VULNERABILITY TO SCHIZOPHRENIA: INFORMATION PROCESSING IN THE PUPIL AND EVENT-RELATED POTENTIAL

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ABSTRACT

The psychophysiological markers of vulnerability to schizophrenia reported in this paper focus on evoked potentials and pupillography as indices of information processing. A counting paradigm was adapted to provide three levels of stimulus probability ranging from low to medium to high. The results indicate that for normals there is a direct relationship between level of uncertainty and the extent of dilation of the pupil, and for most subjects, for the amplitude of the P300 component of the event-related potential. For patients undergoing an episode of schizophrenia, this relationship is not apparent. The data suggest that normals tend to be influenced by the conditional probability of the stimulus regardless of change or redundancy in the stimulus, but patients (while in their episodes) seem less influenced by conditional probability and more influenced by change in the stimulus. Thus, not only the amplitude of a response, but also the pattern of responses under different conditions, differentiate between those vulnerable to schizophrenia from controls. The search for markers of vulnerability must take cognizance of the fact that some of the differentials between those vulnerable to schizophrenia and normals reflect the presence of an episode and hence are episode-markers rather than vulnerability markers. It therefore becomes necessary to reexamine patients after termination of an episode to determine whether the marker persists.

KEY WORDS

Schizophrenia, information processing, pupillary dilation, P300, event-related potentials, orienting

INTRODUCTION

The purpose of this communication is to highlight the usefulness of the information processing approach in the search for indicators of schizophrenia, note the virtues of the neurophysiological model in such searches, and contrast the role of data-driven vs. conceptually-driven processing in psychopathology. The methodological innovation consists of analyzing physiological data as a function of conditional probability in the sequence of presented stimuli, rather than of the overall
probability regardless of sequence, which is the usual method for treating such data. This more detailed analysis of the processing of information provides an unexpected indicator differentiating schizophrenics from controls.

The information processing approach attempts to trace the pathway that the energy of an information-laden stimulus follows from its peripheral physiological beginning at the sensory gateway through the various stages leading up to higher cortical levels where the message is "interpreted." This pathway is presumed to develop in the nervous system from neural templates modified by experience.

One of the hypotheses now favored by experimental psychopathologists is that the source of aberrant overt behavior so characteristic of patients undergoing a schizophrenic episode is a failure on the part of the information processing route to follow the expected normative pathway, resulting in distortion of the message (Kietzman, Spring and Zubin, 1980). Usually, the search for indicators ends when a difference is found between patients and controls. In contrast, the finding of differences is only the beginning step of the search in the information processing approach. The search proceeds to examine where, when and how in the processing of the information the deviation took place. By virtue of the explicitly detailed and quantitative models of information processing that have been developed in work with normals, and through use of sophisticated research techniques for measuring various parameters of these models, it may become possible to identify the portions of the information processing route that remain intact and those which deviate in patients undergoing an episode.

The neurophysiological substrate of behavior is eminently suited for the task of searching for indicators because its measurement is relatively immediate. It springs forth directly, like Minerva from the brow of Zeus, while long latency responses such as verbal reports and psychomotor activity are subject to embellishment and/or deviation between the initial physiological response and the overt report. The brief period between stimulation and neurophysiological response, usually within the first 1,000 msec following an event, and its freedom from surplus activity, renders it relatively free of possibly biasing life experiences of remote or proximate origin in time (Zubin and Kietzman, 1966).

The contrasts between these alternative modes of responding is clearly visible, for example, in the comparison between the event-related potential (ERP) accompanying the observation of similarity between two geometric figures (John, Herrington and Sutton, 1967), and the more complex and often idiosyncratic verbalization of the bases on which such a judgment can be made, even using standardized semantic rating scales. The verbal report is influenced more by language, culture and by our own experience in communication, than is the event-related potential, which can provide objective reference points and replicable results.

