The Schizophrenia Prodrome Revisited: A Neurodevelopmental Perspective

by Barbara A. Cornblatt, Todd Lencz, Christopher W. Smith, Christoph U. Correll, Andrea M. Auther, and Emile Nakayama

Abstract

Despite the widespread acceptance of the neurodevelopmental model of schizophrenia, its application to research concerned with the prodromal phase of illness is limited. Little recognition has been given to the concept of an enduring biological vulnerability to illness that may be responsive to early intervention. Rather, the focus of most prodromal studies is on emerging positive symptoms. The Recognition and Prevention (RAP) program follows the strategy of being equally concerned with the nonspecific symptoms reflecting the core of schizophrenia and those directly related to psychosis. Data were collected from 62 adolescents (mean age = 16.4 years) during the initial 3-year pilot phase of the RAP program (1998–2001). Subjects were divided into three clinical high-risk groups, characterized by (1) negative and nonspecific symptoms (e.g., social isolation, school failures), the earliest prodrome stage; (2) emerging attenuated positive symptoms of moderate intensity; and (3) severe attenuated (but subpsychotic) positive symptoms, considered most proximal to psychosis. Four risk factors, derived from the neurodevelopmental literature, were selected to reflect the vulnerability core: cognitive deficits, affective disturbances, social isolation, and school failure. All four domains were equally unpaired across the three risk groups, supporting the presence of the underlying vulnerability core regardless of the magnitude of emerging positive symptoms. An observational pilot study was also conducted to identify the medications typically used to treat emerging positive symptoms. Antidepressants were used as frequently as antipsychotics to treat adolescents presenting with moderate attenuated positive symptoms. Regardless of type of medication, moderately symptomatic youngsters did quite well over the approximately 1-year followup period. By contrast, adolescents presenting with more severe (but nonpsychotic) attenuated symptoms were treated with antipsychotics, often in combination with other agents. Outcome for the more symptomatic youngsters was, however, more guarded, with nearly half (i.e., 47%) of the group converting to a schizophrenia spectrum psychotic disorder. Nonadherence to medication appeared to be a major risk factor in this group. We conclude that a neurodevelopmental model of schizophrenia is supported by our data and that a range of novel treatment strategies may be neuroprotective by directly affecting the disorder’s vulnerability core.

Keywords: Prodrome, schizophrenia, neurodevelopmental, clinical high risk, vulnerability, risk factors, attenuated positive symptoms, negative symptoms, antipsychotics, antidepressants.


The widely accepted neurodevelopmental view of schizophrenia (e.g., Murray and Lewis 1987; Weinberger 1987; Lieberman et al. 2001) provides an implicit theoretical foundation for early intervention during the prepsychotic or “prodromal” stage of illness. However, the treatment implications of this model have thus far been of peripheral interest to ongoing clinical trials. In this article, we will argue that the explicit application of a neurodevelopmental approach considerably broadens the concept of the prodrome and, by so doing, introduces a number of possible remediative and preventive treatment options. Throughout this article, much of our discussion will be illustrated by early data emerging from the Recognition and Prevention (RAP) program of the Zucker Hillside Hospital in New York. From its inception, the RAP program has adopted a developmental clinical high-risk (CHR) research strategy (Cornblatt et al. 2001, 2002).

Vulnerability Concept

The details of proposed neurodevelopmental mechanisms continue to evolve across the field (e.g., Davidson et al. . . . )

Send reprint requests to Dr. B.A. Cornblatt, The RAP Program, 444 Lakeville Road, Suite 303, Lake Success, NY 11042; e-mail: cornblat@lij.edu.
1999; Tsuang and Stone 2000; Tsuang et al. 2000; Lieberman et al. 2001; Cannon et al. 2003). Figure 1 presents the working model that currently guides the RAP program research strategy. According to this model, fully expressed schizophrenia involves two distinctly different dimensions: (1) a biological vulnerability and (2) later developing positive symptoms. The biological vulnerability is viewed as involving a substantial genetic component and as consisting of deficits and behavioral disturbances directly reflecting underlying brain pathology. These early subtle abnormalities are likely to be major contributing factors to later illness. We hypothesize that the vulnerability core is the necessary, although not sufficient, substrate leading to schizophrenia and is the root of the often crippling disability associated with it. In the absence of positive symptoms, this biological disorder is thought to result in nonpsychotic spectrum disorders (e.g., schizotypy, schizoid and avoidant personality disorders) or more moderate, but related, functional disorders. This view is consistent with family and twin studies that have demonstrated a higher rate of schizotypy in the nonpsychotic first degree relatives of adults with schizophrenia and a considerably stronger genetic involvement in negative as opposed to positive symptoms (Kety et al. 1976; Dworkin and Lenzenweger 1984; Dworkin et al. 1988; Kendler et al. 1995). For heuristic purposes, we have selected four major domains that we hypothesize directly reflect the vulnerability core of schizophrenia: (1) cognitive deficits, (2) affective disturbances (i.e., depression), (3) social isolation, and (4) school failure. We refer to these by the abbreviation CASIS. This cluster clearly does not include all signs and symptoms associated with either pre-illness or prodromal vulnerability; instead, it focuses on risk factors that appear to be particularly good targets for future interventions. We consider a risk factor to be a characteristic that, if present, makes an individual more likely to develop a disorder than a member of the general population who lacks this feature would be (Mrazek and Haggerty 1994). A primary goal of our program is to determine whether remediating these early deficits will substantially reduce the probability that schizophrenia will later develop.

