Premorbid Functioning in Schizophrenia: Relation to Baseline Symptoms, Treatment Response, and Medication Side Effects

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Abstract

Impaired premorbid functioning prior to the onset of acute psychosis has frequently been noted in schizophrenia. This study examined retrospectively the premorbid status of patients in their first episode of psychosis in order to determine relationships with baseline symptoms, treatment response, and medication side effects. One hundred eleven schizophrenic and schizoaffective patients participating in a large prospective study of first episode schizophrenia were evaluated with the Premorbid Adjustment Scale (PAS). Premorbid functioning in males became progressively worse over time. Deficit state patients exhibited worse premorbid functioning. A third of patients exhibited sustained poor premorbid functioning. At various developmental stages, lower “sociability and withdrawal” scores correlated with increased time to treatment response, more severe negative symptoms, increased drug-induced parkinsonism, and deterioration of premorbid functioning. Various mean PAS scores predicted susceptibility to tardive dyskinesia. Our findings suggest that prior to acute psychosis onset there are certain behavioral precursors reflected in premorbid functioning that may predict subsequent illness manifestations. Measures of premorbid functioning indicate that disease pathogenesis is manifest, albeit more subtly, prior to presentation of first psychotic symptoms.

Keywords: Premorbid, schizophrenia, predictor, first episode, psychosis.


There is extensive evidence that there are certain behavioral precursors long prior to the onset of acute psychotic symptoms in schizophrenia (Haas and Sweeney 1992; Done et al. 1994; Larsen et al. 1996). One of the more widely used indexes of precursor features to the illness is premorbid functioning.

Associations between premorbid factors and clinical variables, both at onset and later in the illness course, have been reported by numerous studies. Many of these have demonstrated an association among the presence and severity of premorbid symptoms and an insidious or gradual mode of onset, a more chronic clinical course, and a poorer outcome of illness (Gittelman-Klein and Klein 1969; Bromet et al. 1974; Drues et al. 1978; Farmer et al. 1983; Knesevich et al. 1983; Kay and Lindenmayer 1987; Keefe et al. 1989; Bartko et al. 1990; Jorgensen and Parnas 1990; Fenton and McGlashan 1991; Addington and Addington 1993). Furthermore, better premorbid history has been associated with older age at onset of illness, later age of first neuroleptic use, and later age at first hospitalization (Haas and Sweeney 1992). Males generally score worse than females on a range of premorbid variables (Klorman et al. 1977; Goldstein 1988; Childers and Harding 1990; Dworkin 1990; Haas and Sweeney 1992; Castle et al. 1993; Hafner et al. 1993). Patients with the deficit state have been characterized by poorer premorbid adjustment scores (Buchanan et al. 1990; Mayerhoff et al. 1994), while patients with the paranoid subtype of schizophrenia have better premorbid functioning compared to patients with nonparanoid types of schizophrenia (Jorgensen and Parnas 1990; Fenton and McGlashan 1991).

In addition to the level of premorbid functioning, worsening in premorbid functioning between childhood and adulthood has been associated with the negative or deficit state syndrome (Mukherjee et al. 1991; Kelley et al. 1992; McCreadie et al. 1994), as well as with a longer duration of untreated psychosis (Haas and Sweeney 1992). However, this change in behavior and functioning also has been suggested as possibly reflecting the prodromal phase of the illness, as opposed to the premorbid
phase of the illness, which is defined as occurring closer or immediately prior to the onset of the first psychotic episode.

Most prior studies investigating premorbid functioning in schizophrenia have obtained premorbid history from patients in the chronic stage of their illness—many years from their illness onset (Andreasen et al. 1990). These assessments were based on chart review and retrospective patient recall, which entails a potential bias, as information recalled from the distant past is frequently incomplete or inaccurate. To decrease the potential bias of lengthy retrospective assessment, we examined a cohort of patients presenting with a first episode of psychosis, permitting an assessment of patients’ premorbid status that is closer in time to that premorbid state. Retrospective assessment of premorbid functioning in first episode patients involves a shorter temporal separation for the period being recalled by the patients and their family. In this way we were able to decrease the bias that might accrue from chronic illness, treatment, institutionalization, and advanced age. In addition, most studies that have examined premorbid states have not assessed the changes that may occur over time and that might reflect the mode of onset of illness (i.e., insidious or precipitant). In this study of first episode patients, we were able to relate premorbid states and change to clinical presentation and prospectively to subsequent treatment response over 6 months. Thus, we intend to investigate the above previously described phenomena of premorbid functioning in schizophrenia in a large cohort of patients and to determine whether they and other observations can be replicated in data from a prospective study of first episode schizophrenia. We hypothesized that poor premorbid functioning might provide further evidence for a poor prognostic phenotype of schizophrenic illness that manifests itself in both impaired premorbid functioning and the subsequent onset of more serious illness.

