Impaired Attention, Genetics, and the Pathophysiology of Schizophrenia

by Barbara A. Cornblatt and John G. Keilp

Abstract

Impaired attention is commonly observed among schizophrenia patients and those at genetic risk for the disease. This article reviews over 40 studies that used various versions of the Continuous Performance Test (CPT) as the primary measure of attention. These studies of normal subjects, affected patients, and various at-risk populations demonstrate that the CPT is a psychometrically sound procedure that consistently discriminates affected patients from controls. Sufficiently difficult versions of this task have also demonstrated that impaired attention is (1) evident in schizophrenia patients regardless of clinical state, (2) detectable before illness onset, (3) apparently heritable, (4) specific—in terms of distinct profile patterns—to schizophrenia, and (5) predictive of later behavioral disturbances in susceptible individuals. Selected studies are also discussed that examine the role of attentional deficit in the pathophysiology of schizophrenia and its potential consequences for personality development. With respect to pathophysiology, preliminary data suggest that subcortical brain dysfunction has an important role in the attentional deficits tapped by the CPT. With respect to personality, an association between chronically impaired attention and deficient social skills has been found. It is concluded that the CPT is a cost-effective measure of the attentional deficit commonly found in affected schizophrenia subjects and those at risk for the disorder, and is therefore a potentially valuable screening device for preventive intervention programs.

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The need to identify biobehavioral or "trait" indicators of the schizophrenia genotype has increasingly been recognized by schizophrenia researchers (Gershon and Goldin 1986; Goldin et al. 1986; Cloninger 1987; Moldin et al. 1990*a*; Cornblatt and Keefe 1991; Erlenmeyer-Kimling and Cornblatt 1992). As a result, there has been considerable interest in studying candidate traits in populations at risk for carrying the schizophrenia gene but not necessarily for expressing the full illness (Lenzenweger and Moldin 1990; Moldin et al. 1990*b*). For example, the unaffected or mildly symptomatic first-degree relatives of schizophrenia patients are one type of at-risk population. Such subjects are optimal for studying the biological mechanisms involved in schizophrenia, since they are free of many of the confounds characterizing research with schizophrenia patients—for example, psychosis, generalized performance deficits, long-term medication, and institutionalization.

In our review we emphasize the extent to which current research with at-risk populations has reinforced previous findings suggesting that abnormal attention is an indicator of a genetic susceptibility to schizophrenia. Attention is a complex construct that has been measured in a variety of ways in

Reprint requests should be sent to Dr. B.A. Cornblatt, Dept. of Psychiatry, Rm. D-10-4, Elmhurst Hospital Center, 79-01 Broadway, Elmhurst, NY 11373.

research concerned with both normal development and psychopathology. For example, there is an extensive literature concerned with deficits in selective attention and distractibility in schizophrenia (see reviews by Nuechterlein and Dawson 1984 and Erlenmeyer-Kimling and Cornblatt 1987). Neuropsychological attentional constructs have also shown some promise as indicators of risk for schizophrenia (see Kremen et al. 1994, this issue). In this article, however, we will specifically focus on attentional capacity as measured by the Continuous Performance Test (CPT; Rosvold et al. 1956), since the potential of this aspect of attention to be an indicator of genetic susceptibility to schizophrenia has been most solidly established in the literature. (See this issue for discussions of other promising indicators, for example, eye movement dysfunctions as discussed by Levy et al. 1994, this issue.)

We will begin by presenting an overview of the evolution and reliability of the various CPT measures and then discuss in detail whether attention—as measured by the CPT—appears to be a valid phenotypic indicator of the schizophrenia genotype. In our discussion, phenotypic indicator refers to a stable deficit (i.e., trait) that is intermediate between the genotype and clinical phenotype. Although it can be objectively measured on the behavioral (i.e., phenotypic) level, it is assumed to be a more direct reflection of genetic factors than the more variable and environmentally influenced clinical syndrome. Following our review, we will examine recent research addressing the possible neurophysiologic causes and behavioral consequences of attentional impairment in subjects with a liability to schizophrenia.

The CPT: Overview of the Tasks

Background. The CPT is not a single measure but a family of measures that share a number of features: (1) the rapid presentation of a long series of stimuli; (2) the requirement that a subject respond whenever a designated target or target sequence occurs in the series; and (3) a relatively low probability (generally around 20%) that a target will appear. Although there are a few auditory versions of the CPT, the task is usually presented visually, either on a rear projection screen (in earlier versions using a slide projector) or on a video monitor (in later, computerized versions). A constant, externally paced presentation rate that is not under the subject's control appears to be a critical feature of the CPT tasks that have been used most successfully in schizophrenia research (Kornetsky and Orzack 1964; Nuechterlein 1991).

Evolution of the CPT: Early Versions. In its original version, the CPT consisted of a series of single letters that were visually presented for about 10 minutes (Rosvold et al. 1956). There were two tasks, one very easy, the other somewhat more difficult. In the easier task, the subject was instructed to respond whenever the letter X appeared; in the more difficult one, the subject was to respond to the letter X only when it followed the letter A. These two tasks and their variants will be referred to as the X and AX CPT, respectively.

Rosvold et al. (1956) reported that brain-damaged subjects—whether retarded or with a relatively normal IQ—performed significantly more poorly than retarded and normal-IQ control individuals who were not brain damaged. Thus, this study demonstrated that the attentional deficit measured by the CPT was more directly associated with neurologic impairment than with low IQ. Mirsky, Kornetsky, and Orzack subsequently used the CPT in a series of studies of schizophrenia patients (Kornetsky and Mirsky 1966; Kornetsky and Orzack 1964; Mirsky and Kornetsky 1964; Orzack and Kornetsky 1966, 1971; Orzack et al. 1967; Mirsky 1969; Wohlberg and Kornetsky 1973). Using somewhat more difficult X and AX tasks (e.g., tasks with shorter stimulus duration and lower target probability), the researchers found that schizophrenia patients were impaired in their CPT performance when compared with other patient groups and when compared with their own performance on other measures, such as the Digit Symbol Substitution Test (DSST; Mirsky and Kornetsky 1964; Orzack and Kornetsky 1966; Orzack et al. 1967; Orzack and Kornetsky 1971). This dysfunction appeared, then, to be specific to schizophrenia, rather than a function of general psychopathology, and specific to attention, rather than simply an aspect of a generalized performance deficit (Mirsky and Kornetsky 1964; Kornetsky and Mirsky 1966; Orzack and Kornetsky 1966).

