Recent Studies of Psychophysiology in Schizophrenia

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Abstract

A general introduction is given and followed by a review of recent literature under the following subheadings: electrophysiological, cardiovascular activity, smooth pursuit eye movement, electroencephalogram, and evoked potentials. An attempt is made to assess the clinical significance of the findings reported in each area and to indicate directions for future investigation. The feasibility of defining homogeneous subgroups in schizophrenia using psychophysiological parameters is also considered. The review concludes with the recommendation that peripheral psychophysiological studies entailing (1) comprehensive recording of brain electrical activity and (2) behavioral experimentation on variables thought to be influenced by schizophrenia (e.g., sustained attentional ability) are promising directions for future research. Relationships between behavioral and psychophysiological variables determined by such studies (and possibly subgroupings) may then become the basis for neurophysiological-neurochemical investigations of specific abnormalities underlying such relationships and subgroups.

It seems appropriate at the beginning of this review to draw boundaries around the content area of interest. That is best done by defining psychophysiology and by providing a historical perspective concerning the development of psychophysiological studies in schizophrenia.

Psychophysiological measurement, broadly speaking, encompasses methods of recording and processing bioelectric signals from the surface of the skin. Such bioelectric signals typically reflect the activity of the central nervous system (CNS) and the peripheral nervous system (PNS) in mediating the response of effector systems (e.g., eccrine sweat glands, cardiovascular system) and/or CNS activity itself (e.g., brain waves). The domain of psychophysiology proper is the study of variation in CNS and PNS activity in relation to behavior, and to psychological states and functions inferred from behavior.

Historically, the psychophysiological study of schizophrenia is characterized by three epochs. These epochs overlap temporally but are distinctive in terms of aims, response systems indexed, and conceptualization of mechanisms underlying psychopathology in schizophrenia.

The earliest psychophysiological studies of schizophrenia were largely devoted to attempts to identify reliable differences between nonpsychotic subjects and schizophrenics in tonic and phasic nervous system activity. The nervous system of choice in such studies was typically the autonomic nervous system (ANS). In 1965, Lang and Buss (1965) reviewed, summarized, and evaluated this literature.

Even before the publication of the influential review by Lang and Buss, investigators concerned with the experimental study of psychopathology in schizophrenia had come to recognize that psychophysiology could be a research tool by means of which aberrant internal states and functions might be indexed. This approach also recommended itself because it was addressed to responses and response systems that could be regarded as unequivocally free of such contaminants of schizophrenic behavior as inattention and variable motivation.

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Conceptually, this epoch was dominated by such constructs as “arousal or activation,” typically indexed by tonic levels of ANS activity, and “attention,” indexed by phasic response and by behavior. These constructs were integrated by some investigators in models of mechanisms underlying psychopathology. An instructive example here is Venables’ (1964) theory that schizophrenia is a bimodally distributed input disorder. Chronic, poor premorbid, nonparanoid schizophrenic patients are thought to be hyperaroused (elevated levels of skin conductance or heart rate) and acute, good premorbid paranoid schizophrenics are thought to be hypoaroused (abnormally low levels of skin conductance or heart rate). These two aberrant arousal states were considered to be linked to abnormal attentional response (indexed behaviorally or, for example, by skin conductance response) in the form of excessively narrowed ranges and broadened ranges of voluntary attention, respectively.

Sometime in the last decade there began a shift in interest away from focus on ANS activity and such constructs as arousal and toward a growing emphasis on psychophysiological assessment of brain function. Psychophysiological study came to be regarded as a noninvasive method, par excellence, for examining neurophysiological and neurochemical processes hypothesized to be dysfunctional in schizophrenia. Evoked potential and electroencephalographic (EEG) recording became the preferred modes of assessment in this enterprise.

A number of factors contributed to this still ongoing trend. In the recent past, knowledge of brain function and its relationship to behavior has greatly increased. The discovery of the neurotransmitters and a growing body of knowledge concerning their mediation of psychological states and behavior have led to several theories that locate the core pathophysiologic functions in schizophrenia in particular neurotransmitter systems (e.g., dopamine and acetylcholine). Indeed, the growth of interest in studies of brain function is due in part to the recent determination of a common mode of neurochemical action of all clinically effective antipsychotic drugs. Furthermore, the concept of attention has come to be regarded in some theories as a “phase” in an information processing sequence that encompasses preattentive phases as well. (Preacttentive processing of information includes scanning, registration, and visual trace formation phases.) Some investigators (Braff, Callaway, and Taylor 1977) have identified the preattentive phase as a possible locus of critical dysfunction in schizophrenics and one that lends itself particularly well to evoked potential studies (see p. 598). Finally, increasing sensitivity of electronic equipment and the availability of highly sophisticated laboratory computers has greatly facilitated electrophysiological study of brain functions. An instructive example of this contemporary trend is again that of Venables and his associates whose study of the skin conductance orienting response and its relation to attentional pathology in schizophrenia is currently guided by hypotheses pertaining to dysfunction at the subcortical-neurochemical level (see p. 583).

It should be noted that these contemporary trends in the psychophysiological study of schizophrenia have not completely displaced trends characterizing the preceding epochs. Indeed, a number of studies focused on arousal-attentional linkages will be among those included here.

The primary concern of this review is with studies published since 1975. The review will not, however, be focused exclusively on the research literature from 1975 to the present. Studies preceding this period will be cited to set the conceptual and empirical stage for critical evaluation of more recent studies.

The review is organized in terms of CNS- or PNS-mediated response systems (e.g., electrophysiological and cardiovascular activity) and by method of brain function assessment (e.g., EEG and evoked potential). Separate sections will be devoted to each of these categories. A word needs to be said concerning the rationale for such an organizing scheme. At this stage of the development of the field of psychophysiology, individual investigators still differ from one another in their commitment to a particular response system and associated conceptual domain. Cross-system conceptual synthesis is still the exception rather than the rule in this field. Thus, for example, three different investigators (Shagass 1977; Buchsbaum 1977; Roth 1977) have each laid claim to different phases (early, middle, and late) of the EP (see p. 598). Similarly, the study of the skin conductance orienting response is the special domain of Venables and a small band of associates. To attempt an integration of this diverse research literature at the present stage of its development would be foolhardy and premature.

Finally, mention needs to be made of the fact that the recent developmental history of the psychophysiological study of schizophrenia was temporally paralleled by the increasingly prevalent use of antipsychotic (or neuroleptic) drugs as an effective symptomatic treat-
ment of schizophrenia. It has become evident that these drugs affect (albeit selectively) CNS and PNS activity. In some cases, the direction and degree of effect is known; in many others, it is not. This state of affairs forces a special caution on investigators and on reviewers of their studies. As will be seen below, this caution takes the form of suspending final judgment of the significance of empirical findings in studies in which antipsychotic drug variance was not controlled.

Electrodermal Activity

Both skin conductance and skin potential recording are usually included under this heading. Because of the difficulty in quantification of the amplitude and recovery aspects of the skin potential response, the bulk of the research on electrodermal activity has used the skin conductance response (SCR), although it is frequently recorded in the “orienting” paradigm and is thus referred to as the skin conductance orienting response (SCOR).

This area has produced some rather exciting findings in the past few years, and almost all of them have directly involved the pioneering work of P. H. Venables (York University, England). Venables has been involved in the area since the 1950s and made significant methodological and theoretical contributions to the investigation of potential physiological mechanisms controlling skin conductance (e.g., Venables and Christie 1974; Venables and Martin 1967). No potential experimenter should start work with skin conductance recording before reading the excellent chapter by Venables and Christie (1974) which covers every aspect of the theory and practice of skin conductance recording and data quantification. This is the most significant attempt to produce a standardized methodology for skin conductance yet printed and should, with luck, prevent a repetition of the situation of the 1960s, when results of skin conductance experiments with schizophrenics and normals could not be compared between laboratories because the experimental methodology varied so much. Units that measure skin conductance directly are not commercially available so that each laboratory has to make its own. The design of these units (in electronic terms) is important, and this is discussed by Venables and Christie (1974) where circuitry is presented. However, a new approach to such equipment has been developed by Lowry (1977), whose article also presents new circuitry of considerable elegance. Two excellent reviews of current findings and controversies in this area are available (Venables 1977, in press), and the interested reader is strongly encouraged to consult them.

Almost all of the studies quoted in this section will concentrate on fractionated components of phasic skin conductance responses. These studies generally use some variant of the orienting response to elicit the phasic skin conductance change. Thus, separate components, such as latency, rise time, amplitude, and 50 percent recovery, are usually recorded from each response in the orienting series, as well as the number of responses given by a subject before habituation occurs (i.e., the response no longer appears). Some investigators then change the stimulus (e.g., increase or decrease its intensity) and often observe the reappearance of the orienting response. This is called dishabituation. Another approach (e.g., Bernstein 1968, 1969, 1970; Bernstein and Taylor 1978) is to alter the significance that the stimulus holds for the subject (e.g., to make it imperative in some way) so that perhaps a response is required or the subject has to count the tones or light flashes. This type of experiment is often conducted by investigators who suggest that it is the process of assigning significance to stimulation that is the central problem in schizophrenia. These experiments (e.g., Bernstein 1968, 1969, 1970; Bernstein and Taylor 1978) have interesting data to report, but, by and large, studies of the simple “nonsignal” orienting response have produced the most interesting data relative to schizophrenia. A discussion of stimulus significance is not really warranted in this review, in that the concept is better understood in the context of a discussion of the theoretical and physiological mechanisms involved in the orienting response. However, the interested reader should pursue the following sources relative to “significance”: Bernstein (1968, 1969, 1970), Bernstein and Taylor (1978), Barry (1977a, 1977b), and Pribram and McGuinness (1975).

The use of fractionated components of electrodermal responses is relatively new in the electrophysiology of schizophrenia. Hitherto, the most common approach was to look at skin conductance or resistance level at various periods in an experiment (e.g., the skin conductance level would be sampled every 30 seconds during periods of “rest” and “activation”). By and large, this type of experiment is declining, largely because of the failure to find interesting results. However, the use of skin conductance level in conjunction with two flash fusion threshold has produced interesting results in the hands of at least one experimenter (see Claridge 1978), and this work is discussed below in relation to EEG. These data also
raise the question of arousal and schizophrenia. By and large it is questionable whether the term "arousal" has any value as a clarifying concept in schizophrenia (see the discussion of the work of Lifshitz and his associates below). This question will be returned to again.

Limbic Involvement in the SCOR.
The most significant inspiration of the current wave of interest in skin conductance in schizophrenia was the work of Muriel Bagshaw and her colleagues with monkeys (Bagshaw and Benzies 1968; Bagshaw and Kimble 1972; Bagshaw, Kimble, and Pribram 1965). These experiments showed that amygdalectomized monkeys produced hyporesponsive (or nonresponder) electrodermal records, whereas hippocampectomyed monkeys showed the reverse effect (i.e., a hyperresponsive record in which the orienting response failed to habituate). These findings became known at a time when interest in the limbic brain and control of inhibitory processes was at its height. The interested reader is referred to the summary of limbic brain function in MacLean (1973) and especially to the book Inhibition and Learning edited by Boakes and Halliday (1972), which contains seminal chapters by Warburton (1972) and Douglas (1972). Also influential during this period were the findings of Mednick and Schulsinger (1968) from their longitudinal studies on high-risk children in Denmark. These findings suggested that perinatal birth complications could be etiologically significant in schizophrenia. It had been known for some time that the hippocampus possessed the lowest seizure threshold of any structure in the brain (MacLean 1973) during hypoxia, and, as this condition frequently occurs during birth complications, that hypoxic damage to the limbic brain was implicated as a possible route to schizophrenia. As schizophrenic mothers had greater frequency of difficult births, it was also possible that hypoxic birth damage could account for data hitherto attributed to genetic factors. Consequently in the early 1970s, Gruzelier and Venables in London began the search for data on skin conductance that would demonstrate limbic involvement in schizophrenics.

