PUPILLARY DILATION, P300 AMPLITUDE AND HEART RATE RESPONSES
IN NORMALS AND PSYCHIATRIC PATIENTS: EFFECTS OF
CONDITIONAL PROBABILITY DURING A COUNTING TASK

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This paper presents some of the recent findings from the Biometrics Research laboratory at the Highland Drive Veterans Administration Medical Center in Pittsburgh which explore the possibility of finding markers of vulnerability to schizophrenia in the neurophysiological responses which may underly information processing in normals and patients. The various scientific models for the etiology of vulnerability to schizophrenia have been examined elsewhere (Zubin & Spring, 1977; Zubin, in press). The selection of the neurophysiological model as a starting point is premised not so much on the greater potential of this model for providing markers as on the possibility that neurophysiological markers are less likely to be influenced by the noxious life experiences to which premorbid schizophrenics are exposed. These premorbid experiences might contaminate markers emanating from the other scientific models (ecological, developmental, learning, internal environment) to a much greater extent.

There is a tradition among psychopathologists that the schizophrenic processes information differently from the normal individual. Hallucinations and delusions provide the most clear examples of deviance in sensation, perception and cognition, and many other psychopathological phenomena can be attributed to deviant information processing. Heretofore, most of the explanations of deviant behavior have been couched in psychodynamic terms, but with the development of information processing theory and techniques it has become possible to relate some of these phenomena to deviations in the manner in
which energy is received and information is processed by the schizophrenic (Kietzman, Spring & Zubin, 1980).

One of the best examples of the utilization of the information processing approach in studies of schizophrenia is afforded by the experiments which led to the discovery of the P300 component of the event-related potential (Sutton, Braren, Zubin & John, 1965). The research team had been concerned with the question of shifting of attention in schizophrenia. At first, the effect of shifting attention was examined by changing from visual to auditory signals to see whether the shift would affect reaction time (Sutton & Zubin, 1965). An increase in latency was indeed observed when a cross-modality shift occurred between successive stimuli. Although schizophrenic subjects exhibited longer reaction times than normals for all conditions, their responses in the cross-modality conditions were excessively prolonged.

In performing this experiment, the frequency with which each of the stimulus modalities was presented was varied, and it was soon discovered that there was an inverse relationship between the probability of the stimulus occurring and the latency of the response to the cross-modality shift, i.e., the less probable or more uncertain stimulus was accompanied by a longer latency response. An effort was made to examine the electrophysiological correlates of cross-modality performance by recording the evoked response from human scalp during performance of a guessing task in which stimulus modality was
varied. But as the shift in modality occurred, a new phenomenon appeared in the evoked potential—a positive waveform with a peak occurring approximately 300 msec following stimulation, which also varied in amplitude inversely with the probability of the stimulus to which the shift occurred. This P300 response was prominent under conditions of uncertainty, but was diminished or absent when no uncertainty was present. As a result of this finding, a series of studies was initiated to determine the effect of the variation of probability of stimuli on event-related responses (Sutton, Tueting, Zubin & John, 1967; Tueting, Sutton & Zubin, 1971; Friedman et al., 1973) and subsequently, upon the pupillary dilation response (Levine & Hakerem, 1969; Friedman et al., 1973; Hakerem, 1974).

The event-related potential was recorded from schizophrenics, depressives, and normal subjects during a guessing task by Levit, Sutton and Zubin (1973). Normals showed the largest P300 amplitudes, with diminished but readily observable P300 responses among the depressive subjects. However, schizophrenic subjects tended to show small or entirely absent responses. Employing a similar paradigm with a more stringent behavioral requirement for insuring attention, Steinhauer, Hakerem & Spring (1979) recorded both event-related potentials and pupillary dilation in schizophrenics, depressives and normals, noting that the pupillary dilation response was also deficient or absent among schizophrenics.
At the initiation of the current project, a modification of the guessing paradigm of Levit et al. (1973) and Steinhauer et al. (1979) was employed, and schizophrenics again were found to exhibit smaller P300 and pupillary dilation responses than normals. The guessing paradigm used is unfortunately time-consuming, requiring a prestimulus guess, presentation of stimuli, and post-trial behavioral report. In order to obtain clear averaged responses, many individual trials had to be employed (a minimum of 50 trials is usually required for each experimental condition). In our experience, obtaining the over 400 trials of data necessary for this paradigm can require 3 to 4 hours of preparation and testing time. Although patients can complete such a procedure, they become distracted and tired, and in our opinion, less willing to return for retesting.

We therefore sought an experimental paradigm that would be more efficient for the collection of data, but would nevertheless, satisfy the following criteria: 1) separate responses could be recorded under conditions of various levels of probability, from relative uncertainty (low probability) to certainty; 2) the paradigm should require a behavioral response to insure that the subjects' attention was maintained to at least some minimal level; 3) the paradigm should generate differential responses in pupillary dilation and the P300 component of the event-related potential (ERP) when presented to normal subjects, similar to the responses obtained with the previously used guessing paradigm (Friedman et al., 1973); 4) because both pupillary dilation and event-related potentials can
be contaminated by motor responses, and given that reaction times are more variable in schizophrenics, no motor response should be generated during the period of recording.