Method

Study Design. Patients were part of a large prospective study of first episode schizophrenia, the design and procedures of which have been described previously (Lieberman et al. 1992, 1993; Robinson et al. 1999). In summary, all patients were hospitalized for their first episode of psychotic illness, were between the ages of 14 and 44, and had received less than 12 previous weeks of cumulative lifetime neuroleptic treatment. Diagnoses were made according to Research Diagnostic Criteria (RDC) as assessed by a Schedule for Affective Disorders and Schizophrenia Change (SADS–C; Endicott and Spitzer 1978) patient interview and family member supplemental information. To facilitate the diagnosis of patients, we included only those who were actively psychotic, defined as having a rating of 4 or more on at least one of the psychotic item scales (severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, bizarre behavior) of the Schedule for Affective Disorders and Schizophrenia Change with Psychosis and Disorganization items (SADS–C+PD; Endicott and Spitzer 1978). Subjects were excluded if they had any past or present history of significant neurological or endocrine disorder, or substance-induced psychotic disorder. Written informed consent for the study was obtained from both patients and their families, according to the guidelines of the Institutional Review Board of the Long Island Jewish Medical Center.

Baseline psychopathology was evaluated with the following assessments: the SADS–C+PD (item range 1–6), the Scale for Assessment of Negative Symptoms (SANS) (item range 0–5) (Andreasen 1983), and the Clinical Global Impression (CGI) scale (item range 1–7) (Guy 1976). A composite score of positive symptoms was obtained using the mean SADS items of severity of delusions and severity of hallucinations. Similarly, composite scores were obtained for negative symptoms using the mean SANS scores of global affective flattening, global alogia, global avolition-apathy, and global anhedonia-asociality, as well as for thought disorder, which is composed of mean scores of the SADS–C+PD items of derailment, illogical thinking, and impaired understanding. Thought disorder is considered separately from positive symptoms based on previous work by Bilder et al. (1985) demonstrating the distinctness of thought disorder from the psychotic cluster of hallucinations and delusions. The patient’s socioeconomic status was assessed by means of the Hollingshead/Redlich scale (item range 1–5). Baseline extrapyramidal symptoms were assessed using the Modified Simpson-Angus Extrapyramidal Symptom Scale (SAEPS) (item range 1–5) (Simpson and Angus 1970).

Premorbid Adjustment Scale. At baseline, patients’ premorbid status was assessed by using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al. 1982); age at onset and mode of illness onset were ascertained by interviews with the patients and their families after the patients had responded to treatment. The PAS was selected from various scales to assess premorbid functioning in schizophrenia (Phillips 1953; Gittelman-Klein and Klein 1969; Goldstein 1977; Cannon-Spoor et al. 1982) because it provides a measure of premorbid symptoms at different stages of life and prior to the onset of psychotic symptoms, in contrast to an assessment of premorbid functioning immediately prior to illness onset and initial psychiatric and hospital presentation. Thus, it decreases the confounding of measures by acute illness and provides a clearer measure of premorbid features. In our study,
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"premorbid" was defined as the period ending 6 months prior to the first onset of psychotic symptoms (as evidenced by delusions, hallucinations, or prominent thought disorder). This information was cross-referenced with chart and patient recall information and integrated by research team discussion. When differences between patients' and family members' responses/recollections were evident, a consensus decision was made by research team discussion. All PAS evaluations were done by a single research team staff member blind to subjects' treatment response and trained and reliable in PAS administration.

The PAS is divided into five sections. The first four sections assess four time periods: childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood (19 years and above). The fifth section is a general section providing an overall indication of premorbid educational, occupational, social, and energy level. This nonspecific section was not considered as reliable as the other four and therefore will not be considered any further. Sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and sociosexual functioning were assessed within each period. Items were scored on a scale from 0 to 6, with 0 denoting the best level of functioning and 6 the worst level of functioning. The range of scoring for each developmental period was the same, allowing comparison scores across developmental periods. The PAS was assessed in patients up until the time of their onset of symptoms, at which time they were no longer considered premorbid.

Classification and Change in Premorbid Functioning
To examine the course and consistency of premorbid functioning, we used the criteria of Haas and Sweeney (1992) to examine change in PAS scores across developmental periods. The median score on the PAS scale was used instead of PAS anchors to discriminate between these two groups to maintain conformity with previous studies and to demonstrate replicability of observations. Based on the PAS, three patterns of premorbid functioning in schizophrenia are described: (1) deteriorating premorbid functioning, defined as a progressive or insidious decline over the four age groups of at least a 2-point drop in scores between the childhood and adulthood groups; (2) good premorbid functioning, defined as adequate to good premorbid functioning from childhood to onset of psychosis; and (3) chronically poor premorbid functioning, defined as consistently poor premorbid functioning from childhood to onset of psychosis. The stable good and stable poor groups are formed by using the median of the "nondeteriorating" subjects' scores to divide these subjects into the two groups. Change between age groups was defined as an increase or decrease of at least 0.66 in the mean PAS score, the change corresponding to a 2-point change from childhood to adulthood.

