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Cognitive and behavioral precursors of schizophrenia

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Abstract

Attentional deficits are well-established characteristics of patients with schizophrenia and their at-risk offspring, suggesting a biological connection between attention and schizophrenia. The goal of this study is to clarify the developmental role of attention in the illness. Data has been collected from 87 subjects at high and low risk for schizophrenia who have participated in the New York High-Risk Project from 1977 to the present. Individuals are considered to be at high risk if either or both of their parents has schizophrenia. Analyses of attention and global behaviors, measured at intervals from about 12 to 26 years of age, indicate (a) attentional deficits can be reliably detected in high-risk children who will develop future schizophrenia-spectrum disorders (the prespectrum [PSP] group); (b) these deficits are stable, enduring over time, and appear to reflect a compromised attentional capacity; (c) attention is not affected by the onset of illness in the PSP group; (d) for all subjects, attention and global behaviors follow independent developmental pathways; and (e) behavioral difficulties, but not attention deficits, appear to be highly sensitive to environmental factors, especially rearing by a mentally ill parent. It is concluded that in PSP individuals impaired attention probably results from prenatal developmental abnormalities (possibly on the cellular level) and is likely to be a marker of a biological vulnerability to schizophrenia. In addition, attentional deficits, as opposed to early behavioral difficulties, are concluded to be a useful first step in screening for youngsters in need of early intervention.

Schizophrenia is the most debilitating of the psychiatric disorders. It typically strikes just as adulthood is approaching and, despite recent advances in treatment, continues to have a guarded prognosis for many of its victims. Although schizophrenia has been studied for close to a century, the etiology of this devastating illness remains shrouded in mystery. However, over the past 2 decades a multitude of clues about possible causes, risk factors, and potential prevention strategies have begun

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to emerge. Schizophrenia "high-risk" studies are a central source of such information. High-risk research focuses on young people considered statistically to be at higher risk for eventually developing schizophrenia than individuals in the general population. In the past, the subjects most typically studied have been the children of parents with schizophrenia. A major goal of high-risk research is to identify precursors of illness.

The search for precursors—subtle abnormalities that precede the clinical expression of illness by many years—is consistent with a neurodevelopmental view of schizophrenia. Although always implicit in high-risk studies, this view has become increasingly explicit over the past decade or so (e.g., Cannon, 1998; Cannon, Mednick, Parnas, Schulsinger, Praestholm, & Vestergaard, 1994; Jones & Murray, 1991; Murray, O'Callaghan, Castle, & Lewis, 1992; Weinberger, 1987). According to this approach, the basic biological error leading to schizophrenia occurs very early in development (in many cases, prenatally), is triggered during late adolescence–early adulthood, and may not involve further major deterioration in brain functioning after the initial symptoms have appeared.

The neurodevelopmental hypothesis was originally proposed as a theoretical alternative to the traditional view of schizophrenia as a neurodegenerative illness. The notion that schizophrenia follows a degenerative course dates back to Kraepelin (1919), who believed that schizophrenia was an early form of dementia (i.e., dementia praecox). The alternative viewpoint—that at least some aspects of schizophrenia are neurodevelopmental—has evolved far more recently in response to largely indirect but converging data. For example, the results of several studies have indicated that structural anomalies such as enlarged ventricles are found in schizophrenic patients at their initial episode of illness and do not appear to increase as the illness progresses (e.g., Cannon, 1991; Degreef et al., 1992; DeLisi et al., 1992; Hoffman, Ballard, Turner, & Casey, 1991; but see DiLisi et al., 1995). Moreover, clinically it appears that few patients show the progressive deterioration characteristic of the dementias, and, in fact, some patients improve over time. In addition, developmental abnormalities on the cellular level, including abnormal synaptic pruning, defects in embryonic cell migration, and abnormal myelination of axons, have been reported that support the neurodevelopmental model (e.g., Kovelman & Scheibel, 1984; Jakob & Beckmann, 1986; Falkai, Bogerts, & Rozumek, 1988; and see excellent overviews by Cannon, 1998, and by Green, 1998, pp. 7–8).

Beginning with Meehl's (1962) seminal work, a number of researchers have presented models of the schizophrenia process that are consistent with the neurodevelopmental approach (e.g., Erlenmeyer–Kimling et al., 1982; Nuechterlein et al., 1992). In Figure 1, we present a highly simplified schema that emphasizes the major assumptions incorporated into most of these models.

As mentioned above, it is considered probable that the illness process begins with an early (prenatal) biological error or insult that is most likely genetic, although in some cases other factors (e.g., infection, environmental insult) may be involved; this early error leads to a series of brain abnormalities (the "lesion"). Although an actual lesion has not yet been identified, it is currently believed that structural, functional, and biochemical abnormalities are all involved. These abnormalities, in turn, are thought to cause an underlying susceptibility or vulnerability to later illness. Although frequently described as being "clinically silent" until late adolescence–early adulthood, the susceptibility is reflected throughout development in the form of subtle neurocognitive deficits and other types of difficulties (e.g., neuromotor).

In terms of clinical severity, as seen on the right side of the model in Figure 1, the susceptibility to illness can be expressed in a number of different ways, ranging from full-blown schizophrenia through a variety of less severe but genetically related forms of the illness, including a variety of schizophrenia-like nonpsychotic features that do not fit into any current DSM-IV Axis II diagnosis. Increasing evidence from family studies and neurocognitive research suggests that the milder variants of illness, especially schizotypal personality

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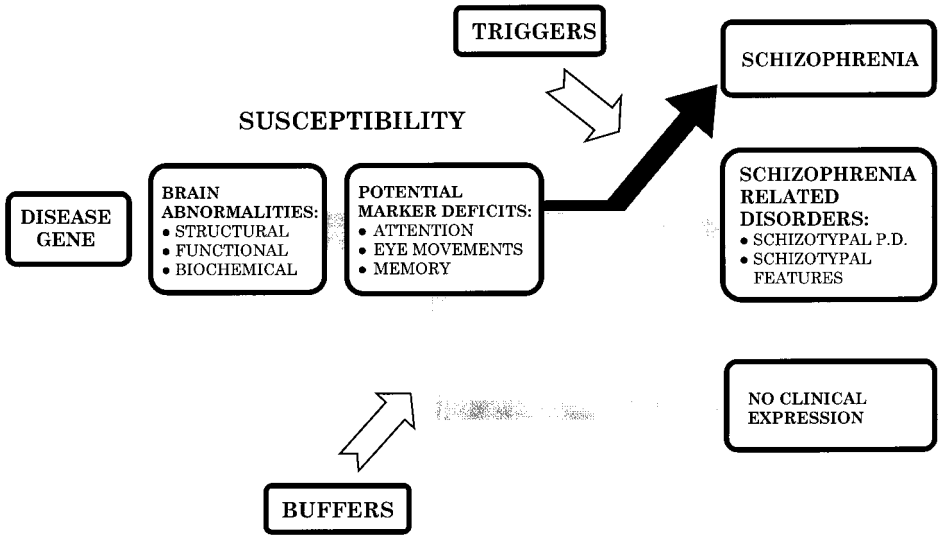


Figure 1. Neurodevelopmental model of schizophrenia.

disorder, may be a more common phenotypic expression of the schizophrenia genotype than full-blown schizophrenia (Baron, Gruen, Asnis, & Kane, 1983; Kendler, Gruenberg, & Strauss, 1981; Kety, Rosenthal, Wender, Schulzinger, & Jacobsen, 1975; Lees et al., 1997; Siever et al., 1990). This is indicated in the model by the thicker arrow. However, whether fully or partially expressed, the distinctive aspect of this process is that some factor, the nature of which remains unknown, triggers the clinical expression of illness relatively late in the process, most typically in late adolescence. Finally, as shown on the bottom right of the model, it is assumed that in some cases there may be no clinical expression at all. It is possible that in these cases some kind of environmental or biological protective factors buffer the underlying vulnerability. In the long run, such protective factors will be of primary interest, although it is not yet possible to identify asymptomatic carriers of the schizophrenia genotype.

