THE PUPILLARY RESPONSE IN COGNITIVE
PSYCHOPHYSIOLOGY AND SCHIZOPHRENIA\textsuperscript{a}

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I. Introduction

The human pupillary response, whose final neural pathways are mediated through the autonomic nervous system, has been shown to reflect more centrally occurring processes when examined from the perspective of information processing activities. This chapter will examine components of information processing as reflected in the pupil, and its relation to other neurophysiological signs of cognitive activity, most notably, the event-related brain potential. Both the constriction of the pupil to light (miosis), as well as the dilation (dilatation; mydriasis) resulting from information delivery, have provided useful adjuncts in the study of psychopathology, especially with reference to schizophrenia; The time course of pupillary dilation, reflected in the morphology of the pupillographic record, indicates a high degree of similarity among related family members; findings from patients and their relatives will be reviewed.

While the contributions of separate physiological components to the cognitive pupillary dilation response have never been adequately delineated, a review of findings indicates the possibility for experimental dissection of components. A model delineating likely psychophysiological contributions to the pupillary response, and approaches for testing the model, will be presented.

II. General Background and Historical Perspective

For centuries, the pupillary aperture has been thought of as a figurative window to the mind; with the advancement of medical sciences, the pupil began to serve as a literal window on brain function. In her 1958 tome dealing primarily with pupillary dilatation, Loewenfeld (1958) cited nearly 1600 references, including 114 dated prior to 1830. Incidental observations of pupillary dilation associated with increased interest or arousal were well known, such as the use of belladonna to enlarge the pupil artificially as a cosmetic effect, and wearing of eyeshades to obscure any sudden dilatation for the poker player who might otherwise give away his hand.

During the early years of this century, aberrations in pupillary responsivity were carefully noted in psychotic patients (cf. Hakerem & Lidsky, 1975; Hess, 1972), especially by German psychiatrists such as Bumke (1904) and Bach (1908), and were followed up with studies by Lowenstein and Westphal (1933), Levine and Schilder (1942), and May (1948) in the third and fourth decades.

The earliest work this century was performed by comparing the pupil with hand-held templates, or through laborious, often Herculean, photographic analyses. The first major leap in technology was provided by Otto Lowenstein's development of an electronic scanning pupillograph. Lowenstein, with Irene Loewenfeld, was responsible for many of the detailed investigations into the physiology of pupillary activity (e.g., Loewenfeld, 1958, 1963; Loewenstein & Loewenfeld, 1952, 1962). By digitizing the analog output, it became possible to utilize computer averaging both in the recording, data storage, and analysis of pupillary activity (Hakerem, 1967). In the past two decades, infra-red TV-based systems, providing both analog and digital output, have permitted direct interface and control with laboratory minicomputers and even personal computers. As an example of the technological effects, we once calculated that a research project investigating the reaction to light, which required seven months of data collection and analysis in 1962, could be performed today within a single afternoon. There is a
caveat to such methodological speed, and that is that the generation of experiments may become more routinized rather than well-conceived, a notion that would be strongly criticized by Samuel Sutton, who played an integral role in some of the research to be discussed below.

The re-emergence of pupillary studies among psychologists is related to a series of reports from several different laboratories in the early 1960s in the areas of experimental psychology and experimental psychopathology. The most polemic approach was generated by the initial papers of Eckhard Hess claiming pupillary dilation to positive affect stimuli and constriction to negative affect (Hess & Polt, 1960), which led to continuing controversies. Hess and Polt also began to report on pupillary dilation during mental activities (Hess & Polt, 1964), and this direction was taken up by Kahneman and Beatty (1966) representing a much stronger commitment to the developing concepts of cognitive psychology. A separate source of interest in pupillographics was developing in investigations of psychopathology. Leonard Rubin, at Eastern Psychiatric Research Institute in Philadelphia, was employing pupillary measurement to develop hypotheses of autonomic imbalance in psychiatric patients (Rubin, 1960, 1961, 1974; Rubin & Barry, 1968, 1972a, 1972b, 1976).

During the same period, both approaches, the psychopathological and the cognitive, were involved in the research program emerging from the Biometrics Research program in New York, involving Gad Hakerem, Samuel Sutton, and Joseph Zubin. Technological changes again played a substantial role in these developments. By the early 1960s, the Lowenstein pupillograph had replaced the camera in Hakerem's laboratory, and Manfred Clynes had introduced the first practical analog signal averager: the Computer of Average Transients (CAT 400). Clynes had been interested in using the device for physiological analysis of pupillary reactions as well as for electrophysiological analysis, and one of the earliest machines was made available to the Biometrics Research laboratories. Data were standardly recorded onto multichannel FM tape, along with trigger pulses preceding stimulus presentations. Off-line, the trigger pulse was used to initiate sampling with the CAT, and the resulting averages were plotted on paper. However, the same technology was appropriate for deriving evoked potentials, and Samuel Sutton's event-related potential laboratory was located directly across the hall. Tape recording allowed collection of data in either laboratory, but initially there was only the single averager. Thus, the CAT began a history of being shuttled back and forth between laboratories, providing averaged pupillographic waveforms one day, averaged evoked potentials the next. Eventually, this traveling show resulted in the detection of the P300 component of the event-related potential (ERP), as it is known today, by Samuel Sutton and colleagues (Sutton, Braren, Zubin, & John, 1965), and one of the keystones of cognitive psychophysiology was established. One of the initial pupillary studies involving cognitive processing activity demonstrated that visual stimuli at a 50% detection level (which were too weak to produce pupillary constriction) resulted in dilation when they were reported as seen, but not when they were missed, when blanks were inserted, or when no detection was required (Hakerem & Sutton, 1966). A further addendum to this story is that the continuing collaborations between the laboratories emphasized a number of parallels between pupillary dilation and P300 activity, so that eventually Hakerem and Sutton decided to add recording of the ERP to the pupillography laboratory. Some of the comparisons of pupillary and P300 findings are reviewed below.