Two types of neurophysiological indicators will be discussed which are related to information processing in schizophrenia, the pupillary response, and the event-related potential recorded from the human scalp. The observation of pupillary abnormalities in schizophrenics dates to the turn of the century when Bumke claimed a poor prognosis for any patient who failed to show pupillary dilation in response to a painful stimulus (see Hakerem and Lidsky, 1975). The event-related potential is a more recently investigated phenomenon, and our interest has been directed primarily to those components which seem to reflect information processing characteristics. Prominent among these is the P300 component of the evoked response, so named because it is a positive wave appearing with an approximate latency of 300 msec. Although P300 has been
studied in greatest detail with reference to normal patterns of information processing (Donchin, 1979; Sutton, 1979; Tueting, 1978), the origin of P300 is of some historical interest for psychopathologists. It had been observed that reaction time was lengthened when the modality of a stimulus differed from that of the immediately preceding trial a cross-modal lengthening of reaction time (Sutton and Zubin, 1965). Schizophrenics exhibited longer reaction times than controls under all conditions, but the effect of cross-modality shift was increased for schizophrenics relative to normals. The cause of this increase in latency was intriguing and a decision was made to investigate the possibility that the then newly developing evoked potential technique might cast light on it. Reaction time did not seem an appropriate task for those preliminary investigations, since motor potentials were known to contaminate scalp recordings. Instead, a guessing task was introduced for normal subjects. As the shift in modality occurred, a previously unreported phenomenon appeared in the evoked potential—a large positive component, which varied in amplitude inversely with the probability of the stimulus (Sutton and co-workers, 1965).

This P300 response was more closely related to the informational characteristics of the stimulus than to its specific modality and physical attributes or to shift in stimulus. As a result of this finding, a whole series of studies was initiated to determine the effect of the variation of probability of stimuli on event-related responses (Sutton and co-workers, 1967; Tueting, Sutton and Zubin, 1971; Friedman and co-workers, 1973) and subsequently, upon the pupillary dilation response (Friedman and co-workers, 1973; Hakerem, 1974).

MODES OF INFORMATION PROCESSING

One of the distinctions made in information processing research is between data-driven and conceptually-driven processing (Lindsay and Norman, 1977). The contrast between these two modes of processing is not dichotomous, but continuous, depending on whether the response is determined more by the attributes of the stimulus (data-driven) than by the attributes of the individual and the ongoing endogenous activity when the stimulus is presented (conceptually-driven). Data-driven processing is thus more closely related to the energy and information provided by the stimulus. Conceptually-driven processing is more related to the attitudes, past history and ongoing brain activity of the subject when the stimulus impinges.

As an example of purely data-driven processing, we may consider the pupillary response to a brief pulse of light. Under non-stressful conditions, the extent of the response is relatively constant. However, the amplitude of the constriction is increased as a function of increasing intensity of the light. Schizophrenic patients show a reduced pupillary constriction to light, and group differences are maintained even when initial diameters are matched between the groups (Lidsky, Hakerem and Sutton, 1971). Differences in the extent of the light reaction between controls and schizophrenic patients have often been reported (Rubin, 1974), and there is some evidence that the light reaction continues to be deviant among schizophrenics even during remission (Ikushema and Matsunaga, 1977; Rubin, 1974) (This would tend to make it a trait rather than a state marker).

The elicitation of the neurophysiological response can serve as a proving ground for determining whether the relative potency of data-driven and conceptually-driven processing can be tested. Hakerem and Lidsky (1975) demonstrated that even complex data-driven responses may be present in normal subjects but not in schizophrenic patients. They recorded pupillary
constrictions during presentation of an irregular, but repeated, sequence of light flashes. The pattern of pupillary constriction in normal subjects indicated that the sequence of lights was encoded in the pupillary response, although delayed by a latency of 480 msec, which is longer than the latency to a single flash at the intensity employed. The data-driven response resulted in some form of temporary neurophysiological storage, allowing the information provided by one stimulus to be encoded and retained even before the response to the previous stimulus had been expressed. No similar pattern characterized the schizophrenic patients. Most patients did not exhibit a pattern of constrictions triggered by the light sequences. This provides an example of a deviant data-driven process among schizophrenic patients.