Since precursor deficits are detectable many years before the overt clinical symptoms appear, these deficits presumably serve as "indicators" or "markers" of an underlying biological vulnerability. In the neurocognitive domain, the deficits most commonly regarded as candidate markers include components of impaired attention, deficits in short-term and working memory, and eye-movement abnormalities (Cornblatt & Obuchowski, 1997). Such dysfunctions are considered to be intermediate between underlying brain structures/functions and complex clinical behaviors. They are often referred to as endophenotypic indicators (Gottesman, McGuffin, & Farmer, 1987) or biobehavioral markers (Erlenmeyer–Kimling & Cornblatt, 1978, 1987a; Erlenmeyer–Kimling et al., 1982). "Biobehavioral markers" is a particularly descriptive label, because these deficits are considered to be closer to the underlying biology than clinical characteristics (i.e., to be *bio*behavioral) while their presence relatively early in development is considered a possible indicator or "marker" of a biological susceptibility to future illness.

In this report, we are concerned with identifying biobehavioral markers of the schizophrenia spectrum (ranging from the least to most severe forms of illness). Our long-range goal is to develop intervention programs that may help to prevent the illness from being expressed clinically, or, at minimum, to lessen clinical severity. Preventive intervention should be quite possible, since, from the neurodevelopmental perspective described above, the unfolding of the clinical illness is a long-term process. Studies of schizophrenic patients un-

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dergoing their first episode of illness have demonstrated that the earlier treatment begins, the better the prognosis (e.g., Loebel, Lieberman, Alvir, Mayerhoff, Geisler, & Szymanski, 1992; McGlashan, 1996; McGlashan & Johannessen, 1996; Wyatt, 1991). It therefore follows that treatment beginning before psychosis sets in may be yet more effective.

Premorbid intervention programs, however, have never been attempted. This is because, although populations at statistical risk can be identified, individuals at true risk cannot. As a result, based on the limited screening procedures now available, the majority of individuals selected for early treatment would be false positives (i.e., individuals not at true risk and not in need of intervention). For example, offspring of schizophrenic parents have the most solidly established statistical risk for schizophrenia. Risk for full-blown schizophrenia in the children of one affected parent has been estimated to be as high as 15% (Erlenmeyer–Kimling & Cornblatt, 1987a; Gottesman, 1991). In this case, if genetic relatedness were the criteria for inclusion in an early intervention program, only around 10 to 15% would actually need treatment and over 80% would be participating unnecessarily. This is an unacceptably high false-positive rate and is the reason that intervention programs have not been feasible in the past. However, this situation can change dramatically with a more accurate way of identifying true-positive individuals—individuals for whom early treatment may be the only way to avoid becoming ill. Neurocognitive precursors or predictors appear likely to meet this need.

For marker deficits to be useful as population screens, they must be reliable, stable, detectable at appropriate ages, specific to schizophrenia-spectrum disorders, cost effective, and relatively easy to administer and score. A number of deficits have been identified that may be markers but do not meet all of these requirements. For example, neuromotor abnormalities have been reported in young children at risk by a number of investigators (e.g., Fish, 1984, 1987; Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Jones, Rodgers, Murray, & Marmot, 1994; Walker & Lewine, 1990). However, these particular marker deficits seem to be displayed only in very early childhood, too early to be included in screening procedures that will probably be administered during adolescence. Moreover, their specificity for schizophrenia-spectrum disorders has not as yet been established.

Furthermore, within broadly defined categories of neurocognitive precursors (e.g., attention, memory, and eye movements), there are numerous component functions which differ considerably in nature and extent of established marker potential. For example, within the category of attention, a number of specific deficits have been proposed as possible markers. These range from deficits in the earliest stages of attentional processing, such as those measured by Backward Masking and Span of Apprehension, to those in the later stages when attention begins to converge with working memory, as, for example, tapped by some versions of the Continuous Performance Test. For our initial step in identifying suitable screening tools, we have chosen to focus on one particular marker deficit within the attentional domain—sustained attention—as typically measured by the Continuous Performance Test (CPT). We have selected this function because it is a particularly well established precursor of illness and because it has also been related to later schizotypal characteristics, such as interpersonal difficulties (see review by Cornblatt & Keilp, 1994). In this report, we will present compelling new evidence that impaired sustained attention can provide the first building block of a test battery intended to screen adolescents and young adults for early warning signs of impending schizophrenia-spectrum illnesses. We will also evaluate whether early behavioral disturbances can add to the predictive validity of attention and thus should also be included in an initial screening battery.

The attentional and clinical data to be presented have been collected over the course of the New York High-Risk Project (NYHRP), a longitudinal, prospective study of two samples of children at high and low risk for schizophrenia that was initiated in 1971 (Erlenmeyer–Kimling & Cornblatt, 1987b, 1992; Erlenmeyer–Kimling, Marcuse, Cornblatt, Firedman, Rainer, & Rutschmann, 1984; Erlen-

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meyer–Kimling et al., 1995). In both samples (referred to as Samples A and B), children at high risk for schizophrenia (HRSz group) are the offspring of one or two schizophrenic parents. There are also two control groups in both samples: a psychiatric control group consisting of the children of one or two parents with a major affective disorder (HRAff), who are considered to be at risk primarily for mood disorders, and a normal control (NC) group, made up of the offspring of parents who have no history of mental illness and who are therefore considered to be at low risk for psychiatric illness in general.

In this report, we focus on the second of the two samples, Sample B. The attentional and clinical data collected from Sample B is uniquely suitable for evaluating potential markers for several reasons. First, Sample B subjects, who were originally recruited at about 9 years of age, are now in their early 30s. These subjects have been clinically assessed every 3–4 years since initially recruited. As a result, behavioral changes have been documented across development and outcome is fairly well established. This enables us to identify individuals who, as adults, have developed schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder, and schizotypal and paranoid personality disorders). The developmental patterns of the individuals with adult-spectrum disorders (to be referred to as the prespectrum [PSP] group) can then be compared with each of the other three groups (HRSz, HRAff, and NC) and with all three combined. Emphasis, however, will be placed on the PSP versus HRSz and PSP versus combined sample comparisons. The former is of interest because the HRSz individuals are optimal control subjects, since they are matched with the PSP subgroup on nearly all major variables other than illness (e.g., subjects in both groups have been raised by schizophrenic parents). The latter comparisons between PSP individuals versus all remaining subjects are important in the present study because they approximate the contrasts to be made between individuals targeted for intervention and members of the general population.

The second major advantage provided by Sample B is that attention was measured at four time points over a 15-year period using the same measure (i.e., the Continuous Performance Test–Identical Pairs version [CPT-IP]) at mean ages of 12.2, 15.1, 22.4, and 25.9 years. Therefore, information is available about the development of attention in individuals who will subsequently develop schizophrenia-related illnesses and about changes in attention following onset of the clinical illness—longitudinal information unavailable elsewhere. These assessments also provide a rare opportunity to assess the relationship between neurocognitive deficits and early behavioral disturbances.

More specifically, we are interested in determining (a) how well attentional deficits function as preillness predictors or markers of later spectrum disorders, (b) whether early behavioral disturbances can be detected that can also function in a predictor capacity, and (c) which of the two—or possibly a combination of both—provides the most accurate way of screening a population for true-risk subjects in need of intervention.

Methods

Subjects

In Sample B, 150 subjects were recruited and initially tested between 1977 and 1979. Recruitment procedures have been described in detail elsewhere (e.g., Erlenmeyer–Kimling & Cornblatt, 1987b; Erlenmeyer–Kimling et al., 1984, 1995). In brief, the children's risk status was based on parental diagnosis. For subjects in the HRSz and HRAff groups, parents were identified by screening consecutive admissions at several large New York state psychiatric facilities. Patients (male or female) who had one or more children in the designated age range (7–12 years) and who had an intact marriage with the biological parent of the eligible children were recruited for the study. Parents were excluded if they had chronic alcoholism, drug addiction, brain trauma, or psychoses of toxic origin. Parents in the HRSz group were diagnosed as either schizophrenic or schizoaffective, mainly schizophrenia. Parents in the HRAff group were diag-

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nosed as either major affective disorder or schizoaffective disorder, mainly affective. All final diagnoses were made according to Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) based on interviews with the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L; Spitzer & Endicott, 1977). Normal control families were recruited by a population sampling firm from neighborhoods similar to those in which the high-risk subjects lived. Normal control parents met the same exclusionary criteria listed above and were also eliminated if either parent had a history of psychiatric difficulties or treatment. All participating children were English-speaking and Caucasian and were free of mental retardation or obvious psychiatric problems.