Clinical Management and Assessment. After completion of baseline assessments, patients received open treatment with a standardized treatment algorithm (Lieberman et al. 1993; Robinson et al. 1999). Patients were evaluated every other week during acute treatment and monthly during the maintenance phase by means of the SADS–C+PD, SANS, CGI, Global Assessment Scale (GAS; Endicott et al. 1976), and SAEPS scales. Treatment response was defined as ratings of 3 (mild) or less on the psychotic item scales of the SADS–C+PD, a CGI severity item rating of "mild" or less, and a rating of at least "much improved" on the CGI improvement item. To be classified as responders, patients had to sustain this level of improvement for 8 consecutive weeks. Patients were assessed at baseline and every 8 weeks for tardive dyskinesia (TD) using the Simpson Dyskinesia Scale (SDS; Simpson et al. 1979), modified to include a global severity item. Presence of TD was defined as two independent raters agreeing on a global judgment of at least 2 (mild) on this scale following independent examinations.

Deficit State Classification. Patients were classified by the criteria for the deficit state of schizophrenia (Mayerhoff et al. 1994) during the followup phase of the study. To classify for the deficit state according to these criteria, patients were required to have been remitted from their acute psychotic episode for at least 6 months, to have a SANS rating of 3 or greater on at least two of the first four global categories (affect, alogia, avolition, anhedonia), to have no "significant" signs of parkinsonism (akinesia, tremor, rigidity) on the SAEPS, and to have no "significant" depression or anxiety on the SADS–C+PD. "Significant" was defined as a depression rating of 4 or greater; an anxiety rating of 6 or greater; and an akinesia, tremor, or rigidity rating of 2 or greater on the Simpson–Angus Neurological Rating Scale. Because our first episode study population differs obviously from the general chronic schizophrenic population, this modified approach slightly differs from other approaches. This can be noted perhaps most importantly with regard to the 6-month period of clinical stability required for deficit state definition—not 12 months, as in the core Carpenter et al. (1988) criteria.

Statistical Analysis. We used mixed models analysis to address the change in premorbid adjustment over the development stages. This method allows analysis of incomplete longitudinal data, given that not all subjects had all four developmental stages rated. We also used
mixed models analyses to study interaction effects of sex, diagnosis, and deficit state with developmental stage to see whether any worsening in premorbid adjustment occurred at similar rates among groups. Effects seen in the mixed models analysis of mean PAS scores were followed up by similar mixed models analyses of the component PAS scales in order to further clarify any differences among groups.

Associations between the PAS measures and other clinical variables were estimated using product-moment correlations. Comparisons among the three PAS groupings (stable good, stable poor, and deteriorating) were achieved using analysis of variance for the continuous measures (e.g., age, age of onset) and categorical data analysis for variables such as sex and race. Survival analysis was used when the outcome of interest was the time to an event (remission, TD). Life table analyses comparing the survival functioning between PAS groupings, and Cox proportional hazards regression analyses looking at the effect of PAS scores on remission and TD, were the survival techniques used.

Because we report the results of multiple analyses, we emphasize the strength of associations rather than their statistical significance. We aim to achieve this by reporting the point estimates of these associations and confidence intervals (CIs) to indicate the precision of these estimates.

Results

Demographics. One hundred and eighty subjects (52% male) who met inclusion criteria and provided informed consent were recruited from consecutive admissions to the inpatient service of Hillside Hospital. One hundred and eleven of these patients (57 males, 54 females) had a PAS interview. The PAS was not administered to one patient who was 5 years old at the onset of psychotic symptoms, and six patients refused to allow interviews with their relatives. Patient diagnoses were schizophrenia (n = 78) and schizoaffective disorder (n = 33) (table 1 contains demographic and clinical characteristics). The mean (standard deviation [SD]) age at study entry was 25.2 years (6.6) and at first presentation of psychiatric symptoms was 23.9 years (6.7). There was a range of socioeconomic class and educational levels, but there was a predominance of patients in the middle class and below (mean Hollingshead/Redlich score was 3.29 [SD = 1.34]).