The vulnerability construct illustrated by figure 1 is highly compatible with a range of epidemiological research, including follow-back studies, such as the British (Done et al. 1994; Jones and Done 1997) and Finnish birth cohorts (Cannon et al. 1999), the large population Swedish

Figure 1. The neurodevelopmental model currently guiding the RAP program
conscript (David et al. 1997; Malmberg et al. 1998), and Israeli Army studies (Davidson et al. 1999), and with traditional genetic high-risk (GHR) research (e.g., Nuechterlein and Dawson 1984; Erlenmeyer-Kimling and Cornblatt 1987; Cornblatt and Keilp 1994; Tsuang and Faraone 1999; Tsuang and Stone 2000; Tsuang et al. 2000, 2002; Cornblatt 2002). Treatment is not generally a concern of these studies, which are typically designed to chart the course of illness and identify risk factors and predictors of illness (Cornblatt 2002). Treatment-focused research, and clinical trials in particular, tend to concentrate almost exclusively on the attenuated positive symptoms foreshadowing psychosis. The positive symptom focus has resulted in an overly narrow definition of the prodrome that, in turn, leads alternative, potentially effective interventions (both pharmacological and nonpharmacological) to be overlooked. This is a significant omission, because negative-like prodromal symptoms are considered a direct link to the often profound functional disability that characterizes schizophrenia (Green 1996) and that often remains even after the successful treatment of psychotic symptoms.

### CASIS Cluster

The four domains of the CASIS cluster have been selected to reflect the vulnerability core because (1) they are supported by a large and consistent literature, (2) they reflect the earliest findings in the RAP program, and (3) they appear causally related to the disability associated with the range of schizophrenia spectrum disorders. Causality is critical because attempting to reduce risk factors may be pointless if such intervention does not affect later illness (Kraemer et al. 2001).

#### Cognitive Deficits

Cognitive deficits are thought to be a direct reflection of the underlying brain pathology and are most likely detectable developmentally as soon as they can be reliably measured. Findings from traditional GHR studies that prospectively follow the children of parents with schizophrenia have indicated that neurocognitive deficits (especially compromised attention and working memory) can be detected in early childhood, at least by age 9, and precede other types of symptoms by many years (e.g., Cannon and Mednick 1993; Cornblatt and Keilp 1994; Cornblatt et al. 1999; Erlenmeyer-Kimling et al. 2000). Cornblatt and colleagues also found that childhood neurocognitive deficits were related to social skill deficits in adolescence and social isolation in adulthood, suggesting a causal relationship with at least the interpersonal component of the vulnerability (Dworkin et al. 1991, 1994; Cornblatt et al. 1992, 1999). This suggests the possibility that early cognitive intervention might reduce multiple vulnerability components. The GHR cognitive findings are well supported by the host of cognitive difficulties in childhood and adolescence reported to precede schizophrenia in the 1946 and 1958 British cohort studies (Done et al. 1994; Jones et al. 1994; Jones and Done 1997), the 1949–50 Swedish conscript study (David et al. 1997; Malmberg et al. 1998), and the Israeli army study (Davidson et al. 1999). However, previous findings have also indicated that neurocognitive functions are complex and multidimensional and may play several roles in the unfolding of schizophrenia, only some of which are causal (e.g., Nuechterlein and Dawson 1984).

#### Affective Disturbances

Although emerging later than cognitive difficulties, affective disturbances, the second CASIS factor, have been reported to be a relatively early prodromal precursor of schizophrenia. As part of their groundbreaking longitudinal study of first episode patients, Hafner and colleagues conducted a systematic, retrospective investigation of the schizophrenia prodrome. Depression was found to be the most frequently reported and earliest prodromal symptom and to precede the onset of psychosis by 5 years or more (e.g., Maurer and Hafner 1995; Hafner et al. 1999). Moreover, additional analyses suggested that depression is not a reaction to the symptoms of schizophrenia or a consequence of medication but a direct expression of the disease process (Hafner et al. 1999).

#### Social Isolation

Hafner et al. (1999) also reported that nonspecific symptoms tended to emerge shortly after the appearance of the first depressive symptoms. In particular, social disability characterized a substantial proportion of patients and preceded the onset of psychosis by 2 to 4 years. These authors further noted that the younger the patients’ age at onset, the lower their social development, leading the authors to conclude that the level of social development attained during the prodromal phase sets the upper limit on social development throughout the course of illness. These observations, in turn, highlight the importance of early intervention. Other retrospective studies have also found social isolation to be one of the prodromal symptoms most frequently reported by first episode patients (e.g., Jackson et al. 1995; Moller and Husby 2000; Gourzis et al. 2002). In addition, deficits in social functioning have been consistently detected in adolescents at genetic risk for schizophrenia (e.g., Dworkin et al. 1991, 1994) and in children and adolescents who later developed schizophrenia across many of the birth cohorts, including in the British 1946 and 1958 studies (Jones et al. 1994; Jones and Tarrant 1999). For example, at age 18, Swedish military conscripts who later developed schizophrenia experienced a range of social difficulties, includ-
ing having fewer than two friends, preferring small social groups, feeling more sensitive than their peers, and being less likely to have a steady girlfriend compared to age-matched controls (David et al. 1997; Malmberg et al. 1998).

School Failure. In studies of at-risk children and adolescents, decline in school functioning can be considered a proxy for deterioration in role functioning. Among those studies with childhood and adolescent developmental data, school difficulties were frequently found to characterize preschizophrenia individuals (Jones et al. 1994; Jones and Done 1997; Cannon et al. 1999; Moller and Husby 2000). Furthermore, these school difficulties are not simply a function of cognitive problems. For example, in their analysis of all individuals who were born in the Finnish birth cohort in Helsinki between January 1, 1951, and December 31, 1960, and who later developed schizophrenia, Cannon et al. (1999) reported that children between the ages of 7 and 11 did not differ from controls academically but nevertheless were considerably less likely than controls to progress to high school. This school problem was interpreted as possibly one of the earliest vulnerability signs.