Evolution of the CPT: Recent Versions. Difficulties with the classic X/AX CPT arose as soon as it was used in studies of the at-risk offspring of parents with schizophrenia. Both the X and AX tasks proved too easy to detect

subtle deficits in subjects who were not yet clinically affected. As a result, the classic X/AX CPT underwent a number of modifications in an attempt to make the procedure sufficiently difficult for nonpsychotic at-risk populations. For example, several investigators added various types of visual and/or auditory distraction to increase the test's cognitive load (Stammeyer 1961; Wohlberg and Kornetsky 1973). Of the alternative versions developed, the two that have become most widely used in schizophrenia research are the Degraded Stimulus CPT (DS CPT) developed by Nuechterlein (1983) and the Identical Pairs version (CPT–IP), which evolved over the course of the New York High-Risk Project (NYHRP; Cornblatt and Erlenmeyer-Kimling 1985; Erlenmeyer-Kimling and Cornblatt 1992).

In the DS variant, the basic X format is maintained (i.e., the subject is required to respond whenever the number 0 appears among a series of single numbers). However, the task is made more difficult than the classic X procedure by blurring the stimuli so that they are very difficult to see. Thus, the DS CPT produces a high processing load on attention by burdening early aspects of stimulus encoding and perceptual analysis (Nuechterlein 1991).

The CPT–IP was made more difficult both by modifying the definition of the target and by increasing the complexity of the stimuli. In the CPT–IP, a target is defined as the second stimulus in any pair of identical stimuli. Thus, no number or number sequence is specified, as in the X/AX design. The subject must keep every stimulus presented in working memory until it can be compared with the one immediately following it, thus greatly increasing the information processing load.

Over the course of the NYHRP, two forerunners of the CPT–IP were administered during various test rounds: (1) the playing card CPT, which introduced the identical-pair target definition but used images of playing cards as stimuli (Rutschmann et al. 1977), and (2) the double-digit CPT (task B), which applied the identical-pair strategy to more traditional two-digit number stimuli (Friedman et al. 1981, 1985; Rutschmann et al. 1986). The CPT–IP was developed to incorporate the best features of the two earlier procedures but to be substantially more difficult than either. Thus, in addition to using the identical-pair target definition, the CPT–IP consists of two independent sets of complex stimuli: nonsense shapes and four-digit numbers.

In the sections that follow, the major studies in schizophrenia research using the classic X/AX CPT, the DS CPT, and the CPT-IP will be summarized. Our discussion will focus on the results of CPT studies conducted with both fully affected schizophrenia patients and various at-risk populations. The at-risk populations include (1) high-risk offspring of parents with schizophrenia, tested before illness onset; (2) unaffected adult offspring and siblings of schizophrenia patients, at risk for having the clinically unexpressed (or mildly expressed) genotype; and (3) individuals (generally college students) without a family history of schizophrenia who display schizophrenia-like personality characteristics on psychological tests, such as the "psychosis-proneness" scales of Chapman et al. (1980).

Psychometric Properties of CPT Tasks

Performance Indices. Traditionally, the indices most widely used to assess performance on the classic CPTs have been correct responses to a target stimuli, or "hits" (also expressed as the complement, "misses" or "omission errors"), and incorrect responses to nontarget stimuli, or "commission errors" (referred to as "false alarms" in some studies). More recently, investigators have tended to use signal detection analysis (Rutschmann et al. 1977) to combine hit and false alarm rates into d' (d-prime) and β (beta). The d' is a measure of a subject's ability to discriminate a signal from background noise. The β (typically expressed as a natural log, ln β) is an index of a subject's tendency either to overrespond or underrespond and is considered a measure of state disposition and motivation. The higher the d', the better the processing capacity. The higher the β, the more conservative the response bias (i.e., sacrificing hits to make fewer errors); a lower β indicates a more liberal response bias (i.e., maximizing hits but making more errors). Typically, schizophrenia patients and subjects in populations at risk for schizophrenia are characterized by lower d's than controls. By contrast, schizophrenia patients, at-risk subjects, and control subjects show no consistent differences in ln β.

Reliability and Stability. Although reliability has been directly examined in only a few studies, all three versions of the CPT appear to have acceptable reliability when administered to appropriate populations. Rosvold et al. (1956) reported that the split/half reli-

abilities for number of correct responses in non–brain-damaged retarded adults were 0.88 for the X version and 0.86 for the AX version. Stability of hits over a 4- to 7-week period was similarly acceptable (0.88 and 0.74 for the X and AX tasks, respectively). Similar findings were reported for brain-damaged retarded subjects. Asarnow and MacCrimmon (1978) reported even higher reliabilities (0.88–0.99) for the X task in acute and remitted schizophrenia patients.

Rutschmann et al. (1977) correlated d′ values across successive trial blocks of the playing card CPT and then converted the correlations into *Z* scores. The resulting average *Z* scores of 0.95 for the offspring of normal parents and 0.97 for those of parents with schizophrenia indicated that the playing card CPT was reliable across blocks of trials. By contrast, reliability estimates for response bias were low and nonsignificant in both subject groups. Similarly, alpha coefficients ranged from 0.86 to 0.92 for the double-digit CPT (task B) and from 0.69 to 0.89 for the CPT–IP, for both hit rate and d′ (Erlenmeyer-Kimling and Cornblatt 1992).

