Neurophysiological Aspects of Information Processing in Schizophrenia

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This discussion focuses on the neurophysiological model as an approach to understanding schizophrenic behavior. One viewpoint is that physiological deviations in themselves are completely responsible for the etiology of deviant behavior, a relatively extreme view, though a possible one. It should also be noted, however, that external influences which modify behavior will be reflected in the physiology. Regardless of the etiological model to which we are bound, it is appropriate to examine psychophysiological changes that accompany behavioral performance. In some cases, the physiological measures mirror the behavioral performance precisely, providing a direct link between behavior and physiology. For further understanding of psychopathology, or differentiation of patient subtypes, such data are redundant, not necessarily being any more informative than the subject's overt behavior. In other situations, however, the physiological data provide insights that cannot be gleaned from overt observation, and teach us not only about which system is involved, but the manner in which information is processed in that system. During the past decade, we have gained sufficient confidence in many psychophysiological measures to accept differences in physiological activity among subjects, or even within the same subject under different conditions, as being indicative of true differences in information processing activities. Our approach has reached the point from which we can attempt to understand what such differences may imply regarding the processing activities of each subject.

Information processing demands may vary over a wide range of complexity, from minimal processing activity to tasks which require a great deal of attention and interpretation by subjects. Many varieties of task demand have been imposed on schizophrenic subjects. At all levels of complexity, there have been efforts to identify potential vulnerability markers for schizophrenia.

Resting Measures

The conceptually simplest level of study involves the recording of tonic physiological response measures under resting conditions, or what Zubin refers to as the "idling state." There is a problem in assuming that there really is any such condition as complete rest or absence of processing activity. We know from the reports of our laboratory subjects that when given no instructions other than to rest, normal subjects often attribute some meaning to whatever is going on, regardless of our instructions. For schizophrenic patients, it is not clear whether they react in the same manner (attending to irrelevant environmental stimuli as if there is some meaning), or whether they withdraw into their own world, including mild delusional states for some. Sutton has called this the problem of "subject option," which we normally try to control by giving specific task instructions to anchor the subject's responses. In practice, many resting response levels must be recorded without being able to control for subject option.

Both resting autonomic levels and resting electroencephalograms (EEG) (typically subjected to spectral analysis) have been used to study schizophrenia. Heart rate has usually been found to be increased in schizophrenics, and differences in spectral composition of the EEG have distinguished schizophrenic groups from normals. An interesting strategy was provided recently by Shagass et al. (1984), who analyzed EEG records of patients with several diagnoses.
using nonspectral procedures. They were especially interested in examining how well the EEG could be used to classify patients with differing diagnoses, such as major depression, mania, latent schizophrenia, and overt schizophrenia. While complete independence of groups could not be established on the basis of the EEG findings alone, initial classification of subjects into larger groups was possible. The authors emphasized that, as yet, the data could not successfully discriminate manics from overt schizophrenics, major depressives from overt schizophrenics, nor major depressives from neurotics, three sets of distinctions which would have major clinical value.

Reactions to Stimuli in Non-Task Situations

Increased processing activity is demanded when a physical stimulus is presented to a subject, even though no overt behavioral reaction to the stimulus may be required. Very early latency brainstem-evoked responses have provided a major neurological tool for detecting intact or deviant reactivity of the nervous system at early stages of processing. No attenuation of brainstem auditory responses was reported for schizophrenics by Pfefferbaum et al. (1980). Somewhat greater complexity is involved in the study of middle latency event-related potential (ERP) components to sequences of paired stimuli, studied extensively by Shagass and his colleagues (1984), in which the response of components to the second stimulus is typically attenuated in normals, but to a greater degree in schizophrenics, although latency recovery of the somatosensory ERP tends to be accelerated in schizophrenics. Augmenting/reducing phenomena, the enhancement or reduction of middle latency components of the ERP to increasing stimulus intensity, especially for visual ERP, has not yet provided consistent results in the study of schizophrenia.

Intense or unusual stimuli often cause an initial series of reactions which habituate after repeated presentation of the same stimulus. The initial reactions are referred to as orientation reactions. Schizophrenics have been characterized on the skin conductance orienting response as nonresponders or fast habituators, with hyporeactivity to orienting stimuli the predominant characteristic across studies (Bernstein et al., 1982).

Another presumably simple response is the pupillary reaction to light pulses, which has most typically been characterized as smaller in extent of constriction by Hakerem and by Rubin. When a series of light pulses were presented at irregular intervals, constriction in normals occurred to each of the stimuli in appropriate sequence, but delayed by an additional 480 msec; schizophrenics exhibited less pupillary following of the temporal sequence (Hakerem & Lidsky, 1975). Such data, as well as the orienting and habituation phenomena, emphasize the fact that even without instructions, some stimuli impact upon the nervous system in complex ways.