It seemed that the counting paradigm with some modification would meet our requirements. A counting task typically requires the subject to 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). We approached this paradigm with some hesitation, which was related to the previous observations that there was often little pupillary dilation when normal subjects were required merely to report the occurrence of a particular stimulus on some blocks of trials, as compared to larger dilations when the subject was actively guessing on other blocks (Levine & Wakerem, 1969). Thus, we had some concern that the counting requirement would be insufficient for eliciting pupillary dilation. This concern ultimately proved needless. However, we investigated the experimental paradigm first in a group of normal volunteers before testing of patients was begun.

It has previously 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 et al., 1979). Consequently, we decided to employ only auditory stimuli during performance of this task.
Responses of Normal Subjects

Subjects: Seven normal volunteers (5 female, 2 male, age 21-23) participated.

Stimuli: 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.

Physiological recording: Pupil diameter and eye movements were measured 60 times/sec with a Gulf & Western infra-red TV Pupillometer, which provided continuous analog outputs corresponding to pupil diameter, and horizontal and vertical eye movements. The eye movement channels were used to assist artifact detection (blinks, eye movements).

For the event-related potentials, five channels of EEG were recorded with gold cup electrodes from midline frontal, vertex and parietal (Fz, Cz, Pz) and left and right parietal (P3, P4) scalp locations, each referred to linked earlobes and amplified X10,000 with Grass 7P3 or 7P5 amplifiers set to a bandpass of 1-75 Hz. An electrode on the forehead served as ground. Inter-electrode impedances were maintained below 5 K ohms. 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).

A calibration pulse was superimposed onto each of the EEG and pupillary data channels at the start of each trial. The calibration pulse was later averaged along with the signal to
provide absolute scaling of data.

The EKG was also recorded for 4 of the subjects. Gold cup electrodes were placed on the right and left forearms. This placement allowed the detection of movement artifacts as reflected in the EKG leads. A Grass 7P4 tachograph amplified the EKG and provided cardiotach output representing heart rate.

Physiological data were monitored on-line with a 4-channel Tektronix storage oscilloscope and stored on FM magnetic tape. A control pulse to mark the start of each trial was recorded on a separate channel.

Procedure: High and low pitched tones were presented in 8 blocks of 80 trials each, with a 3 second interstimulus interval. For every two consecutive blocks, one of the tones was designated as Target (T), and was presented across trials with an overall probability of .25, with the restriction that the Target could never occur in succession, resulting in a total of 17 to 23 Targets presented per block. 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. The subject was also told that there would be fewer Targets (T) than Non-Targets (NT), and also that two Targets would never occur "in a row." The tones were presented several times before the beginning of the experiment to insure ease of discrimination. The subject was also asked to demonstrate an awareness of the fact that the tone being counted was followed by the Non-Target tone and not by another Target.
(e.g., the subject was asked "If you are counting the low tones and you hear a low tone, what will the next sound be?"). The target to be counted was told to the subject at the beginning of each block and was randomly assigned to either the high or low tone for the first two blocks.

After the electrodes were attached, the subject sat in front of the pupillometer, which was in focus when the subject placed his/her head into a chin/head rest. During recording, the subject fixated a small red LED placed 1 meter away. To minimize pupillary oscillations, all recording was performed in darkness, after 7 minutes of adaptation to allow for stabilization of the pupil. The experimenter sat in a separate room and communicated with the subject through an intercom. Fixation during recording was ascertained on the eye view monitor of the pupillometer. The subject was permitted to remove her/his head from the recording position during a two-minute rest between blocks. Data collection required approximately 45 minutes.

Data collection: Generation of stimuli and all timing operations were controlled by a KIM-1 microprocessor system, which also stored codes indicating the condition for each trial. Trials showing blink or other movement artifacts were recorded for exclusion before final analysis. Off-line, the data were played back from the tape recorder and averaged on a Mnemotron CAT 400A Signal Averager at a sampling rate of 10 msec/point (200 points for ERP data, 400 points for pupillary and heart
rate data). Under microprocessor control, only trials for specified conditions were combined into each single averaged response. A Hewlett-Packard X-Y plotter provided an analog copy of each averaged response curve. For evaluation of amplitudes, the digital values computed by the signal averager were read by the microprocessor and printed, allowing absolute scaling from the averaged calibration pulse.

Although the standard analysis of such data is to segregate trials according to rare and frequent stimuli (corresponding to Targets and Non-Targæts in this experiment), the restriction preventing successive presentations of the Target stimulus permitted a further delineation: 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 \( \Pr(\text{NT/\text{T}}) = 1.00 \), a condition analogous to complete certainty. However, when a Non-Target stimulus occurred, it could either be followed by another Non-Target stimulus or by the Target. The respective conditional probabilities for these outcomes are \( \Pr(\text{NT/NT}) = .67 \) and \( \Pr(\text{T/NT}) = .33 \) (since the Target could not be repeated successively, \( \Pr(\text{T/T}) = 0 \)). These conditional probabilities differ from the overall probabilities of .25 for Targets and .75 for all Non-Targæts.