Positive Symptoms

The second dimension essential for the development of psychosis involves the processes leading directly to psychosis, reflected by sharply increasing positive symptoms, typically beginning in mid- to late adolescence. As illustrated in figure 1, full disease expression may require some sort of “trigger,” involving one or more independent environmental or biological stressors. Although no specific trigger has yet been identified, some likely neurobiological candidates include programmed cell death, axonal myelination, and synaptic pruning (Hoffman and McGlashan 2001; Lieberman et al. 2001; Cannon et al. 2003). It is also unclear whether the triggering process acts directly on the underlying vulnerability or affects an entirely independent domain with a different genetic etiology. In either case, it is assumed that without the underlying vulnerability, the positive symptom component would not lead to schizophrenia. Walker et al. (2002), for example, have recently proposed that this latter pattern will lead to bipolar illness, which will essentially have no prodrome because of the absence of the underlying vulnerability.

Because attenuated positive symptoms emerge from mid- to late prodrome, these symptoms can be considered most proximal to onset. As such, attenuated positive symptoms might be expected to be the most accurate predictors of impending illness. The notion that reducing them, or, more optimally, eliminating their pathway altogether, will prevent schizophrenia is logical and intuitively appealing. This possibility, in turn, provides a major rationale for concentrating on the pharmacotherapy of attenuated positive symptoms (with antipsychotics) to the exclusion of interest in the more nonspecific vulnerability risk factors. However, because attenuated symptoms blend into psychosis, such treatment is secondary rather than truly preventive and does not typically improve the disability associated with the vulnerability deficits.

In the following sections, we will first describe the RAP program and illustrate the ways in which our neurodevelopmental model, as discussed above, has provided the framework for our research strategy. We will next present some of the early findings that have emerged from the RAP program that support several of the hypotheses inherent to our model. We will describe an expanded phase of illness model based on differences in the baseline severity of positive symptoms, with the resulting three CHR groups displaying a linear increase in attenuated positive symptoms. Next, we will cross-sectionally validate our selected nonspecific risk factors by demonstrating that they are invariant across the three risk groups and thus independent of increasing positive symptoms. We will close by discussing the implications of our findings for developing future pharmacological interventions.

RAP Program

Subjects are recruited into the RAP program from the RAP clinic, which is an independent treatment facility jointly sponsored by the Zucker Hillside and Schneider Children's Hospitals of the North Shore–Long Island Jewish Hospital Health System in New York. The RAP clinic treats adolescents and young adults between the ages of 12 and 22 (with a primary focus on ages 14–18) who are considered to be in the prodromal stage of schizophrenia (Cornblatt 2002; Cornblatt et al. 2002; and Lencz et al., in press, contain more details). All youngsters accepted into the RAP program are treatment seeking, and most are referred by the intake staff of the Schneider Children’s Hospital Child and Adolescent Ambulatory Services.

Patients are recruited for research from the RAP clinic with the full understanding that research participation in no way affects clinical care. After all procedures are fully explained to potential subjects and their family members and all questions are answered, written informed consent (or assent if under 18) is obtained from participants for each research protocol and, if under 18, from parents as well. All research protocols have been approved by the Institutional Review Board at Long Island Jewish Medical Center.

Initiated in 1998, the RAP program was designed to collect data about the longitudinal progression of symp-
toms and functioning within a naturalistic treatment framework. Throughout the initial pilot period (1998–2001, referred to as Phase I), RAP clinicians treated patients according to best standard practice and had little exposure to RAP research procedures or hypotheses. In terms of treatment research, our strategy during Phase I was observational: to gather information about the type and effectiveness of the medications used to treat prodromal symptoms.

Subjects. In this report, we focus on the initial sample of 62 subjects who participated in Phase I and were diagnosed as being prodromal according to our research criteria. Although we incorporate many of the inclusion criteria developed by McGorry and McGlashan (McGorry et al. 1995, 2002; Yung and McGorry 1996a, 1996b; Miller et al. 1999; McGlashan et al. 2003), the RAP program has a broader definition of the prodrome than is typical of most other studies (see below). It should be noted that we and others have some reservations about the term prodrome, which can be interpreted to imply that illness is inevitable. This problem, although frequently discussed, remains unresolved throughout the field. As a result, for convenience, we use the terms prodromal and CHR interchangeably, with the understanding that in all cases, illness is, at most, only a possibility.

Initial Clinical Subgroups. Although we cast a broader net than most other prodromal studies, we nevertheless attempt to clarify etiology by dividing the overall sample into relatively homogeneous subgroups. Currently, the largest at-risk group within the overall RAP sample includes treatment-seeking subjects with moderate to severe attenuated positive symptoms (the CHR+ group, n = 42). These symptoms largely mirror the primary criteria used by many other major groups (e.g., Yung and McGorry 1996a, 1996b; Miller et al. 1999; McGlashan et al. 2001, 2003). However, consistent with our developmental model, we have also included a somewhat smaller at-risk group, not typically studied elsewhere. The second group is referred to as CHR− (n = 20) and includes individuals who exhibit only nonspecific, attenuated negative symptoms, such as social isolation and deterioration of school (role) functioning (Cornblatt et al., in press). Attenuated positive and negative symptoms are measured by the Scale of Prodromal Symptoms (SOPS; Miller et al. 1999; McGlashan et al. 2001). Presence of one or more attenuated positive symptoms at a moderate level or above is exclusionary for the CHR− risk group.

