinal study. The comparison group comprised 21 healthy individuals recruited from the surrounding community. They had no Axis I disorder by SCID interview. The comparison group was selected to match the patient sample on age, sex, ethnicity, and parental socioeconomic status (Hollingshead 1975) (table 1). All subjects met the following criteria: (1) age between 18 and 55 years; (2) no known systemic or neurologic illness; (3) no prior treatment with electroconvulsive shock therapy; (4) no history of head trauma with loss of consciousness for more than 10 minutes; (5) no lifetime history of substance dependence, or of substance abuse in the 3 months preceding entry into the study; and (6) no anticonvulsants or benzodiazepines for 1 month. The study was approved by the Institutional Review Board of the University of Pittsburgh. All participants gave their written and witnessed informed consent to participate in these studies. Twenty-four patients and 16 healthy controls of the current study were included in our previous investigation on short-term clinical and neuropsychological changes after treatment initiation (Schuepbach et al. 2002). Some of these cases were lost to followup and thus are not included in this report, and additional cases were added since that manuscript was submitted for publication.

Clinical Ratings. The Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1989) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1990) were completed close to the time of the neuropsychological evaluations without knowledge of the findings from cognitive investigations. Similarly, neuropsychological testing was done without knowledge of clinical ratings. Symptom factors were generated as follows (Schuepbach et al. 2002): total SANS score (including global ratings of affective flattening, alogia, avolition/apathy, attention, and anhedonia/asociality) was taken as an index of negative symptoms; global SAPS ratings of hallucinations and delusions were used as an index of psychotic symptoms; and global SAPS ratings of bizarre behavior and formal thought disorder were combined as an index of disorganized symptoms. Additionally, we included the depression item from the Brief Psychiatric Rating Scale (Overall and Gorham 1962) in the analyses to estimate depressive symptoms during the followup and their relation to negative symptoms and cognition. Raters achieved an intraclass correlation coefficient of at least 0.80 on the clinical rating instruments.

Neuropsychological Assessment. Neuropsychological examination took place within 72 hours of clinical ratings. Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT; Delis et al. 1983)
Table 1. Sociodemographic and clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Schizophrenia patients (n = 32)</th>
<th>Healthy individuals (n = 21)</th>
<th>( \chi^2 ) or t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>27.4 (8.2)</td>
<td>23.9 (5.6)</td>
<td>1.85</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/12</td>
<td>16/5</td>
<td>1.09</td>
<td>ns</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20</td>
<td>13</td>
<td>1.60</td>
<td>ns</td>
</tr>
<tr>
<td>African-American</td>
<td>10</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental SES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total education (yrs)</td>
<td>15.1 (2.2)</td>
<td>14.3 (3.6)</td>
<td>0.92</td>
<td>ns</td>
</tr>
<tr>
<td>Word-reading ability</td>
<td>101.2 (14.2)</td>
<td>110.7 (9.0)</td>
<td>2.95</td>
<td>0.005</td>
</tr>
<tr>
<td>Patient's history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of illness (yrs)</td>
<td>25.3 (7.9)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (yrs), median (SE)</td>
<td>1.0 (0.69)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of psychiatics</td>
<td>0.1 (0.3)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom severity at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>6.1 (2.6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganized symptoms</td>
<td>3.5 (2.0)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>2.7 (0.6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average medication dose antipsychotic (CPZE)</td>
<td>139.3 (105.8)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients on anticholinergics (%)</td>
<td>23.44 (9.02)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.—CPZE = chlorpromazine equivalent; NA = not applicable; ns = nonsignificant; parental SES = parents' socioeconomic status, using the Hollingshead Scale; SE = standard error. Values are mean (standard deviation) if not indicated differently.

1 Percentage of patients taking benztropine mesylate during followup.

using the following scores: total recall over all five learning trials, short delay free and cued recall, long delay free and cued recall, and recognition discriminability. Starting with the initial CVLT form at baseline, the alternating form was administered at 1-month followup, alternating with the initial form at subsequent assessment points. We introduced this sequence after we commenced recruitment, so only 21 out of 32 schizophrenia patients and all healthy subjects received the alternating forms of this test over the course of followup. Language skills were assessed by verbal fluency with the Controlled Word Association Test (Benton and Hamsher 1983). Attention was assessed using the Digit Span and Digit Symbol tests from the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler 1981) and the Trail Making Forms A and B (Reitan and Wolfson 1985). Visual perception and learning were assessed with the Benton Judgment of Line Orientation Test (Benton 1975) and with the immediate and delayed visual memory design reproduction of the Wechsler Memory Scale–Revised (WMS–R; Wechsler 1987). Basic manual psychomotor skills were assessed with the Finger Tapping Test (Reitan and Wolfson 1985) and the Grooved Pegboard Test (Klove 1963). Raw scores were converted to standardized z scores, with performance of healthy subjects at baseline set at 0 and standard deviation at 1. Scale scores were inverted where appropriate, so that lower values always represented lower performance.