A comparison between primarily data-driven vs. conceptually driven activity is presented in Fig. 1 for the computer-averaged vertex event-related potential and pupillary dilation response to an auditory stimulus. These data were recorded during performance of a guessing task by a normal subject. When the subject was requested to guess which of two different sounds would be presented (top, Fig. 1) there was a marked dilation of the pupil, and a large P300 component appeared in the event-related potential (in all event-related potential recordings, positivity is represented as a downward-going deflection). In contrast, when the subject was informed which stimulus was to be presented (bottom Fig. 1), there was no pupillary dilation evident in the response, and the event-related potential showed only a minimal positivity at P300 msec in this data-driven condition. The modifications of the pupillary response and ERP during the guessing task represent greater processing attributable to the conceptually-driven mode.

PUPILLARY DILATION RESPONSE EVENT-RELATED POTENTIAL

![Diagram](image)

Fig. 1. Pupillary dilation response and vertex event-related potential recorded from a normal subject under conditions of Uncertainty and Certainty.

The event-related potential was recorded from schizophrenics, depressives, and normal subjects during a guessing task by Levit, Sutton and Zubin (1973). In the guessing condition, normals
showed the largest P300 amplitudes, with diminished, but readily observable P300 responses among the depressive subjects. However, schizophrenic subjects tended to show small response amplitudes. Subjects were selected from patients who had received a hospital diagnosis of schizophrenia, but received an independently assessed RDC diagnosis of depression. Thus, patients in both groups were considered schizophrenic by the hospital staff and were receiving equivalent medication. Similar findings were reported by Verleger and Cohen (1978). P300 is also decreased in schizophrenics relative to controls during performance of reaction time tasks (Roth and co-workers, 1980a, 1980b).

Employing a guessing paradigm similar to the Levit, Sutton and Zubin (1973) design, but requiring all subjects to report the outcome of each trial, Steinhauer, Hakerem and Spring (1979) recorded pupillary dilation in schizophrenics, depressives and normals, noting that the pupillary dilation response was deficient or absent among schizophrenics.

A CONDITIONAL PROBABILITY PARADIGM TO INVESTIGATE INFORMATION PROCESSING

In order to obtain an adequate signal to noise ratio for computing averaged pupillary and ERP waveforms, many individual trials must be employed for each of the several experimental conditions to derive a single averaged response curve. The guessing paradigm is unfortunately time-consuming, requiring a prestimulus guess, presentation of stimuli, and post-trial behavioral report. In our experience, obtaining the over 400 trials of data necessary for this paradigm can require three to four hours of preparation and testing time. Although schizophrenic patients can complete such a procedure, they become distracted and tired, and often, less willing to return for retesting.

We therefore sought an experimental paradigm that would be more efficient for the collection of data, but would still allow informational value to vary as a function of stimulus uncertainty. It seemed that the counting paradigm with some modification would meet our requirements. A counting task typically requires the subject to selectively count one of two stimuli, either of which may be presented on any trial. When the stimuli are presented with unequal probability, P300 is larger for the more infrequently occurring stimulus (see Donchin, 1979).

It has been demonstrated that auditory stimuli can be used to elicit pupillary dilation, but light stimuli used within the same paradigm result in a constriction that obscures any dilation associated with cognitive components of the task (Steinhauer, Hakerem and Spring, 1979). Consequently, only auditory stimuli were employed in this task.