Sample B subjects have undergone six rounds of neurocognitive testing and clinical assessments, with the clinical assessments often, but not always, completed at the time of laboratory testing. In this paper, we focus on attention collected during Rounds 2 (1980–1981), 3 (1983–1984), 5 (1991–1992), and 6 (1994–1995) of Sample B testing and on clinical assessments collected at all six time points: 1980, 1982, 1985, 1987, 1992, and 1995. Testing rounds were selected for inclusion in this study if the CPT-IP was administered as part of the routine test battery. Round 1 attentional data is not included here because a much easier, psychometrically different version of the CPT was administered, confounding longitudinal comparisons. Round 4 was incomplete and due to a large number of missing subjects was also eliminated.

All six clinical assessments included in this study were based on global behavior ratings that varied in source of information (described in more detail below). These ratings were specifically selected from the extensive clinical information available (see Erlenmeyer–Kimling & Cornblatt, 1987b; Erlenmeyer–Kimling, Cornblatt, Bassett, Moldin, Hilldoff–Adamo, & Roberts, 1990) because they most closely approximate the type of information that would be used during a first-phase screening of adolescents.

Axis I diagnoses of all participating offspring were made according to the RDC and based on SADS-L interviews; Axis II diagnoses were derived from the Personality Disorders Examination (PDE; Loranger, Susman, Oldham, & Russakoff, 1987; and see Squires–Wheeler et al., 1993, for details about the Axis II assessments). As of October 1998, six subjects in Sample B had received a schizophrenia-spectrum diagnosis during at least one clinical assessment. The schizophrenia spectrum is considered here to include schizophrenia, schizoaffective disorder, schizotypal personality disorder, and paranoid personality disorder. Since the NYHRP diagnoses are based on the RDC, schizoaffective disorder is divided into mainly affective and mainly schizophrenic subtypes; only the latter is included in the spectrum. The lifetime diagnoses of these subjects (i.e., the most serious diagnosis received) are as follows: Subject 1, schizoaffective, mainly schizophrenic; Subject 2, schizotypal personality disorder; Subject 3, probable schizotypal personality disorder; Subject 4, schizotypal personality disorder, paranoid personality disorder; Subject 5, schizophrenic; Subject 6, schizotypal personality disorder, paranoid personality disorder.

All six subjects were members of the HRSz group (15.3% of the 39 HRSz subjects with follow-up data). Subjects 1 and 2 are not related and are both offspring of one parent with schizophrenia. Subjects 3 and 4 are siblings and offspring of two parents with schizophrenia-spectrum disorders. Subjects 5 and 6 are also siblings and are offspring of a parent with an RDC diagnosis of schizoaffective disorder, mainly schizophrenic. One of the six subjects was diagnosed as an adolescent; the other five were diagnosed between the ages of 19 and 21 years. Since most of the data to be discussed was collected prior to the onset of illness when outcome was unknown, this group will be referred to as the PSP group.

Table 1 presents the number of subjects in each group with complete attentional and clinical data for Round 2, the baseline round in this report. In addition to the six PSP subjects described above, the sample consisted of 15 HRSz, 26 HRAff, and 40 NC subjects. The PSP subjects were, on average, somewhat younger (mean age: 10.8 years) when tested

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Table 1. *Sample B demographic information at Round 2: 1980*

	PSP	HRSz	HRAff	NC	Total
N	6	15	26	40	87
Mean age	10.84	11.67	12.97	12.10	12.19
	(1.47)	(1.99)	(2.02)	(1.97)	(2.03)
Females (%)	33.30	40.00	57.7	40.0	44.8

Note: Ages: PSP < HRAff ($p < 0.05$); PSP = HRSz = NC. Gender: no significant group differences. Standard deviations are in parentheses.

at Round 2 than subjects in the other three groups; these differences were not significant when compared with either the HRSz (mean age: 11.7 years) or NC (mean age: 12.1 years) groups. The HRAff subjects (mean age: 13 years) were, however, significantly older than the PSP subjects. Since age was found not to affect any of the analyses presented in this report, it is not discussed further. Similarly, although there tended to be more males than females in the PSP, HRSz, and NC groups and more females in the HRAFF group, these differences were not significant and gender is not included in the analyses that follow.

Measures

Clinical ratings. The clinical ratings in this study were all derived from various Global Adjustment Scales (GAS; Erlenmeyer–Kimling, Cornblatt, Bassett, Moldin, Hilldoff–Adamo, & Roberts, 1990) and all were either scored on or transformed into a 5-point scale, with the higher the score the healthier the subject. The first three clinical assessments were based on the Behavioral Global Adjustment Scale (BGAS; Cornblatt & Erlenmeyer–Kimling, 1985; Erlenmeyer–Kimling et al., 1990) and were completed in 1980 (BGAS 80), 1982 (BGAS 82), and 1985 (BGAS 85). The BGAS rating categories ranged from gross behavioral disturbance requiring hospitalization (score of 1) through moderate behavioral difficulties (score of 3) to above-average functioning (score of 5). All BGAS ratings were based on information obtained by social workers from the parents of participating subjects every 6 to 12 months throughout the study. In these interviews (conducted mostly by telephone), overall adjustment in three areas was emphasized: family functioning, peer relationships, and school behavior. There was no attempt to evaluate specific clinical signs or symptoms of schizophrenia or any other major disorder.

The three BGAS ratings (BGAS 80, BGAS 82, and BGAS 85) will be used in the current study to assess the predictor potential of early behavioral abnormalities relative to attentional precursors. The reason for focusing on these particular rating scales is that we are not here concerned with fine-grained clinical signs that require an experienced observer, but, rather, our goal is to determine if the everyday information available from parents or teachers can provide useful screening information.

The remaining three GAS scores included in this report were based on different types of information than the earlier ratings and did not use the BGAS scale. In the case of all three (i.e., GAS 88, GAS 91, and GAS 95), the ratings were derived from information gathered during structured clinical interviews (versions of the SADS-L and PDE). The 1988 GAS scale was derived from the 7-point SCID-II Global Assessment of Personality and was reduced to 5 points by collapsing the first two and last two scores of the original scale. For the last two assessments (GAS 92 and GAS 95), ratings were made using the 100-point GAS scale developed by Endicott, Spitzer, Fleiss, and Cohen (1976). For both the 1991 and 1995 assessments, the original 100-point scale was collapsed into 5 points, as follows: 1, scores of 1–20; 2, 21–40; 3, 41–60; 4, 61–80; 5, 81–100. Since all three of the later GAS ratings were based on structured clinical assessments and were completed after the six PSP subjects had become ill, they have

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been included to provide an overview of behavioral changes across early adulthood in all subjects, rather than as generating behavioral predictors of schizophrenia.

CPT-IP. A specific version of the CPT—the CPT-IP—was administered during all of the test rounds included in this report. The CPT-IP measures sustained attention, working memory, and a complex of other related information processing functions. The CPT-IP is considered to be more cognitively challenging than most other versions of the CPT (see Cornblatt & Keilp, 1994, for review). It was developed specifically for use with the clinically unaffected or mildly affected relatives of schizophrenic patients and has been shown to be appropriate across a wide range of ages and clinical states, from at-risk children to chronic schizophrenic patients (Cornblatt & Keilp, 1994; Cornblatt, Lenzenweger, & Erlenmeyer–Kimling, 1989; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer–Kimling, 1988). In particular, the CPT-IP appears to be sensitive to deficits characterizing the full range of schizophrenia-spectrum disorders, including young adults psychometrically considered to be schizotypal (Lenzenweger, Cornblatt, & Putnick, 1991) and patients with a clinical diagnosis of schizotypal personality disorder (Lees et al., 1997).

The CPT-IP has been described in detail elsewhere (see Cornblatt et al., 1988, 1989; Cornblatt & Keilp, 1994). In brief, the CPT-IP is a computer-generated test of visual attention that consists of 12 conditions, tapping verbal and spatial attention. Verbal stimuli are four-, three-, or two-digit numbers (with digit strings of each length presented in separate conditions); spatial stimuli are nonsense shapes. Distraction, speed of processing, and difficulty level are varied systematically across conditions. During each condition, 150 stimuli are presented in rapid, continual sequence on a computer monitor. On the most challenging conditions, each stimulus appears on the monitor for 50 ms, followed by a dark time of 950 ms, for a total trial time of 1000 ms (1 s). A 150-trial condition takes 150 s or 2.5 min to administer. The total 12 condition measure requires about an hour, including time for instructions, practice trials, and rest breaks.