Stability has also been evaluated for several CPT measures. Cornblatt et al. (1988) evaluated test–retest stability over 1½ years for the CPT–IP in 120 normal subjects. Consistent with expectations, d′ ranged from 0.56 to 0.73, whereas ln β showed considerably lower correlations over time. For patients, Nuechterlein et al. (1991; Nuechterlein 1991) examined the stability of d′ across clinical states for both the DS and a version of the AX task, the 3-7 CPT. The 3-7 task requires subjects to respond whenever the number 7 follows the number 3. However, it differs from the standard AX format in containing a greater than usual number of nontarget 3s and 7s. Correlations across clinical states were 0.57 for the DS CPT d′ and a lower 0.33 for the easier 3-7 task. Finally, Cornblatt et al. (1989*b*) and Winters et al. (1991) reported that attentional abnormalities detected in adolescents at risk for schizophrenia (as measured by an index derived from the CPT–IP) were stable over a 6- to 9-year period. Thus, the classic X/AX, the DS CPT, and the CPT–IP all appear to be psychometrically reliable and capable of detecting an attentional trait that is stable over extended time intervals.

Vigilance Properties. CPTs have historically been considered vigilance tasks. It has been assumed, therefore, that the critical deficit tapped in schizophrenia research is a dysfunction in "sustained" attention (i.e., that as a CPT proceeds, the performance of schizophrenia patients will deteriorate to a greater extent than is typical of comparison subjects). The ability to sustain attention over time is clearly essential to successful CPT performance. However, the majority of studies have found that a decline in attention over time is not the critical impairment in schizophrenia. In nearly all cases, deficient processing capacity—evident at task onset and continued throughout—is the overriding deficit manifested (Nuechterlein 1983; Nuechterlein and Dawson 1984; Cornblatt and Erlenmeyer-Kimling 1985; Cornblatt et al. 1989*a*).

Overview. All three of the most common versions of the CPT appear to be reliable measures of the capacity to attend to a continual input of information over time. Whether impaired attentional capacity is a valid indicator of biological susceptibility to schizophrenia, however, depends on the extent to which it is (1) independent of the state of illness, that is, is not a secondary symptom of schizophrenia; (2) associated with risk for illness; (3) transmissible in normal families and coaggregates with illness in families of schizophrenia probands; and (4) acceptably sensitive and specific in predicting illness. (See Moldin and Erlenmeyer-Kimling 1994, this issue for a more complete discussion of these criteria.) Each of these criteria will be discussed below.

State Independence

A sizable number of studies have demonstrated that schizophrenia patients are characterized by impaired attention relative to many kinds of controls, and this is true across all versions of the CPT. There is also considerable evidence that this deficit is not simply a secondary effect of the florid schizophrenia state. Orzack and Kornetsky (1966, 1971) found that attentional deficits were not a secondary product of chronicity, severity of illness, or length of hospitalization and that deficits were detectable in remitted patients as well as those in episode (Wohlberg and Kornetsky 1973). Somewhat later, Asarnow and MacCrimmon (1978) reported cross-sectional comparisons indicating that remitted schizophrenia patients performed similarly to patients in episode and differed from normals to an increasing extent as the CPT task grew more difficult (i.e., as distraction was added).

Secondary effects of chronicity have also been controlled for by testing patients in the earliest stages of illness. Impaired performance on the DS CPT (d' and hit rate) has been found in patients within 2 years of illness onset (Nuechterlein 1991). Similar findings have emerged from the Elmhurst Adolescent Project, a study of drug-free psychotic adolescents in their first year of illness recently initiated by the first author. In an early report from this project, Bergman et al. (1992) found that these subjects did not differ from patients with chronic schizophrenia in level of attentional impairment on the CPT–IP.

A more direct demonstration of state independence is to show that attentional disturbances remain stable within patients regardless of fluctuations in clinical state. Preliminary evidence of this form of state independence has been reported by Nuechterlein et al. (1991). In their longitudinal study of schizophrenia patients in the early stages of illness, these investigators found that comparable deficits (on the DS CPT) were displayed in episode and subsequently during a stable remission of at least 1 month (on medication). Additional support for state independence is provided by Cornblatt et al. (1989*b*) and Winters et al. (1991), who found that attentional abnormalities measured by the CPT–IP remained stable for over 6 years in adolescents at risk for schizophrenia, even with the emergence of increasingly disturbed behaviors.

Medication effects must be taken into account when assessing state independence. Because many of the remitted patients in the above studies were medicated, the effects of medication cannot be clearly separated from changes in clinical state. Furthermore, comparisons of medicated patients with unmedicated relatives in family studies may be confounded by medication effects. Of the investigations addressing the medication issue, the majority are cross-sectional; only two involve longitudinal comparisons.

In the earliest of the cross-sectional studies, Orzack and Kornetsky (1971) compared the performance of 27 drug-free and 42 medicated (with phenothiazines) chronic schizophrenia patients on an X CPT and found that medicated patients performed better than those who were drug free. However, because this study did not include normal controls, the extent to which medicated patients approached normal performance levels could not be determined.

Subsequently, Harvey and colleagues compared performances of unmedicated chronic schizophrenia patients, medicated chronic schizophrenia patients, and normal controls on various versions of the AX CPT. Overall, these studies indicate that medication enhances attention—independently of clinical improvement—but does not elevate it to normal levels (Harvey et al. 1990; Serper et al. 1990; Earle-Boyer et al. 1991). Nestor et al. (1991) similarly reported that schizophrenia patients withdrawn from medication performed more poorly than medicated patients on a version of the DS CPT.

In one of the two longitudinal studies of medication effects, Orzack et al. (1967) tested 18 chronic schizophrenia patients after a 1-month washout and then after 12 weeks of treatment with carphenazine. Medication was found to improve clinical state and CPT hit rate, but to have no effect on the DSST. These findings were subsequently replicated by Spohn et al. (1977) in a more elaborate longitudinal study of 40 chronic schizophrenia patients. Following a 6-week washout, patients in Spohn et al.'s study were randomly assigned to placebo and chlorpromazine groups in a double-blind design and then tested after an 8-week trial. Medicated patients displayed a decrease in omission errors, whereas patients on placebo exhibited an increase in omission errors. There was also a significant correlation between improvement on the CPT and clinical improvement with medication. Both groups of investigators subsequently concluded that medication specifically affected attention and that improvements in the ability to focus attention contributed, causally, to improvements in clinical state.