PAS Scores. Mean (SD) PAS scores were as follows: childhood (n = 111) = 1.19 (0.88), ranging from 0 to 3.75; early adolescence (n = 108) = 1.35 (0.84), ranging from 0.2 to 5; late adolescence (n = 102) = 1.60 (1.07), ranging from 0 to 5; and adulthood (n = 78) = 1.84 (1.34), ranging from 0 to 5 (table 2). The sample number decreased as the age range increased because several patients began experiencing the onset of symptoms and were, therefore, no longer in the premorbid phase. Table 2 summarizes the results of mixed models analyses that investigated the change in premorbid adjustment over the four developmental stages represented in the PAS. In these analyses, the initial developmental stage, childhood (except for socioeconomic aspects, which were not rated in childhood and wherein the initial stage is early adolescence), was coded 0 so that the intercept represents the score during this initial stage. The regression coefficient for developmental stage estimates the degree of change in premorbid adjustment over each subsequent stage. The coefficients for developmental stage were all positive, indicating a worsening in premorbid adjustment in the mean PAS and the five components of the PAS. All of the 95 percent CIs for these regression coefficients excluded 0, indicating that these slope coefficients were all statistically significant. In childhood, premorbid behavior ranged from normal to moderately withdrawn, with a tendency to some mild deviant friendship patterns, and fair achievement and adaptation in school. With a similar analysis of the range of scores around the means of early adolescence, late adolescence, and adulthood, premorbid behavior ranged from normal to significantly withdrawn, with very poor achievement and adaptation to school, limited contacts with those of the same sex, and very rare contacts with those of the opposite sex.

Patients with schizophrenia scored worse on all PAS items, except for sociosexual functioning in early and late adolescence. The only significant effects involving diagnosis in the mixed model analyses related to sociosexual functioning. Patients diagnosed with schizophrenia had better sociosexual functioning during early adolescence; the difference among diagnostic groups during this initial stage was estimated by a regression coefficient of −0.63 (95% CI = −1.20, −0.06). However, the stage-by-diagnosis interaction was 0.64 (95% CI = 0.017, 1.11), indicating a reversal in the difference in sociosexual functioning among adults.

PAS and Gender Differences. Males and females had comparable overall PAS scores during childhood. However, males became progressively worse over subsequent stages, as indicated by a significant stage-by-sex interaction in mixed models analysis (t = 2.41, df = 286, p = 0.016). The rate of change among men was three times greater than among women, increasing by 0.22 (95% CI = 0.04, 0.40) above the female rate of 0.11 (95% CI = −0.14, 0.24). Examination of the component PAS scales revealed that this interaction of sex and developmental stage in mean PAS was mainly due to sociosexual functioning, the only component scale that also had a signifi-
### Table 1. Characteristics of 111 subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Age of patient, mean (SD)</td>
<td>25.2 (6.6)</td>
</tr>
<tr>
<td>Age of onset of psychotic symptoms, mean (SD)</td>
<td>23.9 (6.7)</td>
</tr>
<tr>
<td>Weeks of psychotic symptoms to study entry, mean (SD)</td>
<td>71.5 (149.7)</td>
</tr>
<tr>
<td>Baseline psychoticism, mean (SD)</td>
<td>4.5 (1.0)</td>
</tr>
<tr>
<td>Baseline disorganization, mean (SD)</td>
<td>2.4 (1.2)</td>
</tr>
<tr>
<td>Baseline SANS global without attention, mean (SD)</td>
<td>2.6 (0.9)</td>
</tr>
<tr>
<td>Baseline Clinical Global Impression, mean (SD)</td>
<td>5.5 (1.0)</td>
</tr>
<tr>
<td>Baseline Global Assessment Scale, mean (SD)</td>
<td>27.1 (9.0)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>57 (51.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47 (42.3)</td>
</tr>
<tr>
<td>Black</td>
<td>40 (36.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Parental SES, n (%)</td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>Upper-middle</td>
<td>20 (18.3)</td>
</tr>
<tr>
<td>Middle</td>
<td>30 (27.5)</td>
</tr>
<tr>
<td>Lower-middle</td>
<td>18 (16.5)</td>
</tr>
<tr>
<td>Lower</td>
<td>29 (26.6)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>59 (53.2)</td>
</tr>
<tr>
<td>Disorganized</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Catatonic</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>13 (11.7)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td></td>
</tr>
<tr>
<td>Mainly schizophrenia</td>
<td>20 (18.0)</td>
</tr>
<tr>
<td>Mainly affective</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (8.1)</td>
</tr>
</tbody>
</table>

**Note.**—SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation; SES = socioeconomic status.

### Table 2. Effects of developmental stage on premorbid adjustment

<table>
<thead>
<tr>
<th>Intercept (95% CI)</th>
<th>Regression coefficient for stage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAS</td>
<td>1.17 (1.00, 1.33)</td>
</tr>
<tr>
<td>Sociability and withdrawal</td>
<td>0.83 (0.61, 1.05)</td>
</tr>
<tr>
<td>Peer relationships</td>
<td>1.27 (1.07, 1.48)</td>
</tr>
<tr>
<td>Scholastic performance</td>
<td>2.01 (1.75, 2.28)</td>
</tr>
<tr>
<td>Adaptation to school</td>
<td>0.51 (0.29, 0.73)</td>
</tr>
<tr>
<td>Sodosexual aspects</td>
<td>1.37 (1.11, 1.64)</td>
</tr>
</tbody>
</table>