While negative symptoms are the only basis for selection of individuals in the CHR− group, they do not play a role in selection for the CHR+ risk sample, which is determined by only the presence and intensity of the attenuated positive symptoms. Inclusion in the CHR+ subgroup is based on moderate to severe scores on one or more of the five SOPS items measuring attenuated positive symptoms: (1) unusual thought content/delusional ideas, (2) suspiciousness/persecutory ideas, (3) grandiosity, (4) perceptual abnormalities/hallucinations, and (5) conceptual disorganization. All SOPS items are rated on a scale of 0 (not present) to 6 (extreme or psychotic intensity), with specific probes and detailed anchors provided to determine level of severity. A current or past rating of psychotic intensity (even if present only briefly) on any one of these items is exclusionary for both CHR groups.

Distribution of Positive Symptoms. We have previously questioned (i.e., Cornblatt et al. 2001) whether subjects displaying attenuated positive symptoms are a homogeneous population, as is now assumed throughout the field. To answer this question, we summed the five baseline SOPS positive items (possible range of 3–25) and examined the distribution of the resulting total scores for the 42 subjects in the CHR+ group.

As presented in figure 2, total scores range from 3 to 21 and appear to be distributed bimodally with a relatively clear cutpoint at a score of 10. Nineteen CHR+ subjects (45%) have scores of 10 or more, and 23 (55%) have total scores of 9 and below. As discussed by Lencz et al. (2003), there are a number of alternate ways to establish cutpoints, each of which has its own advantages. However, from the

![Figure 2. Distribution of SOPS total scores for attenuated positive symptoms for all CHR+ RAP participants (n = 42)](image-url)
developmental perspective of interest here, the selected cutpoint appears most appropriate in that it divides the overall CHR+ category into two comparably sized subgroups that clearly differ in terms of symptom severity. CHR+ subjects with total scores of 3–9 are considered to have attenuated positive symptoms of moderate severity and will be referred to as CHR+mod. Subjects with scores of 10 or more are considered to have severe (but still nonpsychotic) attenuated positive symptoms and will be referred to as CHR+sev.

**Expanded Clinical Subgroups.** The division of the CHR+ category into the two subgroups based on symptom severity has expanded the phase of illness schema originally presented by Cornblatt and colleagues (Cornblatt 2002; Cornblatt et al. 2002). The expanded model is presented in figure 3. This schema follows a neurodevelopmental framework in indicating that negative symptoms will precede positive ones and that positive symptoms increase as the illness progresses. The CHR+ groups were selected only on the basis of attenuated positive symptoms, which, by design, display a linear increase across the three groups, as indicated by the mean total symptom scores shown for each subgroup. However, only the CHR− subjects were selected for nonspecific and negative symptoms. Therefore, a major question to be addressed here is the extent to which the “vulnerability” risk factors, which were not part of their selection criteria, nevertheless characterize the two CHR+ groups.

In the sections to follow, the three prodromal risk groups will be compared on selected risk factors measured at baseline to cross-sectionally provide initial support for our neurodevelopmental model and for the validity of the CASIS cluster of risk factors. Preliminary longitudinal findings will also be presented in support of the cross-sectional results. Our specific hypotheses are as follows:

**Figure 3. Evolving phase of illness model, expanded according to differences in severity of attenuated positive symptoms at baseline**

**Phases of the Schizophrenia Prodrome**

<table>
<thead>
<tr>
<th>CHR-</th>
<th>CHR+ MODERATE</th>
<th>CHR+ SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td>N=23</td>
<td>N=19</td>
</tr>
<tr>
<td>ATTENUATED NEGATIVE SYMPTOMS</td>
<td>ATTENUATED POSITIVE SYMPTOMS (SOPS total score ≤ 9)</td>
<td>ATTENUATED POSITIVE SYMPTOMS (SOPS total score ≥ 10)</td>
</tr>
<tr>
<td>M=1.20</td>
<td>M=6.00</td>
<td>M=13.95</td>
</tr>
</tbody>
</table>

*Note.*—M = mean total positive symptom scores (SOPS); SLP = schizophrenia-like psychosis.
All three prodromal risk groups (i.e., CHR-, CHR+mod, and CHR+sev) will be comparably impaired across the four CASIS risk factors (i.e., cognitive deficits, affective disturbances, social isolation, and school failure).

The developmental course predicted by the model represented by figure 3 (i.e., CHR- through CHR+mod and CHR+sev to psychosis) will be supported by preliminary longitudinal outcome data. Movement in the direction of psychosis will therefore typically involve a gradual increase in attenuated positive symptoms.

The level of risk for psychosis will differ markedly among groups, with the highest risk found in the subgroup most proximal to onset of psychosis (i.e., the CHR+sev group). At least in the short term, risk will decrease with nonspecificity of symptoms, and, thus, should be lowest for CHR- subjects.

All demographic variables, clinical ratings, and cognitive measures for the three RAP prodromal groups (CHR-, CHR+mod, and CHR+sev) are compared using chi-squares for categorical data and one-way analyses of variance (followed by pairwise least significant difference comparisons) for continuous variables.

Results

Demographic variables are presented for each of the three groups in table 1. No significant differences were found among groups on age, IQ, or socioeconomic status (SES). Overall, youngsters in the RAP study are, on average, about 16.5 years old and have an average IQ of 98. Parental SES was scored according to Hollingshead (1957), with the scale ranging from the highest SES of 1 to the lowest of 5. The mean SES level for the total sample is 2.30 (standard deviation [SD] = 0.94). Thus, the RAP sample is solidly middle class, and SES level is not associated with severity of symptoms when seeking initial treatment. Although there are more males than females in all three groups, this difference is dramatically increased in the CHR- group, which is 95 percent male ($\chi^2(2) = 8.5, p = 0.013$). Two of several possible explanations for this are (1) an ascertainment bias results from negative/withdrawn symptoms being considered much more dysfunctional in teenage boys than teenage girls, or (2) the marked gender difference is a function of the small sample size and will tend to disappear as the sample size increases.