Separate sets of averages were computed across blocks for which the low pitched tone served as Target vs. blocks on which the high pitched tone served as Target. The number of
artifact-free trials comprising each averaged response was typically between 50-80 for the Target [T] and high-probability Non-Target [NT/T] conditions and 90-150 for the medium probability Non-Target condition [NT/NT].

For evaluation of pupillary dilation and P300, analysis of variance was employed with 3 factors: Conditional Probability (3 levels) X Target Stimulus (2 levels) X Subjects (6; treated as a random factor; data for one subject were excluded from statistical analysis because only one target stimulus had been employed and ERPs had only been recorded from Cz and Pz). Significant F-tests for factors with more than 2 levels (e.g., probability) were evaluated with the Scheffe test at the .05 probability level.

Results: The amplitudes of the P300 component of the ERP and pupillary dilation were greatest 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 & Zubin, 1971). Heart rate showed greater deceleration following the target stimuli than following the non-targets.

Pupillary Response

Greater pupillary dilation has been reported for rare outcomes occurring during a guessing task (Friedman et al., 1973), but have not previously been recorded during a counting task. Typical data for one subject appear in Figure 1, with
Pupillary responses plotted at the top, and vertex and parietal ERPs on the bottom. Positivity at the active electrode is reflected as a downward wave in all ERPs presented.

The typical averaged pupillary response was a dilation beginning several hundred msec after stimulus presentation. The peak of dilation was observed at approximately 1200 msec post stimulus. Initial diameter was calculated from the median activity occurring 130 msec prior to stimulus onset, and peak diameter was measured as the average diameter within the range of 1160-1250 msec post-stimulus, consistent with previous research. The maximum amplitude of peak dilation (peak diameter - baseline) across subjects ranged from .04 to .17 mm for responses to the Target stimuli, reflecting intersubject variability in response magnitude.

Mean amplitude of dilation was .10, .07 and .05 mm, respectively, for conditional probabilities of .33 [T], .67 [NT/NT] and 1.00 [NT/T] (Figure 2). Analysis of variance indicated a significant main effect for conditional probability [F(2,10) = 9.07, p = .006]. The mean dilation for Targets was significantly greater than for either of the Non-Target conditions. Individually, the dilations to the Target stimuli were larger than to the Non-Targets for 6 out of 7 subjects. Although the two Non-Target conditions were not significantly different from each other, a larger dilation was observed for the medium probability Non-Target [NT/NT] than for the high probability Non-Target [NT/T] in 4 of 7 subjects. These effects
are reflected in the significant negative correlation of $-0.95$ ($p < 0.01$, df=5) between amplitude of dilation and conditional probability.

Initial diameters of 8.03, 8.00 and 8.05 mm for the respective probabilities of 0.33, 0.67 and 1.00 were observed (Figure 3). These differences, though significant [$F(2,10) = 10.52$, $p = 0.004$], were due to a significant difference only between the two NT conditions. The larger initial diameter for the [NT/T] condition is considered to be primarily a residual effect of the dilation to the preceding Target stimulus, rather than an effect of stimulus probability. In general, initial diameters under conditions of relative certainty have been found to be smaller than under conditions of uncertainty (Friedman et al., 1973). No significant correlations, however, were found between initial diameter and either amplitude of dilation or conditional probability, either across subjects or as calculated for each subject individually.

Event-related Potentials: The early components of the event-related potential of approximately 200 msec or less were similar across conditions, with marginal stimulus differences observed for the P200 component of several subjects. The most striking difference was observed for the P300 component, but smaller differences could also be observed for the N250 component.
P300 was evaluated as the largest positive wave occurring within approximately 300 msec of the stimulus, which for these subjects actually ranged from 300-350 msec. P300 amplitude was evaluated with respect to a 130 msec prestimulus baseline. Data for the midline frontal, vertex and parietal leads was entered into the analysis of variance as an additional factor. A main effect was observed for electrode placement \( F(2,10) = 33.14, \ p = .0001 \), with a significantly larger response at Pz (7.01 µV) than at either Cz (2.85 µV) or Fz (1.87 µV). Maximum P300 response at Pz (for the Target conditions) ranged from 6.0-16.2 µV across subjects. P300 amplitude at the midline parietal electrode was larger than at either of the lateral parietal electrodes. No differences were observed between the responses recorded at the left and right parietal locations. Data for one subject at all electrode locations are shown for the 'Count Low tones' condition in Figure 4. The N100 (large upward deflection) and P200 components (subsequent downward deflection) are typically observed to be largest at the vertex and then frontal locations. While these components are decreased at the midline parietal location, the P300 component is larger than at the other electrode sites.