Skin Conductance Responding/Nonresponding.
Gruzelier and Venables (1972, 1973) were the first to publish research in which it was specifically noted that a sizable number of adult schizophrenics did not produce any SCORs. During the 1960s electrodermal research produced conflicting findings, some reporting hyporesponding and some hyperresponding in ostensibly similar schizophrenic patients, thus adding fuel to the flames of the argument of whether psychotics were over- or underaroused. Gruzelier and Venables showed that approximately 50 percent of the patient population studied produced no responses (i.e., were nonresponders), and the remaining 50 percent did not habituate the orienting response. The parallels with the work on monkeys by Bagshaw and her associates were obvious, and the findings produced considerable excitement. This was the resolution of the conflicting reports of the 1960s—schizophrenic subjects were hypo- or hyperresponsive, depending upon the number of nonresponders included in the mean values of each group. A number of studies followed (e.g., Bernstein and Taylor 1978; Patterson 1976a, 1976b; see also Venables, in press) which showed that "nonresponding" did indeed characterize close to 50 percent of schizophrenics and perhaps 7 to 10 percent of normal subjects. However, what was not so easily accepted was total limbic control of the SCOR and therefore limbic abnormalities in nonresponders. Zahn (1976) produced data that did not show the "bimodality" so neatly displayed by the Gruzelier and Venables data. At the time of writing, the consensus of opinion is that "nonresponding" is certainly more frequently seen (perhaps as much as 50 percent) in adult psychotics compared to normal subjects (10 percent or less), but many researchers question the simplicity of the original statement concerning the "nonhabituation" of the remainder of the schizophrenic population. Bernstein et al. (in preparation) are attempting to synthesize findings from various laboratories and countries, and the reader is again referred to Venables (1977, in press) for detailed discussion of current controversies. What has also been made obvious is how little is actually known about the mechanisms that control skin conductance phenomena, especially with regard to brain neurochemistry. This will be referred to in later sections.

Skin Conductance Recovery.
The SCOR, if it occurs at all (i.e., if the subject is a "responder"), shows measurable components, such as latency, rise time, amplitude, and recovery. These fractionated components of the SCOR are elegantly discussed by Venables (1975) with special reference to the 50 percent recovery parameter following stimulation. (For a technical explanation of why 50 percent recovery is used, the reader is referred to Venables, 1975.) Great interest has been shown in this parameter since it is perhaps the only known measurable
event that would appear to predict schizophrenia in high-risk prepsychotic children.

This finding came from the longitudinal studies conducted in Denmark by Mednick and his associates (Mednick 1970; Mednick et al. 1977; Mednick and Schwinger 1968) but, as Venables (1975) has pointed out, the exact control of this mechanism is not known. (Some clues as to the underlying mechanisms are suggested in a later section.) It does appear to have considerable significance for schizophrenia research if schizophrenia is conceptualized as a disorder of attentional processes. Venables (1975) has hypothesized that fast skin conductance recovery (which characterized those children who were found to break down in later life) is indicative of exceptional “openness” to environmental stimulation, perhaps leading to the “sensory flooding” seen in schizophrenia. By contrast, Hare (1972, 1975) has presented data on “psychopaths” which suggest that such patients have exceptionally long 50 percent recovery time in the SCOR: psychopaths could be hypothesized to be “closed off” from environmental stimulation. Thus, understanding the control of the 50 percent recovery of the SCOR may give us important clues to controlling mechanisms in schizophrenia.

Skin Conductance Habituation. The original reports of Gruzelier and Venables (e.g., 1972) suggested that all schizophrenics who produce SCORs failed to habituate within 15 trials, whereas almost all normal subjects did. This finding has been confirmed in some studies and refuted in others. Thus C. Firth (personal communication) upheld the original Gruzelier and Venables finding (data included in Bernstein et al., in preparation), whereas Patterson (1976a, 1976b), Patterson and Venables (1978), Straube (in Bernstein et al., in preparation), Zahn (1976), and Bernstein (in Bernstein et al., in preparation) all find that habituation occurs within the normal range or very frequently below the normal range and that nonhabitation in schizophrenia is the exception rather than the rule. Clearly, there are methodological differences and procedural differences that may account for this disparity, and these are explored by Venables (1977, in press). It is readily apparent that as long as measurement techniques differ as widely as they do, much needless controversy will rage between laboratories. For example, the orienting tones can be 400, 500, or 1,000 Hz, with or without controlled rise times (to minimize transient overshoot and “startle” effects), and few experimenters bother to report the intersubject intervals used in their series or to mention their habituation criterion (one, two, or three trials of nonresponse being seen). As all of these variables affect the habituation of the orienting response (OR), it is a matter of considerable surprise that as much consensus as there is has been reached across studies (see Bernstein et al., in preparation).

This matter of alteration of habituation in schizophrenia is fairly important to notions of limbic involvement and is essential to the issue of whether schizophrenics cannot stop themselves attending to stimuli or whether they actually inhibit large amounts of stimulus input and cannot attenuate the inhibition, thus producing severe perseveration.

Considerable agreement has been reached by Patterson, Straube, and Bernstein among others (in Bernstein et al., in preparation) concerning a group of schizophrenic subjects referred to by Patterson (1976a, 1976b) and Patterson and Venables (1978) as “fast habituators.” This name applies to schizophrenic subjects who show a sizable amplitude response to trial 1 (and occasionally trial 2) OR stimuli, then thereafter do not respond even after 80 trials of orienting tones (T. Patterson unpublished data collected with A. S. Bernstein). Such subjects are an utterly distinct electrodermal group, and their skin conductance and skin potential records are systematically explored by Patterson and Venables (1978). Patterson and Venables have suggested that such subjects may fall somewhere in between responders and nonresponders (see Venables 1977, in press), and Patterson has suggested that “an active inhibitory process” could well be evident in these “fast habituator” subjects because of their extremely good auditory signal detection performance. Patterson and Venables (in preparation b) found that sustained attention ability in the fast habituators was indistinguishable from normal when a decision at near threshold discriminability was required once every 3 seconds for 30 minutes in a signal detection task. This was in marked contrast to poor sustained attention for schizophrenic subjects who habituated within the normal orienting range and very poor signal detection ability in schizophrenic nonresponders.

The question of drug interaction with electrodermal findings is one of importance. It is possible that much of the SCOR abnormality reported is a drug interactive effect in schizophrenic patients. This possibility is hinted at in the work of Söhn et al. (1977), who reported that phenothiazines reduced test trial related SCRs in chronic schizophrenics. Gruzelier (1978), however, found no changes due to drug treatment in the pattern
of SCORs to neutral stimuli produced by chronic schizophrenics. Also relevant here is a recent study by Frith et al. (1979) indicating that SCOR habituation (or absence thereof) in acute schizophrenic patients is as effective in predicting response to phenothiazines as the traditional indicators of prognosis—insidious and sudden onset of illness. Habituation shows a positive response to drug treatment, while nonhabituation does not. However, attempts by Spohn et al. (1977) to relate pre-treatment, specific SCR amplitudes to response to treatment and to drug withdrawal were not successful. The main problem is that it is not possible to find an adequate “control” population for schizophrenics on daily doses of phenothiazines. A normal sample on a single acute dose is not an adequate control, possibly for the reasons that all drugs interact with “state of the nervous system” variables. A good example of this is the different effects that a narcotic analgesic may have on the person in pain and the person not in pain. However, potential drug effects are noted and discussed by Zahn (1976), Venables (1977, in press) and Bernstein et al. (in preparation). One of the few direct drug experiments using single acute drug doses in normals is that of Patterson and Venables (in preparation). It is interesting to note that very different effects were obtained for chlorpromazine (CPZ) and haloperidol in normal subjects. This does not, however, answer the question of drug effects in long-term doses in schizophrenics. Clearly with the use of increasingly potent dopamine receptor blockers in schizophrenia (e.g., haloperidol), it would be advisable to look for possible differential effects of these drugs compared to older, less potent phenothiazine compounds.

Clearly there is going to be disagreement for some time to come about SCOR habituation in schizophrenics, although it is most likely to be found to be heterogeneous. However, it would appear to be worth pursuing if it can predict attentional differences within the schizophrenic population. As something of the neurochemistry of sustained attentional ability is known (see Douglas 1972, and Warburton 1972), then it could be that SCOR habituation is a function of highly variable neurochemical parameters (e.g., neurotransmitter turnover rates) that are believed by many to be diverse and manifold abnormalities underlying as yet undifferentiated schizophrenic subgroups.

Modification to a “Limbic” Hypothesis. The “limbic” hypothesis that spawned the work of Bagshaw and her associates with monkeys and the SCOR work of Gruzelier and Venables was derived from Douglas and Pribram (1966), who had put forward a simple theory on the basis of the “then existing” data. They had suggested that the amygdala was an excitatory body and the hippocampus was an inhibitory body and that the excitation/inhibition balance necessary for the control of behavior was a function of the “reciprocity” of the two. This picture was clearly an oversimplification and has given way to much more complex notions of limbic functioning.

In an elegant review of a vast quantity of animal lesion and learning studies, Douglas (1972) showed convincingly that for every effect that could be obtained with hippocampal lesion, the same effect could be obtained by depletion of brain acetylcholine (ACH), and also showed that there is no brain structure more “cholinergic” than the hippocampus.

Elizabeth Fonberg (1972) showed that substantial behavior deterioration could be seen in dogs with exact amygdala lesions but that this deterioration could be completely reversed by an equal sized lesion in another part of the amygdala. Thus, it could be concluded that other “reciprocities” are in evidence in the limbic brain besides the very simple notion of hippocampal/amygdala reciprocity. It must also be borne in mind that brain structures are interconnected by pathways which differ in their neurochemical coding and that brain circuits consist of parts of different structures which are chemically linked by virtue of common neurotransmitter systems.

With reference to the control of “attention,” the work of Warburton (1972) and Warburton and Brown (1971) is particularly enlightening. In their studies, the ability to maintain attention (commonly held to be a central defect in schizophrenia) is manipulated in rats and humans by anticholinergic drugs such as scopolamine. The reader is referred to Warburton’s (1975) review of this research for more substantial and detailed arguments.

A theory based on functional neurochemistry is a possible alternative to the more “static” hypoxic lesion theory discussed on p. 584. One way to investigate such a theory is to combine skin conductance recording with recording of other electrophysiological systems in which the neurochemical innervation is fairly well known. This has been attempted with some success with pupillometry.

Pupillometry and Skin Conductance. Movement of the pupil is not easy to record in that either high-speed photographic techniques or raster-scan television techniques are involved. The formidable technical
difficulties presented by pupillographic research have tended to discourage investigations relevant to schizophrenia. What little research has been done has been reviewed by Venables (1977, in press). It falls mainly into two paradigms: the light pulse where brief flashes of light are given to a dark adapted pupil, and the light/dark reflex where the time/size curve at an “undriven” pupillary response to darkness (over about 60 seconds) and to reillumination (usually 5 to 10 seconds) is obtained. This latter paradigm was explored by Rubin in the 1960s (see Venables 1977, in press) but only on its own (i.e., not in combination with other electrophysiological variables).