In certain circumstances of longitudinal studies, cognitive performance change is of interest. Therefore, the calculation of neuropsychological change was carried out with residualized scores in which variance related to baseline performance of a defined task was partialed out of scores obtained at followup. Residuals are defined as differences between observed and predicted values of the solution. By dividing those values by the standard error of the estimate, standardized residuals were obtained. Where appropriate, residualized scores were inverted, so that lower values always represented less improvement in performance. Average performance change scores within each domain of functioning were computed to estimate
overall performance change. Theoretical considerations of this method are discussed in McSweeney et al. (1993) and Savrie (2002), and an example of residuals in longitudinal data can be found in Piper et al. (1999). Because only the last 21 patients recruited received alternating forms of the CVLT at followup, analyses were separately carried out for the full sample for all tests except the CVLT (all 32 patients), and separately for the CVLT, with analyses restricted to the subset of subjects who had alternating forms of the test administered throughout followup.

Medication. While all patients were neuroleptic-naïve at baseline assessments, antipsychotic agents were given shortly thereafter to treat psychotic symptoms. The type of antipsychotic agent and dosage were prescribed according to the treating physician’s judgment. The same was true for anticholinergic medication. Initial antipsychotic treatment comprised haloperidol (n = 13), risperidone (n = 17), loxapine (n = 1), and perphenazine (n = 1). Anticholinergics were administered according to clinical judgment based on extrapyramidal side effects. Average antipsychotic dosage and the percentage of patients receiving anticholinergics across all of the followup assessments are given in table 1.

Followup Assessments, Missing Data. After study entry at baseline, patients were reassessed after 1, 6, 12, and 24 months. Seven out of 32 patients had no followup assessments at year 2. Three of these patients were lost to followup after year 1, and four had not yet reached the 2-year followup endpoint. We did not detect significant baseline differences of sociodemographic or clinical variables between these patients and the rest of the sample (Mann-Whitney U test, p > 0.05). We therefore assumed a random pattern of missing values and replaced missing values to achieve maximum power and minimal bias in the following way. Using evidence of Rund and Borg (1999) and Hoff et al. (1999), we assumed a stable clinical and neuropsychological pattern between followup intervals of year 1 and 2 and extended the last available data through to the year endpoint. Four patients had no followup at 6 months, and two had no followup at 1 year. For these missing values, we used the linear trend of available data to predict missing values.

Statistical Analyses. The Kolmogorov-Smirnov test was used to test for normality of distributions; non-normally distributed data were transformed. Where transformations were not appropriate, nonparametric procedures were used.

The mixed procedure, PROC MIXED (SAS Institute Inc., Cary, NC), was used to confirm results of the general linear model (GLM), because it can accommodate data that are missing at random. Because findings of PROC MIXED were largely the same as those with GLM, only results of GLM are reported.

Results

Sociodemographic and clinical characteristics are summarized in table 1. Severity of symptoms at baseline was comparable to that in other studies in first episode schizophrenia (Szymanski et al. 1996). Word-reading ability (Wide-Range Achievement Test–Revised; Jastak and Wilkinson 1984) was greater in healthy individuals (table 1). Consistency of raw scores across followup assessments was examined, with Cronbach’s coefficient alpha showing a range from 0.80 to 0.96 in healthy subjects.

Time Course of Clinical Symptoms. Antipsychotic treatment reduced symptoms over time. Significant reductions were seen for psychotic (t(31) = 7.08, p < 0.001), disorganized (t(31) = 5.54, p < 0.001), and negative symptoms (t(31) = 3.73, p < 0.01) after 1 month (figure 1). No other significant changes were observed over the followup period (p > 0.1). We calculated the relative change between baseline and followup at 1 month as an index of clinical response to antipsychotic medication according to our recently published report (Schuepbach et al. 2002). There was no significant association between medication dose and age of onset with either clinical symptoms or neuropsychological parameters.

Neuropsychological Deficits in Schizophrenia. There was a significant overall difference in neuropsychological performance at baseline between patients and healthy subjects as revealed by a 2 (patients vs. healthy subjects) by 18 (all neuropsychological test data) multiple analysis of variance (MANOVA; Wilks’ lambda = 0.35, F(18,34) = 3.48, p < 0.01), and analyses including followup data supported a generally stable pattern of cognitive deficits over time (data not shown).