Subjects are asked to respond (via a finger lift from a reaction-time key) whenever two stimuli in a row look exactly alike. In each condition, 20% of the stimuli are target pairs that are exactly alike and require a response; 20% are catch trials—pairs that are almost alike, but are not quite identical; and 60% are randomly organized fillers. This design generates a substantial number of performance indices, suitable for different levels of analysis (e.g., ranging from overall attention capacity to microcomponents of attention). The major indices include percentage correct, percentage false alarms (responses to catch trials), percentage random errors (responses to the randomly organized fillers), reaction times for all responses, number of times off task (times finger is off the response key for more than one trial) and signal-detection indices d' and $\ln \beta$.

In the present study, analyses are limited to d' for the most difficult verbal condition (four-digit numbers). This specific condition has been selected because (a) performance on the four-digit condition reflects maximal attentional capacity; (b) the verbal condition is most consistent with the versions of the CPT traditionally used, and thus the findings can be compared with those reported throughout the literature; and (c) d' is arguably the single measure most representative of overall processing capacity, since it takes into account both correct responses and false alarms (see Rutschmann, Cornblatt, & Erlenmeyer–Kimling, 1977, for a more detailed explanation of the signal detection indices).

Results

Developmental pattern of attention

Figure 2 displays attention in all four groups across Rounds 2, 3, 5, and 6. Round 2 was conducted from 1980 to 1981 when the mean sample age was just above 12 years. Round 3 took place in 1983–1984, with an overall sample age of 15 years; Round 5 was completed 7 years later, from 1991 to 1992, when the sample was approximately 22 years old, and

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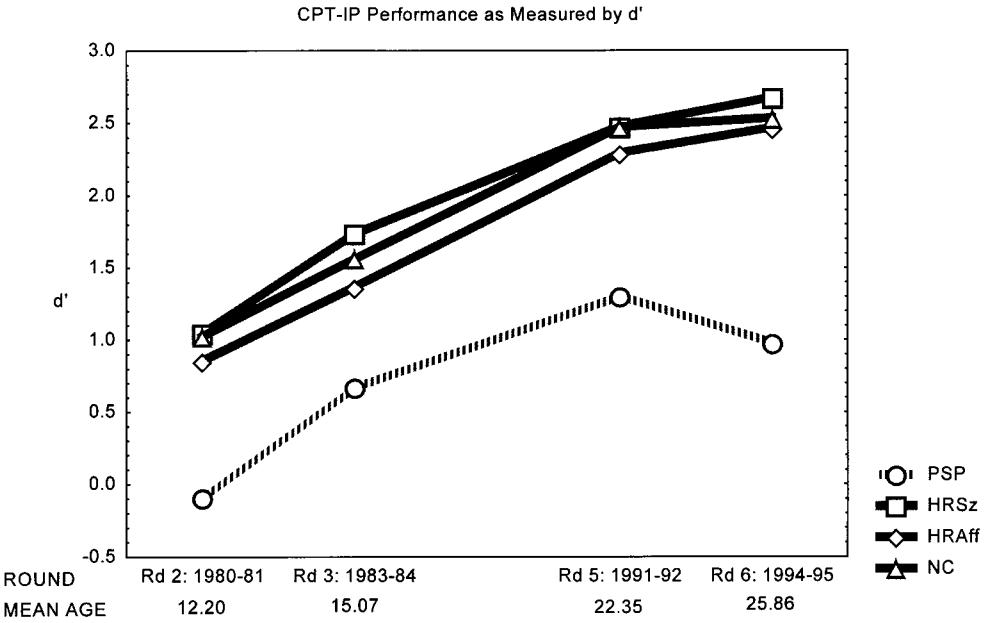


Figure 2. CPT-IP performance on four testing rounds.

Round 6 from 1994 to 1995, at a mean sample age close to 26 years of age. Attentional data were analyzed using Repeated Measures Analysis of Variance (StatSoft, Inc., 1998). Group comparisons were conducted using planned contrasts (StatSoft, Inc., 1998) with the NC group predicted to be the best performers and the PSP group the worst on both attention and behavioral measures. It should be noted that for this set of analyses the number of subjects is 62, since only those subjects with complete attentional data across all four rounds are included (PSP, $n = 5$; HRSz, $n = 10$; HRAff, $n = 18$; NC, $n = 29$).

As indicated in Figure 2, main effects for both Group ($F_{3, 58} = 5.918$; $p = .001$) and Round ($F_{3, 174} = 63.63$; $p < .0001$) are highly significant. The Group × Round interaction, however, is not significant.

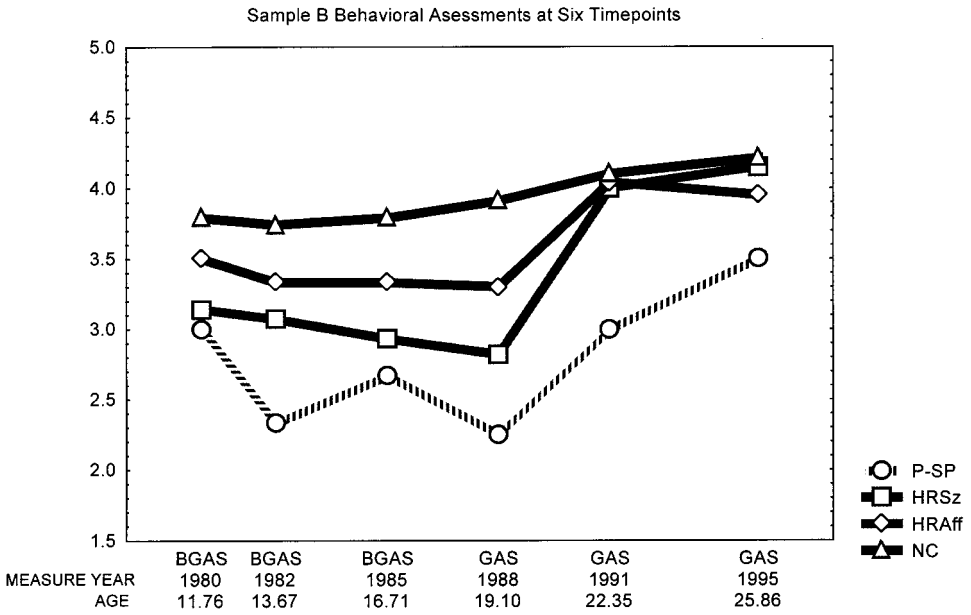
Round effects. Comparisons across rounds indicated that for the sample overall performance improved steadily throughout adolescence, with increases from 1981 ($M = .711$; $SE = .09$) to 1984 ($M = 1.334$; $SE = .115$) and from 1984 to 1992 ($M = 2.135$; $SE = .139$) being significant. However, by their early 20s, all subjects appeared to reach maximum attentional performance and no further improvement was found for any of the groups from 1992 to 1995 ($M = 2.162$; $SE = .134$). Note that for the PSP group, a dip in performance was displayed from 1992 to 1995; this change was small and nonsignificant.

Group differences. A strong and consistent pattern of group differences was displayed across all three rounds: Subjects in the PSP group performed significantly worse than did subjects in all three other groups, and the other three groups did not differ from each other (i.e., NC = HRSz = HRAff). Group means summed across all four rounds were as follows: PSP, $d' = .714$; HRSz, $d' = 1.984$; HRAff, $d' = 1.746$; and NC, $d' = 1.898$.

Developmental patterns of behaviors

In Figure 3, the six behavioral ratings are plotted over time for all four groups. BGAS

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BGAS 90, 82 & 85 results for planned comparisons (all differences are greater than $p < 0.05$); GAS scores not included in these analyses.

GROUP: $F_{(3,78)} = 7.852$, $p < 0.001$: PSP = HRSz; PSP < HRAff, NC; NC > HRSz, HRAff, PSP
ROUND: $F_{(2,156)} = 1.618$, $p = 0.030$: BGAS 80 > BGAS 82; BGAS 82 = BGAS 85
GROUP x ROUND: NS

Figure 3. Behavioral assessments at six time points.

ratings were completed at three time points from early to midadolescence: in 1980, when the sample was close to 12 years old; in 1982, with a mean sample age of about 13.5 years; and in 1985, when subjects were just over 16.5 years. GAS ratings took place in early adulthood: in 1988, when subjects were approaching their 20s (mean age: 19.10 years); in 1991, in their early 20s (mean age: 22.35 years); and finally, in 1995, when subjects were in their mid-20s (mean age: 25.86 years).