Association With Increased Risk for Illness

The results summarized thus far clearly indicate that when the population under study consists of affected schizophrenia patients, the easy X and AX tasks are sufficient to assess substantial performance deficits (e.g., Kornetsky and Orzack 1964; Orzack and Kornetsky 1966, 1971; Orzack et al. 1967). However, as mentioned earlier, in nearly all studies the classic version of the CPT has proven insufficient to demonstrate performance deficits in at-risk populations such as the unaffected first-degree relatives of schizophrenia patients. When evaluating the association between attentional abnormalities and risk for schizophrenia, then, the difficulty level of the CPT task administered is of critical importance.

Standard X versions of the CPT have not proven effective in detecting attentional dysfunctions in at-risk offspring of schizophrenia parents in studies conducted by Grunebaum et al. (1974), Asarnow et al. (1977), Herman et al. (1977), and Rutschmann et al. (1986). By contrast, more difficult variants of the CPT paradigm have been consistently effective in high-risk investigations. Children at risk for schizophrenia displayed attentional abnormalities on an X task with colors as stimuli (difficult for 5-year-olds only, Grunebaum et al. 1974), the playing card CPT (primarily effective with children younger than age 11, Rutschmann et al. 1977; Erlenmeyer-Kimling and Cornblatt 1992) and the double-digit CPT (for children between the ages of 7 and 12 years, Rutschmann et al. 1986). After administering several CPT versions in the same study, Nuechterlein (1983) reported that older (9–16 years of age) at-risk subjects did not differ from comparison subjects on any variants of the classic X task or on the playing card version of the CPT but that they were impaired on the more challenging DS CPT.

Similar results have been reported for adult at-risk populations, primarily first-degree relatives of schizophrenia patients. In a study of adult monozygotic twins discordant for schizophrenia, Goldberg et al. (1990) found that the unaffected cotwin did not display significant performance deficits relative to normal control twins on a dynamically paced (i.e., pacing was partially under subject control) version of the AX CPT. Since the unaffected cotwins displayed marginally impaired performance, however, it is possible that attentional deficits would have been detected with a more appropriate version of the CPT. Mirsky et al. (1992) administered four CPT tasks of varying difficulty levels to two independent family samples and found that patients were significantly impaired, compared with controls, across all tasks. Relatives, however, were similar to normal controls on the three easiest tasks (X, AX, and a version of the DS CPT) and approached patient performance levels only on the most difficult task (an auditory CPT measure).

By contrast, studies using the relatively challenging CPT–IP have consistently demonstrated clear deficits in unaffected offspring of parents with schizophrenia (Cornblatt et al. 1989*b*, 1992*b*), unaffected adult siblings of schizophrenia patients (Maier et al., submitted for publication), and psychometrically defined schizotypal subjects both in this country (Lenzenweger et al. 1991) and in Europe (Obiols et al., in press). In combination, these findings indicate that attentional abnormalities can be detected in a variety of clinically unaffected at-risk populations when an appropriately difficult version of the CPT is administered.

Familiality

Transmission in Families. There have been few studies examining the familial transmission of attention, per se, in normal families. The major findings in this area are from a study by Cornblatt et al. (1988) in which the CPT-IP was administered to 120 normal subjects from 30 families. In each participating family, both parents and two children between the ages of 12 and 22 years were tested. The results indicated that the CPT–IP taps two independent attentional dimensions: verbal, as measured by the numbers stimuli, and spatial, as measured by nonsense shapes. Both dimensions appear to involve a genetic component. In a genetic study comparing normal monozygotic and dizygotic twin pairs, Kendler et al. (1990) also found that attention, measured by a factor combining CPT tasks, was a heritable trait.

Similarly, there has been little research concerned with transmission of attention in families of schizophrenia patients. However, in a recent pilot study in which a version of the DS CPT was administered to first-degree relatives of schizophrenia patients, Grove et al. (1991) found preliminary evidence for the heritability of attention. Although these findings, overall, suggest that there is a heritable biological basis to attentional performance, more definitive family studies are required.

Coaggregation With Illness. As in the case of familial transmission, coaggregation with illness in the families of probands has not been explored in any depth. Some very indirect evidence has been provided by studies comparing attentional disorders in patients with and without a family history of schizophrenia. Orzack and Kornetsky (1971) found that there was more mental illness in the biological relatives (primarily siblings) of chronic schizophrenia patients who performed poorly on the X CPT than in the relatives of those who performed well on the CPT. Walker and Shaye (1982) expanded this finding by reporting that schizophrenia patients with a positive family history for schizophrenia had higher omission and commission errors on the AX CPT

than patients without a family history. No difference in motor dysfunctions was observed between the groups, implying that family history was specifically relevant to attentional processing rather than a more general performance deficit.

More direct evidence supporting the cosegregation of attentional dysfunctions with illness has been provided in a preliminary report by Steinhauer et al. (1991), who compared stabilized schizophrenia outpatients with their siblings and normal controls matched to the siblings. Early results on the DS CPT indicated that schizophrenia patients had significantly lower d' values than normal controls and that the performance of siblings with spectrum disorders more closely resembled patient performance than the performance of matched normal subjects. Similarly, in a family study now under way in Germany, Maier et al. (submitted for publication) have administered the CPT-IP to schizophrenia patients, their siblings, and matched normal controls. Preliminary findings indicate that siblings are more impaired than controls on both the spatial and verbal CPT-IP conditions.

