Recent Studies of Psychophysiology in Schizophrenia

by Philip S. Holzman

Abstract

Eye movement dysfunctions have been shown to be reliably associated with schizophrenia as a trait, suggesting disorders of nonvoluntary attention in association with those brain areas involved in smooth pursuit and saccadic eye movements. The familial distributions of the eye movement dysfunction and of schizophrenia, when considered together, suggest the existence of a latent trait whose transmission fits an autosomal dominant transmission mode. Chronic schizophrenic patients show diminished variation and shorter latencies of early components of somatosensory brain related potentials, which reflect stimulus registration, and investigators have interpreted the finding as indicating impaired modulation of stimulus input, which allows too much information to reach higher brain centers. Laterality differences, in which the left hemisphere may be less efficient than the right, have also been reported. Schizophrenic patients show reduced amplitudes of later component waves of event related potentials, a finding that has been interpreted as reflecting impaired selective attention. The issue of whether these deviations are state or trait related has not yet been resolved. Directed attention in the form of vigilance shows significant performance impairment, as measured by the continuous performance test and the span of apprehension, not only in schizophrenic patients but in some populations at high risk for schizophrenia. Studies of backward masking suggest that the time taken to transfer a stimulus from the stage of registration to short-term memory may be slowed in schizophrenia, although other interpretations are possible. Skin resistance orienting responses are absent in about 50 percent of adult schizophrenics, and there is some evidence that this absence may reflect a trait. Studies should now test the trait status of all these psychophysiological variables and probe into the significance of the measures used. In these efforts, both the testing of first degree family members and the standardization of testing techniques are recommended.

Since the publication of the previous update on the psychophysiology of schizophrenia by Spohn and Patterson (1979), several authoritative reviews have appeared. These reviews provide details of the several areas in which major progress has occurred. Mirsky and Duncan (1986) gave a broad overview of progress with respect to etiological hypotheses. Lipton et al. (1983) and Holzman (1985) reviewed the findings about eye movements in schizophrenia. Dawson and Nuechterlein (1984) surveyed electrodermal and evoked potential measures, as well as information processing and attentional functions in schizophrenia. Erlenmeyer-Kimling (1986) critically surveyed the putative biological markers for liability to schizophrenia. Gjerde (1983) reviewed the literature on arousal, as did Pritchard (1986) for studies of the P300 wave, both with respect to schizophrenia. All of those reviews are useful source material from which to launch further inquiry into the psychophysiology of the schizophrenias.

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The aforementioned reviews alone run to 163 pages. It is therefore obvious that the present update cannot even pretend to be an exhaustive compendium of psychophysiological studies of schizophrenia during the past 6 years. This review will focus on what appear to be the sturdier findings in this area.

There has been a noticeable turn in the nature of psychophysiological studies in psychopathology. Previously, investigators used methods principally because of their availability rather than because of their appropriateness for testing a hypothesis about schizophrenia. And subject groups consisted mostly of the most severely ill patients. This practice was, of course, a bootstrap operation, perhaps a necessary one. Investigators had to start somewhere, and why not use the most available techniques on the most available patients whether or not the methods possessed relevance for the pathology under consideration? Some of the earlier work examined bioelectric signals from the surface of the body as an indicator of central or peripheral nervous system integrity. Other behavioral scientists have tried to study aspects of perception and cognition that might be involved in schizophrenic disorders, such as focused attention, inhibition of distracting stimuli, perceptual distortion, and thinking peculiarities. But many of the tests that have been used to measure those processes failed to isolate the specific components of performance that are relevant to schizophrenia. The yield of these efforts has understandably been disappointing because few of the indicators studied could be depended on to reflect the underlying disease process.

An approach that systematically works its way by degrees from behavior toward physiological, bio-chemical, and genetic levels will be most fertile. Great leaps from behavioral to biochemical events have not worked in the past and are not likely to work in the future. Most putative markers studied in the past, like monoamine oxidase or γ-aminobutyric acid, tried to bridge the gap from mental state to molecules in one jump, and it would have been abiding good luck, never yet a steady companion of schizophrenia studies, to have found correlations that bridged so great a gulf.

Many of the studies reviewed here reflect two simultaneous emphases. They are anchored to the psychology of schizophrenia and at the same time related to processes in the brain. Chief among these is the work on eye movement dysfunctions, which has explored the psychology of schizophrenia with respect to nonvoluntary attention and the higher brain centers that are known to be implicated in smooth pursuit and saccadic eye movements, and the genetic models suggested by the family distribution of eye movement dysfunctions. Because it represents a body of work that has been sustained over about 15 years, and has produced new hypotheses about schizophrenia, I have been requested to give major attention to the studies of eye movement dysfunctions in schizophrenia in this overview. This review will also consider, but in less detail, early and late event related brain potentials, tests of information processing such as the continuous performance test, span of apprehension test, and backward masking, and electrodermal measures. A subsequent issue of the *Schizophrenia Bulletin* will contain an article in greater detail on the psychophysiological concomitants of schizophrenic disorders.

Eye Movement Abnormalities

The study of eye movement dysfunctions in schizophrenic patients has contributed both to the neuropsychological understanding of schizophrenic disorders and to new hypotheses about the genetic transmission of the schizophrenias. Investigations were at first confined to smooth pursuit eye movements, those that are made when following a moving object. Later it became apparent that the eye movement dysfunctions were detectable even when the target was stationary. Although this may appear puzzling, it should be noted that when one fixates on a stationary target, the same eye movement apparatus and mechanisms are employed as when one is fixating a moving object. Fixation is thought to be a pursuit movement with zero velocity.

The eye movement system under consideration can be illustrated as follows: Imagine a small spot of light which begins to move to the right. The eye is delayed by about 200 ms in its pursuit of that target. When the eye begins to move in the direction of the target, it has already fallen behind the target by virtue of its late start; a rapid eye movement, or saccade, must then be executed to put the eye on the target. That saccade is also delayed by about 200 ms. Only after about 400 ms is the eye on the target and able to continue to keep that target on the fovea. If the light now abruptly moves back again to the starting point, the eye continues its pursuit movement for yet another 200 ms, and then a saccadic movement takes the eye the distance the target moved from its stopping point to its final position at the center of the screen. But once again, because of the inherent refractory period, the eye is off target and another saccadic

movement is necessary to bring it on target, a movement that also has a 200 ms latency. The process described is a dual control, coordinated system in which one process is turned on while the other is turned off, to place an object of interest on the fovea and then to keep it there. But for large numbers of schizophrenic patients and almost half of their first degree relatives, when the pursuit system is engaged in a following movement, the saccadic system is only incompletely turned off or, for some, not turned off at all. That finding has generated new hypotheses about schizophrenic pathology and its transmission.

Using a high resolution reflected infrared light technique to record the nature of the eye movement disruptions in schizophrenic patients, Levin et al. (1982*b*) were able to show that schizophrenic patients with irregular pursuit eye movements also have a high prevalence of saccadic intrusions and saccadic tracking. In the latter, smooth pursuit is replaced by small saccadic jumps. These instances of saccadic tracking are generally compensatory eye movements that correct for low gain pursuit which causes the eye to lag behind the target. In pursuit with saccadic intrusions, however, extraneous eye movements, those that have no corrective function, interrupt the pursuit movements. These saccadic intrusions are of various types, some of which have been called "square wave jerks" or paired saccades that range from less than 0.5 degrees to 5 degrees in amplitude. Figure 1 illustrates some of the types of pursuit disruptions found in schizophrenics.

A study published in 1974 by Holzman and his colleagues reported that schizophrenic patients and their first degree relatives ac-

Figure 1. Pursuit eye movements produced by a schizophrenic patient when tracking a constant velocity target moving at 0.33 and 0.10 Hz

SUBJECT 9 (SCHIZOPHRENIC): PURSUIT
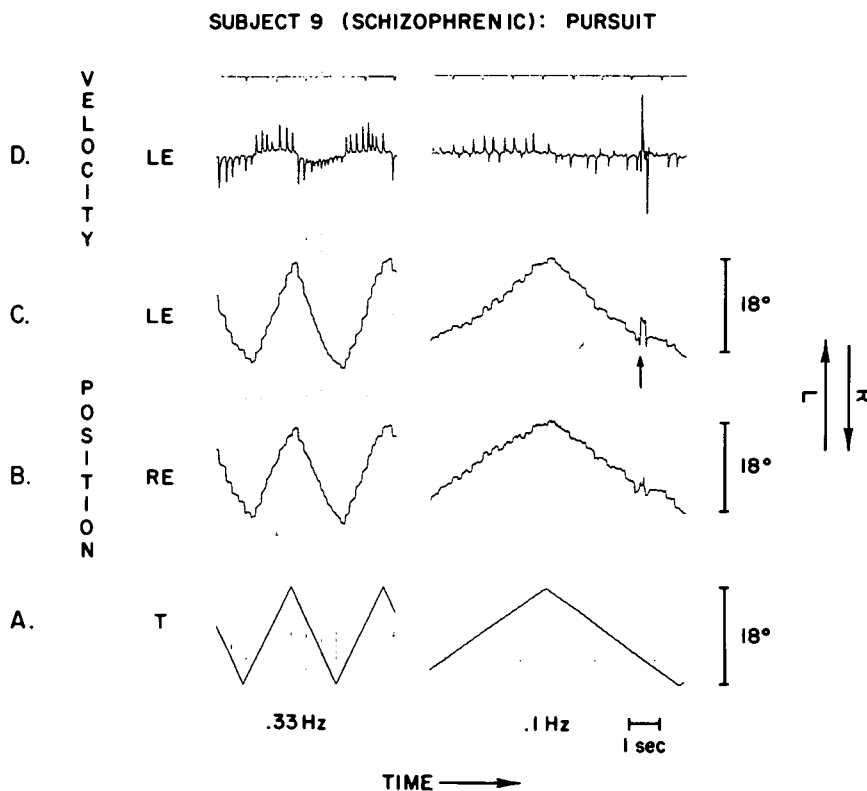
LE = left eye, RE = right eye, T = target. At 0.33 Hz the pursuit movements are mostly saccadic pursuit; the velocity pulses indicate rapid eye movements in the same direction as the target movement. At 0.10 Hz the pursuit movements show many saccadic intrusions; the velocity pulses show rapid left and right eye movements in succession but separated by short intervals of smooth pursuit eye movements. The arrow indicates a blink. The panels illustrate the differences between saccadic tracking and saccadic intrusions.

counted for over 80 percent of abnormal pursuit in a sample of over 200 subjects. About 45 percent of the family members of schizophrenics manifested qualitative disruptions of pursuit, in contrast to about 10 percent of the first degree relatives of nonschizophrenic psychiatric patients. In addition, Holzman and Levy (1977) reported that abnormal pursuit in a schizophrenic proband tended to be associated with poor tracking in at least one of the two

clinically unaffected parents. These findings raised the question of whether eye movement dysfunctions associated with psychosis are genetically transmitted and, if so, whether they indicate an inherited predisposition to schizophrenia.