Early Change of Clinical Symptoms and Its Association With Cognitive Function. Based on findings from our prior study indicating that reduction in negative symptoms is associated with better cognitive functioning after acute treatment in first episode schizophrenia (Schuepbach et al. 2002), this variable was used as a predictor of cognitive performance at followup:

1. A 2 (low vs. high early SANS improvers, split at the group median of 13.33%) by 4 (all followup intervals) by 12 (all tests excluding CVLT) repeated measures MANOVA with residualized scores as dependent measures showed a significant effect of early negative symptom change on cognitive functioning (F(1,30) = 7.53, p = 0.01).
Univariate analyses indicated that those who demonstrated more pronounced reduction in negative symptoms after acute treatment showed better long-term performance in verbal fluency \((p < 0.01)\); WAIS-R Digit Symbol \((p < 0.05)\); WMS-R, visual reproduction, delayed \((p < 0.001)\); and Grooved Pegboard of the nondominant hand \((p < 0.05)\) (figure 2). There were no significant relations between early improvement in psychotic or disorganized symptoms and long-term cognitive performance \((p > 0.1)\). Because dichotomizing the patient group may result in a loss of information, additional correlational analyses between different symptom measures and average cognitive performance change across all followup intervals are presented in table 2. Similar to the findings reported in another recent article of ours (Schuepbach et al. 2002), analyses with this partially overlapping sample indicated that negative symptom reduction after acute treatment was significantly associated with cognitive performance change during that time period (data not shown).

2. We conducted analyses using early symptom change as an independent measure in multiple regression analyses with symptom severity at baseline as a covariate and average cognitive performance change at followup assessment of 2 years as a dependent variable. Negative symptom change was a significant predictor of cognitive performance excluding CVLT \((R^2 = 0.20, F(1,30) = 7.66, \text{standardized beta} = 0.45, p = 0.01)\), and there was no effect of baseline symptoms \((p > 0.1)\) (figure 3A). No other associations with clinical
Figure 2. Time course of neuropsychological functions at followup assessments (residualized scores)

A) Verbal fluency

B) WAIS-R Digit Symbol

C) WMS-R - delayed

D) Grooved pegboard - nondominant hand

Note.—SANS = Scale for the Assessment of Negative Symptoms; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised. On x-axis, breaks were inserted between 0 and 1 month to increase the readability of the figures. Results of independent sample t tests comparing low and high SANS improvers (split along the group median of 13.33%) are shown. For comparison purposes, results of healthy subjects are also shown.

* p < 0.05; ** p < 0.01

measures were significant (p > 0.1). Depression was not a significant cofounder of the above-mentioned associations between cognitive function and negative symptoms (p > 0.1).

Early Change of Cognitive Function and Symptom Prediction. Correlation analysis between early average cognitive performance change and average symptom score at all followup intervals revealed significant inverse associations between cognitive functions when analyses were conducted excluding or including verbal learning and memory performance and negative symptoms (p < 0.05) (table 3). Significant inverse correlations of individual tests with negative symptoms included verbal fluency (p < 0.05); WMS-R, visual reproduction, delayed (p < 0.05); Trail Making Form A (p < 0.05); and CVLT short delay free (p = 0.01) and long delay cued recall (p < 0.05). Early cognitive performance change excluding ver-
Table 2. Correlations between clinical measures and average standardized neuropsychological change scores (1–24 months of followup) in functioning from baseline, after treatment

<table>
<thead>
<tr>
<th>Symptoms symptoms</th>
<th>Average performance Δ functions without CVLT</th>
<th>Average performance Δ CVLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>0.05</td>
<td>-0.10</td>
</tr>
<tr>
<td>Disorganized(^1)</td>
<td>-0.16</td>
<td>0.12</td>
</tr>
<tr>
<td>Negative</td>
<td>0.11</td>
<td>-0.29</td>
</tr>
<tr>
<td>Symptom change at 1 mo(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>0.18</td>
<td>0.12</td>
</tr>
<tr>
<td>Disorganized(^1)</td>
<td>-0.02</td>
<td>0.29</td>
</tr>
<tr>
<td>Negative</td>
<td>0.49(^*)</td>
<td>0.44(^*)</td>
</tr>
<tr>
<td>Symptom change at 24 mos(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic(^1)</td>
<td>-0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>Disorganized(^1)</td>
<td>-0.12</td>
<td>0.35</td>
</tr>
<tr>
<td>Negative</td>
<td>0.09</td>
<td>0.33</td>
</tr>
<tr>
<td>Average symptom score(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>-0.20</td>
<td>-0.19</td>
</tr>
<tr>
<td>Disorganized</td>
<td>-0.07</td>
<td>-0.25</td>
</tr>
<tr>
<td>Negative</td>
<td>-0.18</td>
<td>-0.56(^*)</td>
</tr>
</tbody>
</table>

Note.—CVLT = California Verbal Learning Test (n = 21), except baseline (n = 32); functions without CVLT = functions excluding California Verbal Learning Test (n = 32).