Specificity, Sensitivity and Predictive Validity

Specificity. Although not as solidly established as differences between schizophrenia patients and normal controls, attentional abnormalities—or, at least, particular patterns of attentional abnormalities—appear to be specific to psychosis and possibly to schizophrenia. In studies by Kornetsky, Orzack, and their colleagues (Orzack and Kornetsky 1966), schizophrenia patients not only performed more poorly on the AX CPT than normal controls but were deficient relative to alcoholic controls, a finding recently replicated by Mussgay and Hertwig (1990). Walker (1981) reported that schizophrenia inpatients were significantly more impaired in AX CPT performance than inpatients with either schizoaffective or major affective disorders. (Note, however, that in a separate study Walker and Green [1982] found that differences between schizophrenia and affectively disturbed inpatients—although in the right direction—were not statistically significant.)

Cornblatt et al. (1989*a*) found that affectively disturbed patients displayed attentional abnormalities on the CPT-IP but that these abnormalities were clearly different from the dysfunctions characterizing schizophrenia patients. Schizophrenia patients showed a global deficit across verbal and spatial tasks and were primarily characterized by low hit rates and high numbers of random commission errors. By contrast, affective patients were impaired on spatial tasks only and made an excessive number of false-alarm commission errors.

High-risk findings support the specificity of CPT deficits to schizophrenia. In the study conducted by Nuechterlein (1983), significantly more children of mothers with schizophrenia scored low on the CPT d' factor than did normal control youngsters, children of mothers with nonpsychotic psychiatric disorders, or boys with attention deficit disorder. In the NYHRP, children of affectively ill parents displayed some degree of attentional impairment. However, consistent with the findings for affected adults, the deficits in affective-risk children were (1) of lesser magnitude than those of schizophrenia-risk children, (2) not stable over time, and (3) not directly related to later behavioral disturbances (Cornblatt and Erlenmeyer-Kimling 1985; Cornblatt et al. 1989*b*, 1992*b*).

Predictive Validity. In terms of predictive validity, Cornblatt and Erlenmeyer-Kimling (1985) reported that the attentional deviance index (ADI; a measure composed largely of playing card CPT performance indices for sample A of the NYHRP) had a specificity of 91 percent and a sensitivity of 35 percent for predicting the adolescent disturbances considered most likely to foreshadow eventual schizophrenia-spectrum disorders. This finding was replicated in sample B by Cornblatt et al. (1989*b*) and Winters et al. (1991), who found a comparable ADI (composed entirely of CPT-IP performance measures) to have a specificity of 90 percent and sensitivity of 31 percent for predicting serious behavioral disorders in adolescents. Attentional abnormalities in childhood, therefore, appear to have high specificity but only moderate sensitivity as predictors of subsequent illness. Since a major long-term goal of high-risk research is to develop a screen for preventive intervention, it is necessary to optimize high specificity—often at the cost of lowered sensitivity—to avoid false-positive identification of children (i.e., those with abnormal attention who prove to be clinically normal) who would be subjected to unnecessary long-term treatment.

Moderate sensitivity may also reflect the heterogeneity of the disorder. It is very likely that impaired attention characterizes only one form of schizophrenia. For ex-

ample, Orzack and Kornetsky (1966) found that 44 percent of the schizophrenia patients in their study were extremely poor performers (i.e., they performed more poorly than the worst-performing normal control) on the classic X CPT. Similarly, Walker and Shaye (1982) found that 42 percent of their patient group were poor CPT performers. Therefore, the above sensitivity estimates (ranging from 31% to 35%) may be fairly accurate reflections of the proportion of schizophrenia patients actually characterized by early childhood attentional abnormalities.

Attention and the Pathophysiology of Schizophrenia

The weight of the evidence indicates that abnormal attention is an indicator of biological liability to at least one major form of schizophrenia. With regard to the pathophysiology of this biological liability, it is likely that the attentional impairment involved is associated with an underlying brain abnormality. Impaired attention may also contribute to the development of schizophrenia-like symptoms and play an important mediating role in the expression of the illness. In the following sections, we will examine both of these possible roles of attentional dysfunctions in the pathophysiology of schizophrenia.

CPT Deficits and Abnormal Brain Functioning. Similarities in CPT performance between schizophrenia patients and brain-damaged patients (Mirsky 1969), as well as the relative state independence of CPT deficits in schizophrenia patients, strongly suggest that brain abnormalities underlie attentional dysfunctions in schizophrenia patients. Recent functional brain imaging studies using the CPT as an activation task provide further evidence to support this assumption. In one of the most direct demonstrations of this association, Buchsbaum et al. (1990) observed that schizophrenia patients' performance on the DS CPT was associated with significant abnormalities of regional glucose metabolism, measured by positron emission tomography (PET). Compared with normal subjects, schizophrenia patients showed decreased metabolic activity in the prefrontal cortex and a reduction of normally lateralized activity in temporoparietal regions (differences in activity between right [R] and left [L] sides of this region were much greater in control subjects [R > L] than in schizophrenia patients).