**Note.**—CI = confidence interval; PAS = Premorbid Adjustment Scale.

1 The initial developmental stage, childhood (except for sodosexual aspects, wherein the initial stage is early adolescence), was coded 0 so that the intercept represents the score during this initial stage. The regression coefficient for stage estimates the increase (or worsening) of premorbid adjustment since the preceding stage.
significant stage-by-sex interaction \((t = 3.67, df = 173, p < 0.001)\). While the slope among women showed virtually no change in sociosexual functioning \((slope = -0.04, 95\% CI = -0.33, 0.25)\), the coefficient for the stage-by-sex interaction was 0.78 \((95\% CI = 0.36, 1.20)\). Thus, the sociosexual functioning ratings among males worsened by about three-quarters of a point over each developmental stage, indicating prominent decline in functioning as compared to females.

PAS and the Deficit State. Mixed models analysis of mean PAS scores indicated worse overall PAS scores in patients with the deficit state, with a regression coefficient of 0.36 \((95\% CI = 0.01, 0.71)\). There was interaction of deficit state with developmental stage; the deficit state group had consistently worse scores across stages. Similar results held in mixed models analyses of sociability and withdrawal \((regression coefficient for deficit state = 0.57; 95\% CI = 0.10, 1.06)\), peer relationships \((regression coefficient for deficit state = 0.52; 95\% CI = 0.07, 0.97)\), and scholastic performance \((regression coefficient for deficit state = 0.56, 95\% CI = -0.02, 1.13)\). The effect of deficit state on scholastic performance was, however, not statistically significant at the 0.05 level. A more complicated pattern was seen in the comparison of sociosexual functioning by deficit state. A significant stage-by-deficit-state interaction \((t = 2.77, df = 173, p < 0.01)\) indicated that the deficit state group became progressively worse in sociosexual adjustment.

PAS Correlations With Clinical Variables. Because of the large number of correlation analyses required for the associations between all PAS measures and clinical variables, we adopted a hierarchical analytic method. Thus, the association between mean PAS at each time period was tested first with each clinical variable; only if the association was significant were further analyses of the specific items of the same stage performed. To control for alpha level for multiple comparisons, a Bonferroni correction was implemented for the correlation analysis of the five items using an alpha level of 0.01. This alpha level corresponds to a critical \(r\) value of 0.25 (2-tailed). By means of this hierarchical method, SANS global items \(\) (excluding the attention global item) showed positive correlations with mean PAS score during childhood \(r = 0.23, 95\% CI = 0.03, 0.42\) and early adolescence \(r = 0.22, 95\% CI = 0.02, 0.41\). Analysis of items showed that the SANS was related to childhood sociability and withdrawal \(r = 0.28, 95\% CI = 0.04, 0.52\), and adaptation to school \(r = 0.29, 95\% CI = 0.05, 0.53\). No associations with early adolescence items were significant. In addition, a longer duration of psychosis prior to study entry was negatively associated with mean PAS score for late adolescence \(r = -0.22, 95\% CI = -0.40, -0.02\). Analysis of items during late adolescence did not yield further associations. Lower GAS scores, indicating poorer global functioning, were associated with worse early adolescence mean PAS scores \(r = -0.24, 95\% CI = -0.43, -0.04\). Further analysis showed that lower GAS scores were also associated with poorer early adolescence adaptation to school \(r = -0.25, 95\% CI = -0.49, -0.01\).

PAS and Treatment Outcomes. The relationships of PAS variables to treatment response during the first episode of illness were analyzed using Cox proportional hazards regression. Sex was entered as a covariate in these analyses because females have better treatment response than males. The hazard ratios were all controlled for sex. The only PAS item that significantly predicted worse treatment response was sociability and withdrawal during early adolescence \(\) (hazard ratio = 0.85%, 95% CI = 0.73, 0.99). The sociability and withdrawal item had similar hazard ratios during childhood \(\) (hazard ratio = 0.85%; 95% CI = 0.71, 1.01) and late adolescence \(\) (hazard ratio = 0.87%; 95% CI = 0.76, 1.01), although the upper limits of these hazard ratios only slightly exceeded unity.