The pupil is a dually innervated organ using noradrenaline (NA) for dilation and acetylcholine for constriction. As such, it is difficult to tell exactly which neurotransmitter substance is involved if an abnormality in total pupillary dilation or constriction is observed. Nonetheless, if a correlation between pupillary and skin conductance parameters should be found, then it could give important clues to the mechanisms underlying skin conductance components. A consensus of work with the light pulse (e.g., Lidsky, Hakrem, and Sutton 1971) suggests a weak “parasympathetic” system in schizophrenia by virtue of slow or reduced pupil constriction to light pulses. This work has not been done in conjunction with skin conductance research, however, so little can be deduced from it.

Pupillographic relationships to both SC recovery (Patterson 1976a) and SC responding/nonresponding (Patterson, 1976b) have been found using the light/dark reflex. These findings are discussed by Venables (1977, in press) and are also related to speech perception and decision processes in signal detection (Venables and Patterson 1978). The direction of these findings was that nonresponder schizophrenics showed hypoactive pupils in the light/dark reflex and that fast SC recovery was linked with very slow pupil constriction and vice versa. As these data suggest that SC parameters tap “state of the nervous system” differences of some generality, Patterson and Venables decided to subject both electrophysiological systems to pharmacological manipulations to elucidate underlying neurochemical mechanisms.

Pharmacological Manipulation of SC and Pupilometrics. Little direct work has been done on neurochemical mechanisms underlying SC change. However, early iontophoresis work by Venables and Martin (1967) suggests cholinergic innervation of the eccrine sweat glands. There is also suggestion of adrenergic innervation to a hypothetical “ductal squeeze” mechanism in the glands (see Venables and Christie 1974), but this is still not certain. Some work with drugs has been done on the pupil by Rubin and Barry (1972), among others, and schizophrenics have been reported to show reduced constriction parameters or sluggish parasympathetic systems. The eccrine gland innervation is ACh, pupil constriction is controlled by ACh, and ACh is central to maintenance of attention (Warburton 1975). Therefore, Patterson and Venables (in preparation) carefully manipulated the SCOR and the pupillographic light/dark reflex with scopolamine (a cholinergic blocker), haloperidol (a dopaminergic blocker), and chlorpromazine (a major phenothiazine tranquilizer with anti-catecholaminergic action). The experiment used a within-subject design but because of presentation of a single OR stimulus under each drug condition, nothing could be said about SC habituation effects.

Preliminary results from this work show the total obliteration of the SCOR with scopolamine. But what is perhaps more interesting is that haloperidol in single acute administration looks as though it can produce the SC pattern found in prepsychotic children—that is, the rise time and recovery time are markedly shortened, and the amplitude of the response is increased. The haloperidol and scopolamine effects taken together might suggest some dopamine/ACh controlling and modulating mechanisms for the SCOR, and these are known to exist in the basal ganglia, the caudate nucleus, and the limbic brain, if not in other areas. There is evidence going back for at least 20 years that acetylcholine abnormality is involved in certain schizophrenic subjects (Sherwood 1955; Warburton 1975) and it is currently highly fashionable to attribute schizophrenic symptomatology to altered states of dopamine—hence the high therapeutic efficacy of haloperidol as a treatment in schizophrenia.

The involvement of a dopamine/acetylcholine balance in schizophrenia has in fact been formally stated by Davis (1975). His article is one of a number of recent communications that have attempted to get away from a single amine theory of schizophrenia. Interestingly, Nielsen and Peterson (1976) reported that in normal subjects scored on a scale of “schizophrenism,” those high on the dimension showed fast recovery and high SCR amplitude in some of their experimental conditions. Further experimentation on this notion of dopamine/ACh reciprocity may well be fruitful for both SCOR mechanisms and schizophrenic etiology. Drug effects on the pupil are mostly in keeping with speculations of Pat-
Clinical Implications and Future Research. Electrodermal activity, if carefully recorded with a standardized methodology (see Venables and Christie, 1974), is capable of producing data that could well be integrated with the diagnostic process in psychiatric practice. Much work is still needed to refine specific SCOR wave forms to specific subgroups of adult schizophrenics, but the longitudinal studies in Denmark (Mednick et al., 1977) and the island of Mauritius (Venables, 1977) have shown adequately that electrodermal activity is perhaps the best population-screening tool currently available. Further refinement of SC as a tool could well take place, with the addition of pupillometric and pharmacological studies of the type mentioned above, as well as the combination of SC recording with EEG and evoked potentials. At the time of writing, it is not possible to make definite statements about the use of electrodermal activity as a diagnostic or treatment monitoring tool. In addition to the “population screening” noted above, it would, however, be possible to use it as one of the many instruments involved in diagnosis. For example, if the subject is a non-responder, this is about five times as likely to be found in schizophrenics as normals. If the subject shows the “fast habituator” pattern of SCOR, then it may be more likely that this type of pattern is observed in schizophrenia and not in other conditions.

Moreover, the work of Frith et al. (1979) suggests the possibility that individual differences in response and habituation before treatment may reliably predict response to treatment. However, all of this is by no means certain and awaits further research, especially to see if the single long recovery responses occur in “normal” groups. If fairly specific EEG and evoked potential indices are found to characterize the electrodermal groups reported above, then it may be possible to use the cheaper, quicker recording of electrodermal activity as a diagnostic “shortcut” in the future. For the moment, the measurement of electrodermal activity is predominantly a research procedure.

Cardiovascular Activity
Cardiovascular variables have played a significant role in the history of psychophysiological study of schizophrenia. In their review of such studies, Lang and Buss (1965) based their conclusion that schizophrenics are hyperaroused largely on studies reflecting a pattern of elevated cardiovascular activity. A variety of cardiovascular variables have been used such as, for example, blood pressure, peripheral blood flow, peripheral vascular resistance, pulse rate, and heart rate (HR). In recent years investigators have tended to favor HR (tonic level and phasic response) as representative of cardiovascular activity. Two explanations for this tendency are that HR is more conveniently measurable than the other variables, and it has come to occupy a central position in models of attention-cardiovascular activity relationships (Lacey and Lacey, 1970; Obrist, 1975).

As one examines the research literature in this area over the last several years and since the publication of the Lang and Buss (1965) review, two trends become apparent. There has been a relative decline in the interest in cardiovascular variables. Moreover, cardiovascular studies, by contrast with skin conductance and smooth pursuit eye movement research, do not display the monothematic conceptual guidance and programmatic research development evident in these other areas. This complicates somewhat the organization of a review of the cardiovascular literature over the last several years, but work in the area falls into two general categories: (1) studies involving tonic HR level and (2) studies involving phasic HR response. These categories are based on empirical and scoring distinctions commonly made by investigators in the area. Subdivisions within each of the two categories can also be made. Thus, under tonic HR level, studies involving HR as an indicator of arousal and studies concerned with HR level in infants and young children genetically at risk for schizophrenia will be considered. Research involving phasic HR response will be subdivided into studies identifying HR change as an orienting response (OR) component and studies in which HR phasic response is considered a dependent variable in the study of impaired attention in schizophrenic patients. Before we proceed further, two methodological issues must be considered because they bear significantly on the interpretation of findings in cardiovascular studies.

Two recent studies by Spohn, Thetford, and Cancro (1971) and Spohn et al. (1977) and a series of similar studies reviewed by Tecc and Cole (1972) have indicated
beyond doubt that tonic HR level is elevated in schizophrenic patients treated with antipsychotic drugs. The evidence here is such that had Lang and Buss been aware of it in 1965, they would surely have qualified their interpretation of elevated cardiovascular activity in schizophrenia as reflecting chronic hyperarousal. There is, however, also strong evidence (Fenz and Velner 1970; Spohn, Thetford, and Cancro 1971; Zahn, Rosenthal, and Lawlor 1968) that HR tonic level in unmedicated schizophrenics is elevated relative to normal controls.

Spohn, Thetford, and Cancro (1971), Spohn et al. (1977), and Tecce and Cole (1972) find that HR variability appears to be unaffected by antipsychotic drugs. Reactivity (phasic HR response), however, is reduced by these drugs (Goldstein et al. 1966; Spohn et al. 1977). Clearly, evidence of this kind dictates an examination of the drug status of schizophrenic patients serving as subjects in cardiovascular studies.

In relation to the interpretation of reactivity findings, Law of Initial Value effect (Lacey 1956; Wilder 1950) must also be considered. There is ample evidence from studies of the HR phasic response in normals that phasic HR measures do show a Law of Initial Value effect. Initial level values are typically negatively correlated with change scores, and investigators in this area have commonly applied Lacey’s (1956) statistical solution to this problem.

**Tonic Levels of Heart Rate.** Gruzelier and Venables (1975a) sought to determine whether SCOR “responders” and “nonresponders” (for a definition of these terms, see p. 584) among schizophrenics differ in level of somatic arousal, since they hypothesized that responders and nonresponders might constitute two extreme physiologic groups. Among the measures used to index arousal were HR level and blood pressure. With respect to both of these cardiovascular variables and other non-HR variables, they found differences indicating a significantly greater level of arousal in the responder group. Since responders and nonresponders, were both receiving the same type and average daily dosage level of antipsychotic drugs, these differences could not be ascribed to drug influence. Their finding with respect to tonic HR did, however, require a qualified interpretation by virtue of the fact that HR in both groups was significantly greater than that in nonschizophrenic patient controls. Thus, while responders and nonresponders differ from each other in HR level, they could not be considered extreme physiologic groups in these terms. Moreover, the investigators, aware of the literature on drug effects, pointed out that their findings of greater tonic HR in both schizophrenic groups might reflect the influence of drug variance on tonic HR level.

Tarrier, Cooke, and Lader (1978a) sought to replicate the Gruzelier-Venables findings in both hospitalized schizophrenics and remitted patients living in the community. Their results were largely negative—i.e., they found neither consistent electrodermal differences between patient groups and normals nor a bimodal distribution of responding within the patient group. In only one respect—relevant here—did their findings parallel those of Gruzelier and Venables. Tonic HR levels were higher in all schizophrenic patients than in normal controls. With respect to drugs, they did not find significant HR level differences between medicated and nonmedicated patients.

In the first study of its kind, Schachter et al. (1975) examined information processing in the neonatal offspring of schizophrenic and normal parents by recording both tonic HR level and phasic response to auditory stimuli in the first 3 postnatal days. Their results were essentially negative. A significant interaction between diagnostic groups and level of maternal delivery medication for change in HR in the second but not third postnatal day was found. There were no significant main effects for diagnosis. Among the speculations offered by these investigators, to explain their negative results, is the postulation that schizophrenic disorder may not involve deviant processing of simple sensory information.

A report by Herman (1972) of data from the Mednick and Schul-singer (1968) longitudinal study of high-risk children of schizophrenic mothers speaks to this speculation. It also provides a basis for believing that tonic level HR deviance may be a component in a constellation of developmental psychophysiological characteristics that are etiologically significant. Herman found that tonic levels of HR were not significantly different in high- and low-risk groups during rest. However, differences in tonic HR level were found during a fairly stressful conditioning period, indicating that the HR of high-risk subjects is significantly higher than that of low-risk subjects.