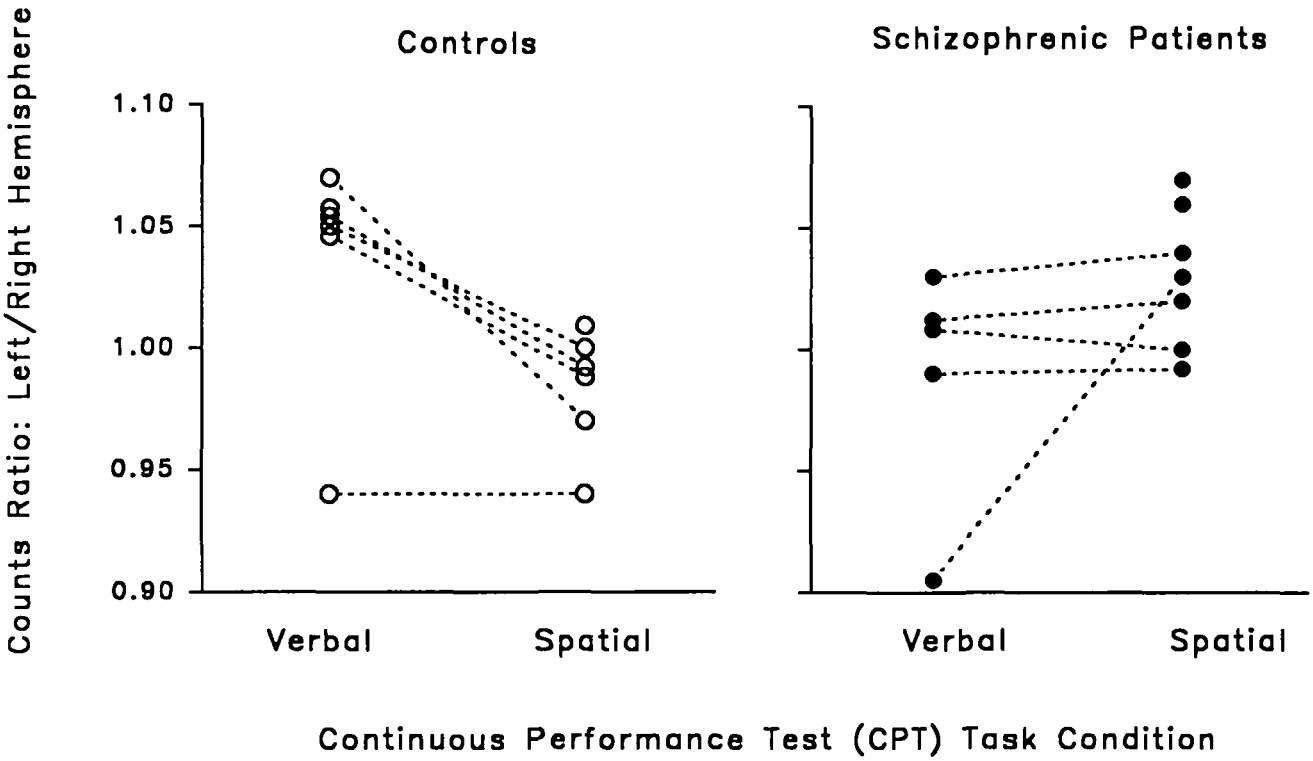
Although Buchsbaum et al. (1990) were able to localize deficits in metabolic activity during CPT performance to regions of the brain that had previously been implicated in schizophrenia (frontal and temporal lobes), these findings have not been consistent across studies using other versions of the CPT. Berman and Weinberger (1990), for example, obtained measures of regional cerebral blood flow during the classic X CPT and did not find evidence of reduced frontal lobe activation among schizophrenia patients. Like Buchsbaum et al., however, they did find laterality differences between schizophrenia patients and normal controls, suggesting that frontal lobe abnormalities may be a function of task difficulty and that disturbances in laterality may play an important role in poor CPT performance. In addition, two pilot studies conducted in our laboratory at Elmhurst Hospital Center suggest that the laterality disturbances observed reflect both aspects of the CPT task and complex interactions between cortical and subcortical brain activity.

Our two pilot studies examined brain functioning during the performance of subtasks of the CPT–IP (Herrera et al. 1991; Keilp et al., in preparation *a* and *b*). Because Cornblatt et al. (1989*a*) had previously established that the number and shape subtasks of the CPT–IP are psychometrically matched for both difficulty level and error variance and that they assess independent verbal versus spatial attentional functions, we were able to use them to determine whether previously observed laterality disturbances were a function of the disease itself or resulted from the nature of the stimuli used in specific CPT tasks.

In the first study, five male schizophrenia patients (consensus *DSM–III–R* [American Psychiatric Association 1987] diagnoses, based on the Schedule for Affective Disorders and Schizophrenia [Endicott and Spitzer 1978] interviews) were compared with five male normal controls (hospital staff members, matched for age) on ^{99m}Tc-HMPAO (single photon emission computed tomography (SPECT) images obtained during performance of the number (verbal) and shape (spatial) CPT–IP tasks (presented separately, 1 week apart). The results of this study are presented in figure 1. Data are presented in terms of a ratio of metabolic activity in the left versus right half of the brain (left divided by right).

In normal controls, the verbal and spatial CPT–IP subtasks produced predictable changes in cerebral activation: for most subjects (four of the five), the left side was relatively more active than the

Figure 1. Relative hemispheric activation during verbal (numbers stimuli) and spatial (nonsense shapes stimuli) CPT–IP subtasks



Data points are perfusion ratios for each individual subject. Unconnected data points represent subjects who did not complete both conditions. CPT–IP = Continuous Performance Test–Identical Pairs Version (Cornblatt et al 1988)

right during performance of the verbal task and the right side was relatively more active than the left during the spatial task. In patients, however, most subjects (four of the five) showed no lateralized change during the performance of either task. Mean differences between patients and controls in the degree of lateral specialization were significant in both conditions. Rather than suggesting an abnormal reversal of lateralized functioning or overactivity of one particular hemisphere, however, these brain activity patterns reflected what appears to be a *failure* of appropriate lateralization in schizophrenia patients under both task conditions.

In the second SPECT pilot study, we used a high-resolution scanning apparatus (Keilp et al., in preparation *b*) to study specific brain correlates of normal performance on the verbal and spatial subtasks of the CPT–IP. Seven normal controls were administered the CPT–IP number and shape subtask during a ^{99m}Tc-HMPAO SPECT scan. The resulting cerebral perfusion pattern was similar to that observed among normal subjects in our first study: greater left-sided activity during the number task and greater right-sided activity during the shape task. However, we also found that the change in lateral distribution of labeled tracer took place primarily within subcortical regions, including the basal ganglia and thalamus. Cortical activity was surprisingly consistent across the two conditions. Data from this second study suggest, then, that the lack of lateralization effects observed among schizophrenia patients in our first SPECT study may be attributable to metabolic dysfunctions primarily within subcortical regions. This conclusion is consistent with recent findings from Buchsbaum et al. (1992), who used PET scans in a sample of

never-medicated schizophrenia patients and found a reduction of normally lateralized metabolic activity within the basal ganglia during performance of the DS CPT.