A main effect for conditional probability was also obtained \( F(2,10) = 17.66, \ p = .0005 \). The mean amplitude for a conditional probability of .33 [T] was significantly greater than the amplitudes for conditional probabilities of .67 [NT/NT] and 1.00 [NT/T] (Figure 5). Four of the subjects showed a larger response for the lower probability Non-Target [NT/NT].
while other subjects showed no differences. One subject showed clearly larger responses to the high probability condition [NT/T] compared to the lower probability Non-Target [NT/NT]. The data for this subject indicate heightened responsiveness to the dimension of stimulus change, which in this experiment was a shift in frequency of the stimulus tone between 800 and 1500 Hz.

The difference in amplitude between the Target and Non-Target conditions was approximately 6.5 μV at both vertex and parietal electrodes, but only 3 μV at frontal, resulting in a significant interaction between electrode location X conditional probability [F(4,20) = 5.66, p = .003].

The latency of P300 was evaluated across stimuli (since no stimulus differences were obtained), and included the data for all 7 normal subjects. A significant main effect was found [F(2,12) = 12.88, p = .001]. The mean latency +/- standard error was 347.8 +/- 4.5 msec for the Target stimulus, 321.4 +/- 8.4 msec for the .67 probability Non-Target [NT/NT] and 318.6 +/- 7.6 msec for the high probability Non-Target [NT/T]. The significant increase in latency for the response to the Target condition is considered to reflect additional processing related to both the rareness and task-relevance of this condition.

Cardiotach data were also averaged across trials for 3 of the subjects. Averaged heart rate responses plotted at .5 sec intervals across subjects [Figure 6] indicate a tendency for an initial acceleration followed by maximum deceleration at 1500 msec. The extent of deceleration (500 msec pre-stimulus - 1500
msec post-stimulus) is plotted across conditional probability in Figure 7, along with similar graphs for peak dilation and P300 amplitude. The similarity between the pupillary and heart rate data is especially striking. The most distinguishing features of the response are the tendency to show a marked deceleration to the Target at approximately 1500 msec after stimulus presentation, and great inter-subject variability in the shape of the waveforms, which nevertheless seem characteristic for a single subject. Pupillary and ERP waveforms characteristic of specific individuals have previously been reported (Bock, 1976; Hakerem, 1974).

For all physiological measures, no differences were observed between the high vs. the low tone serving as Target stimulus.

Discussion: The manipulation of conditional probability resulted in corresponding changes in pupillary dilation, P300, and heart rate. The pupillary results are especially intriguing, since previous work (Levine & Hakerem, 1969) 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), with an association due to novelty of stimulation. From such a vantage point, one would predict that stimulus change would be a major influence upon pupillary dilation. For the present data, however, change of stimulus per se was not as effective in producing pupillary
dilation as was the uncertainty resolved by stimulus presentation. Specifically, the change from a Target to a Non-Target stimulus, a highly probable event, resulted in less dilation than repetition of the same Non-Target, an event that involved greater uncertainty but no change. Subjects were still required to discover for themselves the relative probabilities of the Target and "uncertain" Non-Target [NT/NT].

It has also been shown that presentation of "novel" stimuli is associated with a P300 having a more anterior distribution (Courchesne et al., 1975), but the topographical distribution observed here is more posterior, which has been associated with various information processing tasks (Tuetins, 1978). The amplitude of the P300 component has long been associated with variations in stimulus probability (Tuetins, Sutton & Zubin, 1971; Donchin, 1979; Tuetins, 1978). Sauires et al. (1976) have demonstrated quite clearly the dependence 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 Sauires et al. (1976), the repetition of a Non-Target stimulus (F = .67) indicated a more "surprising" event (in their terminology) than the change from a Target to a Non-Target [NT/T]. Previously, the similar presentation of stimuli has not been evaluated in such detail. Roth et al. (1980a; 1980b) recorded ERPs from both normal and schizophrenic subjects,
requiring subjects to perform a motor response at presentation of the Target stimulus. No attempt was made to compare the high probability of a Non-Target following a Target, with Non-Targets that were less predictable [NT/NT]. We suspect that P300s analyzed according to conditional probabilities would have revealed individuals among the subjects of Rothe et al., whose patterns resembled those obtained in the present study, even though the tasks differed.

Lacey and Lacey (1980) used a paradigm similar to the present one in a study of heart rate, but were examining influences upon period of the cardiac cycle rather than the overall time course of heart rate changes. The response to the rare tone was discriminated from the frequent tones by a decrease in the subsequent period between R waves, an increase in rate. Our findings of a major deceleration to the rare tone was obtained by examining changes in heart rate over a greater time period, and we noted the tendency for subjects to show an initial acceleration, which could be the change measured by Lacey and Lacey. In their data, the inter-subject variability was also a prominent characteristic. Lacey and Lacey also recorded vertex P300 from their subjects. They observed the usual enhancement of P300 to the rare Target, but then compared Non-Targets that preceded the rare tone to those that followed it. No P300 was observed to the preceding Non-Target, and either a small or no P300 was observed following the Target. These findings for the Non-Targets are not fully representative of the ongoing processing activities, however; while the
subsequent standard tone averaged by Lacey and Lacey is equivalent to our Non-Target [NT/T], the tone preceding the Target as reported by them is actually comprised of both types of Non-Targets, those following another Non-Target [NT/NT] and also some of the tones which followed a Target. Moreover, the vertex recording site is less representative for this task than a parietal recording site would have been.