These four studies of tonic HR level in adult schizophrenics and of children at high risk for schizophrenic disorder, taken together with earlier cited studies of the influence of drugs on HR level, would seem to imply the following. Relative to normals and independent of drug effects, HR levels are elevated in schizophrenics, and elevated HR levels are not a secondary conse-
quence of the disease process or institutionalization. These findings are not inconsistent with a functional interpretation that schizophrenics are hyperaroused. They may, however, also be interpreted with the Lacey’s (1970) hypothesis in mind. They have postulated that deceleration reflects cortical activation and openness to environmental input, while acceleration is defensive in nature and represents a “shutting out” of environmental stimuli. Accordingly, the above results, indicating elevated HR levels in schizophrenics, may be viewed as a chronic defense against environmental stimulation. It is of some interest to consider here Venables’ interpretation of SC fast recovery in high-risk children as reflecting susceptibility to “sensory flooding” (see p. 585). Elevated HR in high-risk children may represent the beginnings of an attentional defense against information overload.

**Phasic Heart Rate Response.** Studies to be reported under this heading are further subdivided into two classes: (1) studies in which the responses (accelerative-decelerative) to “neutral” stimuli (e.g., tones) were recorded and (2) studies in which responses to “meaningful” stimuli (e.g., imperative signal in a reaction time task) were examined.

In three studies “paradoxical” HR phasic response to neutral stimuli (OR) was found. Zahn, Rosenthal, and Lawlor (1968) reported HR acceleration to 72 dB tones in a sample of drug-free schizophrenics. Dykman et al. (1968) found HR acceleration to 60 dB tones in a group of schizophrenics whose drug status was not specified. Normals are generally found to manifest decelerative responses to such levels of tone loudness. Lobstein (1974), however, reported deceleration to loud tones of 100 dB—which in normals would have occasioned acceleration.

When investigators have subdivided schizophrenic samples along individual difference dimensions (e.g., SCOR responders and nonresponders), such homogeneity of phasic HR response as is indicated above has not been the rule. Thus, Gruzelier (1975) reported, in a study in which SCOR responders and nonresponders on equal doses and types of antipsychotic medication were exposed to 75 dB neutral tones, that responders manifested HR acceleration, while nonresponders showed brief and shallow deceleration followed by rapid return to basal level.

Houlihan (1975) classified acute schizophrenics by efficiency of performance on a word recognition task involving both neutral and emotional words. He reports that HR decelerators (in response to pretest neutral tones) were significantly superior to HR accelerators in accuracy of recognition of neutral and emotional stimulus words. Moreover, Houlihan found the HR accelerator-decelerator dichotomy to be unrelated to such traditional classification dimensions as premorbid social-sexual adjustment and paranoid symptoms, as well as mediation level and other cardiovascular and SC variables.

Patterson (1977), amassing pupillometric data for 73 schizophrenic patients from several hospitals and subdividing them into three levels of latency of pupillary constriction, reports a general tendency toward a positive correlation of rate of HR deceleration in response to neutral tones and pupillary latency. The fact that this relationship is more striking in some of the hospitals than others is attributed by Patterson to differences in level of maintenance doses of phenothiazines.

Three studies in which phasic HR response to signal stimuli was the dependent variable are relevant here. In contrast to Houlihan (1975), McCormick and Broekema (1978), in a study of size estimation and cardiac rate response in paranoid and nonparanoid schizophrenics, found a dissociation at the behavioral/diagnostic level that was not reflected at the psychophysiological level. All the schizophrenic patients in their study manifested larger magnitudes of HR decelerative response than normal controls. In paranoid subjects, however, HR deceleration was associated with underestimation in the size estimation task, while in nonparanoids HR deceleration paralleled overestimation. These investigators interpret the results as implying that phasic HR response in schizophrenics functions as a moderator variable—i.e., as facilitating differing behavioral response dispositions. Such an interpretation is not inconsistent with the size estimation-HR phasic response findings of Warner (1973) who reported deceleration associated with underestimation in good premorbid paranoid patients and with veridical size estimation in alcoholic patient controls. In poor premorbid nonparanoids in that study, however, overestimation was associated with HR acceleration.

Only one phasic HR study of schizophrenic patients in the recent past was explicitly guided by the Lacey’s (1970) “bradycardia of attention” hypothesis. Using a modified version of the Lacey’s reaction time paradigm, Waddington et al. (1978) found characteristic HR deceleration in normal controls immediately before an aversive stimulus in a signaled escape paradigm. In a small sample of medicated schizophrenic patients, however, both HR deceler-
ation and acceleration responses to the aversive stimulus were absent. Despite similar findings in a three-person group of unmedicated schizophrenics, neuroleptic medication cannot be ruled out as an explanation of the schizophrenic-normal differences. Nevertheless, the investigators believe that the abnormal HR response observed in schizophrenics could represent a deficit central to the disease process. They implicate impairment in a process postulated by the Lacey's (1970) in which cardiac function modulates aspects of cognitive function by a negative feedback loop from the brain stem to the peripheral cardiovascular system and back to the brain stem via baroreceptor afferent input.

Clinical Implications and Directions for Research. As noted above, the empirical picture with respect to tonic level HR seems to be fairly clear. A number of diverse studies involving both high-risk offspring of schizophrenic parents and adult schizophrenics converge on similar findings, namely, elevated tonic HR relative to normal controls. Two relevant functional interpretations of such findings—chronic hyper-arousal or attentional defense—have been proposed by investigators in this area. In all the studies discussed above, distributions of tonic HR in schizophrenics and normals were found to overlap. This fact, taken together with the demonstrated drug sensitivity of tonic HR, suggests that tonic HR has very limited (if any) diagnostic value. Moreover, in none of the above studies was there an explicit attempt to assess the prognostic usefulness of tonic HR or its relation to severity of illness.

With respect to phasic HR responses, the empirical picture is much less clear. Findings reported by investigators in this area diverge considerably and militate against a consistent and coherent interpretation across studies. It seems highly probable that divergence of findings is related to a number of methodological and sampling differences. Thus, sensitivity of phasic HR response to neuroleptic medication and to initial value effects were either not at all controlled or inadequately controlled in several studies. Studies differed considerably in characteristics of schizophrenic patients and procedural detail. Moreover, there were no systematic efforts to replicate results. Clearly, this state of affairs renders phasic HR response in schizophrenia a less than reliable diagnostic or prognostic dimension.

If one sets aside methodological, sampling, and procedural issues and accepts phasic HR response findings at face value, the following picture emerges. It seems evident from studies treating phasic HR response as an OR component that schizophrenics differ from normals in characteristic phasic response to neutral stimuli. With respect to direction of response (accelerative-decelerative), research in this area is less than consistent. It is also evident that there is considerable heterogeneity in direction of phasic HR response in schizophrenics. In those studies discussed above in which schizophrenic samples were subclassified along behavioral or psychophysiological individual difference dimensions, phasic HR response was consistently found to be correlated with the dimension in question. Since the individual difference dimensions differed from study to study, however, no clear picture as to phasic HR correlates or subgroup characteristics emerges.

Only three studies in recent years have used "signal" stimuli to examine phasic HR response in functional terms. The report of Waddington et al. that the Lacey's (1970) "bradycardia of attention" is attenuated in chronic schizophrenics is of interest, not only for its substantive findings but also because it uses the Lacey's' hypothesis as a conceptual tool and their reaction time paradigm as a methodological tool. Indeed, the results of this study would be said to be of lesser importance (because of the uncertainty about the role of drugs in producing them) than the conceptual and empirical context in which they were obtained. The size-estimation studies by McCormick and Broekema (1978) and Warner (1973) are of interest because they suggest a decoupling of behaviorally indexed attentional response and phasic HR response, and thus perhaps the behavioral boundaries within which phasic HR response variation reflects attentional "attitudes" toward environmental input. Here too, however, drug influence was not well controlled since McCormick Broekema's schizophrenics had been drug free for only 2 weeks—too short a period to constitute a "wash-out" of medication in all schizophrenic subjects.

As regards future research directions, a number of studies discussed above, especially the studies of Waddington et al., McCormick and Broekema, and Warner, should be replicated under conditions in which drug variance and initial value effects are controlled. Indeed, without such controls, the results of future research in this area will be suspect. This field would also benefit greatly from standardization of procedure and careful selection and classification of schizophrenic subjects. Finally, it is somewhat surprising that the Lacey's' bradycardia of at-
attention hypothesis, supported by a substantial data base in normal subjects and implicating a heuristic model of neurophysiological-cardiovascular interaction, has not been used more frequently as a conceptual tool in the study of attentional impairment in schizophrenics. Investigators who undertake such work in the future would be well advised to study the recent article by the Lacey's (1978) in which results of earlier and ongoing research dealing with time within the cardiac cycle as an experimental variable are summarized.

Smooth Pursuit Eye Movements

In a series of pioneering studies Holzman, Proctor, and Hughes (1973) and Holzman et al. (1974) have demonstrated the existence of smooth pursuit eye movement (SPEM) anomalies (or eye tracking deviance, ETG) in a substantial proportion of schizophrenics. ETG was first observed in the administration of a common clinical test which uses a pendulum to study lateral eye movements. While most normal subjects can track the sinusoidal motion of the pendulum within a narrow critical range, schizophrenics and other psychotic patients deviated significantly from normal tracking. Holzman, Proctor, and Hughes (1973) developed a quantitative score—"velocity arrests"—which characterizes the degree of deviation from normal tracking. Holzman and Levy (1977, pp. 25-26) have interpreted ETG as a nonvoluntary attentional disorder "which has a neurophysiological substrate...in hitherto unspecified neural noise."

ETG in schizophrenia has gained the interest of investigators concerned with attentional disorder in schizophrenia for two reasons. It is a novel form of abnormal attention, apparently not reflective of the well-known dysfunction of voluntary attention. Moreover, the demonstration that ETG is also found in 45 percent of the first degree relatives of schizophrenic patients and in only 10 percent of the relatives of non-schizophrenic patients (Holzman et al. 1974) has led to the provocative hypothesis that ETG may represent a genetic marker, useful in the study of the transmission of a vulnerability to schizophrenia. The work of Holzman and his group (Holzman 1975; Holzman, Proctor, and Hughes, 1973; Holzman, Proctor, and Levy, 1976; Holzman et al. 1974) has stimulated the development of a small cottage industry of investigations focused on these issues: the role of voluntary attention in ETG, the genetic marker hypothesis, diagnostic specificity of ETG, the role of neuroleptic medication and measurement, and scoring methodology. A review of recent work in these five areas will serve to reflect the state of current knowledge about both the nature and mediation of the ETG phenomenon.

Voluntary Attention. Holzman, Proctor, and Hughes (1973) early ruled out the influence of voluntary attentional dysfunction and of motivational factors on the ETG phenomenon. Schizophrenic and other psychotic patients appeared to be attentively oriented to the SPEM test and showed no change in quality of eye tracking after a realerting signal 30 seconds after initiation of eye tracking. The identification of ETG as a disorder of involuntary attention was challenged by Breznovva and Kendell (1977), who found that conditions designed to distract attention produced abnormal tracking movements in normal subjects quite similar to those observed in schizophrenics. Breznovva and Kendell (1977) reasoned, perhaps suspiciously, that their findings in normals implied that ETG in schizophrenics must be a result of impaired voluntary attention. Fass et al. (1978) addressed this issue directly by visually and audibly distracting poor eye tracking schizophrenics and normally tracking nonpsychotics. Since distraction did not modify eye tracking quality in either group, these investigators conclude "that inattention alone does not account for schizophrenics' tracking impairment" (p. 587).