\(^1\) Spearman's rho.

\(^2\) Partial correlation, controlling for symptom severity at baseline.

\(^* p < 0.05; ** p < 0.01\)

...bal learning and memory predicted negative symptom severity at followup of 2 years only by tendency (figure 3B). No significant effects with psychotic and disorganized symptoms were found (p > 0.05). Overall, these results show an inverse association between measures of early average cognitive performance change and negative symptom severity at followup.

Discussion

This longitudinal study investigating parallels in clinical and neuropsychological changes after treatment initiation in first episode schizophrenia yielded several important results. First, early treatment-induced change of negative symptoms was associated with short- and long-term cognitive outcome. Patients with greater reductions in negative symptoms over the first month of treatment showed significantly better cognitive performance over followup than other patients, particularly in the domains of verbal fluency, attention, and nonverbal learning and memory. Second, early cognitive performance change was significantly associated with negative symptoms during the followup period. Generally, cognitive deficits remained stable after treatment initiation as in other studies, and the relation between negative symptom change with acute therapy to cognitive ability persisted throughout the 2-year followup period.

Our study population was antipsychotic-naïve at baseline, so the analyses we report were not confounded by chronicity of illness or the sequelae of recent or long-term treatment. With reference to our baseline assessments, we observed little evidence for an association of psychotic state with cognitive functioning, consistent with findings from other reports (Bilder et al. 2000). There have been few previous studies following neuroleptic-naïve first episode schizophrenia patients longitudinally (vs. baseline/endpoint design) focusing on neuropsychological performance. Most previous neuropsychological followup investigations on first episode or early-phase schizophrenia had a baseline condition involving testing patients taking medication (Hoff et al. 1999), had a baseline/endpoint design (Censits et al. 1997), or had a combination of first episode and chronic patients (Censits et al. 1997).

Our observation that early treatment-induced reductions in negative symptoms were significantly associated with cognitive function for up to 2 years is especially important. It indicates that those patients who were able to benefit from antipsychotic treatment early in their course of illness in terms of negative symptom reduction had a
Figure 3. (A) Early negative symptom change versus cognitive performance excluding verbal learning and memory at followup of 2 years ($R^2 = 0.20$, $p = 0.01$); (B) early cognitive performance change excluding verbal learning and memory versus negative symptoms at followup of 2 years ($R^2 = 0.10$, $p = 0.08$)

Note.—SANS = Scale for the Assessment of Negative Symptoms. Dashed lines indicate 95% confidence intervals.

Table 3. Correlations between averaged standardized neuropsychological variables and clinical measures (1–24 months of followup) in functioning from baseline and after treatment

<table>
<thead>
<tr>
<th>Average cognitive measures</th>
<th>Average psychotic symptoms$^2$</th>
<th>Average disorganized symptoms$^2$</th>
<th>Average negative symptoms$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functions without CVLT</td>
<td>0.11</td>
<td>-0.16</td>
<td>-0.33</td>
</tr>
<tr>
<td>CVLT$^1$</td>
<td>-0.33</td>
<td>-0.15</td>
<td>-0.16</td>
</tr>
<tr>
<td>Performance change at 1 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functions without CVLT</td>
<td>-0.03</td>
<td>-0.29</td>
<td>-0.42*</td>
</tr>
<tr>
<td>CVLT</td>
<td>-0.31</td>
<td>-0.32</td>
<td>-0.50*</td>
</tr>
<tr>
<td>Performance change at 24 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functions without CVLT</td>
<td>-0.17</td>
<td>-0.02</td>
<td>-0.20</td>
</tr>
<tr>
<td>CVLT</td>
<td>0.00</td>
<td>-0.06</td>
<td>-0.54*</td>
</tr>
</tbody>
</table>

Note.—CVLT = California Verbal Learning Test ($n = 21$), except baseline ($n = 32$); functions without CVLT = functions excluding California Verbal Learning Test ($n = 32$).

$^1$ Spearman's rho.

$^2$ Partial correlation, controlling for symptom severity at baseline.