Developmental Differences in the CASIS Cluster at Baseline

Cognition. Presence or absence of cognitive deficits did not enter into the selection criteria for any of the three high-risk groups. In general, subjects in all three groups were impaired relative to normal controls across a wide range of neurocognitive tasks. In-depth analyses of the neurocognitive variables will be reported elsewhere. For the purposes of this report, however, we have extracted two of the most widely studied neurocognitive functions to illustrate two very different risk factor patterns.

Performance on both the Continuous Performance Test, Identical Pairs version (CPT-IP) and the Wisconsin Card Sorting Test (WCST) (Heaton et al. 1999) is shown in figure 4 for all three prodromal risk groups. Attention is measured by $d'$ on the CPT-IP (four-digit condition, see Cornblatt et al. 1988, 1989; Cornblatt and Malhotra 2001), and executive functioning is represented by perseverative errors on the WCST (Heaton and Pendleton 1981; Goldberg and Weinberger 1988). Performance indexes have been converted into $z$ scores, based on published norms for the WCST and a normative data base for the CPT-IP (available upon request from the first author). For the CPT-IP, all three risk groups are significantly impaired relative to normative performance levels (CHR-, $z = -0.57$, SD = 0.83; CHR+mod, $z = -0.86$, SD = 0.83; CHR+sev, $z = -0.86$, SD = 0.83).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHR- (n = 20)</th>
<th>CHR+mod (n = 23)</th>
<th>CHR+sev (n = 19)</th>
<th>Total (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>95</td>
<td>56</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>16.50 (2.26)</td>
<td>16.46 (2.60)</td>
<td>16.37 (2.02)</td>
<td>16.44 (2.29)</td>
</tr>
<tr>
<td>IQ, mean (SD)</td>
<td>101.88 (22.82)</td>
<td>96.80 (13.66)</td>
<td>95.57 (13.05)</td>
<td>98.00 (16.08)</td>
</tr>
<tr>
<td>SES, mean (SD)</td>
<td>2.22 (0.94)</td>
<td>2.11 (0.88)</td>
<td>2.59 (1.00)</td>
<td>2.30 (0.94)</td>
</tr>
</tbody>
</table>

Note.—CHR = clinical high risk; mod = moderate; SD = standard deviation; SES = socioeconomic status, as measured by Hollingshead (1957) index (high = 1, low = 5); sev = severe.

1 Gender: significantly with more males in CHR- subgroup, $\chi^2 = 8.5, p = 0.013$. 

639
Figure 4. Contrasting performances on the CPT-IP versus the WCST across CHR groups

Performance on the CPT-IP (d') and WCST (Perseverative Errors) across prodromal groups

Performance Indices expressed as z scores

Note.—PE = perseverative errors.

CHR+sev, z = -0.93, SD = 1.06; intercept, p < 0.001), with no differences between groups (F(df 2,48) = 0.72, p = 0.49).

Perseverative errors on the WCST show a very different pattern. In this case, the two early-phase groups are not impaired in their executive functioning relative to normals, and, in fact, both groups perform about half an SD better than population norms (CHR-, z = 0.58, SD = 1.29; and CHR+mod, z = 0.72, SD = 1.07). By contrast, the CHR+sev group is about half an SD worse than normal controls (z = -0.54, SD = 1.63). The difference between prodromal risk groups is significant (F(2,47) = 4.27, p = 0.02), with no difference between the CHR- and CHR+mod groups, but with the CHR+sev significantly more impaired than both the CHR+mod (p = 0.04) and the CHR- (p = 0.009) groups. These contrasting patterns suggest that impaired attention is a long-standing trait whereas executive functioning, at least as measured by the WCST, appears to be associated with the emergence of severe positive symptoms.

Negative and nonspecific CASIS symptoms across risk groups. Table 2 presents the breakdowns for the individual negative and nonspecific symptoms included in the CASIS cluster for each of the three risk groups. It should be noted that for all analyses involving scores for individual negative symptoms, the overall sample is reduced to 40 subjects: CHR-, n = 14; CHR = mod, n = 15; and CHR+sev, n = 11. This is because the SIPS/SOPS rating system was not introduced by McGlashan and colleagues until well into the RAP pilot study. As a result, about a third of the RAP research participants had already been clinically evaluated, using other instruments, at the point where the Structured Interview for Prodromal Symptoms (SIPS)/SOPS became available. While a global negative SOPS score and individual positive symptom SOPS ratings could be calculated from chart reviews, it was not possible to obtain scores for individual negative items. However, negative symptom findings for this reduced sample can be considered representative of the sample.
overall, because no differences were found on the global negative score or any of the positive symptom ratings between the 40 at-risk subjects with in-person SIPS interviews and the adolescents making up the remainder of the sample (see Lencz et al., in press).

As mentioned above, the SOPS negative symptom ratings were the basis for selecting CHR- subjects but did not enter into the selection or differentiation of the CHR+ groups. In support of a primary RAP hypothesis, as shown in Table 2, no group differences were found on any of the three CASIS clinical symptoms: dysphoric mood (affective disturbances), social isolation and withdrawal (social isolation), or deterioration in role functioning (school failure).

To compare the pattern and magnitude of the negative and positive symptoms characterizing the three prodromal phases, we compared mean total scores for the 40 subjects by risk group. As shown in Figure 5, negative scores again...
are quite even for the three groups. Of particular interest, although positive symptoms gradually approach the level of negative symptoms, for all three groups the mean level of negative symptoms is higher than that for positive symptoms. This pattern suggests that despite the level of positive symptoms, prodromal adolescents, in general, are characterized by a consistent and high level of negative symptoms and nonspecific behavior problems (most normal controls, for example, have scores near zero across these items). Thus, the negative symptom dimension appears quite independent, developmentally, from positive symptoms.