A more serious challenge to the position of Holzman and associates in this regard, however, comes from a study by Shagass, Amadeo, and Overton (1974), who found that when psychotic subjects were required to read numbers placed on the visual target (a pendulum), their eye tracking performance improved substantially over a preceding baseline condition, i.e., a reduction in velocity arrests was achieved. When what Shagass, Amadeo, and Overton designated as an attentional aid was removed, psychotic subjects reverted to their poor eye tracking level.

Holzman, Levy, and Proctor (1976), who replicated the results obtained by Shagass, Amadeo, and Overton, also found that the quality of eye tracking in schizophrenics under number reading conditions was still significantly poorer than that of nonpsychotic and normal controls. They argued that while ETG may be temporarily mitigated by an aid to the kind of "cognitive centering" required for SPEM, the underlying impairment in involuntary attention is clearly still evident. To date, there have been no further efforts to challenge this position.

Genetic Marker Hypothesis. The finding by Holzman et al. (1974) of
greater incidence of ETD in first degree relatives of schizophrenics than in the relatives of nonschizophrenic patients and normals has been replicated by Kuechenmeister et al. (1977), which thus strengthens the case for the genetic marker hypothesis. Moreover, Holzman et al. (1977) addressed this issue directly in a study of a sample of Norwegian monozygotic and dizygotic twins discordant for schizophrenia. The finding in this study that ETD is significantly concordant within monozygotic twin pairs, and less so within dizygotic twin pairs, in the view of Holzman et al., justified a genetic interpretation of these results but did not rule out toxic, viral, and environmental causes. Holzman et al. are also cautious in interpreting these results genetically because the twin sample was older than the patient sample in their earlier studies (Holzman et al. 1974; Holzman, Proctor, and Hughes 1973). Age is known to be negatively related to eye tracking efficiency. Accordingly, Holzman et al. (personal communication) have sought to replicate these findings in a younger Norwegian twin sample. The results of this replication are not yet available but, if positive, would further strengthen the genetic marker hypothesis.

Diagnostic Specificity. The question of specificity—whether SPEM disorders are found only in schizophrenics—has an obvious bearing on the genetic marker hypothesis and, of course, on the psychopathological significance of ETD. Shagass, Amadeo, and Overton (1974), who replicated the Holzman group’s findings with schizophrenics, also found deviant eye tracking in nonpsychotic patients; ETD was greater than that in nonpsychotics and normal controls. Holzman and Levy (1977) report similar findings. These findings would seem to suggest that ETD is not specific to schizophrenia but, rather, a phenomenon associated with functional psychosis in general. In their 1974 study, however, Holzman et al. applied diagnostic criteria (psychological test evidence of thought disorder) more stringent than those determining hospital diagnosis to their “schizophrenic” samples. They found that patients diagnosed by psychological test evidence manifested significantly greater ETD than psychotic patients excluded by these diagnostic criteria. Holzman and Levy (1977) call for a replication of this procedure as a means of achieving better understanding of the specificity issue. They grant, however, that in light of evidence to date, ETD cannot be used as a specific diagnostic sign of schizophrenia.

Neuroleptic Medication. The majority of the psychotic patients in the studies of Holzman, Proctor, and Hughes (1973), Holzman et al. (1974), and Shagass, Amadeo, and Overton (1974) were receiving neuroleptic medication—generally phenothiazines. Thus, the question was raised as to whether ETD might be a drug-induced phenomenon. Holzman, Shagass, and their associates have adduced indirect evidence (including the fact that drug-free relatives showed ETD) to indicate that neuroleptic medication is not responsible for ETD. Moreover, Holzman et al. (1975) tested normal volunteers before and after ingestion of single doses of diazepam, chlorpromazine, and secobarbital and found that only secobarbital affected SPEM performance. Thus, there is no evidence to date that suggests neuroleptic drug influence. That possibility, however, cannot be ruled out except in a placebo-controlled study. Such a study remains to be done.

Measurement and Scoring Methodology. In the laboratories of Holzman, Shagass, and Kuechenmeister, SPEM has been recorded by means of electrooculography (EOG) and has been indexed by the velocity arrest scoring procedure. Recording of eye movements by EOG (with electrodes placed at the outer canthus of each eye) has been criticized on the grounds that EOG recording might be sensitive to muscle contraction, EEG, and other extraneous signals. A study by Lindsey et al. (1978) addressed this issue by comparing EOG recording of eye tracking with a reflected infrared light recording method (IR) free of muscle movement and EEG artifacts. These investigators found that EOG and IR recording of SPEM in the same subjects yielded substantially similar qualitative results, but velocity arrest scores based on EOG recording were only moderately correlated with velocity arrest scores in IR and with qualitative ratings. Accordingly, Lindsey et al. have devised a scoring procedure that expresses the goodness of fit of the recorded waveform with the ideal sinusoidal wave form characterizing the perfectly smooth pursuit eye movement, as a signal to noise ratio. EOG and IR records scored by means of IS/N turn out to be highly correlated, which suggests that ETD is reliably recorded by both procedures. Mention must also be made here of a very recent parametric study of both smooth pursuit and saccadic eye tracking in normal monozygotic twins by Iacano and Lykken (1979). These authors addressed a somewhat broader range of measurement issues than those dealt with by Lindsey et al. and devised a computerized scoring system for EOG.
records not so different from that referred to above. Investigators planning eye-tracking research in psychiatric populations would be well advised to study both the Lindsey et al. study and that of Iacano and Lykken for current state-of-the-art information.

Clinical Implications and Directions for Future Research. Although ETD in schizophrenics is a theoretically interesting phenomenon, its clinical and etiological significance remains in doubt. In light of present knowledge, the use of ETD in differential diagnosis is likely to be misleading. If currently ongoing research indicates unequivocally that ETD reflects a genetically determined vulnerability to functional psychosis, however, the presence of ETD in nonpsychotic individuals may well become a basis for prevention and genetic counseling.

The empirical work of Holzman and his associates has stimulated considerable interest among other investigators, who are now pursuing a variety of issues raised by the Holzman group's initial studies. Thus, the attainment of greater clarity about the nature and mediation of the phenomenon in the near future seems likely. One area that merits further study is the relationship of ETD to other forms of attentional dysfunction (e.g., SCOR) and to cognitive dysfunction (e.g., thought disorder) for which schizophrenic specificity has been more firmly established.

Vestibular Responses. Studies of vestibular response disorder in schizophrenia conclude our review of SPEM deviance for two reasons. In a recent study of eye and head movement during SPEM in trained monkeys, Lanman, Bizzi, and Allum (1978) interpret their findings by postulating an internal smooth pursuit command which, in the case of eye movement, is combined with vestibular feedback from head movement before being forwarded to eye movement centers. It is of some interest to note that in all of the eye tracking studies reviewed above, subject head movement during tracking was interdicted either by instruction or physical restraint. Also, vestibular response dysfunction is relevant at the present juncture because ETD was first identified by Holzman, Proctor, and Hughes (1973) in the course of studies aimed at determining vestibular and proprioceptive deficit in schizophrenics.

It is a longstanding hypothesis, and one which has received ample empirical attention, that vestibular response (or nystagmus response) is diminished in schizophrenics. Indeed, biological and psychological models of schizophrenic processes have been predicated on the assumption of vestibular deficit. Levy, Holzman, and Proctor (1978) undertook a comprehensive and well-controlled test of this hypothesis in a large sample of psychiatric patients, relatives, and normal controls. Their findings did not support a diminished response hypothesis. They did find, however, that chronic, deteriorated schizophrenics and recent schizophrenics manifested more dysrhythmic responses (i.e., diminished orderliness of nystagmus response in a temporal interval of 60 seconds). As in most past studies, Levy, Holzman, and Proctor found no evidence compatible with peripheral vestibular disease. They speculated that the dysrhythmic response in adult schizophrenics may reflect disturbances in alertness.

This interpretation is also placed on results obtained by Fish and Dixon (1978) who did find, in the offspring of schizophrenic mothers, "transiently decreased vestibular responses [incident] with severe developmental disorders that were related to psychopathology at 10 years" (p. 963).

Clinical Implications and Directions for Future Research. By virtue of its comprehensiveness and its use of relevant methodological and subject controls, Levy, Holzman, and Proctor's attempt to test the vestibular response hypothesis could be regarded as definitive. It should be noted, however, that by subdividing 158 subjects into seven diagnostic groups, the investigators traded power in statistical analysis for comprehensiveness; the study had very limited power to detect small vestibular differences among the diagnostic groups. This consideration, however, does not qualify the conclusion that vestibular response dysfunction cannot be regarded as pathognomonic of schizophrenia. Both the studies of Levy, Holzman, and Proctor and Fish and Dixon may be interpreted as suggesting that disturbed vestibular response in schizophrenics is an epiphenomenon of disorder at the level of involuntary attention.

It may be of some interest in future research to examine SPEM in psychotic patients under conditions of free head movement. Given the role of vestibular feedback in controlling SPEM centrally, as suggested by Lanman et al., it is not inconceivable that ETD may be enhanced or diminished under circumstances when SPEM is more complexly mediated than under head movement restraint.

Electroencephalogram
The brain electroencephalogram (EEG) has been recorded in schizo-
phrenic patients since the 1930s, and a short history with a summary of the findings from early studies is provided by Ilil (1977). Basic background is given by Fink (1973) and, with respect to attention, by Haider (1970). However, the excellent and clearly written review by Ilil (1977) contains an orientation, some information on methodology, and a consensus of recent findings.

By and large, a visual inspection of the EEG record does not produce much data that could be used to differentiate schizophrenics and normals. However, when data are subjected to power spectral analysis by the use of such techniques as Fast Fourier Transform, changes can be seen within specific band widths that may well differentiate psychotic from normal states. It is important to realize that only very sophisticated computer-based data analysis can be helpful here, with data produced from as many placements of the international 10/20 electrode placement system as possible.

Moreover, careful recording of eye movements, muscle tension, and adequate reference electrodes (usually linked earlobes) are also necessary. These artifacts in the EEG record must be "filtered off" for both normal and patient subjects. There is controversy concerning EEG abnormalities in psychosis, and these will be dealt with below. It should be noted, however, that much of this controversy has to do with whether certain findings are artifactual or not. If such EEG differences do exist, then it should be remembered that evoked potential data are elicited on top of potentially "abnormal" background activity. The reader is again referred to the recent review by Ilil (1977).

Findings Relative to Schizophrenia.