The potential link between poor CPT performance in schizophrenia and dysfunction of the basal ganglia is intriguing in light of older data suggesting that CPT performance is more sensitive to subcortical than cortical brain dysfunction (Landsell and Mirsky 1964). Both empirical findings (Kornetsky and Orzack 1964; Rappoport et al. 1980; Klorman et al. 1984; Peloquin and Klorman 1986; see also review by Pantelis et al. 1992) and neural network simulations (Servan-Schreiber et al. 1990; Cohen and Servan-Schreiber 1993) suggest that dopamine neural transmission (primarily localized within the basal ganglia) is crucial to attention performance. In addition, an association between abnormal attention and neuromotor dysfunction has been reported in both schizophrenia patients (Walker and Green 1982; Nuechterlein et al. 1986) and children at risk (Erlenmeyer-Kimling et al. 1982; Erlenmeyer-Kimling and Cornblatt 1992). Further research on the functional brain correlates of CPT performance is needed to confirm these associations.

Attention and Adult Personality. In addition to providing a window to abnormal neuropathological processes, impaired attention appears to play a role in the personality development of subjects with a susceptibility to schizophrenia. A number of studies have attempted to relate attention to either positive or negative symptom domains in schizophrenia (e.g., Nuechterlein et al. 1986; Kendler et al. 1990; Nestor et al. 1990). Although not entirely consistent, these studies have found a loose association between impaired attention and various negative symptoms.

By studying the unaffected adult offspring of parents with schizophrenia (high risk for schizophrenia individuals) in sample A of the NYHRP, Cornblatt et al. (1992*b*) have specifically linked childhood attentional problems to social deficits in adulthood. In this study, abnormalities in childhood attention were assessed by means of the ADI originally calculated by Cornblatt and Erlenmeyer-Kimling (1985). Adult personality disorders were measured by the Personality Disorder Examination (PDE, 1985 version; Loranger et al. 1987), a semistructured interview assessing *DSM–III–R* Axis II personality disorders, which was administered approximately 14 years after the attentional data had been collected (Squires-Wheeler et al. 1989).

The first question we asked was whether chronic attentional abnormalities were associated with a biological liability for schizophrenia (Cornblatt et al. 1992*b*). We found that clinically unaffected adult subjects at high risk for schizophrenia (many of whom are presumed to have some degree of genetic loading for schizophrenia) were significantly more impaired in attention in childhood (when they were about 10 years old) than were adult subjects in either the group at high risk for affective disorders or the normal control group.

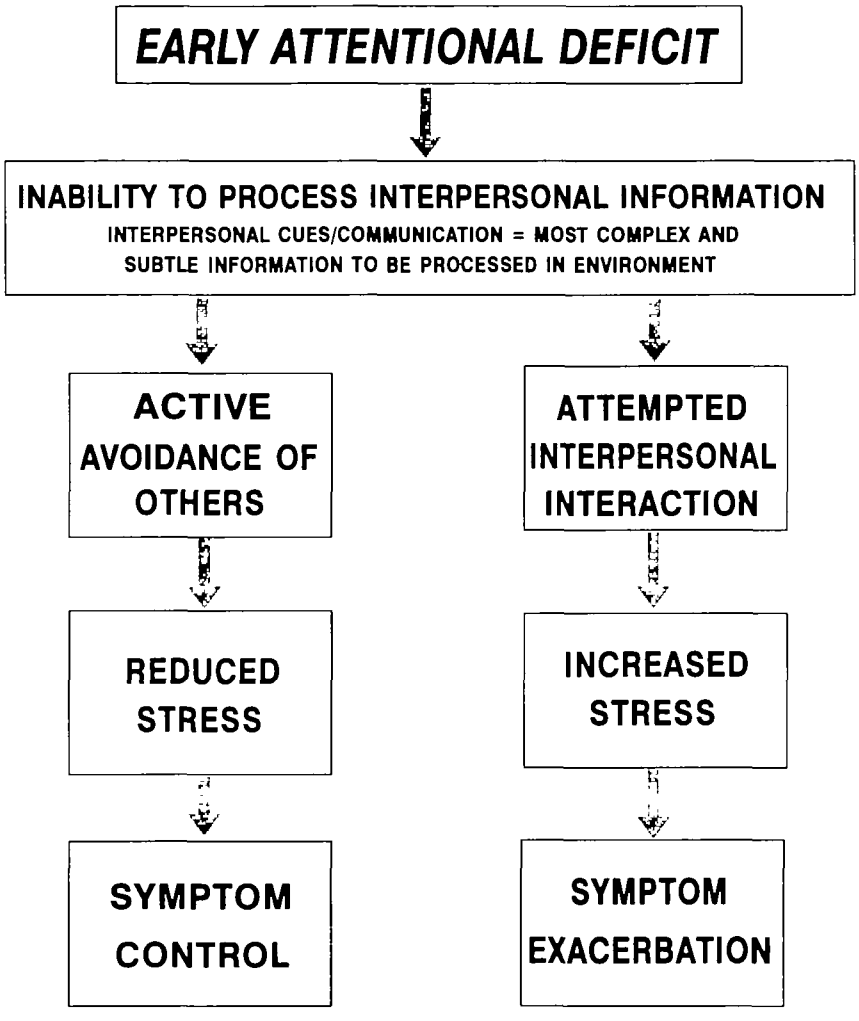
We then related childhood attentional problems to the adult personality features measured by the PDE. To detect underlying Axis II traits, we conducted a factor analysis on selected PDE scales (the schizoid, schizotypal, histrionic, narcissistic, avoidant, and dependent scales). Two major factors emerged that were related to attention. These were labeled "social insensitivity" and "social indifference." A composite scale combining the two factors was designated "social isolation."