**Preliminary Longitudinal Validation of Cross-Sectional Findings**

**Preliminary outcome by group.** Figure 6 depicts initial outcome (mean followup of approximately 1 year). Included in this analysis are 48 Phase I subjects with a minimum of 6 months of clinical followup at the time that the data base was closed (CHR−, n = 14; CHR+mod, n = 19; CHR+sev, n = 15; see Lencz et al. 2003 for details of followup procedures). As indicated in the figure, 47 percent (7/15) of CHR+sev, 11 percent (2/19) of CHR+mod, and 0 percent of CHR− have thus far converted to psychosis, supporting our hypothesis that risk would rise as specificity and proximity to onset of psychosis increased. Furthermore, the developmental pattern of change appears consistent with this prediction. In addition to the conversions thus far observed, one CHR− adolescent has progressed to CHR+mod and one CHR+mod adolescent has progressed to CHR+sev. Of the two CHR+mod adolescents undergoing conversion to psychosis, one first stabilized as a CHR+sev before further progressing. Thus, clinical deterioration appears to be following the types of transitions predicted by our model, and, as expected, conversions have all been to psychotic disorders within the schizophrenia spectrum.

**Outcome as a function of baseline severity: Validating CHR+mod versus CHR+sev.** Data generated by preliminary analyses of the RAP clinic naturalistic treatment data have supported the validity of a differential diagnosis based on the severity of positive symptoms at presentation. Selected for study were 24 CHR+ adolescents (CHR+mod, n = 12; CHR+sev, n = 12), referred to as the treatment sample, who had at least 6 months of followup at the close of Phase I, had received pharmacological treatment with either a second generation antipsychotic (SGAP) or an antidepressant (ADP), and had complete medication data available. Within the naturalistic treatment framework, medication was administered by physician choice according to best practice standards.

As shown in table 3, the pattern of treatment administered according to physician choice differs quite dramatically between the two subgroups ($\chi^2(2) = 6.7, p = 0.03$). For CHR+mod adolescents, ADPs were clearly the medication of choice, whereas the opposite pattern was the

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**Figure 6. Overview of short-term outcome across clinical high-risk (CHR) groups, with a minimum of 6 months of followup (n = 48)**

<table>
<thead>
<tr>
<th>CHR−</th>
<th>CHR+mod</th>
<th>CHR+sev</th>
</tr>
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<tbody>
<tr>
<td>SUM OF ATTENUATED POSITIVE SYMPTOMS: 0 - 2 N=14</td>
<td>SUM OF ATTENUATED POSITIVE SYMPTOMS: 3 - 9 N=19</td>
<td>SUM OF ATTENUATED POSITIVE SYMPTOMS: ≥ 10 N=15</td>
</tr>
</tbody>
</table>

1 The reduced sample of 48 represents the subset of adolescents from the full Phase I sample (n = 62) who have had at least 6 months of clinical followup. Within each box, range of total scores (i.e., sum of attenuated positive symptoms) is indicated.
Table 3. Medication type by CHR group

<table>
<thead>
<tr>
<th>Medication class</th>
<th>CHR+mod, (n (%))</th>
<th>CHR+sev, (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGAP</td>
<td>3 (25%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>ADP</td>
<td>7 (58%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>SGAP/ADP combination</td>
<td>2 (17%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Total subjects</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Note.—ADP = antidepressants; SGAP = second generation antipsychotic.

1 Overall \(\chi^2(2) = 6.77, p = 0.034\).
2 In the CHR+mod group, one SGAP subject and one ADP subject also received adjunctive medication (i.e., anxiolytic or mood stabilizer).
3 In the CHR+sev group, two SGAP subjects and one ADP subject also received adjunctive medication (i.e., anxiolytic or mood stabilizer).

and, as mentioned, displayed a high rate of clinical improvement/stability. By contrast, a substantial proportion of the CHR+sev teenagers were not adherent to medication. In this context, an adolescent is considered to be nonadherent if there is substantial evidence, provided by self-report, physician observation, or lapsed prescription, that no medication has been taken for at least 1 month prior to the onset of psychosis. Nearly all of the adolescents in the CHR+sev group converting to psychosis were considered nonadherent to medication. This pattern suggests that adherence to medication as prescribed may be an important protective factor in preventing, or at least delaying, psychosis.

Discussion

The early data emerging from the RAP program support the hypothesis that schizophrenia is a neurodevelopmental disorder consisting of two interacting but possibly independent symptom domains. A strong undercurrent of negative and nonspecific symptoms runs through all three RAP risk groups, suggesting that the core vulnerability is present at the earliest stages of emerging illness. Moreover, although based on a very small sample, CHR+ adolescents who converted to psychosis during Phase I followup were characterized by the same level of negative and nonspecific symptoms displayed by the overall at-risk sample. Thus, psychosis does not appear to emerge in the absence of the underlying vulnerability. Furthermore, the presence of the vulnerability factors specifically predicted the emergence of schizophrenia spectrum psychoses and not major affective psychotic disorders. Considered overall, these findings tend to suggest that the vulnerability core may be a necessary component of schizophrenia. Our results provide the first prospective confirmation of previous retrospective research indicating that schizophrenia begins with nega-
tive and nonspecific symptoms (Hafner et al. 1999, 1993; Yung and McGorry, 1996a, 1996b) and progresses systematically through attenuated positive symptoms to frank psychotic features.

CASIS Cluster. The current findings also support our selection of the four CASIS cluster variables as both defining an adolescent clinical entity in need of treatment and representing important building blocks of the vulnerability core. All three clinical risk groups in this study were comparably characterized by variables in each of the CASIS domains.