We will report two longitudinal analyses of the behavioral data. In the first, we will include only the three BGAS ratings (BGAS 80, 82, and 85). As discussed above, we consider these to have the most relevance for our screening battery. The total sample size in the BGAS (80, 82, and 85) analysis is 82: PSP, $n = 6$; HRSz, $n = 14$; HRAff, $n = 24$; NC, $n = 38$. In the second longitudinal analysis, we included all six behavior ratings. We regard this as an overview of behavioral changes from early adolescence to early adulthood, rather than as an evaluation of the predictor potential of behavior ratings. It was necessary to conduct a separate analysis when all six assessments were included because a number of subjects are missing during the later rounds. As a result, in the second set of longitudinal analyses the sample size is reduced to 55 subjects: PSP, $n = 3$; HRSz, $n = 9$; HRAFF, $n = 17$; NC, $n = 26$). It should be noted that in Figure 3 the BGAS data points are derived from the first set of longitudinal analyses with the larger sample size, and the last three data points (i.e., for GAS scores 88, 91, and 95) are taken from the second longitudinal analysis based on the reduced sample. Despite the reduction in number of subjects for the second set of analyses, the pattern of group differences and session effects for the BGAS ratings is the same in both analyses.

BGAS 80, 82, and 85 longitudinal analyses. Across time and for each of the three assessments analyzed separately, a consistent pattern was displayed: NC subjects were signifi-

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cantly better adjusted than all other subjects, and PSP and HRSz subjects were similar to each other.

A significant main effect for group was found using a repeated measures ANOVA ($F_{3, 78} = 7.852$; $p < .001$). Planned contrasts indicated that NCs were significantly better adjusted across all rounds than subjects in any of the other three groups (overall mean BGAS scores for NC = 3.772. vs. PSP = 2.667, $p < .001$; NC vs. HRSz = 3.048, $p = .001$; NC vs. HRAff = 3.389, $p = .027$). Planned contrasts also showed that during adolescence (i.e., from ages 12 to 17), there were no differences in behaviors between at-risk subjects who would develop spectrum disorders (i.e., the PSP group) and those who would not (i.e., the HRSz subjects). Thus, early behavioral ratings did not predict future schizophrenia.

A relatively weak, but statistically significant, main effect ($F_{2, 156} = 1.618$, $p = .03$), was also found for round, with scores dropping slightly (indicating an increase in behavior problems) from BGAS 80 to BGAS 82, when subjects were entering their early teens. No further decrease, however, was found for BGAS 85. These findings suggest that—consistent with popular observation—entrance into the teen years may be somewhat problematic for all subjects and particularly problematic for individuals who will later develop schizophrenia (i.e., the PSP group).

Full longitudinal behavioral analyses. When all six behavioral ratings were analyzed longitudinally on the reduced sample of 55 subjects, patterns consistent with the preceding BGAS analyses were found. For the reduced sample, both Group ($F_{3, 51} = 7.478$, $p < .0001$) and Round ($F_{5, 255} = 17.732$, $p < .0001$) main effects were found. However, unlike the earlier analyses, there was also a significant Group × Round interaction ($F_{15, 255} = 1.862$, $p = .040$), reflecting behavioral changes occurring at older ages.

Planned contrasts indicate that the significant Group × Round interaction resulted from the improvement in behavior ratings in both the HRSz and HRAff groups as these subjects entered early adulthood. As can be seen in Figure 3, during the fourth assessment (i.e., GAS 88), when all subjects are in their late teens, NC subjects continue to be significantly better adjusted than subjects in any of the three risk groups, continuing the pattern displayed throughout adolescence. However, for the GAS 91 (subjects in their early 20s) and GAS 95 (subjects in their mid-20s) ratings, both the HRSz and HRAff groups improve and converge with the NC scores. Therefore, by early adulthood there is no longer any behavioral difference between NCs and the two risk groups. In contrast, the PSP subjects remain significantly disturbed relative to the other subject groups, even though the PSP group also improves on the last two assessments.

Predictive potential of adolescent attention and behaviors

To assess the relative predictive potential of attention deficits relative to adolescent behaviors, we conducted a series of discriminant function (DF) analyses (StatSoft, Inc., 1998) assessing the accuracy with which the attentional precursors alone and in combination with the early behaviors (as measured by the BGAS ratings) accurately assigned group membership. BGAS scores were not analyzed independently, since the developmental patterns discussed above indicated a lack of specificity for schizophrenia throughout adolescence. The DF analysis included only the first two rounds of attention (i.e., 1981 and 1984) and combinations of attention and selected BGAS ratings (i.e., BGAS 80, 82, and 85). The remaining data was collected at ages considered too old to contribute to effective intervention screening procedures.

The questions asked by the DF analyses are (a) How accurate is attention in predicting who will eventually be in the spectrum group (i.e., the true positives) and in avoiding false positives and (b) can this accuracy level be improved by adding early behavioral abnormalities? For these analyses we combined the HRSz, HRAff, and NCs into a single overall sample. This resulted in a comparison group that is more representative of the general pop-

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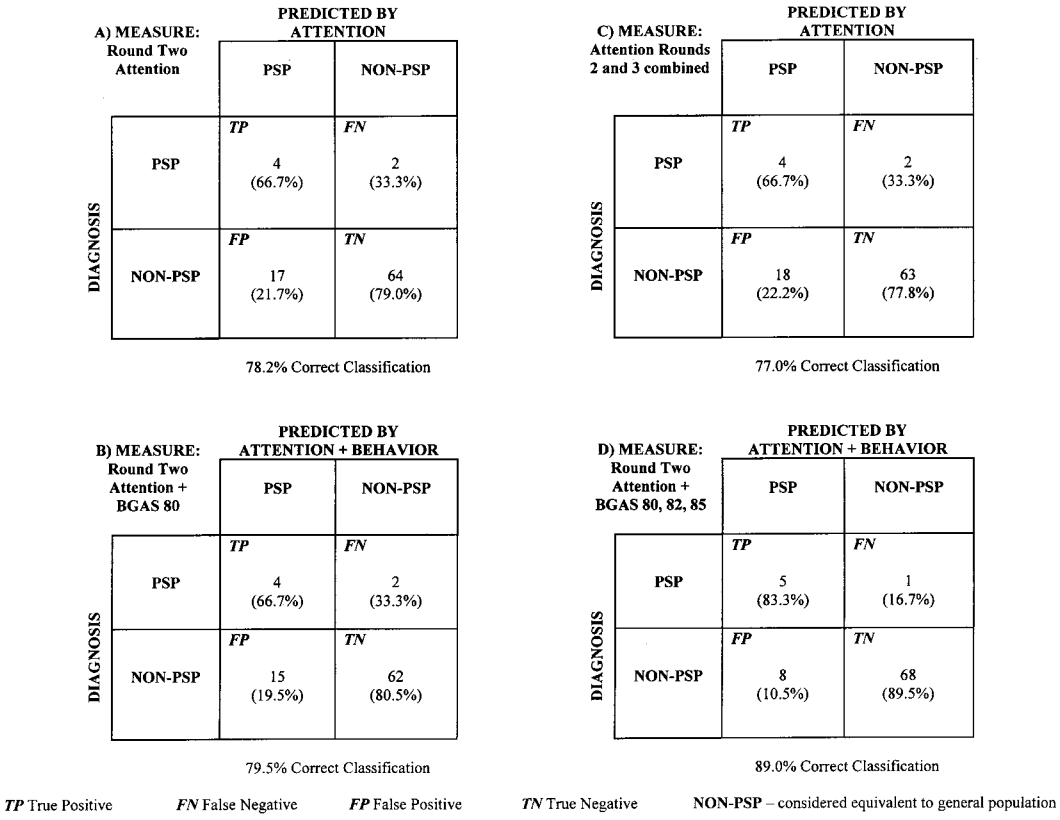


Figure 4. Discriminant function analysis: predictive accuracy of attention alone and in combination with clinical ratings.

ulation than is the NC group used alone. This strategy is considered the closest approximation to the type of real-world situation in which initial screening is likely to take place. The results of these analyses are presented in Figure 4.