$^*$ $p < 0.05$; $^{**}$ $p < 0.01$
superior long-term cognitive outcome. These findings indicate that cognitive changes associated with short-term, treatment-induced change of negative symptoms can be still seen 2 years later and extend results from our recently published study (Schuepbach et al. 2002) by showing a persistence of these early treatment-related cognitive changes in first episode schizophrenia. Until now there have been no other reports that have systematically investigated this association. Bilder et al. (1991) found an inverse association of reduction of negative symptom ratings and improvement of neuropsychological performance over 1 year. The results of our study also lend support to the notion that early cognitive performance change predicts average negative symptom severity, and hence confirm widely accepted assumptions that cognitive deficits may represent a core feature of the illness (Elvevåg and Goldberg 2000). At baseline, patients were psychotic, were unmedicated, and had never taken antipsychotic medication. In accordance with another report (Szymanski et al. 1996), reduction of psychotic and disorganized symptoms was greater than reduction of negative symptoms. Peralta et al. (2000) investigated treatment-induced changes of negative symptoms in neuroleptic-naïve patients and suggested that negative symptoms at this stage were mainly primary or illness related. Although negative symptoms at baseline responded partially to antipsychotic treatment in our study, patients varied in the degree of benefit they received in this regard. These results are in agreement with evidence that antipsychotic agents—typical (in lower doses) (Seidman et al. 1993) and atypical medications (Kane et al. 1988; Chouinard et al. 1993)—reduce negative symptoms. Goff and Evins (1998) reviewed a large body of literature on negative symptoms in schizophrenia and concluded that there might be a subgroup of patients that are unlikely to respond to pharmacological interventions.

From our study’s findings, one could argue that the initial improvement in negative symptom severity is attributable to a state-related phenomenon, where patients went from an untreated and psychotic state to a treated and non- or less psychotic state. This happened during a relatively short time period of 1 month. From these findings, it may be concluded that change in negative symptoms plays an important role in the modulation of cognitive performance in schizophrenia, and that a reduction in negative symptoms may be an even more important target for treatment than has been previously appreciated. Although this study does not provide extensive analysis on clinical and neuropsychological variables at baseline, one might hypothesize that differences in early change measures represent a neurobiological correlate of this illness at baseline.

An important psychopathological model linked to concepts of negative symptoms deserves to be mentioned in this regard: the deficit syndrome (Carpenter et al. 1988). This syndrome is defined by enduring negative symptoms that are essentially unrelated to secondary causes. While only approximately 10 percent of first episode schizophrenia patients fulfill criteria of a deficit syndrome (Fenton and McGlashan 1994), it is possible that the patients we characterized who show low treatment-induced improvement of negative symptoms linked to neuropsychological deficits may be more likely to develop or manifest this syndrome later in their illness. Our findings further illustrate the importance of clarifying the neurobiological basis of negative symptoms in schizophrenia, which likely involves the frontal cortex, the limbic system, the basal ganglia and temporal lobe structures, and dysregulation of several neurotransmitter systems, including dopamine, norepinephrine, glutamate, and serotonin (for review, see Goff and Evins 1998).

Certain limitations of our study need to be considered. First, this was a naturalistic study where antipsychotic treatment was administered according to the decision of treating physicians. It was therefore not possible to draw definite inferences about differential medication effects or dosage effects on clinical and neuropsychological variables. Second, the sample size of groups was relatively small; despite strategies to circumvent this drawback, further investigations with larger study groups are necessary. Last, the study raises a number of questions that need to be addressed regarding the neurobiological basis of cognitive enhancement with antipsychotic treatment, to move toward prescriptive selection of different pharmacotherapies for schizophrenia based on their suitability for particular patients and targeted change in clinical status.

Conclusion

In this 2-year followup study with first episode antipsychotic-naïve schizophrenia patients, we observed significant associations between early negative symptom change and cognitive abilities over a 2-year followup as well as an impact of early cognitive performance change on negative symptoms during that time period. To the best of our knowledge, this is the first demonstration in neuroleptic-naïve first episode schizophrenia of a direct linkage between, on the one hand, the early benefits of antipsychotic medications in terms of reductions in negative symptoms and, on the other, long-term neuropsychological outcome. This finding is important because it emphasizes the relevant role of one early treatment target (negative symptom reduction) that may have especially
decisive long-term benefits for neuropsychological functioning in schizophrenia. It raises new questions for future studies, including the differential benefit of various treatments to said linkage between symptomatology and cognitive performance, the replicability of this effect in chronic patients with long courses of illness and treatment, and the neurobiological mechanisms through which treatment reduces negative symptoms to enhance long-term neuropsychological outcome in schizophrenia.

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