The effect of conditional probability on these physiological measures offers an opportunity to infer the various information processing strategies characterizing each individual. Six such strategies will be described:

A) An individual who shows no differences between responses evoked by Target and those evoked by Non-Target stimuli since either little or no response is observed. This would usually be considered to occur normally when the subject's attention is directed away from the stimuli (e.g., by reading a book). It is, therefore, necessary that some behavioral manifestation of attention be required in order to assure attentiveness. If the subject has at least been able to provide a behavioral report, that usually accompanies some physiological change, and the physiological change is absent, the normalcy of the information processing mechanisms is suspect (the relationship between physiological response and accuracy of the report is examined in a later section). The non-responder is, thus, distinguished from other individuals who show evidence of a vigorous response.

B) An individual may show a physiological response
(pupillary dilation; P300, heart rate deceleration) which, though present, does not differentiate among the conditions of the experiment.

C) An individual whose responses were larger to frequent Non-Targets than to rare Targets would be expected to be using an alternative, possibly deviant, hypothesis in processing the available information. It would be enlightening to examine the strategies that such a subject adopts.

Three remaining patterns are all characterized by a maximum response to the Target (relevant, rare) stimulus:

D) There may be no differential response to the Non-Target stimuli, which suggests that the subject has categorized all Non-Targets together regardless of their conditional conditional probabilities.

E) If a larger response is recorded to the more probable Non-Target following a Target [NT/T] than to the less probable repetition of a Non-Target [NT/NT], it would imply that the individual was especially sensitive to changes in the physical characteristics of successive stimuli rather than to their different conditional probabilities; this pattern may be conceptualized as fitting an "orienting" model of processing.

F) The final pattern differs from the others in so far as the conditional probabilities are inversely related to response amplitudes. A larger response occurs to the Non-Target [NT/NT, p = .67] that is a repetition of the previous stimulus than to the highly probable stimulus shift to a Non-Target from a Target. An individual displaying this pattern seems to make
maximum use of the information regarding conditional probabilities, and is considered to be operating at a more complex level than individuals characterized by any of the other patterns of responses. This final pattern (F) seemed most characteristic of the normal subjects, although not necessarily present in all of the physiological responses measured in the same subject. It remains an intriguing problem to integrate the varying patterns of physiological responses for the same subjects with individual processing strategies. This analysis may provide a general framework for examining the response patterns of psychiatric patients.

Responses of Psychiatric Patients

The diminished amplitude of P300 in schizophrenics has been observed during performance of guessing tasks (Levit, Sutton & Zubin, 1973; replicated by Verleser & Cohen, 1978) and of reaction time tasks recorded to infrequent stimuli (Roth et al., 1980a; 1980b). The current paradigm builds on these reported findings and permits in addition an analysis of the patterning of response amplitudes across different conditional probabilities.

The procedure employed was the same as described above except for the addition of a performance incentive: if the subject reported the correct number of targets presented during
a block of 80 trials a reward of 25 cents was given. If the
error ranged between +/- 1 or 2 counts, the reward was decreased
to 10 cents, and 3 or more errors were not rewarded at all.

During preliminary use of the paradigm, several patients
were tested only under the "Count low tones" condition.
Event-related potentials were recorded from all subjects, using
the electrode montage reported above. Pupillary diameter was
not recorded from several subjects who could not suppress high
rates of blinking, and who were therefore instructed to keep
their eyes closed. For subjects on strongly anticholinergic
agents, which dilate the pupil but allow little pupillary
motility, the pupillary data was not considered. Pupillary
contraction on accommodation to a near stimulus was examined in
all subjects to verify pupillary motility. Heart rate was also
recorded from most of the subjects, but will not be discussed at
the present time.

The patients were drawn from recent admissions to the
psychiatric wards of the Highland Drive VA Medical Center.
Exclusions were made for excessive alcohol abuse or use of
narcotics, or organic involvement (present or past). Subjects
were between 21 and 35 years of age, with the exception of a 42
year old male subject. Only one of these patients was female;
the twin sister of this subject was also tested.

Each patient was given a structured psychiatric interview
(either the Combined Interview Schedule developed by the Dept.
of Psychophysiology at the N.Y.S. Psychiatric Institute, which
incorporates the Schedule for Affective Disorders and Schizophrenia (SADS), or the Renard Diagnostic Interview (RDI) developed at Washington University in St. Louis. A diagnosis according to Research Diagnostic Criteria (RDC) was based on the interview data. To facilitate testing of patients who were in a drug-free state on entering the hospital, laboratory procedures were often carried out prior to the administration of the clinical interview. Of 18 patients tested, 10 received a diagnosis of schizophrenia; 6 were classified as depressive; and 2 were considered to have no mental disorder.