The accuracy with which attention deficits, measured at about 12 years of age (i.e., Round 2), can be used to identify the "true-positive" subjects are presented in Figure 4A. True positives are those in the PSP group who will eventually become ill and therefore are in real need of intervention. Round 2 attentional measures are of primary interest, since subjects are just entering their teens, which is likely to be the optimal time to begin the intervention process. As indicated in Figure 4A, correct classifications occurred for 78.2% of the cases. Sensitivity was quite high, with 66.7% of the true-positive (PSP) subjects accurately identified by the attentional screen. However, the false positive rate of 21.7% is also quite high, indicating that close to a quarter of the population of individuals who will not develop a future spectrum disorder are inaccurately flagged as needing intervention. As shown in Figure 4B, adding the behavioral ratings (BGAS 80) completed at approximately the same time resulted in little change, with correct classifications 79.5%, representing an increase in accuracy of only 1.3%.

Round 3 (1984) attention, measured when subjects were about age 15, was then added to the Round 2 attentional measure to determine whether screening subjects at two time points would increase accuracy levels. As indicated by the results in Figure 4C, combining testing rounds did not improve accuracy levels.

In the fourth analysis, shown in Figure 4D, all three BGAS rounds were combined with Round 2 attention. This particular combination was selected for the following reasons:

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(a) Comparing Figure 4A and 4C demonstrated that only one attentional assessment was necessary, and we therefore chose the results of the earliest testing round available; (b) adding concurrent behavioral ratings did not improve accuracy (Figure 4A vs. 4B); and (c) additional analyses (not shown) indicated that Round 2 attention combined with limited longitudinal behavior ratings spanning a 2-year period (i.e., BGAS 80 and 82) only increased accuracy levels to 82.6%.

Figure 4D contains the optimal combination of the predictors available in this study: attention, measured in early adolescence (around age 12), combined with behavioral assessments spanning early to middle teens (from 12 to close to 17 years old). In this case, 89.0% of the subjects are correctly classified, improving accuracy by nearly 10% beyond the levels of the previous analyses presented in Figures 4A–4C. In the Figure 4D screening data, sensitivity (i.e., identifying true positives or the PSP subjects) is substantially improved from 66.7% (Figures 4A–4C) to 83.3%. False positives are also reduced from approximately 20% (Figures 4A–4C) to 10.5% in Figure 4D. Thus, if the individuals making up Sample B of the NYHRP had been screened for an early intervention program using attentional performance at age 12 and periodic behavioral ratings from 12 to around 17 years of age, over 80% who needed it would have been identified. At the same time, however, 10% of the comparison population are also targeted for intervention, although these individuals will never develop a spectrum disorder—a percentage that will need to be reduced to optimize the intervention process.

Discussion

In Sample B of the NYHRP, 15.3% of the 39 HRSz subjects with follow-up data developed a schizophrenia-spectrum disorder by age 21. All diagnoses are continually updated; those listed in this report were based on information collected through October 1998.

Since the Sample B subjects are now, on average, in their mid-30s, it is unlikely that many more will break down. No individuals in either of the two comparison groups (i.e., NC or HRAff) have developed a schizophrenia-spectrum disorder as of the above cutoff time. Four of the six spectrum diagnoses are for schizotypal personality disorder (SPD). Two of the four HRSz individuals with SPD also have a comorbid paranoid personality disorder. Thus, Sample B outcome is consistent with the literature in supporting the importance of genetic factors across the schizophrenia spectrum.

The primary goal of this study, however, is to evaluate attentional precursors of schizophrenia within a developmental context. The data collected from Sample B provides a unique opportunity to address the following questions: (a) whether attentional precursors of schizophrenia appear to be biobehavioral markers of schizophrenia-spectrum disorders; (b) whether attentional precursors play a role in the subsequent development of symptoms related to schizophrenia; and (c) whether attentional markers provide a means of screening populations for true risk individuals in need of early intervention. A secondary question is whether preillness behavioral disturbances can improve the predictive validity of attentional markers used alone.

The third issue is of particular interest from a treatment perspective. Accurate screening procedures are the essential first step toward developing preventive interventions. Once identified, such youngsters can then elect to participate in programs that are expected to stop, or at least delay, the progression of illness and thus, hopefully, prevent psychosis. Little previous research has been directed at evaluating the effectiveness of potential markers or predictors for screening large number of subjects. We therefore consider the results of this study an important first step in providing a gateway to intervention.

Impaired attention: A biobehavioral marker of illness?

To be a biobehavioral marker of a genetic vulnerability to illness, a deficit must be displayed more frequently by both affected individuals and their unaffected first-degree relatives than by individuals in the general

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population. It must also be a stable trait that precedes illness and be independent of clinical state (Cornblatt & Keilp, 1994; Moldin & Erlenmeyer–Kimling, 1994).

A great deal of indirect evidence obtained from affected patients suggests that attentional deficits are markers of a biological liability to schizophrenia. First, individuals with schizophrenia have long been established to display a broad array of attentional impairments (see reviews by Nuechterlein & Dawson, 1984; Cornblatt & Keilp, 1994). Considerable evidence has also indicated that in affected patients attentional deficits are present in both acute episode and in remission and thus they appear to be independent of clinical state (e.g., Asarnow & MacCrimmon, 1978; Cornblatt et al., 1997, 1998; Steinhauer, Zubin, Condray, Shaw, Peters, & Van Kammen, 1991; Wohlberg & Kornetsky, 1973; and see review by Cornblatt & Keilp, 1994).

While studies of first-degree relatives of schizophrenics also support the marker status of impaired attention, the data available thus far has mainly demonstrated that the rate of attentional deficits in at-risk offspring is higher than in various types of control subjects. As described in several reviews (e.g., Asarnow, 1988; Cornblatt & Keilp, 1994; Cornblatt & Obuchowski, 1997; Erlenmeyer–Kimling & Cornblatt, 1987a; Hans & Marcus, 1991; Nuechterlein & Dawson, 1984), high-risk studies conducted since the 1960s have consistently detected attentional deficits, comparable to those characterizing affected patients, in the children of schizophrenic parents but not in the children of normal parents or other types of patient parents. However, few of these studies have followed the offspring sufficiently long to trace the stability, developmental history, interaction with clinical aspects of illness, or predictive validity of these attentional difficulties. Such information is critical for directly establishing true marker status. The NYHRP findings in this report provide initial information about these issues.

Stability and developmental history. Overall, the findings presented here indicate that in preschizophrenic individuals, impaired attention is highly stable across time. As shown in Figure 2, all four subject groups display parallel slopes indicating that verbal attention improves steadily with age, until the early 20s, when it appears to level off. The same pattern of improvement with age was previously found in a cross-sectional study of 120 normal controls ranging from midadolescence to midadulthood (Cornblatt et al., 1988). Subjects in the PSP group show the same age pattern as normal controls. However, from the earliest ages tested (i.e., beginning with the first round of testing in the NYHRP, not included in this report, when subjects were about 9 years of age), PSP subjects display impaired attentional performance relative to all three groups of controls. Of particular importance, the magnitude of this impairment remains constant across ages. This pattern suggests a compromise in overall attentional capacity—described by Green (1998, p. 53) as a "a smaller than normal pool of attentional resources." This capacity reduction most likely occurs very early in development, possibly in utero, and does not appear to be affected by maturation, ongoing neurological processes, or environmental influences. As will be discussed below, this pattern might result from abnormalities on the cellular level that take place during prenatal development.

Independence from early behaviors and clinical states. Four findings presented in Figures 2 and 3 are particularly illustrative of the independence of attention and behavioral dimensions. First, the attentional curve characterizing the PSP group in Figure 2 clearly supports the independence of attention from the clinical syndrome. As pointed out above, the NC, HRSz, and HRAff groups all show a steady improvement in attention with age up until early adulthood that presumably reflects normal brain maturation. The PSP subjects show the same degree of improvement, although performing at a lower level. If this reduction in capacity is in any way related to clinical state, then a major decline in attention should have been observed in the PSP group from Round 3 to Round 5, since it was during this time period that all but one of these subjects became ill (one subject had an earlier onset). Nevertheless, attention shows the

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same trajectory (i.e., same degree of improvement from Rounds 3 to 5) as do the three control groups.