The general finding that a large number of schizophrenic patients, particularly chronic schizophrenics, show eye tracking dysfunctions has been confirmed in several independent studies (Shagass, Amadeo, and

Overton 1974; Klein et al. 1976; Brezinova and Kendell 1977; Kuechenmeister et al. 1977; Pass et al. 1978; Salzman, Klein and Strauss 1978; Cegalis and Sweeney 1979; Karson 1979; May 1979; Mialet and Pichot 1981; Tomer et al. 1981; Iacono et al. 1982). There have been no published reports of failures to replicate.

The previous "update" of this area of investigation (Spohn and Patterson 1979) concluded that although the appearance of eye tracking disruptions in schizophrenia was a robust phenomenon, its specificity for that disorder had not yet been established. That review also called for studies that probed into the nature of the phenomenon, particularly its relation to cognitive dysfunctions that involved attentional deployment. In the intervening years, it appears that specificity for schizophrenia has indeed been demonstrated, although the precise psychological and neurological import of the eye tracking dysfunctions for schizophrenia has not yet been established. Nevertheless, researchers have already begun to use the dysfunction as a marker for schizophrenia, and have constructed a model for the genetic transmission of schizophrenia based upon the distribution of the dysfunction within families.

At this point in the study of eye movement dysfunctions in schizophrenia, artifacts that could have invalidated the finding have been ruled out. These artifacts include the effects of drug treatment, methods of recording eye movements, and attentional or motivational vicissitudes.

With respect to drug effects, there is sufficient evidence that the phenothiazines, butyrophenones, and thioxanthenes do not induce eye movement dysfunctions. The evi-

dence emerges from several direct and indirect assessments of the effects of those neuroleptics on eye tracking integrity. For example, studies of single dosages of chlorpromazine, secobarbital, ethanol, and chloral hydrate produced significant sedative effects on normal volunteer subjects, but only secobarbital, ethanol, and chloral hydrate produced pursuit disruptions (Holzman et al. 1975; Levy, Lipton, and Holzman 1981). These studies established that single doses of central nervous system depressants disrupt smooth pursuit eye movements in normal volunteers, but neuroleptic drugs do not. There are no reported studies of the effects of tricyclic antidepressants, monoamine oxidase inhibitors, and lithium carbonate on eye tracking performance of normal subjects.

Several investigators failed to find a relation between eye movement dysfunctions and whether the patients were medicated or unmedicated (Shagass, Amadeo, and Overton 1974; Holzman et al. 1974; David 1980; Mialet and Pichot 1981). Withdrawing patients from neuroleptic drugs did not result in change in pursuit movements (Holzman et al. 1974; Spohn 1981). Of considerable interest are the several reports of eye movement dysfunctions that appeared decades before the appearance of the antipsychotic medications. These include the initial study by Diefendorf and Dodge in 1908, and subsequent ones by Couch and Fox (1934) and by White (1938). All three of those studies reported large numbers of schizophrenic patients with eye movement dysfunctions which, of course, could not be attributed to neuroleptic medication. Levy et al. (1984) found that tricyclic, bicyclic, and tetracyclic antidepressants had no effects on depressed patients' eye movements.

Of decisive importance for concluding that antipsychotic drugs do not account for the eye movement dysfunction in schizophrenic patients, however, is the appearance of large numbers of unaffected first degree relatives of schizophrenic patients who show impaired pursuit movements. These people had never been hospitalized or treated for a mental illness (Holzman et al. 1974; Kuechenmeister et al. 1977). The reports make it clear that the eye movement dysfunctions can occur in the absence of treatment with neuroleptic medication. The aforementioned studies of patients and normal volunteers established that neuroleptic medication does not disrupt eye movement. Two studies demonstrated that neuroleptics do not change eye tracking performance, even in the presence of improved clinical condition (Spohn 1981; Levy et al. 1984).

The effect of lithium carbonate, however, may be quite different from that of the other antipsychotic drugs. Levy et al. (1985) tested 15 inpatients and 16 outpatients who had bipolar affective disorder. The patients were tested serially. In eight of the nine patients in whom pre-lithium testing could be undertaken, pursuit was normal. Following lithium treatment, however, seven of those eight showed abnormal pursuit. All of the other inpatients showed abnormal pursuit, as did 9 of the 16 outpatients in remission. Iacono et al. (1982) reported similar data, in that patients with major affective disorders in remission who were continuing to receive lithium carbonate showed more pursuit disruption than did those patients in remission who were not receiving lithium. These two studies strongly suggest that lithium carbonate interferes with smooth pursuit eye movements. This finding assumes

importance for the question of the specificity of these dysfunctions for schizophrenia.

Recording Methods. There are many ways to record eye movements. Each has advantages and disadvantages. The most widely used methods are electrooculography (EOG) and infrared reflectometry (IR). EOG requires the use of skin electrodes which record, in addition to the corneo-retinal potential, other bioelectric signals whose origins may be skin, muscle, retinal, and cortical. The IR technique, while somewhat more complex to manage, in that careful calibrations are indispensable, contains none of the bioelectric intrusions characteristic of the EOG. Both IR and EOG produce very similar results with respect to differences between schizophrenic patients and control populations. It is therefore unlikely that the appearance of eye tracking dysfunctions is an artifact of method of recording.

Psychological Implications. Almost any investigation involving psychotic patients raises questions about patients' motivation, comprehension of the task requirements, and sustained attention during the test period. Indeed, both Kraepelin (1896/1919) and Bleuler (1911/1950) postulated an underlying disorder of attention in the schizophrenias. But the term *attention* does not refer to one process. There are many different psychological processes that have merited the term *attention*. For example Kraepelin distinguished between the apprehension and grasping of information (*Auffassung*, in German) and the active, sustained, directed attention (*Aufmerksamkeit*, in German). The former, a more automatic, almost reflexive process, was believed to be

unimpaired, while the latter, a voluntary process, was asserted by Kraepelin (1896/1919) to be almost always impaired. Researchers have been able to confirm that voluntary attention is indeed impaired in schizophrenic patients. It is therefore of importance to determine whether schizophrenic patients show impaired eye tracking because they are simply not doing the task of following the moving target, in which case the findings of impaired pursuit are trivial and reflect nothing more than the usual inattentiveness of schizophrenic and other psychotic patients. Later in this survey we shall return to the topic of attention when we review event related potentials and specific tests of sustained and directed attention.

Several studies have concluded that inattention and lack of motivation are not involved in the findings of pursuit abnormalities in schizophrenic patients, and that if any attentional quality is involved, it is the automatic, nonvoluntary deployment of attention that seems defective. This conclusion emerges from studies that manipulated the target characteristics so as to make the target more salient and engaging. These manipulations consisted of placing arabic numerals on the target and requiring the subjects to read them silently, changing the shape or color of the target, or turning on and off a target within the target. This enhancement of voluntary attention did not change the quality of pursuit, although all subjects, normal as well as psychotic, tended to be somewhat more accurate with respect to decreasing the amount of overshooting and sporadic looks away from the target. Differences between groups remained, and the number of impaired tracking records within the schizophrenic groups did not

change (Holzman, Levy, and Proctor 1976; Shagass, Roemer, and Amadeo 1976; Iacono and Lykken 1979; Cegalis and Sweeney 1979; Iacono, Tuason, and Johnson 1981; Levin, Lipton, and Holzman 1981). It is quite relevant to the question of the nature of the attentional involvement that subjects were unaware of the poor quality of their tracking or of its improvement with the attentional engagement, suggesting that conscious motivational variables do not explain the occurrence of abnormal pursuit.

Another perspective on attentional correlates of disrupted pursuit is provided by attempts to interfere with eye tracking performance in normal subjects. Brezinova and Kendell (1977) studied the effects of stress, distraction, and fatigue in nonpatients with normal tracking. They found that in several experimental conditions smooth pursuit deteriorated only during the most difficult of their tasks, which was serially subtracting 13's from 200 while following the target, and continuously tracking the target for 60 minutes. They judged that the abnormal pursuit movements produced in the face of these manipulations were indistinguishable from those observed in schizophrenics, and concluded that impaired voluntary attention or heightened distractibility accounted for deviant pursuit in schizophrenics. A repetition of that experiment by Lipton, Frost, and Holzman (1980) showed that pursuit of normal subjects during the distraction tasks used by Brezinova and Kendell (1977) was characterized by large amplitude saccades, in a setting of otherwise intact pursuit, in contrast to the continuous disruptions observed in schizophrenics. With minimal training, naive raters who were unaware of the subjects' identities and diagnoses were able to distinguish normal tracking from the

disordered tracking of distracted subjects, and both of the former from the impaired pursuit of schizophrenics. Thus, although distraction and simple inattentiveness produce tracking disruption, those disruptions are not the ones that characterize the impaired tracking of schizophrenics, which suggests that different processes are involved in the effects on pursuit eye movements of distraction and of being schizophrenic. In this respect, Spohn (1981) studied 54 medicated chronic schizophrenic patients, and obtained correlations between a quantitative measure of tracking integrity and several different measures of voluntary attention, which included reaction time, short-term memory, and size estimation. There were no significant correlations between pursuit scores and any of the voluntary attentional measures, nor was there a correlation with severity of illness.