The data to be presented here are drawn from 7 of the schizophrenic patients who were tested soon after admission, while still judged to be undergoing an active episode of illness. Five of these patients were receiving no medications at the time of testing. ERP data for 5 of the depressed patients will also be presented.

Data was analyzed either with the CAT 400 signal averager, as described previously, or with a MINC-11 minicomputer. The sampling rate was increased to 125 samples/sec for data analyzed with the latter system.

Results: Schizophrenic patients were generally characterized by small or absent P300 responses and minimal pupillary dilation. Representative data for one unmedicated subject are presented in Figure 8. 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 (bottom, Figure 8) 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 fact that the stimuli were properly received and processed initially.

Data for several patients was obtainable using only one of the physical stimuli as the Target. Since no differential stimulus effects were observed for the normals or in the averaged waveforms for patients with a complete data set, data for these patients were averaged across stimuli. Only responses recorded during blocks for which the subject's report was correct within +/- 2 counts were included for this analysis.

No significant differences were seen for initial pupillary diameter \( [F(2,12) = 1.50, \text{n.s.}] \) among the schizophrenics (Figure 9). However, a main effect for amplitude of peak dilation was obtained \( [F(2,12) = 15.67, p = .0005] \) (Figure 10). Pupillary dilation was larger for the [T] and [NT/T] conditions than for the [NT/NT] condition. The two events which represented a change from the previous stimulus resulted in the greatest dilation, analogous to pattern [E] described previously, which has been characterized as an orienting pattern. P300 amplitude (Figure 11) was not significantly different across probabilities for the schizophrenics \( [F(2,12) = 2.45, \text{n.s.}] \), although the
trend across subjects was similar to the pattern observed for pupillary dilation [Figure 10].

There was no significant effect of conditional probability on the latency of P300 for the schizophrenics. Mean latencies and standard errors were 320.7 +/- 14.1, 322.7 +/- 14.8 and 326.7 +/- 14.8 msec for the respective probabilities of [T] = .33, [NT/NT] = .67 and [NT/T] = 1.00.

Depressives: Depressive patients tended to show responses that were most similar to those of normal subjects (e.g., Figure 12). However, 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 submitted for analysis of variance, but did not reveal any significant differences due to conditional probability. However, the pattern of P300 amplitude was similar to that observed for the normal subjects.

Means and standard errors of P300 amplitude at the midline parietal scalp location are plotted in Figure 13 for normals (solid line), depressives (dashed line) and schizophrenics (dotted line). Only the differences between the normal and schizophrenic subjects are significant [F(1,12) = 13.37, p = .003]. The order of amplitude across groups - largest for normals, 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 \( F(1,13) = 1.93, \text{n.s.} \), which was 7.87 mm for the normals and 7.30 mm for the schizophrenic patients. The amplitude of pupillary dilation (Figure 14) was significantly larger for the normals than for the schizophrenics \( F(1,13) = 7.79, p = .015 \), with a mean dilation of .07 mm across conditions for the normals but only .02 mm for the schizophrenics.

Discussion: As in previous studies, both pupillary dilation and P300 amplitude were found to be smaller for schizophrenic patients than for normals. The response deficits are not likely to be attributable to lack of attention, since a behavioral response was required (counting the number of target stimuli). In comparison to the earlier data of Levit et al. (1973), who noted that the waveforms for schizophrenic subjects were aberrant, often with no clear appearance of early components (100-200 msec), all subjects showed readily observable N100 and P200 components in the present study. We attribute this difference in large part to the behavioral requirements imposed on the subjects. In the Levit et al. study, subjects were required to make a pre-stimulus guess, but were not asked to identify trial outcome after the stimulus had been presented. It may be that their patients were less attentive than in studies requiring post-trial behavior (Roth et al., 1980b; Steinhauer et al., 1979). Our subjects were required to count the number of target stimuli in addition to
maintaining position in a head rest and fixation during the recording period. Furthermore, the current procedure and apparatus enabled a direct monitoring of fixation.

The task employed is relatively easy for normal subjects, who rarely make an error of more than one count. On the other hand, some patients often make errors from block to block, and at the suggestion of Samuel Sutton, we examined the contribution of errors to generation of the P300 response. ERPs for one depressive patient are shown in Figure 15 (top) for all blocks on which the subject counted accurately (a stimulus artifact is observable in some of these tracings, especially at P4). A large P300 is visible in response to the Target stimuli (the leftmost column). But when the subject did not count accurately (Figure 15, bottom), P300 was greatly diminished. In Figure 15 (bottom), we do not know exactly which trials the subject has counted, or even whether all of the Targets were among the tones counted. Perhaps, in this case, the subject merely guessed the number of tones presented, and paid little attention to the actual presentation of stimuli. These waveforms indicate that greater accuracy in performance will result in larger P300s for the rare tones, and that a lapse of attention will be indicated by P300 decrement.