Subjects in our preliminary studies included seven control subjects, aged 21-23 (five females), seven schizophrenics (one female) and five depressives (all male): patients were 21-35 years of age, with the exception of one 42 year old male, and met RDC criteria for either schizophrenia or depression. Additional subjects who performed the behavioral task poorly have been excluded from the present discussion. Pupil diameter was measured with an infra-red TV pupillometer, and event-related potentials were recorded from midline frontal, vertex, and parietal locations, and from lateral parietal sites, referred to linked ears (with forehead as ground). The left and right parietal leads were selected to assess potential laterality effects because counting tasks typically produce maximum P300 amplitude over parietal locations (Donchin, 1979). Stimulus tones of either high (1500 Hz) or low (800 Hz) pitch were presented for 40 msec at 65 dB SL through a speaker located in front of the subject. Tones were presented in eight blocks of 80...
trials each, with a three second interstimulus interval. For two consecutive blocks, the same tone was designated as Target (T), and was presented across trials with an overall probability of .25, yielding a complementary overall probability for the non-target stimulus of .75. The subject was told that the task was to silently count the number of Targets presented, and report the total during the two minute rest at the end of each block. He or she was told that there would be fewer Targets than Non-Targets (NT), and also that two Targets would never occur "in a row." The subject was rewarded 25 cents for reporting the correct number of targets presented during the block. If the subject reported accurately within one or two counts, the reward was decreased to ten cents, and three or more errors were not rewarded at all. Although the standard analysis of such data is to segregate trials according to rare and to frequent stimuli (corresponding to Targets and Non-Targets in this experiment), the restriction which eliminated successive presentations of the Target stimulus permitted a more refined analysis: all stimuli were separated according to the conditional probability established by the preceding stimulus. Thus, a Non-Target always followed the presentation of a Target stimulus, so that p[NT/T] 1.00, a condition analogous to complete certainty. However, when a Non-Target stimulus occurred, it could be followed by either another Non-Target stimulus or by the Target. The respective conditional probabilities for these outcomes are p[NT/NT] = .67 and p[T/NT] = .33 (since the Target could not be repeated successively, p[T/T] = 0). These conditional probabilities differ from the overall probabilities of .25 for Targets and .75 for all Non-Targets.

Averaged response curves were computed from artifact-free trials, and represent blocks of trials for which the subject's report was accurate to within one or two counts.

For control subjects, the amplitudes of the P300 component of the ERP and pupillary dilation were largest for responses elicited by the rare Target stimuli, a finding consistent with previous studies for the ERP (Donchin, 1979; Squires et al., 1976; Tueting, Sutton and Zubin, 1971). Greater pupillary dilation has been reported for rare outcomes occurring during a guessing task (Friedman and co-workers, 1973), but have not previously been recorded during a counting task.

Analysis of variance for control subjects indicated a significant main effect for conditional probability [E < .01], with the largest dilation occurring to the Target stimulus (p[T/NT] = .33) for controls. A larger dilation was observed for the medium probability Non-Target (p[NT/NT] = .67) than for the high probability Non-Target (p[NT/T] = 1.0) in six of seven controls. These differences were not due to differences in the initial diameter of the pupil. The averaged pupillary response and event-related potentials at the midline vertex and parietal locations are presented for a representative control subject (Fig. 2).

The early components of the event-related potential of approximately 200 msec or less were similar across conditions. The most striking difference was observed for the P300 component, and was largest at the midline parietal location. No amplitude differences were observed between the left and right parietal electrodes. A main effect for conditional probability was obtained for P300 [p < .01]. The most consistent trend was for P300 amplitude to increase as conditional probability decreased, although not all control subjects evidenced differential responses to the two non-target conditions whose probabilities were 1.0 or .67.
Depressive patients tended to show responses that were most similar to those of normal control subjects, both in the pattern of P300 amplitude and pupillary dilation. Representative data for one depressive subject appear in Fig. 3. Several of the depressives were unable to suppress blinks, so that pupillary diameter could not be recorded. Consequently, no attempt was made to statistically evaluate pupillary activity in the depressives. P300 was not significantly affected by conditional probability among depressives.

Schizophrenics were generally characterized by small or absent P300 responses and minimal pupillary dilation. Five of the schizophrenics were drug free at the time of testing, and illustrative data for one drug-free schizophrenic are shown (Fig. 4). The pupillary response in this subject indicates a lack of dilation, although some slight motility is observed, rather than an entirely flat response. The event-related potentials from midline vertex and parietal leads show definite early components (N100 and P200), but only a small positivity is apparent at approximately 300 msec,
with little differentiation among the experimental conditions. The presence of the early components lends credence to the notion that the stimuli were properly received and processed initially.