PAS and Extrapyramidal Side Effects. Patients who exhibited Parkinsonian signs during the first 16 weeks of treatment had worse sociability and withdrawal during childhood compared to patients who did not develop Parkinsonian signs during this period \((1.23 \pm 1.18\) vs. \(0.68 \pm 1.19\); CI for difference = 0.05, 1.05) \(\) (see also Chatterjee et al. 1995). The development of dystonia and akathisia during the first 16 weeks of treatment was not correlated with any PAS variables. Worse childhood mean PAS scores were associated with greater risk for TD \(\) (hazard ratio = 1.65%; 95% CI = 1.12, 2.43) \(\) (figure 1). Controlling for antipsychotic drug dose and clozapine use as time-dependent covariates and treatment response to the first episode, the effect of childhood PAS was reduced to a hazard ratio of 1.50 \(95\% CI = 0.99, 2.26\). The lower 95 percent confidence limit for this adjusted hazard ratio was slightly below unity, so the possibility of no effect is not ruled out. The hazard ratio of 1.50 remains nevertheless substantial, indicating an estimated 50 percent increase in the hazard of TD with each unit increment in childhood PAS mean scores. The individual childhood PAS item that significantly predicted TD was peer relationships \(\) (hazard ratio = 1.35%; 95% CI = 1.03, 1.76). The hazard ratios for the other childhood PAS items were of similar direction but were not significant. Peer relationships during early \(\) (hazard ratio = 1.33; 95% CI = 1.01, 1.74) and late \(\) (hazard ratio = 1.33; 95% CI = 1.03, 1.72) adolescence were also significant predictors of TD. Adult sociosexual functioning was also a predictor of TD \(\) (hazard ratio = 1.31; 95% CI = 1.004, 1.71).
Classification and Change in Premorbid Functioning.

From childhood to early adolescence, 80.6 percent of patients showed no change in premorbid functioning, 14.8 percent worsened, and 4.6 percent improved. From early adolescence to late adolescence, 75.5 percent showed no change, 19.6 percent worsened, and 4.9 percent improved. From late adolescence to adulthood, 53.2 percent showed no change, 28.6 percent worsened, and 18.2 percent improved. Thus, the greatest change was seen in the transition from late adolescence to adulthood.

When analyzed for stable good, stable poor, and deteriorating premorbid functioning as defined above (table 3), 25 (22.5%) subjects exhibited a deteriorating course over the four age groups. The median of 1.2 points on the PAS scale was used as the cutoff between stable good and stable poor groups as per the Haas criteria (Haas and Sweeney 1992). Forty-three (38.7%) subjects demonstrated a pattern of good premorbid functioning, and 43 (38.7%) showed a pattern of chronically poor functioning from the childhood phase up until 6 months prior to the onset of psychotic symptoms. Mean change in PAS total scores for each of the three PAS course groups was 0.01 (SD = 0.58) for the stable good, 0.16 (SD = 0.97) for the stable poor, and 2.81 (SD = 0.85) for the deteriorating course group, respectively. The differences among the three groups were analyzed, and no significant differences in race, age, or diagnosis were found. However, in examining gender, we observed that males formed 72 percent of the deteriorating group, 51.2 percent of the stable poor group, and 39.5 percent of the stable good group ($\chi^2 = 6.67$, $df = 2$, $p = 0.036$). Moreover, those in the stable poor and deteriorating group had an earlier age of onset of psychotic symptoms ($F = 3.2$, $df = 2,108$, $p = 0.043$). The three groups did not differ statistically in the number of weeks of psychotic symptoms prior to study entry, although the mean of the deteriorating group (84.8 weeks) was greater than both the stable poor mean (75.7 weeks) and the stable good mean (35.6 weeks). There were no significant differences at entry into the study among the three groups in delusions and hallucinations, disorganization (defined as an aggregate of bizarre behavior, inappropriate affect, impaired understanding, derailment, and illogical thinking scores on the SADS–C+PD), and negative symptoms (defined as an aggregate of affective flattening, alogia, anhedonia, and apathy). The prevalence of the deficit state was 20.9 percent in the stable good group,
32.6 percent in the stable poor group, and 36 percent in the deteriorating group ($\chi^2 = 2.23, df = 1, p = 0.33$). To determine whether significant correlations were due to outliers, scatterplots were examined and it was proved that this was not the case. Also, similar measures were used to examine between-group differences to determine whether any differences were driven by outliers, but once again this proved not to be the case.

Survival analysis of treatment response among the three groups revealed no statistically significant differences. When patients were categorized into full remitters, partial remitters, and nonremitters after 1 year of treatment, the proportion of stable good patients who had fully remitted was 85.4 percent, compared to 65.8 percent and 68 percent in the stable poor and deteriorating groups, respectively. Nonremitters composed 4.9 percent of the stable good group compared to 13.2 percent and 12 percent in the stable poor and deteriorating groups, respectively. The pattern of results was, however, not statistically significant (Mantel-Haenszel $\chi^2$ for trend = 2.79, $df = 1, p = 0.10$).