This specific paradigm has the disadvantage that a behavioral response is not obtained after each stimulus presentation, as was obtained by Steinhauer et al. (1979) in the guessing paradigm and by Roth et al. (1980b) using a
reaction time task. We consider the elimination of an immediate report (motor or verbal) by the subject which identifies the stimulus as quite justifiable, since it was important to eliminate any motor activity during the block. We also sought to present stimuli over relative short intervals to increase the number of trials; inclusion of a verbal report would have greatly increased trial duration. Moreover, the task requires that subjects maintain the current count of Target stimuli throughout the block, so that reliance on only immediate information is not satisfactory for correct performance, as it is in the RT task of Roth et al.

Schizophrenics, however, have smaller responses than normals even when their performance is accurate. Since appropriate counting was performed, it is apparent that information regarding the stimulus was processed and retained by the subject. What, then, is 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 with respect to the catalogue of types of patterns described earlier. As noted, the only significant effect for schizophrenics was that pupillary dilation to both the Target and the Non-Target following the Target (that is, T and NT/T stimulus conditions) were larger than to the repeated Non-Target [NT/NT]. This was similar to pattern "E" as described earlier, except that there
was no difference between the [T] and [NT/T] responses. Comparison of pupillary dilation and P300 for the schizophrenics in Figures 13 and 14 indicates an unusual similarity in profiles, even though both sets of responses were small compared to normals, and that the P300 for the schizophrenics was not significantly different across conditions.

On the basis of these patterns, it is suggested that the schizophrenics do make use of information, but do so differently from normal subjects, and perhaps, from depressive patients. The schizophrenics show a greater response (if any) to stimuli that differ physically from the previously presented stimulus. That is, they show an orienting response when the stimulus changes, but do not show evidence of utilizing information regarding change in conditional probability which involves attention to the overall presentation of stimuli.

Roth et al. (1980b) report that even though schizophrenics show consistently smaller P300s than normals, the amplitude of P300 was still increased for schizophrenics when RT was faster, further supporting the contention that even in schizophrenics, differences in P300 amplitude reflect differential utilization of information. Roth et al. hypothesize that the reduced P300 amplitudes indicate a general deficit in responsiveness to unexpected stimuli, and also a failure to use information regarding probabilities of stimulus presentation. The present data indicate agreement with the notion that schizophrenics fail to use the information regarding overall event probability (even
though they report accurately the count of Targets). However, the pattern of both pupillary and ERP responses suggest that there is a trend for responding to changes in stimuli with an orienting response, which is detected despite the overall low amplitude responses of the schizophrenics. This finding is opposite to the more general notion, based primarily on data from the skin conductance literature, that schizophrenics fail to show an orientation response (Spohn & Patterson, 1980; Venables, 1977). Perhaps the difficulty is that orienting must be discriminated as a small signal within a background of high non-signal noise. Thus, signal-averaging as applied in this study contributed to detection of the signal. It is, however, the basically small amplitude of responses that remains the most intriguing problem. The schizophrenic appears to use the data from each trial less effectively than the normal, particularly with reference to future trials (i.e., if the schizophrenic bears in mind the instructions, there should be little surprise that the stimulus following a Target is always a physically different stimulus).

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; in this case, the probability of a Target is decreased to its overall probability of .25. In normal subjects, decreasing the event probability increases P300, but this was not observed for the schizophrenics.
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. That is why a change in stimulus has a greater effect than differences in conditional probability for the same stimulus.

It is not yet possible to determine whether this underutilization of information represents an interference in normal cognitive ability, or a decrease in the affective meaning of the stimulus. For example, does the schizophrenic continue to count, but fail to consider the reward associated with correct performance?

Zubin and Spring (1977) emphasized that detection of individuals vulnerable to episodes must rely on the identification of those markers that can be associated with beginning and ending of the episode (state markers) and on those markers that are relatively independent of the episode (trait markers), which may theoretically be observed in unaffected individuals. A more detailed discussion of markers has been provided (Zubin, 1980).