Three studies have shown that saccadic latency is normal in schizophrenic subjects (Iacono, Tuason, and Johnson 1981; Levin, Lipton, and Holzman 1981; Levin et al. 1982a). These studies taxed the attentional capacities of the subjects much more than pursuit tasks did, since they required patients to pay close attention for 15 minutes at a time and to respond rapidly to shifts in target position. It is, therefore, unparsimonious to attribute pursuit dysfunctions to impaired voluntary attention and yet to find normal saccadic reaction time in experiments that require prolonged sustained voluntary attention. Furthermore, the finding of impaired pursuit in so many of the first degree relatives of schizophrenic subjects strains the explanations that posit distraction, inattention, generalized deficit, and motivation. At this point it is reasonable to conclude that the reports

of eye movement dysfunctions in psychotic patients are not artifacts of drug treatment (except in the case of lithium carbonate and central nervous system depressants), recording and scoring errors, special characteristics of targets, or inattention on the part of subjects. The particular stage of the illness does not seem to be a factor in these reports since schizophrenic patients, tested at admission to a hospital, at discharge, and again at followup, show no change in their eye tracking records (Salzman, Klein, and Strauss 1978; Levy et al. 1983). Nor do subtypes of schizophrenia affect the results; paranoid and nonparanoid patients and those with good and poor premorbid social adjustment showed the same prevalence of eye tracking dysfunctions (Holzman et al. 1974; Bartfai et al. 1985). There is, however, a tendency for hospitals that serve patients with long-time chronic psychoses to show a higher prevalence of eye tracking dysfunctions than hospitals that serve as treatment centers for more acute cases. These parameters point to the trait characteristics of eye movement dysfunctions in schizophrenia.

Specificity of Eye Tracking Dysfunctions and the Family Transmission of Schizophrenia. Early reports of eye tracking dysfunction in psychotic patients indicated that these abnormalities were more strongly associated with schizophrenia than with other psychiatric conditions (Holzman, Proctor, and Hughes 1973; Holzman et al. 1974). Nonschizophrenic psychotic patients accounted for about 22 percent of the eye tracking dysfunctions, and only 8 percent of normal subjects showed pursuit disturbances. The variation in prevalence from about 50 percent to over 85 percent for schizophrenia apparently reflected the hospital

from which the samples were drawn, with the long-term chronic patients in State hospitals showing the highest prevalence. Shagass, Amadeo, and Overton (1974), however, reported a significant amount of pursuit disruptions among patients with major affective disorders, and Lipton, Levin, and Holzman (1980) reported that of the patients meeting strict criteria for schizophrenia and major affective disorders, half of both groups showed eye movement abnormalities.

It is well known that pursuit abnormalities are associated with many neurological disorders, such as Parkinson's disease, multiple sclerosis, and those following brainstem and hemispheric lesions. Therefore, these dysfunctions do not occur only in schizophrenic patients. No identified central nervous system diseases have been reported in association with the functionally psychotic patients or their family members who show eye tracking disorders. The question of the specificity of eye tracking disorders involves issues that extend beyond the prevalence figures cited above. In the central nervous system disorders, for example, eye tracking dysfunction is a symptom of the disease processes themselves. In the psychoses it is unclear whether the pursuit impairments are a trait variable or whether in some conditions they reflect a state-related impairment— that is, a consequence of having the disease or of having been treated for it. The high prevalence of eye tracking disorders among the first degree relatives of schizophrenic patients argues for the trait status of those tracking disorders. As has already been noted, lithium carbonate is associated with pursuit eye disruptions in significant numbers of patients with major affective disor-

ders (Iacono et al. 1982; Levy et al. 1985). The increased prevalence of tracking impairments in patients with major affective disorders may be at least partly attributed to the effects of lithium carbonate. In such patients, therefore, the appearance of eye tracking disorders may be state related, an epiphenomenon of the treatment.

Clarification of the trait and specificity status of eye tracking dysfunctions in schizophrenia came with more family prevalence data. In 1974, Holzman et al. reported that 45–50 percent of first degree relatives of schizophrenics showed eye tracking dysfunctions that were indistinguishable from those shown by the schizophrenic patients. In contrast, only 10 percent of the relatives of nonschizophrenic psychiatric patients showed similar dysfunctions. In a recent and more systematic article in which newer diagnostic criteria were used, Holzman et al. (1984) reported that 34 percent of the parents (or 55 percent of parental pairs) of schizophrenic patients compared to 10 percent of the parents (or 17 percent of parental pairs) of manic-depressive patients showed eye movement dysfunctions. Parental eye movement dysfunctions were significantly related to the diagnosis of schizophrenia in the patient, but not to whether the patient's eye tracking performance was normal or abnormal. Almost identical family data have been reported by Siegel et al. (1984). Levy et al. (1983) also showed that of 47 first-degree relatives of 21 patients with bipolar affective illness, only 13 percent showed abnormal pursuit, a figure that is not significantly different from the normal population prevalence. When those relatives who were receiving lithium were excluded, only 2 percent of the sample

showed impaired pursuit. These data strengthen the claim that abnormal pursuit eye movements are associated with schizophrenia and tend to occur in families in which there is a member with clinical schizophrenia. The presence of abnormal pursuit, however, cannot be assumed to be pathognomonic of schizophrenia, since it can occur in asymptomatic relatives of schizophrenic patients as well as in some central nervous system diseases. In the absence of such diseases, however, these eye tracking dysfunctions seem to represent familial markers of schizophrenia. Demonstration of the genetic transmission of these dysfunctions relied on the outcome of several studies of twins.

An early twin study was mentioned in the last update (Spohn and Patterson 1979). That study examined monozygotic (MZ) and dizygotic (DZ) twins in Norway who were clinically discordant for schizophrenia. These twins had been previously identified and studied by Kringlen (1967). In a study of a Norwegian national sample of twins, Kringlen had determined that the clinical concordance of schizophrenia was 25 percent for MZ twins and 9 percent for DZ twins, using a set of strict criteria for schizophrenia. This pool of Norwegian twins, then, provided the sets of MZ and DZ twins discordant for schizophrenia. A finding that among those clinically discordant twins, the eye tracking dysfunction was twice as concordant among MZ as among DZ twins would provide encouraging, but not yet conclusive, evidence of a trait marker for schizophrenia that is genetically transmitted. Such a result would provide some evidence for a stable trait that is associated with schizophrenia but is not a symptom of the disorder itself. The trait should be present in

those who are predisposed to schizophrenia, and the trait should be present whether or not those susceptible people are actually clinically ill. An example of such a trait marker in general medicine is the presence of hemoglobin X for sickle cell anemia.

The first twin study (Holzman et al. 1977, 1978) showed results that were quite consistent with the genetic transmission of the eye tracking dysfunction as a trait. But the numbers of subjects (11 sets of MZ and 15 sets of DZ twins) were too low for statistically significant differences to emerge. In addition, the subjects were, on average, about 55 years old, and it is known that eye tracking integrity tends to degrade with age. Therefore, a second study with younger discordant twins was undertaken. The results of the second study were almost identical with those of the first (Holzman et al. 1980).

These two twin studies showed statistically that regardless of age, clinically discordant MZ twin pairs have greater eye tracking similarity than do clinically discordant DZ pairs, and that these concordance rates for eye movement dysfunctions are about 80 percent of the theoretically predicted values for a trait under polygenic control. These studies suggest that there is a significant genetic contribution to eye tracking efficiency. The studies, however, do not unequivocally rule out nongenetic mechanisms that may be responsible for both psychosis and eye tracking dysfunctions, such as viral, toxic, and prenatal influences. Nor do these studies address the relation of eye tracking dysfunctions to schizophrenia, since the investigators did not employ comparison groups consisting of twins with other psychoses. The family studies do,

however, support the view that eye tracking dysfunctions are associated with schizophrenia and tend to occur within families in which there is a member with clinical schizophrenia.

There is one puzzling feature in these data. A number of schizophrenic patients with unimpaired pursuit movements have parents with eye tracking abnormalities. Furthermore, in the two twin studies described above, there were five sets of DZ twins in which the schizophrenic twin had good eye tracking, but the unaffected cotwin had impaired eye tracking. Matthysse, Holzman, and Lang (1986) suggested a model to account for these paradoxes. The model postulates a latent trait that is transmitted in quasi-mendelian fashion. That is, although the presence of the latent trait is determined by a single major locus, the latent trait can occur without the allele that is responsible for it—as a phenocopy—and the allele can be present without the trait—as in partial penetrance. The model further proposes that the central nervous system disease process that is the outcome of the latent trait produces clinical schizophrenia or bad eye tracking or both, because it can invade one or another region of the brain independently or together; the symptoms that arise reflect the brain regions invaded.

The model assumes that the smooth pursuit system is invaded with higher probability than the system that is involved in schizophrenic psychosis—whatever that system is. The model also assumes that this disease process is at least partially genetically determined. This situation resembles that of type I diabetes. The deficiency of insulin is transmitted by a gene. Those who have this gene are susceptible to the disease, but the disease is not inevi-

table. Triggering events like viral invasions or chemical injuries are presumed to be necessary. And some experiences can be protective; a recent Scandinavian study indicated that being breast fed longer than 3 months may be such a protective factor. In the model, schizophrenia with good tracking occurs when the disease invades the less probable area and spares the more probable one. First degree relatives will also be at risk for having the same disease process, and that process will cause eye movement dysfunctions with high probability, and schizophrenia with low probability.

The disease process is, of course, a hypothetical one and therefore it is called a *latent* trait. Unlike schizophrenia and eye tracking dysfunctions, the trait is not observed, although, in principle, it is capable of being observed. When the necessary tools for observing it become available, we presume it will be found. Matthysse, Holzman, and Lang (1986) chose a single gene model because it is the simplest one, and they constructed an equation for testing its fit to the data. The equation includes the following variables: (a) the probabilities of the latent trait giving rise to good and bad tracking; (b) the probabilities of the latent trait giving rise to schizophrenia in the general population; (c) the probabilities of the occurrence of phenocopies; (d) the penetrance of the latent trait in heterozygotes and (e) in homozygotes. The equation is then used to search for the probability of any family member's having the latent trait. If an individual has the latent trait, the likelihood that he has schizophrenia, eye movement dysfunction, or both can be computed. The mathematics are those of maximum likelihood estimates. The equation permits one to test whether the eye

movement dysfunctions in schizophrenia or in manic-depressive illness are an independent expression of the latent disease process or an epiphenomenon, that is, an outcome of having the disease itself.