Psychophysiological Responses During Task Performance

The imposition of tasks requiring behavioral performance imposes the greatest demand for information processing activities, in contrast to the responses elicited under relatively passive conditions described above.

Certain psychophysiological measures are especially useful for studying information-processing activities because they occur with a relatively short latency (approximately 1000 msec or less); the components of the ERP offer a temporal resolution on the order of msec accuracy, dependent on sampling rates. This may be contrasted with such measures as the positron emission tomography (PET) scan and cerebral blood flow, which provide an indication of direct or indirect metabolic activity, but integrate activity over much longer periods of time, and are thus not capable of monitoring reactions to single events.

From among the variety of measures, the long-latency components of the ERP have proven to be most closely related to information processing activity across a variety of experiments. The most prominent aspects include the P300 component, a scalp-recorded positivity with a latency of approximately 300 msec, which was first noted by Sutton et al. (1965), and related long-latency activity such as slow wave and processing negativity, as well as the contingent negative variation (CNV) of Grey Walter, which precedes an expected imperative stimulus.
Schizophrenics tend to show reduced P300 amplitude compared to normals; this has been one of the most replicated findings in the ERP psychopathology literature (for a more detailed review, see Zubin et al., 1985). Other patient groups tend to lie somewhat between the normal and schizophrenic groups in amplitude. The increased latency of P300 which is seen in organic patients is not typical for schizophrenia, however, suggesting that what may be occurring in schizophrenics is a true deviation in processing rather than a function of brain damage. Earlier components of the ERP, such as N100, are clearly related to attention, and also tend to be attenuated in schizophrenics. Baribeau-Braun et al. (1983), using an auditory selective attention task, showed that N100 in schizophrenics was reduced at one rate of stimulus presentation but not at another, P300 was reduced in both cases. Apparently, P300 amplitude reduction is not merely a consequence of reduced attention.

A paradigm currently employed in our laboratory permits us to examine P300 simultaneously with two autonomic responses, pupillary diameter and heart rate, during task performance by schizophrenics. Averaged pupillary dilation responses have been shown to parallel P300 changes in several studies, and are reduced in schizophrenics during a guessing task (Steinhauer et al., 1979). A modification of the "oddball" task is employed: normally, when subjects are asked to count a rare auditory or visual stimulus embedded in a sequence of different but more frequent stimuli, a large P300 response is evoked by the rare event. Our subjects were informed that two "rare" stimuli (high-pitched tones) never occurred in a row, so that every high tone was followed by a frequent stimulus, a low-pitched tone. Thus, the frequent tone which follows a rare, counted tone is predictable (probability = 1.00), while after a frequent tone, either another frequent tone may occur (probability = .67) or a rare tone may be presented (probability = .33). The subject's task is to report the number of rare target tones at the end of every block of trials.

Normal subjects show a large amplitude P300 response to the rare tone, a smaller P300 to the unpredictable frequent tone (i.e., the repeated frequent tone, probability = .67), and the smallest response to the predictable frequent tone which follows each rare tone (probability = 1.00). A parallel effect occurs in the pupillary response: dilation is largest to the rare tone, and decreases with increasing sequential probability of frequent tones.

Hospitalized schizophrenic patients, as a group, showed two major differences from the normals. Firstly, both pupillary and P300 amplitudes were significantly decreased in amplitude. Secondly, a different pattern was observed across conditions even at the reduced amplitudes: both for pupillary dilation and P300, responses were larger in amplitude for the rare and the predictable frequent events than for the frequent event which was less predictable (probability = .67) (Steinhauer & Zubin, 1982). The data were interpreted as indicating that the patients were, in effect, more physiologically, responsive when the stimulus differed physically from one trial to the next, rather than utilizing information regarding sequential event probability, which characterized the normals.

Some comments are needed regarding the task requirements. All subjects were required to count rare tones, but were not required to pay any additional attention to sequences, even though some information was made available to them at the outset. In the analyses of the data, only blocks of trials for which the subject has counted accurately to within ± 3 counts are included so that, in general, all subjects considered (including patients) have been performing adequately. It has been instructive to look at the data for several subjects whose performance varied during the course of the experiment. For blocks of trials in which poor counting occurred, patients meeting criteria for depression showed little P300 activity, but the same subjects usually showed virtually normal responses for blocks in which counting was accurate. In contrast, the reduced amplitudes for schizophrenics which are reported above were derived only from blocks with accurate counting. Insuring adequate performance is a necessity before inferring that P300 is reduced because of processing difficulty. Some reports of reduced P300 amplitude in demented patients note that performance was also poor in those subjects. Thus, the reduced P300 may merely reflect their poor performance on the task.