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 et al. (1973) reported recovery of P300 for one patient who showed signs of clinical improvement, but not for another patient still exhibiting symptomatology.
Data for two schizophrenics is presented in Figures 16 and 17 comparing original and follow-up testing. Subject 33 was originally tested with a guessing paradigm during hospitalization, at which time he was receiving Haldol and Cogentin. P300 is not apparent in Figure 16, and no pupillary dilation is observed at the same time (Figure 17). Medications may have diminished his pupillary motility. He was retested six months later during an out-patient visit, after having been free of all medication for over 3 months. By this time we had changed to the counting paradigm. Despite this change, it is readily apparent that P300 is present in the second set of data, during which time the patient was functioning quite well outside of the hospital, and even attending college classes. A second schizophrenic patient (S36) was tested with the counting paradigm on three occasions: soon after admission (under treatment with Mellaril), and at 4 and 7 weeks subsequently. Medication had been stopped one week after the initial testing. Data for this subject indicates a recovery of both P300 and pupillary dilation, which accompanied subjectively evaluated improvement in the patient’s behavior, even though he was hospitalized during all testing periods. An additional patient (S40, not pictured) was tested drug-free at the time of admission, with no pupillary or P300 response evident. One-month later, while receiving Haldol and Cogentin, he was retested, with only a slight increase in the clarity of a minor P300 response evident; pupillary data were not obtained.
Such data suggest that P300 is probably valuable as an episode marker, showing recovery during clinical improvement, a notion that had been expressed previously (Levit et al., 1973; Shagass, Ornitz, Sutton & Tueting, 1978). The pupillary data suggest that for some subjects, the dilation response may serve as a long term indicator of vulnerability (Zubin, 1980) for a subgroup of patients.

The role of neuroleptics with regard to response decrements is not yet clear. One might take the position that administration of medication during the original test period for Ss 33 and 36 had been responsible for suppression of P300. However, the data for the schizophrenics who were tested prior to medication clearly indicate that low amplitude responses are observed during an episode prior to pharmacotherapy. Shagass et al. (1978) suggest that clinical improvement due to neuroleptics is associated with improvement in ERP waveform and amplitude. 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.

Summary

The search for psychophysiological markers of vulnerability to schizophrenia which this paper reports has been limited to evoked potentials and pupillography as indices of information processing. To substitute for the cumbersome guessing paradigm
Previously employed, a counting paradigm was adapted to provide three levels of probability ranging from low to medium to high.

The results indicate that for normals there is a definite negative relationship between level of uncertainty and the extent of dilation of the pupil, cardiac deceleration, and for most subjects, for the amplitude of the P300 component of the event related potential.

For schizophrenic patients during their episode, this relationship is not apparent. However, for two patients who were followed-up past the end of their episode, there was a recovery of P300 amplitude. It is suggested by the data that while normals tend to be influenced by the conditional probability of the stimulus regardless of change or redundancy in the stimulus, patients (while in their episodes) seem less influenced by conditional probability and more influenced by change of stimulus. This is consistent with Salzinger's immediacy hypothesis.

This preliminary report indicates that the search for markers of vulnerability must take cognizance of the fact that some of the differentials between schizophrenics and normals reflect the presence of an episode and hence are episode rather than vulnerability markers. It therefore becomes necessary to follow-up the patients after their episodes end to see whether the marker persists.


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PUPILLARY DILATION RESPONSE

Stimulus Onset

1 second

Low Probability Stimulus (p=.33)
High Probability Stimulus (p=.67)
High Probability Stimulus (p=1.00)

EVENT RELATED POTENTIALS

VERTEX

PARietAL

N=77
N=106
N=85
N=105
N=146
N=112

.1 mm

10 uv

.5 second

Fig. 1
Fig. 2. Mean amplitude of dilation vs. conditional probabilities for normal subjects
Fig. 3. Mean amplitude of initial diameter vs. conditional probabilities for normal subjects
FRONTAL (Fz)

15
uv
+

VERTEX (Cz)
P = 1.00
P = .67
P = .33

PARIETAL (Pz)

LEFT
PARIETAL (P3)

RIGHT
PARIETAL (P4)

.5 sec

Fig. 4
Fig. 5. Mean amplitude of P300 vs. conditional probabilities for normal subjects at Pz and across subjects 42-48 at Fz, Cz, Pz
ACROSS 3 Ss

**AVERAGE HEART RATE (BEATS PER MINUTE)**

**TIME (SECONDS)**

- **P = 1.00**
- **P = 0.67**
- **P = 0.33**

Fig. 6
Across 6 Ss

Pupillary Dilation

Across 6 Ss

P300 Amplitude

Across 3 Ss

Heart Rate Deceleration

Fig. 7
PUPILLARY DILATION RESPONSE

.1 mm

Stimulus Onset

1 second

Low Probability Stimulus (p=.33)
High Probability Stimulus (p=.67)
High Probability Stimulus (p=1.00)

EVENT RELATED POTENTIALS

VERTEX

PARietal

10 μV

.5 second

Fig. 8
Fig. 9. Mean amplitude of initial diameter vs. conditional probabilities for schizophrenic subjects.
Fig. 10. Mean amplitude of dilation vs. conditional probabilities for schizophrenic subjects.
Fig. 11. Mean amplitude of P300 vs. conditional probabilities for schizophrenic subjects
Fig. 12 Data from a Depressive subject
Fig. 13: P300 at Pz
Fig. 14: Pupillary Dilation
Fig. 15 Top: Accurate counting  
Bottom: Inaccurate Counting
Fig. 16
PUPILLARY DILATION: Count "LOW"

S33

GUESSING 3/16/79

COUNTING 9/17/79

S36 (COUNTING)

6/8/79

7/10/79

7/30/79

.10 mm

↑

1 sec

Fig. 17