The results of the mathematical test are that in schizophrenia the data fit the latent trait model, but in manic-depressive illness the data are more easily explained as an epiphenomenon. That is, in manic-depressive illness, poor eye tracking is an outcome of the disease; in schizophrenia, it is an outcome of familial transmission. In schizophrenia, the latent trait can lead to schizophrenia, bad eye tracking, or both, but eye tracking dysfunctions are about 3.5 times more likely to occur than schizophrenia. The prevalence of the latent trait in the general population is calculated to be about 4.4 percent. Among schizophrenics—83.6 percent have it, and so do 36.1 percent of bad trackers, which is 6.8 times more likely than the general population. The model suggests that about 16.4 percent of patients whose condition is diagnosed as schizophrenic by *DSM-III* or ICD-9 criteria have different pathogenic dynamics. But the latent trait can be present without the gene, as in a phenocopy, although about all of those who carry the latent trait have the gene that the model postulates.

The study of people who have the underlying disease process without the obvious symptoms of the disease is an extremely valuable undertaking because those people are free of the biological, social, and psychological complications of the disease. The picture of schizophrenia that emerges from this work is not unique in the annals of medicine. A similar model of transmission is represented by neurofibromatosis (Von Recklinghausen's disease), the gene

for which is an autosomal dominant, but with variable expressivity. Thus, the full syndrome occurs much more rarely than one or two indicators of it. Tumors of peripheral and cranial nerves, subnormal intelligence, cafe-au-lait spots, and areas of depigmentation as well as skeletal abnormalities are among the numerous manifestations of the disease. As in schizophrenia, it is not unusual that a family history of neurofibromatosis may be well hidden or unnoticed in the case of a proband with the full syndrome. Furthermore, family members with the disease may be overlooked because they manifest only the mildest of symptoms.

Neuroophthalmologic Considerations. As outlined earlier in this report, the pursuit system may be regarded as an outcome of a dual control system in which position and velocity errors are separately regulated and controlled; the pursuit system corrects velocity errors and the saccadic system corrects position errors. This view permits the separate examination of the saccadic and pursuit systems, their integrity, and their central nervous system control. A series of studies strongly suggests that the dysfunction observed in the smooth pursuit of psychotic patients and in the relatives of schizophrenics is localizable higher in the central nervous system than the brainstem. For example, Lipton, Levin, and Holzman (1980) showed that every patient with impaired horizontal pursuit had disrupted vertical pursuit. Since it is known that vertical and horizontal eye movements are regulated separately at the level of the brainstem, they concluded, reasonably, that the congruence they found is attributable to a single process that is common to

both vertical and horizontal tracking tasks, and that this process must be localized above the brainstem. Lipton, Levin, and Holzman (1980) also found that 96 percent of their subjects showed a normal oculocephalic reflex—that is, eye movements that are triggered by the movement of the head and not by the movement of a target. The oculocephalic reflex requires an intact brainstem and vestibular system; smooth pursuit that is generated by following a moving target requires an intact cortex as well. In addition, Levin et al. (1982b) showed that compensatory eye movements made while fixating a target with both head and eyes, called the vestibuloocular reflex, were entirely normal in a group of schizophrenic patients with abnormal smooth pursuit in response to tracking a moving target with their head and eyes. The refixations attendant upon the vestibuloocular reflex occur in the context of vestibularly generated signals, whereas head and eye tracking of an external target implicates the cortex as well.

Levy, Holzman, and Proctor (1978) examined vestibularly generated nystagmus in schizophrenic patients, using caloric irrigation. They reported normal latency, duration, slow phase eye speed, and symmetry of responses, although many of the responses were dysrhythmic. Latham et al. (1981) found that full field optokinetic nystagmus (OKN) in schizophrenic patients was normal, whereas partial field OKN was abnormal in those patients who demonstrated abnormal smooth pursuit. Since full field OKN is regulated in the paramedian pontine reticular formation of the brainstem and partial field OKN is essentially cortical in its pathways, Latham et al. (1981) concluded that the pursuit abnormalities seen in schizophrenic patients reflect cortical dysfunctions,

a conclusion supported by the study of Levy, Holzman, and Proctor (1978).

There is, furthermore, evidence that the saccadic system functions essentially normally in schizophrenic patients. Levin et al. (1981), Levin, Lipton, and Holzman (1982), and Iacono, Tuason, and Johnson (1981) reported that saccadic latencies were normal in schizophrenics whether or not the patients had impaired smooth pursuit. These results were obtained in responses to uncomplicated saccadic refixations. When more complicated refixations were required, as in a choice paradigm, Done and Frith (1984) reported increased saccadic latencies. The findings of normal saccadic eye movements occurring without the complication of a superimposed cognitive choice make it unlikely that the pursuit dysfunctions are localized at the horizontal gaze center in the paramedian pontine reticular formation (PPRF) in the brainstem, since the subcortical control center of saccadic movements and of horizontal pursuit meet at the PPRF.

Although the above-mentioned studies suggest the need for further neuroophthalmologic investigations, there are no further data about the locus of the dysfunctions. Nor is there any greater clarity about the relation of eye tracking dysfunctions to the symptoms of schizophrenia or to structural brain patterns. The abnormality that manifests itself as saccadic intrusions—the saccadic system, which should be turned off during pursuit, is not—seems to be essentially a disinhibitory phenomenon. These tracking impairments point to nonmotivational processes in attention that involve higher cortical functions but appear to be nonvoluntary (Holzman et al. 1974; Holzman, Levy, and Proctor 1978).

Levin (1984a, 1984b) has suggested that frontal lobe dysfunctions play a role in these impairments. Arguing from neuroanatomical circuitry, she observed that the frontal eye fields exert an inhibitory effect on the superior colliculus, and their inhibitory function may be mediated by other eye movement centers such as the substantia nigra. Further, the frontal eye fields project to the caudate nucleus, which in turn projects to the substantia nigra pars reticulata. These cells send inhibitory γ-aminobutyric acid (GABA) projections to the superior colliculus, and these inhibitory neurons exert a tonic restraining effect on saccadic movements (Hikosaka and Wurtz 1981). When the effect of the substantia nigra is blocked by GABA antagonists (e.g., by muscimol), as in a recent experiment in monkeys (Hikosawa and Wurtz 1983; Wurtz and Hikosawa 1984), the result is eye movements very much like those seen in schizophrenic patients and their first degree relatives: the presence of square wave jerks and saccadic tracking. Of course, it is possible that the disinhibitory process simply implicates the frontal lobes, but does not originate there. It is, however, of great interest that these neuroanatomical speculations are consistent with other psychophysiological and cognitive work, to which we now turn.

Event-Related Potentials

Present a flash of light, or a tone, or a very mild electrical stimulus to a subject and monitor the ensuing effects in the electrical activity from the cortex. The electroencephalographic signals from those events assume typical wave forms that can be recognized with great reliability. When recorded with reference to sensory stimuli, the term "sensory evoked potentials" is used; when recorded relative to motor events, the term "motor potentials" is used; when recorded in response to touch or pain stimuli, the term "somatosensory potentials" is used. Event-related potentials (ERPs) embrace the broad spectrum of brain electrical activity related to sensory, motor, and cognitive processes. These electroencephalographic signals are of low voltage when compared with the spontaneous electrical activity of the brain (EEG). Detecting those signals, therefore, requires a process that eliminates the random activity of the EEG and enhances the specific activity associated with the eliciting stimulus. This process relies upon an averaging technique which calls for a number of repetitions of the stimulus presentation. The ensuing wave forms are then averaged, and in this process, the background, spontaneous, and essentially random EEG activity is reduced to a uniform level which permits the time-locked responses to the stimulus to assume prominence. Because these changes in electrical potentials reflect the neural activity associated with perceptual and cognitive processes, they promise to be noninvasive probes into brain function in health as well as in disease.

A large literature exists describing ERPs elicited by a variety of experimental paradigms in a number of neurologic and psychiatric disorders. At first, scientific scrutiny focused on the relatively early waves, defined as those occurring before 250 ms after stimulus onset, and sometimes referred to as the exogenous components. The term indicates that these early components vary with the physical properties (such as intensity) of the evoking stimulus. These components found clinical applications in neurology, for example, in the diagnosis of multiple sclerosis.

In contrast with the exogenous potentials, Sutton et al. (1965) demonstrated a component that reflects the cognitive work done on the stimulus by the subject, and not merely the physical characteristics of the stimulus. This late component is generally referred to as the P_{300}, which designates its electrical polarity as a positive wave and its time of occurrence at approximately 300 ms after the stimulus. The components believed to reflect the subject's cognitive processes are sometimes referred to as the endogenous components.

As data on the P_{300} accumulated, it became apparent that this later component is complex, probably consisting of several electrical potential changes. Consequently there are two other designations of these later events: P_3, which refers to the third major positive aspect after stimulus presentation, and "late positive component" (or LPC). Both the exogenous and endogenous components of the ERP have been studied in schizophrenic patients.

As was already mentioned, the early components have generally been interpreted as indicators of stimulus registration. The N_{100} wave appears in the presence of stimuli that a subject is instructed to attend to, as, for example, in a dichotic listening task when a subject is told to listen for tones of a specified pitch in the left ear (Hillyard et al. 1973). All stimuli presented to the selected ear elicit an augmented N_{100} wave. In contrast, the P_{300} is enhanced in response to low probability, task-relevant, attended-to, and consciously apprehended stimuli. It is therefore possible to interpret the N_{100} as an indicator of selective attention.

Shagass et al. (1979) have reported that chronic schizophrenics show less variation and higher amplitudes in the early *somatosensory* evoked po-

tentials than do normal subjects. The authors interpreted these results as reflecting impaired reticular filtering or subcortical modulating, which results in abnormal amounts of information reaching higher brain centers. Buchsbaum et al. (1986) reported that somatosensory responses (to mild shocks to the right forearm) from the left hemisphere in normal subjects were highly localized in the sensorimotor and parietal areas of the brain, as noted from topographic mapping. Schizophrenic patients, however, showed responses that were diffused rather than localized. The authors interpreted this relative absence of localization as a deficit in sensory control. Shorter latencies of the auditory P_{50} in chronic schizophrenics, and particularly those with thought disorder (Saletu, Itil, and Saletu 1971), suggest a similar interpretation. Laterality differences have also been noted to the extent that in chronic schizophrenics the left hemisphere appears to be functioning less efficiently than the right, or the balance between the hemispheres is altered with relatively less activity on the left than on the right. While there is need to study the specificity of these findings, the laterality shift has been found by Morstyn, Duffy, and McCarley (1983) with respect to the P_{300} wave, a study that will be discussed below.