There were no differences among the three groups in the incidence of parkinsonism, akathisia, or dystonia over the first 16 weeks of treatment. However, there were significant differences in the incidence of TD among the three groups (Wilcoxon $\chi^2 = 8.58, df = 2, p = 0.014$). Survival curves of TD onset (figure 1) show that the deteriorating functioning group commenced treatment appearing similar to the stable good group and then fairly rapidly declined, more closely matching the stable poor group in TD onset. TD incidence rates for the stable good, stable poor, and deteriorating premorbid groups, respectively, were 2.4, 12.5, and 4.0 percent at 1 year; 2.4, 15.1, and 8.2 percent at 18 months; 5.0, 23.1, and 8.2 percent at 2 years; 7.7, 32.6, and 13.3 percent at 3 years; and 18.6, 45.1, and 37.7 percent at 5 years.

When the three categorical PAS groups were compared on individual PAS items, analysis of variance demonstrated significant differences among the three groups at all four age categories on the individual item of sociability and withdrawal ($F = 14.19-42.35, df = 2, p = 0.0001$). The deteriorating group scored best at childhood compared to the two other groups but then rapidly declined in functioning, as evidenced by significantly worse sociability and withdrawal scores in late adolescence and adulthood.

### Discussion

#### Relevance of Current Study. Our data are consistent with the findings of previous studies that a subgroup of patients with schizophrenia exhibit poor premorbid functioning and that males have progressively worse premorbid functioning than females. This pattern suggests that the gender differences in the disease expression precede not only the formal onset of the illness but also puberty. While differential social demands on males compared to females may account for these differences, other more independent illness-specific factors may more likely play a role. While at least one other first episode study has investigated premorbid functioning in schizophrenia (Bromet et al. 1996) and found progressively poorer premorbid functioning from adolescence onward, our findings provide further and more detailed descriptive information on the patterns of premorbid functioning in the first episode psychosis population. More specifically, the current study describes in a comprehensive manner in a large prospective cohort of schizophrenia patients the relationship between premorbid functioning and baseline clinical features, treatment response, and side effects.
Our findings shed light on and confirm the probable existence of a more severe subtype of schizophrenia, one that is characterized by worse premorbid functioning (in particular, impaired sociability and social withdrawal), deficit state, negative symptoms, and susceptibility to TD. This information is clarified by means of analysis of a first episode sample, one that permits a more thorough investigation of premorbid functioning because of the shorter separation in time, thus excluding the potential bias of a lengthy retrospective assessment.

The relationship between the deficit state and PAS scores and the relationship between negative symptoms and PAS scores differ from each other because these are overlapping but distinct measures. The criteria for deficit state define a more severe subgroup of the illness, rather than the broader SANS clinical characterization of negative symptoms in all patients, and this may account for the stronger association with PAS scores across all four developmental stages. It should be noted that the correlation coefficients of the PAS scores with clinical variables are somewhat low (up to 0.3). Although this is a potential limitation of the strength of our findings, the low correlations may perhaps be explained by the "restriction of range artifact." While correlation analysis requires high variability of scores (i.e., a heterogeneous sample), the present study included only patients suffering from schizophrenia and schizoaffective disorder, which may have represented a restricted part of the range of the variables, thus leading to a ceiling effect of the correlation coefficients' value. A further potential limitation of the study includes the possibility of spurious results emerging from the study findings. Thus, it is possible that to some extent the pattern of results is cohort specific, limiting the external validity of study findings and thus the generalizability of the observations to other subpopulations of patients with first episode schizophrenia. While this possibility certainly exists in investigations of such nature, in the present study we aimed to minimize the problem by using a hierarchical approach of data analysis.

While several of our findings replicate observations from other studies (e.g., impaired overall premorbid functioning in schizophrenia, gender differences, association with deficit state), we achieve this in the context of a comprehensive, well-described cohort of patients, with important new findings illustrating the centrality of impaired sociability and withdrawal aspects of impaired premorbid functioning, a clear relationship with TD (to the exclusion of other extrapyramidal symptoms), as well as a broad description of the clinical aspects of the subgroup of schizophrenia patients exhibiting a deteriorating pattern of premorbid functioning.

**Impaired Sociability and Withdrawal.** We found poorer scores on the sociability and withdrawal scale correlating significantly with an increased time to treatment response, more severe negative symptoms, a higher incidence of parkinsonism, and deterioration of premorbid functioning. It should be emphasized that these observations were noted in contradistinction to other PAS items that did not consistently demonstrate any such pattern. One may therefore infer that asociability and withdrawal may manifest as an early marker of a more severe and complicated form of schizophrenia.