For subjects in both the high risk for affective disorders and normal control groups, no relationship was found between the childhood ADI and the three adult personality dimensions. However, all three adult personality dimensions were significantly related to the childhood ADI in the high risk for schizophrenia group. These results indicate that subjects at risk for schizophrenia who also have a chronic attentional disorder dating back to childhood tend to be both indifferent and insensitive to other people in adulthood.

On the basis of these findings, we have proposed a heuristic model (Cornblatt et al. 1992*b*) represented here in figure 2 and summarized as follows:

1. In subjects with a biological liability for schizophrenia, impaired attention is likely to be a chronic disturbance evident throughout the subject's development.
2. This attentional impairment leads to an inability to efficiently process information from the environment, especially subtle and highly complex interpersonal cues and communications.
3. As a result, the processing of social information is particularly disrupted by attentional difficulties.
4. Deficiencies in processing social and interpersonal information make interactions with others increasingly difficult and stressful.
5. In predisposed individuals, such escalating stress levels result in one of two outcomes, indicated by the two arms of the model. Over time, continued unsuccessful

Figure 2. Hypothesized role of attention deficits in the development of social dysfunctions among persons with a genetic susceptibility to schizophrenia



attempts to initiate or maintain relationships can exacerbate symptoms and, in some cases, act as an environmental trigger for the full clinical expression of the disease (right arm). Alternatively, susceptible individuals may reduce stress and control their overt symptomatology by actively avoiding intense interpersonal contacts and situations requiring active relationships with other people (left arm). Thus, we hypothesize that for some predisposed persons, the active avoidance of others acts as a compensating mechanism that provides a measure of symptom control.

Recent data from sample B of the NYHRP support this model. Using measures of social competence developed by Dworkin et al. (1991, 1993), Cornblatt et al. (1992*a*) compared childhood attentional disturbances in sample B subjects with social competence at three time points over the adolescent development of these subjects. Attention was measured by an ADI comparable to the index used for sample A. (The scale was based primarily on the double-digit CPT; see Cornblatt et al. 1989*b* for details.)

Consistent with the findings for sample A, correlations between the ADI (obtained when the subjects were approximately 9 years old) and social competence (measured at ages 9, 11, and 15) were not significant at any age for subjects in either the high risk for affective disorders or normal control groups. For high risk for schizophrenia subjects, correlations between attention and social competence were nonsignificant at ages 9 and 11 but significant at age 15 ($r = 0.52$, $p = 0.017$). It should be noted that the youngsters in the high risk for schizophrenia group began to show social skill deficits—relative to both comparison groups—only as they reached midadolescence (between 12 and 15 years of age; see Dworkin et al. 1991, 1993). Thus, attentional disturbances appear to precede social deficits; the latter may not emerge until interpersonal relationships are sufficiently sophisticated to challenge information-processing skills.

Summary and Conclusions

All three of the most widely used forms of the CPT—the classic X/AX, the DS CPT, and the CPT-IP—are reliable procedures that measure a stable attentional deficit in schizophrenia patients. Compa-

rable abnormalities can also be reliably detected in a variety of at-risk populations (i.e., clinically unaffected subjects assumed to be carrying the schizophrenia genotype), but only when the attentional system is challenged by more difficult versions of the CPT, such as the DS CPT or the CPT–IP.

On the basis of the literature summarized in this review, we have concluded that abnormal attention is highly promising as an indicator of a biological susceptibility to schizophrenia. This conclusion is based on the following evidence:

1. In affected individuals, impaired attention is detectable regardless of clinical state, and remitted patients display abnormalities similar to those characterizing psychotic schizophrenia patients. Although medication generally improves attention, it does not fully normalize it.
2. Deficits in attention are displayed by unaffected children of parents with schizophrenia at early ages, preceding clinical symptomatology by many years, and are therefore not secondary to illness or treatment factors.
3. Attention appears to be heritable both in normal families and in families of schizophrenia probands.
4. Although attentional disturbances are also found in patients with major affective disorders and children with attention deficit disorder, particular patterns of impairment appear to be specific to schizophrenia.
5. In unaffected at-risk children, attentional difficulties clearly predict later behavioral disturbances thought to be related to schizophrenia.

Our review of the literature further suggests two important directions for future research concerned with attention. First, little has been established about the genetics of attention itself. The few studies that have examined this issue have been uniformly positive, but more work needs to be done. Future research should focus on the heritability of both normal attention and attentional abnormalities, as well as on the extent to which the latter coaggregate with clinical disturbance in families of schizophrenia probands.

Second, because trait indicators, unlike molecular genetic markers, are considered to play a role in the pathophysiology of the illness (Gershon and Goldin 1986), future research should be concerned with the way attention is involved in the pathogenesis of the illness. Such studies will provide a means for better understanding the mechanisms through which genetic susceptibility is expressed as clinical schizophrenia. Two examples of this type of research have been presented in this review: one suggests a relationship between attentional impairment and dysfunctional subcortical brain structures such as the basal ganglia, and the other describes a developmental association between impaired attention in childhood and social skills deficits in adulthood. These preliminary findings require considerable further study and replication, but they illustrate how findings regarding the indicator status of impaired attention might be extended.

Finally, it should be emphasized that the evidence to date strongly supports the inclusion of appropriate CPT assessments in research concerned with prevention. Computerized versions of the measure, such as the CPT–IP, are easily administered at low cost and are available for general use, allowing comparable data to be generated across a range of studies. Thus, CPT assessments are a highly cost-effective means of initially screening large numbers of subjects potentially in need of preventive intervention programs.

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The Authors

Barbara A. Cornblatt, Ph.D., is Associate Professor of Psychiatry, Mount Sinai School of Medicine, and Director of Psychology, Elmhurst Hospital Center, Elmhurst, NY. John G. Keilp, Ph.D., is Assistant Professor of Psychiatry, Mount Sinai School of Medicine, and Head, Neuropsychological Assessment Service, Elmhurst Hospital Center, Elmhurst, NY.