Shagass, Roemer, and Straumanis (1982) confirmed earlier reports of higher somatosensory amplitudes before 100 ms in chronic schizophrenics as well as in nonpsychotic psychiatric patients. They noted, however, that the chronic schizophrenics showed greater than normal posterior amplitude, which was exaggerated in the hemisphere ipsilateral to the stimulation. This finding suggested to them that normal inhibitory processes that limit

ipsilateral hemispheric discharge may be impaired in schizophrenia. These findings are quite consistent with the interpretation of failures of inhibitory mechanisms at an early stage of information processing in schizophrenic patients. Similar suggestions about failures of inhibitory mechanisms in schizophrenia have been offered to explain the eye movement dysfunctions and the thought disorders (Holzman 1978).

In an important experiment, Baribeau-Braun, Picton, and Gosselin (1983) presented auditory stimuli to schizophrenic patients, using two different intervals between presentation, one fast (between 250 and 750 ms) and one relatively slow (between 500 and 1500 ms). Schizophrenics showed a lower N_{100} amplitude than normal subjects, a result others had previously reported (e.g., Shagass et al. 1977, 1978; Roth et al. 1981). Of interest, moreover, is the finding that control subjects showed the expected N_{100} increase for both the slow and fast rates of presentation, but the schizophrenics showed it only for the faster rate. The authors interpreted their results as indicating a breakdown of sustained selective attention during the slow intervals. They also assessed later occurring waves, around 300 ms, which are related to the amount of information the subject processes from a target. The P_{300} wave was attenuated in schizophrenics even when targets were accurately detected, suggesting that these patients had difficulty in extracting information from the stimulus. The P_{300} attenuation in the schizophrenics was not related to the rate of stimulus presentation, as was the case with the N_{100} wave; nor was it an effect of stimulus interference. This phenomenon has been confirmed by Saitoh et al. (1984).

The study of Baribeau-Brown, Picton, and Gosselin (1983) indicates

that in schizophrenia there is both a stimulus input and a cognitive processing abnormality, with the former detectable principally during slow rates of stimulus presentation or during conditions of divided attention, and the latter probably more or less continually present. Schizophrenics can indeed direct their attention appropriately and can apprehend stimuli, but at normal rates of speed.

The conclusion that attentional processes in schizophrenics tend to break down when long intervals are required for maintaining attention is consistent with findings from other experimental paradigms that manipulate attentional deployment. For example, the reaction time crossover effect (see review in Nuechterlein 1977) tends to occur in schizophrenics when about 5 to 7 seconds separate the preparatory interval from the onset of the imperative stimulus. But a similar effect takes place in normals much later, at about 20 seconds.

There is evidence to suggest that the N_{100} component, like the later components, is a composite wave. It is composed of a stimulus-provoked component and a subject-related component. The latter is related to the deployment of attention during the processing of the target stimulus (Hillyard et al. 1973). The latter has been referred to as "processing negativity" by Näätänen, Gaillard, and Mäntysato (1978) and as "Nd," for "negative displacement," by Debecker and Desmedt (1971). Thus, components as early as 50 ms can be influenced by the attentional set the subject adopts. Näätänen (1982) has offered a theory of selective attention based on the processing negativity, which involves comparison of target features with internal representations. None of the studies employing schizophrenic patients have distinguished the N_{100} from

processing negativity.

Very few studies of the early components have included non-schizophrenic psychotic subjects as comparisons, and therefore the issue of specificity has not been adequately addressed. Studies of patients with major affective disorders are called for, and in this regard, as with the eye movement studies, there is evidence that lithium carbonate alters the ERPs in all three modalities. Lithium carbonate augments the positive waves, reduces the negative waves, but has little effect on latency shifts. Similar to the data on lithium-induced pursuit dysfunctions, these changes are correlated with plasma and red blood cell lithium levels and not with therapeutic response, and therefore seem to be a pharmacological effect of lithium salts and not an effect of clinical condition. Antipsychotic drugs, such as the phenothiazines, butyrophenones, and thioxanthenes, and the antidepressant agents produce relatively small changes in ERPs, in the direction of normalizing the response (Shagass, Straumanis, and Roemer 1982).

The later components of the ERPs have been examined by many investigators. Since Sutton et al. (1965) first described the P_{300}, it has been interpreted as a reflection of cognitive activity that accompanies a search for a specific target. Regardless of sensory modality, the amplitude of the P_{300} varies inversely with stimulus probability. Its latency also varies as a function of the complexity of the stimulus. Consequently, the P_{300} has been assumed to provide a measure of state-related selective attention, which is affected by the complexity, redundancy, and relevance of the stimulus and which may be quite independent of a more abiding general attentiveness.

Although most ERPs have been

assessed from passive responses to uncomplicated stimuli, there have been a number of studies that have manipulated task requirements for selective attention, with quite similar results. These tasks have included (a) dichotic listening, in which the subject has to attend to one channel, perhaps to detect some infrequently occurring stimulus, and simultaneously to ignore the other channel; (b) the simple recognition of one set of stimuli embedded in a larger series; (c) an anticipation or guess about which stimulus will occur next in a series; (d) attentional selectivity in the presence of distractors.

Data with respect to the latency of the P_{300} in schizophrenics are ambiguous. Pfefferbaum (in press) suggests that in spite of the inconsistent data about latency of the P_{300} in schizophrenics, there may be a small but significant delay in latency in schizophrenics that has been overlooked.

In an interesting study, Morstyn, Duffy, and McCarley (1983) studied P_{300} responses using brain topographic mapping. The normal subjects showed an auditory P_{300} with symmetrical topographic distribution around the centroparietal area. The schizophrenic subjects, on the other hand, showed a P_{300} maximum response that was displaced to the right of and anterior to that of the normal group's responses. This topographic shift in the schizophrenic subjects suggested to the authors a deficiency of response activity in the left and posterior temporal areas. These data were replicated in a separate and better controlled study (Faux et al., submitted), although neither the effects of medication nor other psychotic groups without schizophrenia were studied. Nevertheless, the finding is quite consistent with morphometric

studies that show a structural anomaly in the left temporal and frontal areas for some schizophrenics (Brown et al. 1986). This lateral shift occurred in the experimental condition that requires no voluntary attention, and thus implicates a dysfunction in the automatic processing of information.

Strandburg et al. (1984) compared schizophrenic children (mean age 11.5) with a group of age-matched controls. They reported a small and slowly developing contingent negative variation (CNV) (to be discussed below) to a warning tone, and diminished amplitudes for the N_1 (the first negative wave after stimulus presentation) and P_3 components of the ERP. These investigators found a right lateral shift in N_1 activity over the right parietotemporal cortex for the normal children. The schizophrenic children, on the other hand, produced no such lateralization of this epoch. The schizophrenic children, however, did produce very asymmetrical activity in the P_1 component, with less activity in all of the electrode sites except that at the right hemisphere, a finding that is similar to that of Morstyn, Duffy, and McCarley (1983) with respect to adult schizophrenics.

The results with schizophrenic patients, regardless of task requirements, are quite consistent: Schizophrenic patients, compared to normal subjects, show reduced amplitudes of P_{300} waves. The effect of severity of illness is not so clear-cut. Some investigators report that amplitude of the P_{300} varies inversely with clinical condition (e.g., Roth et al. 1979, 1980; Josiassen et al. 1981). But Roth et al. (1981) failed to find this effect in a later study. In this respect, Duncan, Perlstein, and Morihisa (in press) report that P_{300} increased substantially (that is, tended to normalize) following the

administration of neuroleptics, an effect that occurred in both the auditory and visual modalities, and related directly to the degree of clinical response. One patient who showed no clinical amelioration by antipsychotic medication showed no change in the P_{300}, whereas the patient with the greatest clinical response showed the greatest increase in the P_{300}. These data must be reconciled with those of Brecher and Begleiter (1983), Josiassen et al. (1981), and Roth et al. (1980), who reported essentially no effects of neuroleptic medication. The study by Duncan, Perlstein, and Morihisa, although based on very few patients, was a repeated measures design which gives it greater cogency than a cross-sectional design. If replicated on larger numbers of subjects, it suggests that the P_{300} attenuation seen in schizophrenic subjects may be a state rather than a trait marker.

State or Trait. Friedman, Vaughan, and Erlenmeyer-Kimling (1982) reported that P_{300} was reduced in the offspring of parents who had once been schizophrenic patients. Saitoh et al. (1984) tested the well siblings of schizophrenic patients and, in contrast to findings in normal controls, found attenuation of the late ERP. A later reanalysis of the data of Friedman, Vaughan, and Erlenmeyer-Kimling, however, using more stringent diagnostic criteria (the RDC) in addition to the inclusion of offspring of patients with affective disorders as an additional comparison group, failed to substantiate a difference between the offspring of schizophrenic parents and those with affective disorders.

Pritchard (1986) suggests that the discrepancy between the studies of Friedman, Vaughn, and Erlenmeyer-Kimling (1982) and Saitoh et al. (1984) hinges on the complexity of the tasks performed by the subjects. In the Saitoh et al. (1984) study, the task demands were greater than in the study of Friedman, Vaughn, and Erlenmeyer-Kimling (1982), and for clinically well subjects, the processing load may have to be at a greater level than for patients before differences between family members of patients can be detected. Such a strategy, as will be described, has been adopted by Nuechterlein and colleagues with respect to cognitive performance, with promising results.

Late positive somatosensory ERPs were tested in college students who had high scores on Chapman's Physical Anhedonia Scale. Their ERPs were significantly lower than those of a matched control group and did not differ from those of a schizophrenic group (Josiassen et al. 1985). Simons (1981, 1982) had previously found similar results.

These studies of relatives of schizophrenics compare group differences in amplitude of ERP. That method may actually underestimate the degree of family transmission of the ERP dysfunctions. It would be of interest to count the number of first degree family members whose ERP amplitudes fall beyond a threshold that has been previously established on the basis of normative data.