Typical early EEG findings in schizophrenia are that there is a "nonspecific diffuse" record (see Ellingson 1954; Greenblatt 1944; Hill 1956; and the review by Ilil 1977). Lemere (1938) suggests that "weak alpha" is evident in schizophrenics, as well as high beta (Berger 1937). It would be fairly true to say that great heterogeneity is evident in groups of schizophrenic subjects with respect to EEG findings. Thus Ilil, Saletu, and Davis (1972) reported that both normals and schizophrenics (100 matched subjects in each category) showed 2 percent focal changes, with the absence of EEG abnormalities in 13 percent of schizophrenics and 12 percent of controls. These data strongly suggest that we do not know enough about normal data and the distribution of EEG peculiarities in the general population. However, it is more common these days to assume that schizophrenia has "continuous" distribution in the population at large. These findings, therefore, speak positively to the subject of "schizophrenia proneness." The same study also showed that 31 percent of schizophrenics and 11 percent of controls had general dysrhythmia, that 11 percent of schizophrenics and 7 percent of controls had spikes, and that 41 percent of schizophrenics and 28 percent of controls had atypical sharp waves. In 1954, Ellingson reviewed studies that indicated similar results; yet in the 20 years separating the studies many clinicians have not taken cognizance of the fact that EEG changes could well characterize some schizophrenics.

EEG has been extensively studied during sleep, and a study by Gibbs and Gibbs (1963) pointed to 80 to 100 ms "B mitten" activity in a number of subgroups of schizophrenics. Ilil (1964) suggested that reduced alpha characterized schizophrenics relative to depressives.

Because almost all brain wave activity is recorded from surface electrodes, a study by Heath (1966) should be noted for its recording of activity "deep" in the brain. Heath noted spikes from the septal area in schizophrenics when they were agitated, but not when they were calm. However, without normative data, it is difficult to interpret these findings.

With respect to drugs, Ilil (1964) suggests that very stable "hyper-normal" EEG records indicate resistance to neuroleptic treatment. Ilil (1973) suggests that subjects resistant to psychotropic drugs exhibit more slow waves and less fast activity. EEG could thus play a part in chemotherapeutic prescription.

Using power spectral analysis in a study in which medication was carefully controlled, Rodin, Grissel, and Gottlieb (1968) found less alpha and lower EEG amplitudes in schizophrenics. Perhaps one of the clearest studies that has been done so far is that of Ilil, Saletu, and Davis (1972). In this study, power spectral data show very clear differences between normals and schizophrenics. (Diagrams from this study were reprinted in Ilil, 1977.) These differences are in the direction of a significant increase in early delta (3 to 4 Hz), a significant reduction in late alpha (10 to 13 Hz), and a significant increase in fast beta (24 to 33 Hz). One of the fascinating things about these findings is that almost exactly the same power spectral shape can be seen in normal adults using LSD-25 and also in some prepsychotic high-risk children (see Ilil 1977).

As these findings of Ilil, Saletu, and Davis (1972) appear to represent a carefully controlled data source, the data are close to being a statement that reflects an integration of data from other studies also. Therefore, it is necessary to see
whether there is evidence that does not agree with the delta, alpha, and beta findings noted above.

Lifshitz (1978) and Lifshitz, Susswein, and Lee (1979) suggest that high beta activity is seen more strongly in acute than chronic schizophrenics, but they also suggest that it is mostly due to muscle tension (i.e., of electromyographic origin). This crucial question has been addressed by Itil, Saletu, and Davis (1972). They recorded EEG from schizophrenics and normals during rapid eye movement (REM) sleep, when muscle tension is generally believed to be drastically reduced. Their results indicate that fast beta activity remained in schizophrenics and that it is therefore not due to muscle tension potentials (see, also, Itil 1977, p. 72). A second line of evidence of the authenticity of fast beta findings comes from a large number of drug studies in which medication has been shown to increase extrapyramidal effects and muscle tension (Itil et al. 1970, 1971). Here the fast beta actually decreased, i.e., became more normal: this runs counter to a muscle tension explanation.

It has also been argued that reduction of late alpha could be caused by the same muscle tension. Itil (1977, p. 73) presents the argument that subjects with normal EEG alpha recordings do not reduce their alpha when fast muscle potential artifacts are introduced. Thus, it does not appear likely that the reduction in alpha noted above in schizophrenic subjects could be due to muscle artifacts. If it is postulated that increases in muscle tension are not likely to be found in the premorbid state (i.e., that these increases could be a response to the distress of the disease and manifested as the disease develops), then high-risk studies are also pertinent here. Itil (1977, p. 73) goes so far as to say that the fast beta activity may be the electrophysiological marker for a genetic predisposition to schizophrenia (see Dumermuth 1971; Itil, Simeon, and Coffin 1976). Longitudinal studies (e.g., the one being conducted in Mauritius) will obviously contribute positively or negatively to this speculation.

The question of delta wave increase is at once easier to evaluate and also more difficult. The difficulty arises especially with regard to the use of delta waves as an index of arousal (see Lifshitz, Susswein, and Lee 1979). Arousal is not a concept that is easily understood, and it cannot be adequately discussed here. Nevertheless, arousal must be mentioned, especially with regard to phenothiazine effects. In studies of psychotic children (Itil, Simeon, and Coffin 1976), an increase in 3- to 5-Hz activity has been found. It can therefore be hypothesized that this would be a likely finding in unmedicated schizophrenics (see Bente and Itil 1954). The effect of phenothiazines is mostly to reduce the abnormally high delta and also to reduce the high beta (Itil et al. 1974a, 1974b). These effects are most clearly seen by power spectral analysis. From data reported by Itil (1977, p. 73) and Itil et al. (1975), it would appear that high-risk children also show abnormally high (1.3 to 3.5 Hz) low voltage delta waves.

Lifshitz, Susswein, and Lee (1979) have used amount of power in the 2- to 3.8-Hz region to index “arousal” when recording the auditory evoked potential, and they quote Stevens, Lonsburg, and Goel (1972) as justification for this procedure. Lifshitz and his group have also found an increase in 1- to 3-Hz delta waves, especially in chronic schizophrenics. Thus, high power in the delta band appears to constitute “overarousal,” and this interpretation fits well with a number of theories of schizophrenia (e.g., Broen 1968). If antipsychotic medication reduces delta, it presumably reduces arousal; but, as stated above, it also increases muscle tension, which could be thought to increase “arousal.” What seems obvious is that the difficulty comes not from the data but from trying to fit the data to the notion of “arousal.” Perhaps it would be best to look at the data without too many preconceptions— and to set the concept of “arousal” aside.

Lifshitz (1978) reports some fascinating data, all the more so in that it uses a novel triangulated placement of three electrodes and therefore reveals “electrical field vectors.” This is an ingenious combination of EEG and evoked potential methodology, and the conclusions Lifshitz has drawn from its use are that increases in arousal in normals are not at all similar to the increased arousal states that are believed to characterize psychotics. It is therefore evident that arousal does not mean the same thing in each type of subject and its usefulness as an explanatory concept is probably limited. The evoked “electrical field vector” seems to be a promising technique for future EEG research, as an addition to the existing methodology of power spectral analysis.

Clinical Implications and Future Research. The idea of abnormal electrocortical activity is not new to schizophrenia research, but the field may now have reached the stage where this notion can be integrated with theory and experimentation from other areas. Gruzelier and Venables (1975b) and Venables and Wing (1962) have obtained data to suggest links between two-flash
fusion threshold (held to reflect cortical activation) and skin conductance phenomena. Claridge (1978), who has explored skin conductance (or potential) and two-flash threshold relationships to a greater extent, has reported that hallucinogenic (LSD-25) states resemble those of schizophrenia in two-flash threshold. Using power spectral analysis, Itil (1977) has shown that LSD-25 produces the same abnormal EEG patterns characteristic of schizophrenia. It would therefore appear that the link between EEG abnormalities and the abnormal two-flash threshold has been made.

The EEG abnormalities described above were found in subjects comparable to those discussed by Shagass (1976) in a review of evoked potential research. It could well be possible that the same mechanism postulated by Shagass (alteration to hypothetical brain stem filtering capacity) could be involved. This speculation is supported by the anticholinergic hallucinogen research of Itil (1966, 1969), in which exactly the same increase in delta and beta and decrease in alpha activity were noted. Warburton (1972, 1975) has noted the involvement of acetylcholine in attention, and Venables and Patterson (1978) have produced tentative data to suggest that alterations in schizophrenic and normal attention can be indexed by pupillometric variables under cholinergic control. Added evidence for a possible connection between these hitherto separate areas comes from the work of Patterson and Venables (in preparation a). They found that alteration to dopamine (and possibly to dopamine/acetylcholine balance in the CNS) produced SCOR records in normals that closely resembled those of prepsychotic children who later developed schizophrenia. These data recall Shagass’ (1976) hypothesis of a defect in brain stem filtering capacity. All the dopamine pathways originate in the substantia nigra, where important dopamine/acetylcholine balance is seen in the caudate and the basal ganglia of the forebrain as well as the limbic brain. Thus, the defective brain stem filter of Shagass could reflect an alteration in the brain stem neurotransmitter activity of dopamine and acetylcholine. This would also account for the EEG and the two-flash threshold data reported by Claridge and the attentional data of Warburton and of Venables and Patterson. This alteration of brain dopamine/acetylcholine is also hypothesized to underlie the abnormal EEG findings reviewed by Itil (1977).

Future research in this area promises to be both productive and exciting, as many pieces of a complex puzzle seem to be already at hand. For the moment, it would appear that EEG could well be a diagnostic tool and a “monitor” of the therapeutic efficacy of various treatments, chemical or otherwise. EEG techniques might be still more powerful, if used in conjunction with averaged evoked potentials. Perhaps the best possible approach is offered by the standardized neurometric test battery of John et al. (1977); through its use, investigators could develop a “schizophrenic data base” out of which would come “subgroups” of schizophrenia that show functional brain wave similarity. The next step would be to find experimentally the most efficacious treatment for each of these subgroups.

The use of “telemetered” EEG—a procedure whereby the subject need not be restricted to a laboratory setting but can interact in a more normal way with the environment—is both methodologically difficult and expensive. However, it is a technique that has produced interesting results, suggestive of temporal lobe defects, in the hands of Stevens and her coworkers (Stevens 1976; Stevens et al. 1979). A temporal lobe hypothesis of schizophrenia has been advocated for a number of years by Flor-Henry, who in 1976 presented data suggesting an 85 percent discriminability of schizophrenics from other groups using power spectral analysis EEG. (This work is also summarized in Flor-Henry 1978.) Further arguments indicating left hemisphere or temporal lobe involvement in schizophrenia are given by Gur (1977, 1978), Roemer et al. (1978), and Taylor (1975). Hemispheric asymmetry and neuroleptic compounds are the subject of a review by Myslobodsky (1976), and the question of EEG changes during task performance is addressed by Gevins et al. (1979). The latter article strongly suggests that some of the “laterality” arguments put forward over the past few years could well be based on artificial data.

It is possible that a specific EEG “fingerprint” is produced by each different neuroleptic compound, and this question is taken up by Herrmann et al. (1979). EEG effects of the new neuroleptic clozapine are reported by Spatz et al. (1978) and Roubicke and Major (1977). EEG effects of major tranquilizers are the subject of a report by Milstein et al. (1977). There has been a suggestion in schizophrenia research circles for some time that the subpopulation giving rise to the greatest incidence of schizophrenia is also that in which “creativity” is high. This question received some demographic support from the long-term studies in Denmark, but it has recently been the subject of a laboratory investigation by Whitton, Moldofsky, and Lue (1978). Among the other topics...
recent EEG investigators have addressed are the following: subclassification in schizophrenia (Giannitrapani and Kayton 1974), prediction of outcome (Itil et al. 1975), and differences between patients in the hospital and in the community (Tarrier, Cooke, and Lader 1978).