The basis of dysfunctional sociability and withdrawal is unclear. Some have hypothesized that this impaired sociability and withdrawal may be manifested more as a deficit in social skills (Mueser et al. 1990), defective emotional rapport (Parnas et al. 1982), or thought disorder (Carpenter 1983). Others have considered that poor sociability may essentially be the expression of negative features on behavior (Jackson et al. 1989), such as anhedonia and lack of social purpose and will (Chapman et al. 1976), or that negative symptoms are essentially the persistence or exacerbation of schizoid/asocial traits prior to the onset of the full schizophrenic illness (Peralta et al. 1991). This study, however, indicates that the problem may be more central to the sociability item, as there were no significant differences shown among the stable good, stable poor, and deteriorating groups in negative symptoms at study entry, but there were differences on sociability and withdrawal items. While sociability and withdrawal appear to predict outcome early in the illness, our results suggest that sociability and withdrawal do not add any predictive value information about treatment response over and above that which negative symptoms may provide at onset of psychotic illness. It may be that patients who have premorbid asociability have postmorbid social withdrawal manifested as negative symptoms later in the illness. It is unclear whether this predictive value may hold true later in the disease process (McGlashan 1986). Interestingly, children considered genetically at high risk for schizophrenia appear to exhibit poor social competence in early and late adolescence (Dworkin et al. 1991). It remains to be seen whether this is a reversible factor that may be corrected by a pre-illness intervention in high-risk populations—an intriguing possibility of disease modification at an early stage.

**Premorbid Symptoms and TD.** We found that PAS scores predicted susceptibility to TD but not to dystonia, parkinsonism, or akathisia. In particular, overall severity of childhood premorbid functioning predicted TD occurrence. Others have demonstrated an association of premorbid asociality with TD (Wegner et al. 1985). There are at least two potential explanations for this predisposition to TD. First, TD has a different pathophysiology than other extrapyramidal side effects (APA 1992). We have
previously suggested that TD vulnerability may be a constitutional feature of a more severe schizophrenia phenotype that requires typical antipsychotic drug exposure for its expression and also includes poorer therapeutic response and greater severity of negative symptoms (Chakos et al. 1996). However, several studies involving older patients have failed to demonstrate this association (Lindenmayer et al. 1984; Opler et al. 1984; Richardson et al. 1985; Iager et al. 1986). TD has also been observed in nonmedicated individuals with schizophrenia, suggesting a more intrinsic biological process independent of the exogenous use of antipsychotic medication (Owens et al. 1982; Fenn et al. 1996; McCreadie et al. 1996). In addition, the observation of oral-facial dyskinesias in schizophrenia patients prior to medication initiation has been associated with an illness type characterized by more negative symptoms (Fenton et al. 1994). Interestingly, and supporting the above hypothesis of a more severe subtype of schizophrenia, TD has also been associated with progressive cognitive dysfunction (Waddington and Youssef 1996) and overall a poorer long-term outcome (Crow 1985).

Change in Premorbid Symptoms. In the majority of patients, premorbid functioning remained stable over time as defined above, even when analyzed from each developmental stage to the next. There was only slightly more of a change from late adolescence to adulthood, perhaps signifying an early subclinical prodromal period prior to the first overt clinical psychotic episode. This is not unexpected because the closer the PAS assessment is to the formal onset of the illness, the more likely that premorbid functioning is reflecting the prodromal phase of imminent clinical illness to come. Thus, many patients remain relatively stable in their poor premorbid functioning over the successive age periods, and the PAS scores highlight the fact that significant dysfunction occurs before the onset of prodromal symptoms of the illness in many cases. These early abnormalities in premorbid functioning therefore do not merely reflect the prodromal phase of the illness.

These data also replicate previous findings that approximately 25 percent of schizophrenia patients experience deteriorating premorbid functioning from childhood to adulthood (Haas and Sweeney 1992). This group clearly demonstrated a worse illness presentation, including earlier onset, greater prevalence of the deficit state after the first episode, longer duration of psychosis, and poorer outcome. Similarly, we replicate findings that a third of schizophrenia patients exhibit chronically poor premorbid functioning. Our findings are particularly significant considering that, to our knowledge, this sample is the largest individual cohort published to date describing the nature of premorbid functioning in schizophrenia. In contrast to previous descriptions of premorbid function-
individuals to future dysfunction and disease manifestation. These processes may be genetic, environmental, or both. These findings therefore provide further support for the previously suggested hypothesis (Weinberger 1987; Done et al. 1994; Murray 1994) that for some patients the illness of schizophrenia may start long before the onset of the first psychotic presentation.

In summary, these findings provide further descriptive information on the patterns of premorbid functioning in the first episode psychosis population. Our results demonstrate poor premorbid functioning in schizophrenia patients, but with a range in severity correlating with clinical severity of disease at first formal clinical assessment and with treatment response. Male schizophrenia patients demonstrate worse premorbid functioning than females. Sociability and withdrawal appear to be overall the most important features predicting clinical aspects of the illness. Premorbid symptom assessment remains an important clinical tool in the evaluation of schizophrenic illness and is of potential prognostic value.

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