Specificity is perhaps suggested by studies reporting differences between depressed patients and schizophrenics, with the former showing P_{300} levels close to those of normal subjects (Shagass et al. 1979; Roth et al. 1981; Steinhauer and Zubin 1982; Pfefferbaum et al. 1984). Nevertheless, it is noteworthy that P_{300} and, in general, P_3 attenuation occurs in many clinical conditions, such as dementing diseases (Goodin, Squires, and Starr 1978; Josiassen et al. 1984), infantile autism (Novick et al. 1980; Courchesne et al. 1985), states of fatigue, and as a result of some drugs which can dampen as well as normalize the late occurring ERP.

The lack of specificity in the schizophrenic patients should not be taken as evidence for the triviality of the findings on the ERPs. Studies of the nonpsychotic relatives of patients, as in the studies of eye movements, offer a powerful strategy for testing the robustness and the generality of the findings. And, as Duncan (in press) has remarked, the extent to which reduction in P_{300} amplitude represents general organismic impairment regardless of clinical diagnosis, or represents processes that are specific to a clinical condition or diagnosis has not yet been determined. In this regard, she recommends two strategies. The first is to use the P_{300} to identify specific stages of information processing that are responsible for deficit performance. Simultaneous recordings of ERPs and behavior would provide valuable data for this desideratum. A second paradigm would use the P_{300} to study brain processes presumed to underlie schizophrenic disorganization, and in this regard to study the effects of certain centrally acting drugs that affect particular brain areas implicated in schizophrenia.

In a heuristically important series of experiments, a conditioning-testing paradigm with ERPs was employed. The paradigm presented two auditory stimuli successively. The first, called the conditioning stimulus, and the second, called the test stimulus, produce cortically registered responses. The response to the test stimulus is often smaller in magnitude than that to the conditioning stimulus. The phenomenon may be considered a species of the orienting response. When expressed as a ratio of test response to conditioning response, a higher ratio (or percentage, when multiplied by 100)

may indicate a weak sensory gating or inhibition. Adler et al. (1982) reported that when 500 ms separated test and conditioning stimuli, the ratio, expressed as a percentage, for the P_{50} component of the ERP was 13.9 percent for normal subjects, compared with 90 percent for unmedicated, acutely psychotic schizophrenic patients. Treatment with neuroleptic drugs did not change these ratios (Freedman et al. 1983). It is important to note that the amplitude and latency of the P_{50} responses to the first stimulus, the conditioning stimulus, were significantly smaller in the unmedicated schizophrenics, but in the medicated patients they were of normal magnitudes. Similar effects of medication were observed by Shagass, Straumanis, and Roemer (1982). Thus, in unmedicated schizophrenic patients, there seems to be inadequate registration of the response to the first stimulus, possibly because of neuronal hyperexcitability, a phenomenon noted also by Patterson et al. (1986); this failure of adequate registration is perhaps partially corrected by drugs that block catecholamine transmission.

In a third experiment by Freedman's group (Siegel et al. 1984), 44 first degree relatives of 15 schizophrenic patients and 35 normal controls were tested in the conditioning-test paradigm. The schizophrenic patients again showed the expected abnormally high ratios— that is, a relative failure to show diminished P_{50} amplitude to the second stimulus. The normal controls showed the expected low ratios, or high inhibition of response to the test stimulus. The first degree family members, however, fell into a bimodal distribution with respect to the conditioning-test ratios, although the P_{50} amplitudes and latencies themselves did not differ from those of the normal controls. The abnor-

mal ratios were found in at least one of the two parents of 14 of 15 families studied. The investigators also reported that 61.5 percent of the schizophrenics and 39 percent of their first degree relatives showed abnormal smooth pursuit eye movements, similar to the prevalence of 34 percent in first degree relatives reported by Holzman et al. (1984). If a schizophrenic patient had an abnormal conditioning-test ratio, he or she also had abnormal smooth pursuit eye movements. Although the two abnormalities are associated quite closely in schizophrenic patients, they tend not to be so closely associated in their first degree relatives. Twenty-three percent of the relatives had both defects, compared to 61.5 percent of the patients.

Like smooth pursuit eye movement dysfunctions, the inhibitory deficit appears to be a strong candidate for a biological marker of schizophrenic disorders. It is not correlated with clinical state, and it occurs in unaffected members of the families of schizophrenic patients. Although similar ratios are found in patients with major affective disorder, these ratios tend to normalize when the patients become euthymic (Franks et al. 1983). It would be important to see if, in another sample of first degree relatives of schizophrenic patients, the inhibitory deficit and smooth pursuit eye movement abnormality again segregate separately, which they ought not to do if they are part of the same latent structure hypothesized for eye movement dysfunctions and schizophrenia. Several independent replications are now called for.

Contingent Negative Variation. The contingent negative variation (CNV) is a negative voltage that builds slowly in response to a warning about the imminence of a target. It has been interpreted as an indicator

of arousal or anticipation. Data with respect to the CNV have been reviewed in the previous update (Spohn and Patterson 1979). The general conclusion was and remains that the CNV is reduced in amplitude in schizophrenics, but that this is not a finding specific to schizophrenia. Nevertheless, the findings of low CNV amplitude are obtained even after the schizophrenic patients are in clinical remission (Rizzo et al. 1983). In patients with affective disorder, however, the CNV amplitude returns to normal when patients are in clinical remission (e.g., Knott et al. 1976). It is thus possible that the CNV may be a measure of a trait variable. The interested reader is referred to reviews in Tecce (1972) and Callaway (1975).

Because event-related potentials objectively record the neural activity associated with perceptual and cognitive processes, these procedures possess enormous face validity in the study of diseases such as schizophrenia. To realize their full potential in the study of psychiatric disorders, however, additional fundamental studies are required. These studies include efforts to relate ERP components to their neuroanatomical and neurophysiological substrates on the one hand and to psychological processes on the other. When these data become available, it will be possible to use ERPs to probe psychological and physiological derangements in schizophrenia. Until then, the intriguing ERP differences that have been described cannot be fully integrated with psychological and biological theories of schizophrenia.

Attention and Information Processing

Focused Attention. In 1956, Rosvold et al. reported on the use of a

test, the continuous performance test (CPT), to detect impaired sustained alertness in subjects with diagnosable brain damage. The CPT is essentially a test of vigilance. It requires a subject to detect a particular letter—for example, an "X"—in a series of letters presented one at a time for brief periods, from 40 ms to 200 ms, and separated by brief intervals, from 100 ms to 1500 ms. The subject indicates detection of the target letter by pressing a button. The task can be made incrementally more difficult by complicating the selection of the target. For example, the task can be to detect an "X" only when it is preceded by a vowel.

The CPT has been used in studies of schizophrenic patients, particularly in investigations of the effects of antipsychotic medication (e.g., Kornetsky et al. 1959; Kornetsky and Orzack 1964; Kornetsky and Mirsky 1966). Sustained, voluntary, committed deployment of attention has, of course, been cited as a fundamental symptom of schizophrenic psychopathology. But "attention" is not a simple, unitary process. As cited earlier in this article, Kraepelin distinguished between the automatic grasping or intake of a stimulus *(Auffassung)* and the voluntary turning of one's notice to a stimulus *(Aufmersamkeit)*. The former, he thought, was unimpaired in schizophrenia, while the latter showed obvious breakdown.

Both qualities imply that attention is available in limited quantities and that attention can be deployed either automatically or effortfully. This conception of attention as a limited reservoir of "energy" was one proposed by Freud (1900, Chapter 7) to account for consciousness as an experience. Freud assumed that for something to become conscious, it must depend on drawing to itself a quantity of an unspecified type of energy, attention, which he as-

sumed to be available in limited amounts. People differ in this attentional capacity, he believed, and individual organismic differences also affected the availability of this quantity. Thoughts or percepts that failed to attract sufficient attention "cathexis" were simply deprived of consciousness, but not of their further processing and storage in memory. Freud's cognitive theory had no experimental tradition to provide for testing and revision, and as a consequence, it failed to influence cognitive science.

A theory quite similar to Freud's, but one that is nourished by lively experimentation, was proposed by Kahneman (1973). The theory may be paraphrased as follows: Cognitive activities vary in the amount of attentional effort they require. At the early stage of information processing, that of registration and reception, smaller amounts of attention are required than at the later response stages. Shiffrin and Schneider (1977) have characterized these two processing requirements as automatic and controlled. Posner and Snyder (1975) and Posner (1978) have made an equivalent distinction. Impaired attentional capacity can be manifested in either automatic or controlled processing, or both, but the demands on a limited attentional capacity apparatus, such as that under consideration here, would be detected when higher processing loads are levied as task requirements. The effects of impaired attentional capacity or deployment would be hard to discern in the performance of automatic processes because those processes are presumed to occur effortlessly, with the recruitment of overlearned or habitual organizing modes, and are generally refractory to the effects of organismic variations such as states of arousal.

Using a simple version of the

CPT, Kornetsky and Orzack (1978) found that about 40 percent of schizophrenic patients showed deficit performance. They also found it in some schizophrenic patients who were in remission. But CPT deficits are not as prevalent among patients receiving antipsychotic medication. No nonschizophrenic psychotic patients were compared in these early studies. No CPT deficits—using the simple version of the test—were found in populations considered to be at risk for schizophrenia (e.g., Asarnow et al. 1978; Nuechterlein 1983; Cornblatt and Erlenmeyer-Kimling 1984). Populations at risk for schizophrenia do show clear deficit performance on the CPT, however, when, processing load is increased. The processing load is increased by requiring two simultaneous judgments or by degrading the images of the targets, that is, by throwing the letters somewhat out of focus. The critical score used in these risk studies is perceptual sensitivity as assessed from signal-to-noise discriminations (d'). Other independent studies of children of schizophrenic parents also reported impaired perceptual sensitivity in the degraded stimulus CPT (Erlenmeyer-Kimling and Cornblatt 1978; Nuechterlein 1983; Rutschmann, Cornblatt, and Erlenmeyer-Kimling, in press), supporting the finding that when processing load is increased, sustained attention is impaired in asymptomatic persons who are related to a schizophrenic patient. Furthermore, Nuechterlein demonstrated similar d' deficits in a group of asymptomatic young adults who had a 2-7-8 profile on the Minnesota Multiphasic Personality Inventory (MMPI), which has been implicated in schizophrenic disorders (Nuechterlein, Edell, and West, submitted for publication). In still another probe of the generality of vigilance impairments, when the d' score was used as the independent

variable, it was associated, in otherwise asymptomatic adults, with high scores on the MMPI schizophrenia scale, the Physical Anhedonia Scale of Chapman, Chapman, and Raulin (1976), and the Schizophrenism Scale of Nielsen and Petersen (1976).