Within the cognitive domain, findings were relatively complex, with constancy across groups observed for the CPT-IP but not the WCST. Identification of the CPT-IP as part of the core vulnerability is consistent with a substantial body of literature. Research spanning close to 5 decades has consistently demonstrated impaired attention to be a core characteristic of schizophrenia (e.g., Cannon et al. 1994; Kremen et al. 2001; and see review by Nuechterlein and Dawson 1984). On the same version of the CPT used in the RAP neurocognitive battery (i.e., the CPT-IP), deficits in attention have been reported in chronic schizophrenia patients (Cornblatt et al. 1989, 1997), adolescent and adult patients in the earliest stages of illness (Cornblatt et al. 1997, 1998), nonschizophrenic relatives of schizophrenia patients (Franke et al. 1994; Laurent et al. 1999), and individuals with schizotypal personality disorders (Lenzenweger et al. 1991; Roitman et al. 1997). The current findings are consistent with these earlier findings.

Executive functioning as measured by the WCST has also been widely demonstrated to characterize patients with schizophrenia (e.g., Heaton and Pendleton 1981; Goldberg and Weinberger 1988), although findings in unaffected first degree relatives have been equivocal (e.g., Stratta et al. 1997; Laurent et al. 2001; Wolf et al. 2002). The results of the data presented in this report suggest that executive functioning is not, in fact, a vulnerability indicator but rather is associated with the increase in positive symptoms. This might suggest that impaired executive functioning, at least as measured by the WCST, taps into the cognitive disability associated with psychosis, quite likely involving thought disorder. Thus, the comparison between deficits in attention versus executive functioning in RAP at-risk subjects suggests that only some cognitive dysfunctions are tied to the brain pathology underlying the core vulnerability. Other cognitive deficits appear to be associated with later evolving pathology. These differences may, in turn, be highly informative about the developmental pathophysiology of schizophrenia.

The current findings also support the validity of the additional three components of the CASIS cluster, including the one nonspecific (dysphoria) and two negative SOPS symptoms (increasing social isolation and withdrawal and deterioration in role functioning, here school failure). The question of causality and the interrelationship among the CASIS variables remains to be determined. Cornblatt and colleagues (e.g., Cornblatt et al. 1992) have demonstrated an association between childhood attentional deficits and later emerging social and interpersonal problems, suggesting that the remediation of attention may have multiple benefits. School failure, which is as reflective of refusal to attend and/or participate in school activities as it is of academic skills, does not appear to be closely related to impaired cognition in the RAP data. School failure is, however, related to avolition, as measured by the SOPS ($r = 0.56$, $p < 0.001$, $n = 40$). These findings support the conclusions by Cannon et al. (1999), van Oel et al. (2002), and Hafner et al. (1992) that academic failure is likely to reflect early negative symptoms rather than cognition per se. Similarly, the fact that moderate to moderately severe levels of depression are common to all three RAP risk groups implicates depression as one of the core features of the prodromal phase, as suggested by Hafner et al. (1999), rather than as simply a reaction to increasing symptoms.

Phases of Illness: Schizophrenia as a Developmental Disorder. The phase of illness schema (CHR– to CHR+mod to CHR+sev) was derived directly from our neurodevelopmental model and is operationally defined on the basis of presence and intensity of attenuated positive symptoms. If valid, this perspective has substantial implications for the pathophysiology and treatment of the illness. Nevertheless, although the cross-sectional findings presented here support the proposed developmental sequence, several alternate possibilities should be taken into consideration. First, inclusion of false positives, especially in the two early-phase risk groups (i.e., CHR– and CHR+mod), might account for some of the findings. The likelihood of false positives increases as the nonspecificity of the criteria increases. As a result, more false positives are expected in the CHR– group (e.g., individuals with social phobias or affective disorders), leading to a lower overall rate of true risk. With continued followup, false-positive cases will be identified and will serve as controls for refining our risk factor profile and for examining specificity of the proposed risk factors. For example, identifying adolescents at risk for bipolar disorder has emerged as a major interest within the RAP program. In contrast with individuals at high risk for schizophrenia, individuals with attenuated positive symptoms in the absence of significant CASIS cluster problems would be considered at risk for bipolar disorder (cf. Walker et al. 2002).
Etiologic heterogeneity is a separate issue that should also be considered. This might particularly affect the CHR– risk group. In this case, many of the CHR– youngsters might not be destined to follow the developmental pathway proposed here. Rather, many CHR– subjects may represent the insidious-onset, poor-prognosis subtype of schizophrenia that is found largely in males and is associated with an early age of onset and predominantly negative symptoms. This syndrome would be comparable to simple schizophrenia as defined in the ICD–10 European criteria (WHO 1992). From a DSM–IV framework, the CHR– criteria could select for adolescents with schizoid personality disorder who will never become psychotic but who are likely to remain marginally functional as adults. In either case, however, if the CHR– is a valid early developmental phase of schizophrenia, risk will increase with continued followup.

Treatment Implications

The notion of an underlying biological vulnerability, such as represented by the CASIS cluster, is highly consistent with the concept of schizotaxia developed by Tsuang and colleagues (e.g., Tsuang et al. 2002). The CASIS constellation, however, has been selected from a more developmental framework, because it is considered most applicable to emerging illness in adolescents and young adults. Consistent with the Tsuang et al. (2000) formulation, the CASIS cluster not only flags risk for future psychosis but also represents a clinical condition that, in itself, is in need of treatment. Immediate intervention is needed for adolescents who have cognitive difficulties, are depressed, and are experiencing increasing levels of social isolation and trouble at school. Establishing the most effective type of treatment for this syndrome is the focus of the RAP clinic naturalistic research project.