**Evoked Potentials**

The evoked potential is a "special case" of EEG analysis. Any sensory event—auditory, somatosensory, visual—has an effect on the brain EEG, and this can be observed by collecting only that part of the EEG record exactly time locked to the occurrence and duration of the stimulus event. When a light flash is used to obtain a visual evoked potential, the light flash may last 100 ms, but the EEG is collected for perhaps 1,000 ms beginning at the time of stimulus onset and continuing for a considerable period after to enable observation of "information processing" components of the stimulus and its significance to the subject. Because the effects of a single stimulus are very hard to discern against the continuously changing background of the EEG, an "averaging" process is usually necessary. In the averaging technique, the time epochs of EEG collection for many stimuli of the same type are all laid on top of each other, so that the background EEG noise tends toward a straight line at basal level and the component wave forms of the evoked potential get bigger and bigger. In the past, this averaging process was the only way to obtain a visually inspectable evoked potential (EP) record. With modern high-gain, low-noise amplifiers plus digital filtering and computer-based methods, it is often possible to look at EPs from single trials. This methodology promises some exciting research for the future, but little has been made of it so far in schizophrenia research.

A demonstration of the power of single trial EPs can be seen in a film on general release from the laboratory of E. Roy John at New York University; the film shows the differences between imperative and nonimperative stimuli in a discrimination task, trial by trial, with cats. There are, however, technical problems of considerable difficulty involved in the application of single trial EP methods to intact human subjects. John's cat data was obtained using electrodes passed through the skull and placed on the cortical surface. This procedure was necessary in order to obtain an adequate signal-to-noise ratio. EPs obtained from the surface of the scalp have much more noise, and hence the value of single (nonaveraged) EPs is reduced. With schizophrenics, it is possible that greater variability may be evident between EP trials and thus the problem of noise is even more acute (see Coppola, Tabor, and Buchsbaum 1978). The interested reader is referred to books by Callaway, Tueting, and Koslow (1978) and Begleiter (1979) as well as the research of Buchsbaum (1974, 1975, 1976), Buchsbaum, Coppola, and Bittker (1974), Buchsbaum and Henkin (1975), and Schoeller, Buchsbaum, and Carpenter (1976).

More for the sake of convenience than for any powerful theoretical reason, this survey of recent developments in EP research is organized around early, middle, and late EP components. This is not to state that such divisions actually exist in reality, but rather to suggest that it is currently thought that different information about brain function can be gleaned from each of these categories. In practice, the boundaries between early, middle, and late EP components are at best arbitrary. The interested reader is fortunate that three excellent reviews have recently appeared—early EPs (Shagass 1977), middle EPs (Buchsbaum 1977), and late EPs (Roth 1977). In addition, Shagass (1976) has reviewed his own work in relation to EP components and schizophrenic etiology and updated this review in recent communication (Shagass 1978) with highly detailed reference to subclassifications in psychoses. Venables (1977) has also briefly reviewed literature in this area.

Abbreviations that will appear in this section are as follows: auditory evoked potential (AEP), visual evoked potential (VEP), somatosensory evoked potential (SEP). Unless otherwise stated, all data referred to will be from "averaged" and not single trial EPs. Recording sites of EP work vary quite a lot, and as much information as possible will be given (if authors have actually stated the sites). In the main, however, the vertex site gives the clearest results (not in all cases), and most authors use the international 10/20 system for other electrode placements, mostly referenced to linked earlobes and usually with eye movements (EOG) also recorded and "subtracted" from the background EEG record. For more detailed recording methodology, the reader is referred to the reviews cited above.

**Early Evoked Potentials.** As a totally arbitrary rule of thumb, EP events that occur within about 50 ms of stimulation are usually referred to as early components. There are a number of "fast" peaks, and the frequency response of recording equipment must be high enough to allow these to be seen. If later "slower" moving peaks are the main focus of concern, however, the high frequen-
cies are frequently attenuated in the interest of having less noise in the recordings; thus, to some extent, experimenters have had to choose which components of the EP they wished to look at beforehand and set their amplifiers and filters accordingly (see Shagass 1977). Difficulties are compounded by artifacts such as muscle tension, eye movements, surface skin potential shifts, and sex differences. In addition, EP data may show records where within and between subject variation occurs, not only in amplitude of peaks but in their latency also. Comparisons between subjects and conditions involve complex mathematical manipulations in this case (see Shagass, Overton, and Straumanis 1972). The data obtained from such experiments are considered important, however, because the very early components of the EP are believed to represent “stimulus registration” at the cortical level. As such, the data speak directly to the question of brain stem reticular intactness and functional correctness in schizophrenia. These early EP components, often referred to as “far field” potentials, and their origins through the brain stem and via thalamic relay to the cortex are better known than those of later components. A number of previous experiments have suggested reticular dysfunction in schizophrenia, but usually on the basis of extrapolation from behavioral observation (see McGhie, Chapman, and Lawson 1964) or psychological experimentation (Buss and Lang 1965; Lang and Buss 1965). When that research was done, the brain stem reticular formation was a highly popular structure to which to attribute inexplicable findings (as the limbic brain became a few years later). In addition, SEP data are usually attained by direct electrical stimulation of the median or ulnar nerves and, as such, might reflect stimulus input processes that precede stimulus “significance” or attentional factors. Shagass (1977) discusses the methodology and differing wave forms found in the SEP, AEP, and VEP. It is important to recognize that the shape of the wave changes, depending upon modality, because the different peaks correspond to different brain processing structures for each type of material. Shagass’ conclusion with regard to single (i.e., unpaired) stimuli is that chronic schizophrenics show elevated early SEP components with less variability than normal subjects or acute patients. These findings could indicate impaired reticular filtering, which results in abnormal amounts of information reaching higher brain centers (see Shagass, Overton, and Straumanis 1974). In his 1976 communication, Shagass suggests that attenuated later components (a fairly usual finding) could represent an active inhibitory mechanism attempting to overcome the inadequate brain stem filtering that is reflected in enlarged early EP components. Ikuta (1974) has produced data that corroborate elevated early SEP amplitude in schizophrenics, relative to normal. Data obtained using paired stimuli in the SEP, where the object of interest is the rapidity of recovery to the second stimulus, show a complex but potentially interesting picture. The amplitude recovery is usually attenuated relative to normal (e.g., Shagass 1968), although recovery latency may well be augmented (see Shagass, Overton, and Straumanis 1974). These results interacted to some extent with stimulus intensity and patient subgroup and were best observed in chronic schizophrenics. Drug effects have complex interactions with evoked potential phenomena (see Saletu et al. 1971a, 1971b), and the N20-P30 component in the SEP seems particularly vulnerable to the influence of drugs. Despite the high variance of the effects seen in different patients and with different histories of antipsychotic medication, it would appear that patients who show SEP changes also show clinical improvement with medication.

With auditory EP studies by Saletu, Itl, and Saletu (1971) there is evidence of short latency P50 components in both chronic schizophrenics and those with active thought disorder. Itl et al. (1974a) have looked at preschizophrenic children at high risk for the disorder. Although their data are not especially strong in terms of high statistical probability of abnormal peaks, there was strong visual resemblance between latency components observed in the records of the high risk children and those of chronic schizophrenics.

Results with the VEP have been somewhat variable. In the early 1960s, reports tended to suggest that schizophrenics had increased amplitude and reduced latency in some early VEP components. However, much of this work became invalid in the late 1960s, with increased awareness of the necessity to immobilize the pupil or subtract the EOG record from the background EEG. More recent work shows great heterogeneity within patient groups. The finding of heterogeneity in some ways may be an asset to future research, for it could be the basis of subtle subclassification. For example, Ishikawa (1968) showed that delayed VEP recovery (paired stimuli) characterized a subgroup of schizophrenics with marked hallucinations. Perris (1974) looked at early components of the VEP in both right and left occipital electrode
placements and suggested that greater asymmetry could be observed in psychotic depressives (marked reduction on the left) than in neurotic depressives or schizophrenics. Drugs mainly reversed the asymmetries.

In future research, bilateral recordings from a multiplicity of placements, related to subtle clinical symptoms, could help reduce the variance seen within patient groups that are too heterogeneous to allow group differences to appear, relative to a "normal" population. At present, however, the significance of "early" EP components is unclear. Shagass has described the "augmented" nature of schizophrenia and used this observation to form the basis of a theoretical framework. The "augmented" nature of early components is still not generally found (including in recent communications by Shagass 1978), but this could well be due to patient heterogeneity within groups.

A good example of the type of "comprehensive EP" assessment recommended for the future is that of Shagass et al. (1978) and Roemer et al. (1978). Using three sensory modalities and 15 electrode placements (from the international 10/20 system) with all the necessary controls, Shagass and his associates observed attenuated post-100 ms components and an increase in 60 ms components, especially in the SEP. What is especially important about this work is that it shows how a wave shape changes from anterior to posterior regions of the brain, and also in terms of laterality. Thus, the N60 potentials mentioned above as differentiating chronic schizophrenics from other groups are seen to be abnormally high in central locations. In normals this wave is at its height in frontal leads and very small in central and posterior leads.

Thus an abnormality appears not only in the EEG and EP wave shape, but can be precisely located in a specific brain location. This research integrates well with studies that have looked at regional cerebral blood flow (rCBF) in the brain and found considerable differences between schizophrenics and normals, especially during the performance of psychological tests (Franzén and Ingvar 1975a, 1975b). Franzén and Ingvar have proposed that the abnormal distribution of brain function in schizophrenia, fitting the reversed rCBF pattern, might be caused by a defective function of the nonspecific mediothalamic fronto-cortical projection system. This well-explored system has an important activating influence upon the frontal cortex, and also exerts an inhibitory control upon the cortical reception of afferent impulses. In animals, a transient blockade, or destruction of this system, leads to severe behavioural disturbances with ambivalence, inattention, disinterest, and aimless wandering about, but it does not lead to neurological disturbances or somnolence. The blockade also gives rise to an increase of the amplitude of evoked potentials in postcentral and in sensory cortices, as well as a number of other electrophysiological disturbances. On the whole, such a functional change would be consistent with a low frontal and high postcentral level of activity. [Franzén and Ingvar 1975a, p. 211; emphasis added]

Middle Evoked Potentials. To most people not directly concerned with measurement of EPs, the "middle" evoked potential is regarded as the evoked potential. There is, in fact, some truth in this view; amplifier filters that are set to record these wave forms (which are slower than early potentials) and to minimize noise will ordinarily show very little early EP response activity (500 to 3,000 Hz bandwidth for early potentials versus 40 Hz bandwidth for middle potentials). The middle EPs also show by far the biggest and most visible wave forms, and these center around a positive peak at about 100 ms (P100), a negative trough at about 140 ms (N140), and another positive peak at around 200 ms (P200). These wave shapes tend to be very stable in that they can be recognized in almost all EPs from somatosensory, auditory, or visual stimuli, although their amplitudes can vary considerably and (depending upon stimulus modality) their latencies can be quite variable also. As distinct from early EPs, they are almost completely bilateral in appearance and seen most clearly at the vertex. Early potentials tend to appear directly over primary areas and to be heavily lateralized. Thus, in the case of early potentials, direct brain mechanisms can be attributed to each piece of the wave form (see Shagass, 1977). The same cannot be said of middle potentials. Middle potentials probably originate postsynaptically near the cortical surface, but their neuroanatomical underpinnings are not precisely known.