Nuechterlein (1983) reports that lower d' scores also occur in children of nonpsychotic, psychiatrically disordered mothers and in hyperactive children, although not to the same degree as in the offspring of schizophrenic parents. This apparent absence of specificity is not necessarily inconsistent with the status of poor CPT performance as a risk variable. Yet the nonspecificity raises some question about its status as a biological marker. Erlenmeyer-Kimling et al. (1984a, 1984b) studied 80 children who have one or two parents with a schizophrenic disorder. Of the 15 children from that group who appeared to be clinically deviant, five have been hospitalized with schizophrenic conditions. All five showed impaired CPT performance. Seven of the remaining 10 clinically deviant children also showed impaired CPT, including a lower d' than a normal group.

There is also evidence that the d' deficit found in response to the "high processing load" version of the CPT (as well as with a span of apprehension task, to be discussed later) may be associated with "negative" symptoms of schizophrenia and with both total amount of thought disorder and with certain forms of thought disorder, particularly "fluid thinking," and to some extent "confused thinking," as assessed from the Thought Disorder Index (Johnston and Holzman 1979). Although the correlations are moderate, and they emerge only when the patients are in relative remis-

sion, it is noteworthy that the relation between CPT d' and qualities of thought disorder emerge only for those thought disorder categories that are characteristic of schizophrenic conditions and not of manic conditions (Nuechterlein et al., in press).

The CPT is a complex measure of performance. In both the simple and high-processing versions of the CPT, the subjects are required to marshall many cognitive functions—among which vigilance may be the most prominent—to respond appropriately. Because the CPT is not a pure task, the specific component processes responsible for deficit performance in each of the pathological groups are not apparent. Probably the CPT does tap some specific dysfunction in schizophrenia. Yet the analysis of the specificity should now transcend the CPT in order to search for the specific component process involved in the deficit performance.

The results of a set of studies of "span of apprehension" are similar to those found with the CPT. The task, adapted from a procedure developed by Estes and Taylor (1964), requires subjects to detect whether a "T" or an "F" is flashed on the screen directly in front of them. The letters are exposed for very brief periods, generally 50 to 70 ms. At times, the target letters appear alone and at other times embedded in 2, 4, 9, or more different letters. Obviously, the greater the number of irrelevant letters that appear with the target letter, the greater the processing load becomes, and the more difficult the task. Subjects are required to guess even if they are unsure. The test, then, like the degraded stimulus CPT, imposes successively greater loads on the grasping of information presented for very short intervals.

Asarnow and MacCrimmon (1978) showed that schizophrenics, both inpatients and outpatients in partial remission, detected significantly fewer target stimuli in a 10-letter condition than normal subjects did. In a later study, Asarnow and Mac-Crimmon (1981) showed that schizophrenic outpatients detected fewer targets correctly than did manic-depressive patients on both a 5- and 10-letter condition. A longitudinal study showed that schizophrenics who were in partial remission displayed the same level of deficit performance on a 10-letter paradigm as they did when they had been hospitalized 3 months earlier. The test-retest correlation for the schizophrenics over 12 weeks was 0.72, indicating that the span of apprehension measure is quite stable, at least for 3 months (Asarnow and MacCrimmon 1982).

Subjects with no history of psychiatric disturbance were tested on the span of apprehension test and were divided into good and poor performers. Those with poor performance had higher scores than the remainder of the group on the schizophrenia scale (Sc) of the MMPI and on three other indices of schizoptypic behavior and thinking (Asarnow, Nuechterlein, and Marder 1983). Another study reported a correlation of .55 between the span of apprehension scores of young adult schizophrenics and those of their mothers (Wagener et al. 1986). An early study showed that foster children who had been born to a schizophrenic mother showed low scores on the span of apprehension test comparable to those of acute and remitted schizophrenics, especially when tested in a 10-letter display (Asarnow et al. 1977, 1978).

There is, thus, strong evidence that the span of apprehension test, like the degraded CPT, shows that

processing load elicits or accentuates deficit performance in schizophrenics, remitted schizophrenics, those who are at biological risk for schizophrenia, and normals with some nonsymptomatic schizophrenic characteristics. Yet, span of apprehension performance is improved by neuroleptic drug treatment, and those patients who show the least change in span of apprehension after the introduction of neuroleptic treatment also show the least reduction in thought disorder (Marder, Asarnow, and Van Putten 1984). For the span of apprehension performance to have the status of a trait, it should be, generally speaking, unaffected by medication that affects the symptoms of the disease.

The span of apprehension test and the CPT show similar patterns of relations with several clinical variables, such as thought disorder and subscales of the Brief Psychiatric Rating Scale (Nuechterlein et al. 1986), suggesting that both instruments are measuring similar processes that are probably involved in the deployment of controlled attention (Callaway and Naghdi 1982). A necessary task now is to search for the unitary process that is disordered and to trace its relation to brain-related potentials that are presumed to measure the effectiveness with which information is processed at particularly demarcated times after stimulus reception.

Backward Masking

The psychophysiological investigation of schizophrenia has been profoundly influenced by contemporary cognitive theory and experimentation. Common to most of these theories is the assumption that information is processed automatically in a predetermined sequence that, in the simplest of terms, begins with sensory registration and pro-

ceeds to short-term memory and then to long-term memory. The process can presumably be interrupted at any point in the sequence. Each phase has its minimal time for activation and for operation. For example, the registration of sensory information, sometimes referred to as iconic storage, can be retained for about 250 ms before it dissipates, or transfers its information, or is replaced by more recent incoming information. Short-term memory, which has a limited storage capacity, can retain the information passed on to it from iconic storage for about 500 ms, unless a quantity of attention is focused on its contents. Long-term memory, which has a comparatively unlimited storage capacity, receives information from both short-term memory and stimulus registration (Atkinson and Shiffrin 1968).

A technique that has been widely used in the study of the early phase of the information processing sequence is called "backward masking." Several investigators have used this experimental paradigm to study whether the early stage of information processing is disordered in schizophrenic conditions. In this paradigm, the experimenter ascertains a subject's recognition threshold, say, for perceiving the letter T. After determining the time the T must be exposed for that subject to recognize it unequivocally as a T, the experimenter follows exposure of the T with a patterned mask, perhaps a pattern of X's. If the mask of X's follows the T by 120 ms, the subject reports seeing only the X's but not the T. If, however, the X's follow the T by 500 ms, the subject reports seeing both the T and the X's in rapid succession. The second target, when presented 120 ms after the first target, obstructs the experience of having seen the first target. That is, the presentation of the X's

at a critical time period after the T was flashed on the screen interferes with the identification of the T.

An inference made from this paradigm is that it takes time for a stimulus to be moved from the stage of stimulus reception to the stage of short-term memory. This time period can be measured by varying the interval between the presentation of the target stimulus, the T in the example above, and the backward mask, the X's in the example.

In a series of studies using the backward masking paradigm, Braff and Saccuzzo have shown that schizophrenic patients, compared with normals and depressed inpatients (e.g., Braff and Saccuzzo 1985), show more profound effects of the backward mask. The differences between the groups are statistically significant when up to 500 ms separate the presentations of target and mask. After 500 ms, group differences disappear. That is, whereas the backward mask ceases to obscure the target stimulus after about 200 ms in normal subjects, it begins to lose its effectiveness after 500 ms in schizophrenic patients. The probability that medication effects account for the differences is low, inasmuch as antipsychotic medication has been shown to speed up rather than slow information processing (Braff and Saccuzzo 1982). Nor does generalized impairment that accompanies a disorganized clinical state account for the slowness of information processing, since Miller, Saccuzzo, and Braff (1979) and Braff (1981) found that schizophrenic patients in remission and unmedicated schizotypal patients also show similar patterns of slowness, and Braff and Saccuzzo (1985) showed that the differences obtained between schizophrenics and depressed patients were not related to gross psychopathology as measured by the Brief Psychiatric Rating Scale (BPRS) or the Global

Assessment Scale (GAS). Green and Walker (1986) present some evidence that a greater effect of the backward mask tends to be associated with symptoms of withdrawal, sometimes referred to as "negative symptoms."

The generally favored interpretation of these data emphasizes that schizophrenics transfer information from iconic storage to short-term memory more slowly than unaffected people do. It is also possible, however, that for schizophrenics, the T is registered appropriately enough, but it persists too long in iconic storage after the actual target has been shut off. The first interpretation emphasizing slowed information processing would reflect higher level neural events, analogous to those implicated in the P_{300} studies; the interpretation that emphasizes prolonged visual persistence of the target would reflect peripheral sensory events, perhaps analogous to those implicated in the very early epochs of the ERPs.

It would be of interest to study the schizophrenic subjects' "sensory memory" of a target—that is, the length of time a person maintains the visual image of a stimulus after it disappears. There are experimental methods for determining that parameter. For example, the experimenter can display two brief pulses of light separated by a dark interval. The experimenter can adjust the dark interval until the subject sees two flashes rather than a single flash. The persistence of the first flash bridges the dark interval and results in the experience of the two light pulses seen as a single one. This time interval, which would indicate the visual persistence of a target, can be precisely measured. Another explanation for the differences between schizophrenics and others emphasizes the possibility that the mask degrades the

clarity of the target, and thus is like the degraded CPT (Nuechterlein 1983). This explanation may be weakened by an experiment which used forward masking and in which schizophrenics showed normal performance (Saccuzzo and Braff 1981).

At this point, the use of backward masking is promising enough to test the unaffected first degree relatives and other subjects considered to be at genetic risk. It would also be important to test systematically the effects of medication on the backward mask. In addition, standardization of the following also seem to be desiderata for discerning consistency in results from different laboratories: (1) The types of masks, the effect of which varies with the degree of patterning, as Knight, Elliott, and Freedman (1985) have shown; (2) the procedure for establishing thresholds; (3) establishing (a) the length of the interstimulus interval, (b) the duration of the mask, (c) the visual angle for viewing the targets, and (d) whether contralateral masking was used (cf. Fein and Brown, in press).