Second, for all subjects studied, the patterns of impaired attention versus behavioral disturbances are quite different from each other, suggesting independent developmental courses. As mentioned, for attention the curves are parallel for all groups across the full age range studied. By contrast, the four behavior curves are not closely parallel across development and, in particular, show divergences among groups in the early adult years, with significant changes occurring in the HRSz and HRAff groups relative to both NC and PSP subjects.

Third, at the baseline round of this study, Round 2, as the sample overall enters their teens (i.e., around 12 years of age), PSP and HRSz children are nearly identical behaviorally (on the BGAS 1980 scores). However, the two groups are clearly different in attentional performance, with the PSP children showing substantial deficits relative to HRSz subjects. This pattern is maintained throughout adolescence. HRSz subjects are considered the optimal controls for the PSP group, since these two groups are matched on virtually all major variables other than subsequent illness. Differences between the two groups therefore directly pinpoint factors involved in susceptibility to later schizophrenia disorders. Consequently, attention appears to be a clear indicator of future illness while behavior does not—suggesting the independence of the two domains.

Fourth, changes in GAS ratings for the two risk groups suggest that the types of behaviors being assessed are sensitive to environmental stressors, in contrast to attention, which appears not to be affected to any great extent by the environment. GAS ratings for both HRSz and HRAff undergo a marked shift to normal behaviors as the subjects enter early adulthood. These changes suggest that living in turbulent households with parents who suffer from either schizophrenia or major affective disorders exacerbate the behavioral difficulties of adolescence. At the point that these youngsters leave home and establish their own households, their behaviors change and become indistinguishable from controls who have consistently displayed high levels of functioning. There is no comparable change in attention in either risk group. In essence, attentional performance was normal for HRSz subjects, as a group, throughout development.

Summary. Comparisons between the developmental pathways of attention versus behavioral adjustment supports the independence of the two domains. The parallel age-related improvement in attention across the four subject groups suggests that clinical state does not affect attention. If it did, then the PSP group should display a different developmental trajectory than the other subjects. Overall behavioral adjustment during the teen years, in contrast, appears to reflect environmental rearing factors, since PSP and HRSz individuals show the same level of behavioral problems, and both groups display significantly more behavioral problems than do normal controls.

Consistencies with a neurodevelopmental view of schizophrenia. In this report, two major observations are consistent with a neurodevelopmental view of schizophrenia. First, individuals in the PSP group display attentional deficits relative to the other subjects beginning in childhood, long before the appearance of symptoms, a result consistent with the findings of many other high-risk studies. Second, attention does not further deteriorate as the illness progresses, a result supported by studies of affected patients (e.g., Cornblatt, Obuchowski, Schnur, & O'Brien, 1997, 1998). Taken together, these findings suggest that impaired attention results from a brain insult, possibly on the cellular level, most likely occurring in utero. Recent evidence of positional and distributional abnormalities thought to result from disturbances in prenatal cell migration are consistent with this view. Examples of positional disturbances that might be involved are a disorientation of pyramidal cells in the hippocampus and abnormal arrangement of cells in the prefrontal and temporal cortices (see Cannon, 1998, and Green, 1998, for excellent descriptions of these findings). Reduction in the number of cells available or disarrayed positioning of cells might, in turn, interfere with the neural connections leading

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to optimal information processing and result in a lifelong lowered attentional capacity. After the initial compromise in attentional capacity has developed, no further deterioration appears to take place. This suggests that the process is completed by early childhood and that neurological processes taking place subsequently do not impact further on attention although they may trigger the onset of psychosis.

Validity as a vulnerability marker. Marker deficits—in this report, attention deficits—should be displayed to a greater extent by first-degree relatives of patients than by members of the general population. This includes clinically unaffected relatives, which in the current study are individuals in the HRSz group. The results of previous research with Sample A of the NYHRP were consistent with this requirement: HRSz subjects who were asymptomatic as adults nevertheless displayed significantly greater deficits in attention during childhood than did NC subjects (Cornblatt, Lenzenweger, Dworkin, & Erlenmeyer–Kimling, 1992). For Sample B, the data presented thus far appears contradictory to this expectation, since the mean performance level for the HRSz group, also consisting of asymptomatic adults, overlaps closely across development with the mean performance levels for the control groups.

However, when examining the distributions of attentional scores, a somewhat different picture emerges, one that is more consistent with the earlier Sample A results. Scatterplots were constructed for HRSz and for NC groups separately for Rounds 2–4. (Round 5 is missing too many subjects to be included in this analysis.) Inspection of the plots for the three rounds indicate that there are both good-performing and poor-performing outliers in the HRSz group, but not in the NC group, for each of the three rounds. As a result, the presence of the deviantly performing HRSz subgroup was not reflected in the HRSz group mean, since extremely poor performers were canceled out by the handful of extremely good performers.

Following procedures established earlier for Sample A (see Cornblatt & Erlenmeyer–Kimling, 1985), attentional deviance was defined as the poorest performing five subjects in each test round (i.e., individuals falling in the bottom third of the distribution in the current small HRSz group). When tallied across rounds, three HRSz subjects fell into the deviant performance tail during all three rounds. This subgroup represents 20% of the clinically unaffected HRSz group, a proportion consistent with expectation and with the earlier Sample A results. By comparison, no NC subjects were similarly deviant across all three testing rounds. Thus, a subgroup of the asymptomatic HRSz sample can be identified that is characterized by the same enduring, stable attentional impairment displayed by the affected PSP subjects. As adults, one of the three individuals making up this subgroup was free of all clinical disturbances; the other two (who were siblings) did display some clinical problems (suspected alcohol abuse in one case and possible anxiety disorder in the other), but neither were considered to have a disorder falling within the schizophrenia spectrum. In the long run, subjects within this "clinically silent" subgroup will be very important for both research and treatment, since it is assumed that some set of factors (either environmental, biological, or both) acts to buffer the vulnerability represented by the attentional markers and prevent the expression of illness.

Summary. The current results suggest that attention is a long-standing, enduring trait that precedes illness by many years and that is not related to acute episodes of illness. Nuechterlein and Dawson (1984) discriminate between three types of markers: stable vulnerability markers, mediating vulnerability markers, and episode markers. The evidence from this report suggests impaired attention is a stable vulnerability marker of schizophrenia spectrum disorders.

The involvement of attention in the formation of clinical symptoms

As indicated in the above discussion, the evidence that attention is independent of early

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behavioral disturbances and later psychotic symptoms of illness is rather compelling. However, the question can still be raised as to whether impaired attention simply signals a vulnerability to schizophrenia or has some involvement in the clinical illness. Cornblatt and colleagues (e.g., Cornblatt, Dworkin, Wolf, & Erlenmeyer–Kimling, 1996; Cornblatt et al., 1992) have previously speculated that impaired attention is indeed involved in the illness process but is not related to either positive or negative symptoms but rather to the development of social skills. This notion was based on early findings emerging from studies of both samples A and B of the NYHRP.

In Sample A, Cornblatt et al. (1992) found that impaired attention in childhood was related to adult social insensitivity and social indifference in HRSz individuals who did not develop schizophrenia-spectrum disorders. No similar pattern was found for either HRAff subjects or NCs. On the basis of these findings, Cornblatt et al., 1992, proposed that (a) in subjects biologically vulnerable to schizophrenia, impaired attention is likely to be a chronic disturbance throughout development; (b) this attentional impairment leads to an inability to efficiently process information from the environment, especially subtle and highly complex interpersonal cues and communications; and (c) as a result, in these subjects social competence, which is dependent on the processing of social information, is particularly disrupted by attentional difficulties.