A considerable literature on schizophrenia and middle EPs has been critically reviewed by Buchsbaum (1977), and his article is strongly recommended to interested readers. To avoid redundancy, this section will build upon what Buchsbaum has already reviewed. In general the P100, N140, and P200 components can be observed in most subjects in experiments using a nonsignal "OR" type of tone. The N140 component appears to reflect "stimulus selection" processes (Schweng, Snyder, and Hillyard 1976), while P200 seems strongly related to habituation and novelty. Many studies suggest that this whole complex is reduced in amplitude in schizo-
At this writing, there is some consensus that the middle components of the EP, with most stimulus modalities, are reduced in schizophrenia. This finding has been integrated into a conceptual framework by Shagass (1976, 1978) in his discussion of “early EP” components. Although Shagass’ theoretical statements are the most comprehensible yet offered, the “active inhibitory mechanisms” Shagass invokes to explain the middle component attenuation remain to be described. However, it is a beginning, and the phenomena appear to be robust enough to warrant substantial and careful investigation in the future.

Late Evoked Potential Components. In general, events that occur in the evoked potential at about 300 ms or later, in addition to long slow waves such as the contingent negative variation (CNV) and the readiness potential (RP), are regarded as late EP components. The argument is made, on the basis of known neuroanatomical involvement, that early EPs represent stimulus-registration, “hardware”-mediated processes, and thus abnormalities in this respect reflect physiological or biological alterations to the organism. Some investigators clearly wish to pursue this path, and their data are discussed above. The later components, however, are generally held to reflect psychological processes, and therefore abnormality in these components would indicate a more “functional” disorder. Background in this area is given variously by Tecce (1970, 1971, 1972), Shagass (1972), and Callaway (1975). The interested reader is also referred to Roth’s (1977) excellent review, which is brief and will give adequate orientation.

Methodology for recording late EP components and especially the CNV is described by Roth (1977, p. 106). The most important aspects of this methodology are an adequate amplifier time constant (5 to 10 seconds) and the removal of muscle, eye movement, and skin potential artifacts. Put in very simple terms, the CNV was, until recently, believed to be an “anticipation” potential; that is, if a subject was delivered an alerting stimulus followed by an imperative stimulus a few seconds later, a slow negative potential drift (at the vertex) could be seen as the subject “anticipated” what was about to happen. The more “attention” the subject paid to the task, the bigger the CNV, whereas distraction reduced CNV amplitude (this research is summarized by Tecce 1972). However, separate manipulation of “attentional” and “arousal” phenomena has cast doubts on this very simple formulation (Loveless and Sanford 1974; Naatanen and Gaillard 1974).

As Roth (1977) points out, there is evidence that CNVs are larger when subjects are instructed to concentrate on a quick response to the imperative stimulus. But in that case (i.e., if the attention is directed to preparation for motor activity), why is there so little concurrence between CNV and reaction time? This question has considerable import for schizophrenia research in that reaction time is held to be almost universally lengthened in all forms of schizophrenia (see Steffy and Galbraith 1974) for a detailed analysis of this deficit. Exactly what underlies the CNV is not known, but pieces of evidence that contribute toward understanding the mechanisms involved are presented by Roth (1977).

A general finding in this field is that amplitude of the CNV is reduced in psychotics (Abraham, McCallum, and Gourley 1976;
McCallum and Abraham 1973; Wing, Cooper, and Sartorius 1974). However, Timsit-Berthier et al. (1973) and Timsit-Berthier, Delaunoy, and Rousseau (1973) suggest that this finding could well be due to severe CNV amplitude reductions in certain patients. Thus, there is a need to isolate this subgroup (if it exists) and then to try to discern neurological or biochemical differences between patients with CNV amplitude reductions and other patients who do not show this phenomenon. Such an effort shows promise because the CNV appears to be relatively stable over time (Timsit-Berthier and Gerono 1976) and is not necessarily “normalized” after patients recover from severe bouts of mental illness (Abraham, McCallum, and Gourley 1976). CNV alterations would appear to be sensitive to neuroses, anxiety, depression, and attentional phenomena and to “tap” enduring aspects of personality (for further discussion see Roth 1977). The CNV reflects some degree of “information processing,” since continued information processing after response to the imperative stimulus delays CNV resolution (return to basal level) from about 200 ms post-response to in excess of half a second (Roth, Tinklenberg, and Kopell 1977). The CNV is particularly sensitive to experimental manipulations that include information processing, task-directed attention, and subjective uncertainty (see Roth 1977, p. 108).

The CNV has been studied extensively by Tecce and Cole, and their findings relative to psychopathology are as follows: Within the framework of their “distraction-arousal” hypothesis, Tecce and Cole (1972, 1976) suggest there is a “pattern of neuropsychological functioning” that can be used to assess psychopathology. The pattern includes a lowering of CNV amplitude, lengthened reaction time, elevated tonic heart rate level, and increased eye blink rates (Tecce 1977; see also, Tecce, Savignano-Bowman, and Cole, 1978; Tecce, Savignano-Bowman, and Meindresse 1976; Tecce et al. 1978). With respect to drugs, these authors suggest that schizophrenics with slow rise CNVs respond more favorably to thioridazine than patients with fast rise CNVs (Tecce et al. 1978). Although the findings of Tecce et al. could contribute substantially to treatment planning in schizophrenia, the findings of Timsit-Berthier et al. (1973) must also be borne in mind, i.e., that the aberrant CNV wave shape in schizophrenia appears not to be altered by medication. These findings are substantially corroborated by Dubrovsky and Dongier (1976); partial confirmation also comes from Abraham, McCallum, and Gourley (1976), despite different methodology; and most investigators seem to agree that the duration of CNV becomes more “normal” with clinical improvement. Roth (1977) makes the point that CNV failure to neutralize after response to the imperative stimulus is in keeping with clinical observations that schizophrenics cannot rapidly shift attentional set.

The “readiness potential” (RP) is the cortical evoked potential component associated with voluntary movement and, if a repetitive movement is used, it can be recorded, averaged, and inspected (see Roth 1977, p. 111). This potential would appear to be prolonged in schizophrenics (Dongier, Dubrovsky, and Garcia-Rill 1974; Timsit-Berthier, Delaunoy, and Rousseau 1973). Once again, this is not an absolute categorization but instead is a phenomenon displayed by 45–75 percent of psychotics investigated. The phenomenon may also be more evident in acute schizophrenics than in chronic. The “late component” waves of the EP proper are usually those that follow the 250–300 ms period. Of these components, the P300 wave is probably best understood, but some articles (e.g., Timsit-Berthier, Delaunoy, and Rousseau 1976) have shown that a late negative wave with very long duration characterizes some psychotics. The exact interpretation of this phenomenon is not known, but Roth (1977, p. 112) suggests that it could well indicate a “failure to resolve” aspects of attention. Late positive waves (LPWs) are usually induced in conditions of uncertainty about the occurrence of the stimulus and appear across all modalities. Ruchkin and Sutton (in Roth 1977, p. 114) have noted, “LPW amplitude increases monotonically with the amount of information received, which is equal to the subject’s a priori uncertainty of event occurrence minus the subject’s a posteriori uncertainty about having correctly perceived the event.” The general finding with respect to LPWs is that they are substantially attenuated in schizophrenia (Roth and Cannon 1972; Shagass et al. 1978; Timsit-Berthier and Gerono 1976). Shagass et al. (1978) showed that a number of middle and late components of the EP across sensory modalities (the “comprehensive EP” approach) were attenuated in schizophrenia, e.g., P360 auditory, P300 visual, and P280 somatosensory, as well as N130 and P180 somatosensory and N100 and P200 auditory. An earlier study by Levit, Sutton, and Zubin (1973) is also applicable here, as it manipulated stimulus uncertainty (which had a marked effect on LPWs) and also showed very substantially reduced LPW components in schizophrenics compared to both depressives and normals (see also...
Waldbaum, Sutton, and Kerr 1975). However, the interpretation of these findings should be tempered by the additional hypothesis that the LPW may not in itself be altered in schizophrenics but that the task or experimental instructions failed to engage the “attention” of the schizophrenics as much as they did the normals. Roth (1977) makes the pertinent point that the effects of drugs on LPWs are similar to the effects seen in schizophrenics; the common link. Roth suggests, may well be an increased “internal preoccupation” rather than externally oriented attention. It is interesting to note that in the Mauritius long-term study of prepyschotic high-risk children a constellation of measurements refined by discriminant function analysis reveals precisely this “internal preoccupation” in the skin conductance nonresponder 3-year-olds. (Skin conductance nonresponding is more prevalent in schizophrenics than in normals.)

Clinical Implications and Future Research. The field of schizophrenia and brain wave activity now has a substantial data base. However, very little attention has been paid to patient subgrouping and subclassification. This oversight will have to be remedied in the future, and the time is ripe for studies that take behaviorally restricted subgroups and look at EEG and evoked potentials of the types discussed above. Especially needed are fine manipulations of attentional performance and the EP recorded during these “psychologically active” periods. As in skin conductance research, there is also a need to standardize methodology between laboratories. The “comprehensive EP” approach of Shagass and his colleagues is a welcome direction. Perhaps the most exciting new research approach is the work of E. Roy John and his colleagues in New York. John has developed a total neurological assessment “package” that uses complex computer control of the full 10/20 recording system. Assessment is made of subjects who are tested with almost every conceivable type of stimulus suitable for use in EEG and EP studies. The output of this “neurometric” assessment is subjected to complex computer discriminant analysis and, in the case of children, is related to a substantial normative data base. The extension of this type of recording to adult schizophrenics and high-risk prepyschotic populations is an exciting possibility (John et al. 1977). It should be emphasized, however, that “neurometrics” is still in its infancy as a diagnostic tool, and many of the preliminary findings require confirmation by independent investigators using separate subject populations. Nonetheless, the approach’s greatest contribution is the high quality of its standardized methodology and artifact rejection capability. Despite 20 years of methodological refinement, results are often not comparable between laboratories because of different recording techniques. In addition, the inclusion of EP trials that contain noise due to eye movements or movement artifact certainly increases variance. In a branch of science in which variance within a population (e.g., schizophrenia) is often the subject of investigation, the question of experimental variation is often underrated in its importance. Thus, a highly sophisticated computer-controlled, standardized methodology, which uses a broad range of EEG and EP data, could well be a rewarding direction to follow. Such a comprehensive approach will be especially useful if it is combined with the “contour mapping” of brain electrical activity as used by Lifschitz, Susswein, and Lee (1979) and demonstrated by Lehmann and Julesz (1978) and Lehmann, Skrandies, and Lindenmaier (1978).

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Booklet on Premorbid Adjustment

A five-part review article Premorbid Adjustment in Schizophrenia: Concepts, Measures, and Implications, by John S. Strauss, Ronald F. Kokes, Rafael Klorman, and James L. Sackstder, has recently been reprinted. Single copies are available free of charge from the Center for Studies of Schizophrenia. Multiple copies will be supplied to requesters who wish to use the review for teaching purposes.

Aspects of the topic that are covered in the review include: The Concept of Premorbid Adjustment; Measuring Premorbid Adjustment—The Instruments and Their Development; The Relationship of Demographic and Diagnostic Factors to Measures of Premorbid Adjustment; Some Biological Approaches to Research on Premorbid Functioning; The Implications of Findings for Understanding, Research, and Application. The review was originally published in Schizophrenia Bulletin, Vol. 3, No. 2, 1977.

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