Electrodermal Responses

The electrodermal response system has been assumed to represent activity of the sympathetic nervous system and, in particular, the changes in arousal that accompany responsiveness to incoming stimuli. Tonic skin conductance level (SCL) and response (SCR) are two measures of electrodermal responses that are frequently studied in schizophrenic patients. With respect to SCRs, there are several quantitative scores, including (1) the frequency of SCRs, which is a relatively stable characteristic of a person; and (2) the skin conductance orienting response (SCOR), which occurs in the presence of a novel stimulus

that bids for the person's attention. The separate components of the SCOR—its latency, its time to peak response, and its habituation—have been extensively studied in normal subjects as part of the psychology and psychophysiology of attentional process (Sokolov 1963). Spohn and Patterson (1979) reviewed the then current findings with respect to skin conductance, and in particular the SCOR, and schizophrenia. Dawson and Nuechterlein (1984) have provided a more recent review.

The basic finding with respect to the SCOR is that many adult schizophrenics do not produce SCORs. Whereas from 40 to 50 percent of adult schizophrenics do not show an SCOR (e.g., Gruzelier and Venables 1972; Patterson and Venables 1978; Bernstein et al. 1981), only 5–10 percent of normals fail to show an SCOR (Simons et al. 1983). The failure to elicit the SCOR in this substantial proportion of schizophrenics can be reversed, however, by increasing the intensity of the novel stimulus, indicating that the absence of the SCOR represents a raised threshold for the orienting response. In that case, it is quite possible that the data do not describe a bimodal distribution of responders and nonresponders to novel stimuli, as seems to be the case for schizophrenics with eye tracking dysfunctions, but a continuum. It is important to note, however, that large numbers of SCOR nonresponders have been reported among patients with major affective disorders, both unipolar and bipolar (Dawson, Schell, and Catania 1977; Iacono 1982).

In their original study, Gruzelier and Venables (1972) reported that the SCOR failed to habituate in the schizophrenic subjects who did show an SCOR. This failure to habit-

uate, however, has proved difficult to replicate, even by those who at times have found it. A particularly thoughtful review of this area is provided by Öhman (1981).

The SCOR nonresponders tend to be more withdrawn and disorganized than the responders, who tend to show excited, dramatic, obvious, schizophrenic symptoms (Straube 1979; Bernstein et al. 1981). The nonresponders tend to have lower tonic SC levels (interpreted as lowered arousal levels) than the responders (Gruzelier and Venables 1972, 1975), and in that sense resemble those with an attenuated P_{300}. But the P_{300} and SCOR probably represent different aspects of information-processing sequences, as suggested by a finding of small P_{300} amplitudes in schizophrenic patients whether or not they were SCOR responders (Cohen, Sommer, and Hermanutz 1981).

It is noteworthy that SCOR nonresponders are significantly prevalent among schizophrenics in remission (Zahn, Carpenter, and McGlashan 1981; Iacono 1982), suggesting that in this subgroup the SCOR nonresponsiveness may represent a trait. In this regard, Simons (1981) reported that SCOR nonresponders were a majority of subjects who, although clinically unaffected, scored high on the Chapman Anhedonia Scale, a measure of a personality trait assumed to be associated with schizophrenia.

The data, however, are quite ambiguous with respect to non-affected first degree relatives of schizophrenics. Mednick and Schulsinger (1968) reported that 20 high-risk subjects who later showed serious psychological symptoms demonstrated larger SCRs to noxious stimuli than did 20 matched high-risk subjects who seemed clinically well. The separation of the groups was particularly strong

when SCR recovery time was the variable. The subjects who later showed clinical symptoms had shorter latencies and faster recovery time for the SCR. In testing 7- and 10-year-old boys who had a schizophrenic mother, however, Prentky, Salzman, and Klein (1981) failed to find differences in recovery time, although they did report larger SCRs to noxious stimuli, as in the Mednick and Schulsinger data. Van Dyke, Rosenthal, and Rasmussen (1974), too, had earlier reported large SCRs to mild tones on the part of adopted children born of a schizophrenic mother. Erlenmeyer-Kimling et al. (1984b) also failed to find differences in SCR recovery time between children at genetic risk for schizophrenia and those not at risk.

While it may appear trite to call for more research on this issue, such a call is required to determine the source of the ambiguity. Drug effects must be carefully controlled, since tonic arousal levels are affected by neuroleptics. Longitudinal studies should replace cross-sectional studies to determine if there is stability in SCRs and SCORs in different clinical states. First degree relatives of the probands should be tested to chart the familial pattern of electrodermal responses. This last recommendation is particularly necessary in view of the fact that SCOR nonresponders are found in patients with major affective disorders, even in remission.

Overview and Future Needs

During the past 6 years, investigators have shown that several psychophysiological indices have a robust relation to schizophrenic illness. Eye movement dysfunctions, early and late components of ERPs, tests of attentional deployment, backward masking, and some as-

pects of electrodermal response all to some extent indicate that schizophrenic patients manifest dysfunctions of both automatic and controlled deployment of attention. The problems in automatic attention deployment are presumably reflected in eye movement dysfunctions, absence of SCORs, and early components of ERPs. Problems in controlled attention are presumably reflected in late epoch ERPs and tests such as the CPT and the span of apprehension task. Schizophrenics show a more enduring effect of backward masks, a finding that has been interpreted as sluggish transfer of information from the stage of registration to short-term memory. Although there is much evidence for these dysfunctions in patients with manifest schizophrenic symptoms, the evidence is not so clear with respect to their first degree relatives.

At this time, several lines of investigation seem to recommend themselves.

1. The meaning of most of the psychophysiological procedures requires refinement. Although much work has been accomplished on ERPs, and several reviews indicate the intricacy and subtlety of these waves (e.g., Pritchard 1986; Näätänen 1982), there is a need to study further the meaning of the separate components of the ERPs, inasmuch as veteran investigators do not fully agree on the meaning of the separate components.

The eye movement dysfunctions have been characterized as consisting in saccadic tracking, saccadic intrusions, and low gain pursuit. There is a need to establish whether the impairment resides in the saccadic system, pursuit system, or both, and then to establish the functional significance of the abnormalities.

The meaning of absent SCORs in up to 50 percent of schizophrenics also requires exploration, particularly to see if it is an expression of a failure to gate incoming stimuli which could lead to stimulus flooding, an experience of many psychotic schizophrenic patients.

The above considerations hold also for studies using the CPT and the span of apprehension test. Both tests have an obvious rationale that emphasizes sustained attention and vigilance, but they are composed of many tasks performed almost simultaneously. Investigators have established that both tests discriminate schizophrenics from other patients, and studies are showing sturdy familial prevalence of dysfunctions. Investigators should begin to scrutinize the crucial aspects of the tests that produce the performance decrements.

These psychophysiological and cognitive measures are not pursued only in their own right in studies of schizophrenia. Rather, they can also be regarded as temporary vehicles to convey us closer to the basic etiology and pathogenesis of the schizophrenias. When these tasks have brought us as close as they can to the basic disease processes, investigators should change vehicles for more appropriate ones. It is not the test that is "the thing," but the processes and mechanisms represented by the test.

2. The strategy of testing first degree relatives should be pursued as a matter of course. The study of chronically ill patients can take us only a limited way toward understanding schizophrenia. Investigators should therefore study the apparently unaffected first degree relatives and people considered to be at risk for the disorder. This strategy has been followed mainly for eye movement studies and the attentional tests with energizing

results. It remains to be exploited for ERPs and backward masking, and requires more vigorous application in electrodermal measures.

In this reviewer's opinion, the most useful model for that strategy is the latent trait model, described by Matthysse, Holzman, and Lange (1986) and Matthysse and Holzman (in press). The model emphasizes the value of studying mildly affected and clinically asymptomatic members of the families of schizophrenic probands. These people have been a neglected resource for psychophysiological investigations. Most investigators seek to study the sickest patients and the families with the highest concentration of illness. But families with a high density of schizophrenia are not only rare; they are often uncooperative. And the social withdrawal, suspiciousness, and interpersonal incompetence that are parts of the schizophrenic syndrome make these interesting families the hardest to reach. The technique suggested here places an emphasis not on finding families of a particular type, but on a thorough study of each of the relatives, including those who seem well.

The term "generalized deficit" was introduced by Chapman and Chapman (1973) to refer to the many impairments of schizophrenic patients on most psychological tasks. Indeed, all severe disorders, as they progress, gradually become secondary etiological factors in their own right, causing general systemic collapse that may have little to do with the original causes of the disease. This process is characteristic of chronic physical as well as mental disorders. When such patients die, the cause of their death is generally not the disease that began their decline, but a myriad of systemic failures that become quite similar

among patients whose disease processes started quite differently. Generalized deficit has made the task of identifying specific and etiologically relevant abnormalities in schizophrenia difficult, and much effort has been needlessly spent studying deficits that are only secondary consequences of the disease. If the biological factors leading to schizophrenia can manifest themselves in subclinical or functionally unremarkable forms as well as in pathological forms, then the opportunity presents itself for studying those factors without the interference of the formidable dysfunctions in attention and motivation that characterize all forms of schizophrenia.

3. There is a need to standardize procedures and scores. When investigators deviate from those standard procedures, they could state so clearly. Standardization, to some extent, seems desirable to help reconcile apparent discrepancies in experimental results. For example, in backward-masking studies, it is necessary to know if a patterned or a plain mask was used, how the recognition thresholds were obtained, the length of the interstimulus interval, and the duration of the mask, since those procedures will affect the effectiveness of the mask. In ERPs there should be a way to quantify the degree of attenuation of a wave, a procedure that would permit one to judge the extent of the abnormality. A related point: studies generally report mean differences between groups, and usually without any indication of effect size. To look for familial patterns, investigators should be able to classify performance as defective or normal, even though the variable under consideration is a continuous one. That procedure is followed in general

medicine—for example, in assessments of blood pressure or glucose tolerance. Perhaps a cutoff of two standard deviations beyond the mean of a representative normal sample would be helpful, in order to study the functional meaning of deviant scores.

In physical medicine there are more or less standardized levels for judging deviation from the norm of such measures as sedimentation rates, blood pressure levels, or white blood counts. The same standards should be sought for psychophysiological measurement. We need to know how much attenuation of the P_{300} wave, how much reduction of gain of pursuit eye movements, and what levels of d' are to be considered pathological. Within-group differences can be used to explore the heterogeneity of the schizophrenia category.

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