There were no significant differences attributable to initial pupillary diameter among schizophrenics. A main effect for amplitude of peak dilation was obtained [$E = .0005$]; pupillary dilation was larger for the (p[T/NT] = .33) and (p[NT/T] = 1.0) conditions than for the (p[NT/NT] = .67) condition. P300 amplitude was not significantly different across probabilities for the schizophrenics, although the trend across subjects was similar to the pattern observed for pupillary dilation.

Means and standard errors of P300 amplitude at the midline parietal scalp location are plotted in Fig. 5 for controls, depressives and schizophrenics. Only the differences between the control and schizophrenic subjects were significant [$E = .003$]. The order of amplitude across groups -- largest for controls, next largest for depressives, and smallest for schizophrenics -- replicates the trend observed by Levit, Sutton and Zubin (1973).

There was no significant difference between the schizophrenic and normal groups in initial diameter of the pupil. The amplitude of pupillary dilation, shown in Fig. 6 for controls and schizophrenics only, was significantly larger for the normals than for the schizophrenics [$p = .015$].

DISCUSSION

The manipulation of conditional probability resulted in corresponding changes in pupillary dilation and P300 in control subjects, and to some degree, in depressives, i.e., there was generally a negative correlation between conditional probability and response amplitude. Schizophrenics differed from the controls in two major characteristics: 1) Response amplitudes were significantly diminished in schizophrenics, and 2) the pattern of responding characterizing schizophrenics differed from the pattern observed in normals.

The pupillary results are especially intriguing, since previous work (Hakerem, 1974) suggested that the counting task would not have an effect on the dilation response. Historically, pupillary dilation has been relegated to the realm of orienting activity (Bernstein, 1979; Friedman, 1978; Sokolov, 1963), and has been especially associated with novelty of stimulation. From such a vantage point, one would predict that stimulus change would be a major influence upon pupillary dilation. For control subjects, however, change of stimulus per se was not as effective in producing increased pupillary dilation as was the uncertainty resolved by stimulus presentation. Specifically, the shift from a Target to a
Fig. 3. Representative data for one depressive subject in the counting task.
Fig. 4. Representative data for one schizophrenic subject in the counting task.
Fig. 5. Pupillary Dilation vs. conditional probability for controls, depressives and schizophrenics.

Fig. 6. P300 at Pz vs. conditional probability for controls and schizophrenics.
Non-Target stimulus, a highly probable change (p = 1.0), resulted in less dilation than repetition of the same Non-Target, an event that involved greater uncertainty (p = .67).

It has also been shown that presentation of "novel" stimuli is associated with a P300 having a more anterior distribution (Courchesne and co-workers, 1975), but the topographical distribution observed for controls in the present study was more posterior, which has been associated with various information processing tasks (Tueting, 1978).

The amplitude of the P300 component has long been associated with variations in stimulus probability (Tueting, Sutton and Zubin, 1971; Donchin, 1979; Tueting, 1978). Squires and co-workers (1976) have demonstrated the dependencies of P300 amplitude on sequences of preceding stimuli, with larger P300s associated with longer preceding runs of different stimuli. The current paradigm was analyzed with respect to conditional sequential probabilities. In contrast to the data of Squires and co-workers (1976), the repetition of a Non-Target stimulus in the present study indicated a more "surprising" event (in their terminology) than the change from a Target to a Non-Target [NT/T]. Similar presentations of stimuli have not been evaluated in such a manner before. Roth and co-workers (1980a) compared P300 in controls and schizophrenics during performance of a reaction time task (rather than counting) using a non-repeating Target stimulus. No attempt was made to compare high probability Non-Targets following a Target with Non-Targets that were less predictable. We would predict that P300s analyzed according to conditional probabilities would have revealed subjects whose patterns resembled those obtained in the present study, even though the tasks differed.

As in previous studies, both pupillary dilation and P300 amplitude were found to be smaller for schizophrenic patients than for normals. Schizophrenics, however, had smaller responses than normals even when their performance was accurate. Since appropriate counting was performed, it is apparent that information regarding the stimulus was processed and retained by the subject. What, then, was happening to the utilization of this information among the patients who show such a decrement in amplitude?