Of primary importance is the shift in focus from an exclusive reliance on the treatment of attenuated positive symptoms to the earlier emerging disturbances reflecting the fulminating vulnerability. The guiding assumption is that if the vulnerability at the core of the disorder is reduced with early treatment, it may be possible to reduce or eliminate the impact of the factors that trigger the pathway to psychosis. Figure 7 maps out a variety of pharmacological treatment options within the framework of our working model. While beyond the scope of this report, a diversity of psychosocial interventions, including cognitive remediation, cognitive behavior therapy, social skills training, and supportive educational environments, may also be mapped onto this model.

The two interrelated goals of early treatment are reducing the risk of future psychosis while eliminating the functional disability associated with the vulnerability deficits. Impaired cognition is a major candidate for early intervention. As indicated above, cognitive deficits have been shown to be detectable quite early, stable across development, and possibly causally related to later emerging social and interpersonal difficulties. As a result, improving cognition early in the illness process might be expected to ameliorate a number of downstream abnormalities, especially those leading to increasing social isolation. Unfortunately, no treatment (pharmacological or other) has yet been identified that can reliably remediate impaired cognition in any substantial way. In affected adults, traditional neuroleptics have been found to have no effect on cognition (e.g., Cornblatt et al. 1997, 1998). In addition, although SGAPs have been found to improve cognition (Green et al. 1997; Meltzer and McGurk 1999), these deficits did not come close to being normalized. There is, however, some hope on the horizon. Both industry and academic researchers are in the process of trying to identify and develop cognitive enhancers. Agents now actively being studied include cholinesterase inhibitors (Kirrane et al. 2001; MacEwan et al. 2001; Friedman et al. 2002; Buchanan et al. 2003), nicotine (Levin et al. 1996) and nicotinic agonists (Levin and Rezvani 2002; Simosky et al. 2002), COMT (catechol-o-methyltransferase) inhibitors (Gasparini et al. 1997), psychostimulants (Riccio et al. 2001; Turner et al. 2003), ampakines (Goff et al. 2001, Marenco et al. 2002), and 5-HT2A antagonists such as mianserin (Poyurovsky et al. 2003).

As the illness progresses to more behavioral disturbances in the social and role functioning (i.e., school) domains, a variety of other agents may prove to be beneficial. The preliminary RAP naturalistic treatment data discussed above suggested that ADPs, often in combination with mood stabilizers and/or anxiolytics, may have a protective effect if initiated sufficiently early in the illness process. None of the clinically at-risk adolescents treated with ADPs who have been followed up for close to 2 years has developed a psychosis. Because these data were collected in a naturalistic, observational study without random assignment, these findings are only suggestive. It remains a clear possibility that some portion of the adolescents treated with ADPs are false positives who might be affected by other illnesses compatible with ADP treatment (e.g., major depression or anxiety disorders). However, regardless of whether the CASIS syndrome reflects a risk that is specific for schizophrenia or represents a core risk state for multiple disorders, effective early treatment will be of considerable benefit (Jones and Tarrant 2000). It is, however, unclear whether standard treatment principally with SSRIs, as identified in the RAP treatment study, is the optimal strategy for prodromal adolescents, especially when
We are not proposing that ADPs are directly reducing positive symptoms in the same way antipsychotics do. Rather, we are suggesting a different mechanism: that, in support of our hypotheses, ADPs plus adjunctive medications are targeting many of the core features, and that the accompanying reduction in depression, interpersonal problems, and school failures relieves the stress that might otherwise exacerbate the attenuated positive symptoms that are present. Furthermore, antidepressants as well as mood stabilizers seem to possess some neuroprotective properties (Chen et al. 1999; Michael-Titus et al. 2000; Sanchez et al. 2001; Xu et al. 2003). As a result, it is possible that these agents may intervene to delay or even prevent neurodegenerative processes that have been hypothesized to be involved in the progression to frank psychosis (Pantelis et al. 2003). In agreement with Hafner et al. (1999), this suggests that, in some cases, treatment might be most effective when started earlier than is typical. Moreover, it is possible that a combination of ADPs and antipsychotics may be optimal for both controlling the underlying stressors and reducing moderate positive symptoms.

The only medications as yet established to treat attenuated positive symptoms in randomized clinical trials are antipsychotics, which have been shown to be effective for symptom reduction (Woods et al. 2003) and, possibly, for short-term prevention (McGorry et al. 2002). In none of these studies has baseline severity been addressed as a possible confounding factor, and compliance remains a major issue requiring further study (see McGorry et al. 2002). In summary, it can be concluded that the findings emerging from the RAP program support both a developmental approach and flexibility in the choice of therapy, with optimal treatment...
likely to be different for each critical period within the schizophrenia prodrome.

References


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The Authors

Barbara A. Cornblatt, Ph.D., is Professor of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, Senior Research Scientist and Psychologist, The Zucker Hillside Hospital, Glen Oaks, NY, and Director of the Recognition and Prevention (RAP) Program, The Zucker Hillside Hospital and Schneider Children's Hospital, Lake Success, NY. Todd Lencz, Ph.D., is Assistant Professor of Psychiatry, Albert Einstein College of Medicine, Bronx, NY; Research Attending Psychologist in the Department of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY; and Associate Director, The Recognition and Prevention (RAP) Program of the Zucker Hillside Hospital, Glen Oaks, NY; and Associate Director, The Recognition and Prevention (RAP) Program of the Zucker Hillside Hospital and Schneider Children's Hospital, Lake Success, NY. Christopher W. Smith, M.A., is Assistant Director, the RAP Program. Christoph U. Correll, M.D., is Research Scientist, Department of Psychiatry Research, The Zucker Hillside Hospital and Schneider Children's Hospital, Glen Oaks, NY. Andrea Auther, Ph.D., is Assistant Psychologist, the RAP Program, Lake Success, NY. Emilie Nakayama, Ph.D., is Assistant Psychologist, the RAP Program, Lake Success, NY.