Confidence in using differences in the pattern across measures to infer how the subject
is using available information is bolstered by similar findings in the pupillary and ERP data. Preliminary analyses of the cardiac data indicate, for normals, a deceleration in heart rate prior to an unpredictable frequent or rare stimulus event, followed by acceleration after stimulus delivery; greater acceleration occurs to the rare stimulus. The predictable frequent event causes no pattern of anticipatory deceleration or subsequent acceleration. In comparison to the normals, schizophrenics show no significant cardiac changes, even though average heart rate is significantly faster. The lack of cardiac changes, however, represents a group effect and points out that in order for any of these measures to be useful clinically or prognostically, we must be able to make statements regarding the psychophysiological response of an individual subject. Careful examination of the schizophrenic patient data indicates that while the majority respond as shown by the group average, some individuals respond as do normal subjects on pupillary and ERP measures. We expect a similar finding when the cardiac data is examined more closely.

These data permit a distinction to be made not only between the patient and normal groups, but also among members of the patient group. Patients may initially be grouped according to whether response amplitudes are similar to or differ significantly from normals, a traditional type of distinction. Another means of discrimination now available is to classify patients on the basis of whether the pattern of responses across conditions represents utilization of sequential probabilities, or whether it indicates either little differentiation or increased response only to stimulus change. Thus, the processing style which each set of patterns represents now becomes the mode of classification. The practical utility of these distinctions will then require further evaluation.

The nature of these specific measures as vulnerability or episode markers remains unclear. The patients were first tested during hospitalization for an active episode, few being drug-free. Follow-ups on the original sample and on a much larger patient group suggest that, at least for the P300 response, more normal response amplitudes and relation to event probability are observed among patients who are improved clinically, whether or not they are on neuroleptics. Limited but similar findings have been reported by others. It thus appears that P300 is more likely to represent an episode rather than vulnerability marker.

It is not clear whether gradual normalization of responses is related to a gradual decrease in severity of symptomatology. While we can measure the ERP in tenths of a microvolt, or pupil diameter to the nearest hundredth of a millimeter, measures of severity do not even approach such resolution, and we look to the advances of diagnosticians for refinement of their measures on the behavioral side.

The psychophysiological data reinforce current suggestions that limbic functions are implicated in the generation of schizophrenic-like behavior. Control of sympathetic pupillary activity, the major component of the dilation response, is directly linked to limbic regions via hypothalamic pathways, as are other autonomic functions. Increasing evidence has implicated limbic regions as at least a parallel system for P300 activity, if not a possible generator, based on depth electrode studies in humans undergoing surgery and on neuro-magnetic recordings. P300 is especially responsive to such factors as incentive or motivation to perform, and an evaluative function has been proposed for P300 which is consistent with classical notions of limbic activity (Sutton & Ruchkin, 1984). We have suggested that this evaluative function is deviant in schizophrenia, and thus is reflected in P300 generation (Zubin et al., 1985). Weinberger (unpublished) has presented further evidence for limbic involvement in schizophrenia.

The interpretation of whether psychophysiological deviations represent a true physiological aberration, or whether they provide a window on how an essentially normal physiological substrate is responding to a particular idiosyncratic style of processing, is still an open question. For example, all of the ERP, pupillary, and cardiac differences noted among schizophrenics in our data could be due to some essential physiological deviation in processing. A contrasting possibility, however, is that they are accurately related to difficulty in the focusing of attention. Normal subjects appear to be easily capable of performing the task (counting) and, in addition, use the sequential probabilities engendered by the conditions of stimulus presentation. Thus, the counting task
itself does not require all of the subject's available capacity for processing, as inferred from the physiological data. Similarly, the counting task also does not require all of the patient's available capacity for processing in that even with accurate counting, patients respond in addition to events representing a change in stimulus from one trial to the next. If we postulate that responding only to change from one trial to the next represents less complex processing than the discrimination of overall sequences based on the conditional probability of successive events, we may attribute the patient performance to either a problem in the recognition of sequential dependencies, or to a limited attentional capacity that is maximally allocated when attention is paid to the physical difference between successive stimuli. From this perspective, it appears that the patients are not merely performing the task using the least effort necessary, but are probably doing the best that they can at the time of testing. Clarification of these issues is not yet at hand.

Future research plans require the investigation of psychophysiological measures under different treatment conditions. Furthermore, the usefulness of psychophysiological measures in describing information-processing activities suggests that our ability to investigate complex functions in psychiatric patients will be increased as we learn to apply more sophisticated experimental paradigms.

References