In an attempt to deal with this question, we examined the patterns of responses shown by the schizophrenics. As noted, the only significant effect for schizophrenics was that pupillary dilation to the Target following the Non-Target, and the Non-Target following the Target (that is, T/NT (p = .33) and NT/T (p = 1.00) stimulus conditions) were larger than to the repeated Non-Target [NT/NT] (p = .67). Comparison of the relationships between conditional probability and the measures of both pupillary dilation and P300 as shown in Figs. 5 and 6 indicate that the patterns differed between controls and schizophrenics, but were consistent for each subject group across both response measures. These patterns of response suggest that if schizophrenics respond at all they show a greater response to stimuli that differ physically from the previously presented stimulus. That is, they show an orienting response when the stimulus changes, but they do not show evidence of utilizing the information provided by the different conditional probabilities. This information, to have an effect, requires subjects to be influenced by the overall sequence of previous presentations of the stimuli. Current schizophrenic research on orienting responses, based primarily on data from skin conductance studies, is complicated since about 50% of the schizophrenics show an orienting response to which they habituate slowly while the remaining group of schizophrenics show no orienting response at all (Spohn and Patterson, 1979, Venables, 1977). The schizophrenic subject seems to utilize information, but does so differently from the control or depressive subject. Furthermore, if the subject did not make use of this sequential
relationship, but instead classified stimuli only into the categories of Target or Non-Targets, then a larger P300 would be expected to the Target condition: in this case, the probability of a Target would be decreased to its overall probability of .25. In normal subjects, decreasing event probability increases P300, but this was not observed for the schizophrenics. Thus, schizophrenics apparently not only fail to make use of conditional probability but also fail to utilize overall event probability.

In comparison with controls and depressives, information processing among schizophrenics apparently operates more in the data-driven than in the conceptually-driven mode. These data are consistent with the "immediacy hypothesis" (Salzinger, 1973), according to which the schizophrenic is influenced more by the immediately preceding stimulus than by prior stimuli or instructions. The "immediacy" of the stimulus on the preceding trial has a greater effect than differences in conditional probability for the same stimulus.

Zubin and Spring (1977) emphasized that detection of individuals vulnerable to episodes must rely on differentiating between those markers that can be associated with beginning and ending of the episode (state markers) and those markers that are relatively independent of the episode (trait markers), and which theoretically may even be observed in unaffected individuals. A more detailed discussion of markers has been provided (Zubin and Steinhauer, in press).

To distinguish vulnerability from episode markers it becomes necessary to follow-up patients after initial data collection, particularly through periods of remission and/or relapse. Levit, Sutton and Zubin (1973) reported recovery of P300 for one patient who showed signs of clinical improvement, but not for another patient still exhibiting symptomatology. In our present studies, follow-up examination of two schizophrenics who showed little or no pupillary dilation or P300 on admission indicated a recovery of P300 during a period of clinical improvement, but recovery of pupillary dilation did not appear in one of the patients, who was drug-free at the later testing. In contrast, a third schizophrenic showed diminished P300 both initially and one month later, at which time little clinical improvement had been noted.

Such data suggest that P300 is probably an episode marker, showing recovery after clinical improvement, a suggestion that has been expressed previously (Levit, Sutton and Zubin, 1973; Shagass and co-workers, 1978). The pupillary dilation response may serve as a long term indicator of vulnerability (Zubin, 1980) for a subgroup of patients. It is evident that the direct association between psychophysiological activity and schizophrenic symptomatology can only be evaluated by examining the same patients both during episodes and during periods of clinical remission. An examination of patients during hospitalization and at follow-up is now being undertaken by our laboratory.

ACKNOWLEDGEMENTS

Preparation of this report was supported by the Medical Research Service of the Veterans Administration and by NIMH grant MH-30915. The authors wish to acknowledge the assistance of Drs. Usim Odim and Peter Stajduhar at the Highland Drive VAMC, and Drs. Samuel Sutton, Gad Hakerem and Mitchell Kietzman at the Department of Psychophysiology of the New York State Psychiatric Institute. Technical aid was provided by P. Bryan Heidorn, Frederick Ayre and Steven Elmore.
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