Further support for this speculative notion was provided by several early analyses of Sample B data. Cornblatt, Dworkin, and colleagues found that although attention is impaired in HRSz subjects as early as 9 years of age, these children do not begin to experience social difficulties until they enter their midteens (Cornblatt et al., 1996; Dworkin, Lewis, Cornblatt, & Erlenmyer–Kimling, 1994; Dworkin et al., 1991). A lack of significant correlations between attention and social skills suggest that the two domains do not relate to each other throughout late childhood and early adolescence. However, by midadolescence a very substantial and significant relationship develops between attention and social skills—at the point in development when HRSz subjects first begin to display social deficits. This latter finding is quite consistent with Weinberger's (1987, 1995) notion that deficits do not become apparent on the behavioral level until the brain matures enough for these functions to come "on line." As pointed out by Cornblatt and colleagues, social skills are probably not sufficiently well developed in childhood to be greatly affected by the relatively subtle attentional impairments. However, as the maturing individual becomes involved in increasingly complex social situations, there is an increasing dependence on relevant cognitive functions, especially attention to social cues and communications. At this point, the lack of full capacity becomes a handicap and affects the processing of social information, leading to difficulties in interpersonal relationships. These difficulties tend to be expressed as insensitivity to others (i.e., inability to process what others are trying to communicate) and as avoiding social interactions (a likely result of previously unsuccessful relationships). While this process does not necessarily lead to schizophrenia in itself, it may predispose vulnerable adults to a life characterized by social isolation and an absence of normal relationships. Such individuals may be self-supporting and not seek treatment, but may live on the fringes of society. They are likely to meet criteria for personality disorders within the schizophrenia spectrum or be considered to have subclinical features of spectrum disorders.

Summary. Impaired attention appears to be independent of psychotic symptoms, but may be causally related to chronic social difficulties. According to this notion, a reduced capacity to attend to information in the environment limits the individual's abilities to process and understand social communications, in turn interfering with the development of appropriate social skills and relationships. This suggests that impaired attention is likely to be a marker of the full spectrum of schizophrenia-related disorders, since major components of schizophrenia and the nonpsychotic spectrum disorders (e.g., schizotypal person-

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ality disorder) are social isolation and reduced social competence.

How effective are attentional markers in predicting illness and can they provide the screening essential for early intervention programs?

The data discussed above supports impaired attention to be a stable vulnerability marker as defined by Nuechterlein and Dawson (1984). However, stable vulnerability markers are not necessarily useful for screening populations to identify individuals in need of intervention. For example, it appears that specific disturbances in neuromotor development are likely to be early markers of later illness (Jones, Rodgers, Murray, & Marmot, 1994; Walker & Levine, 1990). However, as mentioned earlier in this paper, it would not be possible to include these early deficits, which tend to go underground by late childhood, in a screening battery that will be administered during adolescence. The question addressed here is whether attentional markers provide a cost-effective and valid way of screening populations for true-risk individuals.

Predictive validity of attentional precursors of illness. The results of the discriminant function analysis (Figure 4) suggest that impaired attention, used alone, can serve as a moderately accurate predictor of future schizophrenia-spectrum disorders. Attention deficits measured at the cusp of adolescence led to 78.2% correct classifications, with a sensitivity of 67% and specificity of 79%. Thus, a single assessment of attention at a relatively young age will correctly identify about two thirds of the individuals who should receive intervention—a considerably better success rate than currently otherwise available. However, the false positive rate of just over 20% suggests a further refinement in screening procedures is necessary.

The current results indicate that false positives will not be eliminated either by measuring attention at several time points or at later ages. Attention measured at around 15 years of age was no more accurate as a predictor than when measured at around 12 years of age. Combining the two testings did not improve the initial results. This follows from the developmental findings. Since group differences in attention remain stable across testing sessions, later rounds should not be more accurate than earlier ones, and adding two or more together would not be expected to improve accuracy over any given individual testing. As a result, measures of attention such as the CPT-IP should be regarded as only the first building block of a future screening battery; other neurocognitive measures should be individually added to gradually improve overall predictive accuracy.

There is a cautionary note: although attentional deficits such as those tapped by the CPT-IP are specific to individuals at genetic risk for schizophrenia relative to youngsters at risk for affective disorders and to NCs, no studies have yet demonstrated specificity when compared to adolescents with attention deficit disorder or other types of childhood illnesses. Such studies must be completed before screening on any sizable scale can take place.

Predictive value of impaired attention combined with behavior ratings. In contrast with attention, as discussed earlier, adolescent behaviors appear to be highly sensitive to environmental stressors and, when evaluated at individual time points, to have little value in predicting future schizophrenia-spectrum illnesses. This is the case despite the clear contrast between individuals in the NC and PSP groups. Across development, NCs consistently displayed well adjusted behaviors (i.e. the slope of their scores was relatively flat and hovered around a rating of 4, signifying health). PSP subjects, on the other hand, were equally consistent in displaying serious problems in functioning. Although PSP individuals did show some improvement as young adults, most likely due to treatment, they never approached normal levels (i.e., mean ratings were never above 3.5).

The lack of predictive potential is due to a lack of specificity when compared to the other risk groups. Particularly damaging, HRSz subjects closely resemble the PSP group throughout adolescence. In three of the four

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early rounds (BGAS 80, BGAS 85, and GAS 88), there was no difference between the PSP and HRSz subjects in behavioral adjustment, and their scores were only marginally different for BGAS 82. It is only as the HRSz subjects reach adulthood and begin to leave home that there is a dramatic shift in scores: by their early 20s, HRSz subjects show a marked normalization in adjustment. HRAff individuals showed a similar pattern, although they are more similar to the NCs from the outset. Thus, children raised by an ill parent, especially one with schizophrenia, generally undergo difficulties at home, at school, and in maintaining peer relationships throughout their teenage years. Unlike attentional deficits, however, these difficulties do not necessarily foreshadow later schizophrenia-spectrum disorders. As a result, these types of overall behavior ratings have little predictive validity in their own right.

While concluding that adolescent behavior problems do not predict future schizophrenia, a question can still be raised as to whether some combination of behavioral ratings and attention might improve predictive accuracy. Adding behavior problems measured (by BGAS 80) at the same time as Round 2 attention did not improve accuracy level. Only a very moderate improvement resulted when adding both BGAS 80 and 82 ratings to Round 2 attention, which is not surprising, since the two ratings are only 2 years apart. However, combining all three BGAS scores (80, 82, and 85) with Round 2 attention (Figure 4D) did substantially increase accuracy levels when compared to using attention alone (by close to 11%). As a result, if the subjects in Sample B of the NYHRP had been screened using the combined index, 83% of the subjects who eventually became ill would have received intervention. As importantly, the false-positive rate, which was around 20% in the other analyses, dropped to 10.5% with the combined longitudinal index. Thus, using the longitudinal index, only about 10% of the population not at risk, and therefore not in need of intervention, would also have been selected to participate. Whether a 10% false-positive rate is acceptable at this stage depends to a considerable extent on the nature of the intervention. This rate might be considered reasonable if the intervention to be offered did not cause negative side effects, was nonstigmatizing, and could provide some benefit even for subjects who are not actually at risk for a schizophrenia-spectrum disorder.

Finally, although combining longitudinal behavior assessments across a 5-year period (from approximately 12 to 17 years old) did lead to a nontrivial improvement in correct classifications, the extent to which such ratings are feasible in a screening battery remains to be determined. The first screening phase will be administered to large populations. The screening battery therefore needs to be cost effective and easy to administer, score, and interpret. While the information on which the BGAS ratings are based can be collected from parents in a relatively brief telephone interview, the need to accumulate several ratings over a substantial time period may be unwieldy. In addition, the need for a long follow-up period runs the risk of delaying intervention until after psychosis begins, thereby considerably reducing its effectiveness. The benefits of adding longitudinal behavior ratings therefore remain to be determined.

Summary. Overall, the findings of this study suggest that attentional deficits detected in late childhood provide a starting point in screening for subjects who are susceptible to adult schizophrenia spectrum-illnesses. In the data reported here, behavioral difficulties measured at any given point in time during adolescence do not improve the screening process. By the time true-risk subjects can be distinguished from other individuals behaviorally, it is too late to intervene effectively. Thus, the most reasonable strategy for primary prevention, at least at this time, appears to be to develop a neurocognitive screening battery as the first screening phase. This battery should include an array of cognitive functions to increase predictive precision. Subjects selected as being at cognitive risk would then undergo a second, clinical, screening phase to further reduce false positives. This might consist of a single in-depth clinical assessment shortly after Phase 1 is completed or a series of less intense clinical follow-ups (compara-

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ble to those on which the BGAS ratings were based) across several years. A two-step program of this type may create the most accurate selection process. Which neurocognitive precursors should be selected to augment attention and the nature of the clinical phase await future research. However, the results of this study strongly suggest that developing such a screening process is not only timely and important, but also has become increasingly possible with the steady increase in knowledge about the neurocognition of schizophrenia that has taken place over the past decade.

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