Further study of constriction to light, and dilations in normal subjects and schizophrenic patients evoked during cognitive tasks has continued to be one of the primary aims of a second Biometrics Research Program that was established by Joseph Zubin in 1977, with Stuart Steinhauer, at the Highland Drive VA Medical Center in Pittsburgh. The research conducted in
the Pittsburgh program was strongly influenced by the original findings in New York, and continued the collaborative efforts between the institutions (indeed, in order to be able to begin averaging procedures, Sutton loaned the original CAT 400 to the Pittsburgh laboratories for several years!).

III. Cognitive Psychophysiology and Pupillography

Psychophysiological Measurement of Processing Effort, Capacity, and Information. Among those measures for which a correlate of both attentional effort and processing activities have been studied, perhaps the most widely emphasized is the pupillary dilation response (Beatty, 1982; Beatty, 1986; Goldwater, 1972; Janisse, 1977). Pupil diameter enlarges with increasing effort during performance. This can be observed for purely mechanical effort, as when varying weights are picked up (Nunnally, Knott, Duchenowski, & Parker, 1967) or even when a simple finger press occurs, in which both response preparation and execution contribute to the dilation (Richer, Silverman, & Beatty, 1983). Mental effort has been manipulated by a number of means, including arithmetic problems of varying difficulty (often a typical "mental stress" paradigm), language-based tasks (including reading of material forward and backwards; Metalis, Rhoades, Hess, & Petrovich, 1980), and especially the effect of increasing memory load during the digit span task, in which pupil diameter increases as the number of digits stored is increased (Kahneman & Beatty, 1966). Of special interest is that as maximum effective storage (judged by performance) is reached, pupillary dilation reaches a maximum (Peavler, 1974). When memory is overloaded, the pupil may even decrease in diameter, suggesting that it is sensitive to both the extent of processing capacity as well as the breakdown of capacity (Poock, 1973). Kahneman (1973) relied heavily on results from pupillary experiments in the development of his treatise dealing with basic components of attention and effort.

Pupillary dilation can also be evoked by tasks in which there is little effort employed in recognizing a stimulus, but for which the "informational value" of the stimulus is high. Thus, simple click patterns show a quick habituation when the subject knows what each subsequent stimulus will be, but a clear dilation occurs to the clicks when the subject is asked to guess what stimulus pattern will occur (Hakerem, 1974). Moreover, when the subject is not certain whether a click will actually occur at a specific point in time, but the absence of a click indicates a particular outcome (e.g., correct or incorrect, different amounts of monetary payoff), the "absence" of the stimulus itself elicits a pupillary dilation (Levine, 1969) which is related to the information conveyed by the stimulus absence.

Greater payoff will produce a dilation response of greater amplitude either when it is evoked (when the feedback cue is present) or emitted (when absence is the cue) (Steinhauer, 1982). Figure 1 presents average pupillary waveforms in which different amounts of money (0, 25, or 50 cents) were associated with each trial. The stimulus at S1 was a single 1 msec click. At S2, the informational stimulus was either the absence of a click (emitted) or an additional, identical click occurred at S2 (single click evoked). These events indicated whether the subject had won or lost money on those trials. The set of data on the bottom was recorded when a pair of clicks separated by 10 msec was presented instead at S2, indicating that no money was either won or lost.
Figure 1. Pupillary dilation in 8 normal subjects during a task associated with monetary value and outcome. A single click at S1 was followed by one of three informational cues at S2: either no additional stimulus (emitted response), another identical click (single click evoked), or a pair of clicks (double click evoked). Little dilation was seen when the subject was told what each S2 would be (Certain). Pupillary dilation increased with the amount of money wagered on each trial (0, 25 or 50 cents), and was greater when the subject, rather than a computer, selected the values (adapted from Steinhauer, 1982).

Several aspects of the pupillary response are depicted in these data. First, regardless of whether the presence or absence of a click was used to provide critical feedback, the pupil
showed a dilation reaching its widest diameter approximately 1200 msec after the time of the feedback. Second, the amplitude of dilation was related to the amount of money associated with the trial. Third, the extent of dilation was much greater when the amount of money involved was selected by the subject (Subject-Bet condition), rather than when the value was told to the subject as selected by a computer randomization prior to each trial (Computer-Bet condition). Finally, there was little dilation to conditions in which no money was involved, and the subject was merely told which stimulus would occur on the next trial (Certain condition). (Similar results were seen for the amplitude of the P300 component recorded simultaneously with the pupillary data.)

The phenomena of evoked and emitted pupillary responses directly parallel the initial findings for evoked (Sutton et al., 1965) and emitted (Sutton, Tueting, Zubin, & John, 1967) P300 components of event-related potentials, which were the templates for the design of several pupillary studies (Levine, 1969). A number of specific comparisons between ERP and pupillary data were subsequently conducted (Friedman, Hakerem, Sutton, & Fleiss, 1973; Bock, 1976; Richer & Beatty, 1981; Steinhauer, 1982; Steinhauer & Zubin, 1982).

Following the demonstration by Patricia Tueting that P300 was inversely related to stimulus probability (Tueting, Sutton, & Zubin, 1970), David Friedman simultaneously recorded pupil diameter and the vertex ERP during a guessing task, with the relative probabilities of two events changing across blocks (Friedman et al., 1973). Friedman compared pupillary and P300 data to the subjective probabilities (an interaction of the subject's guessing behavior and the stimulus probabilities), and found that the amplitudes of both dilation and P300 were inversely related to the subjective probabilities. Thus, larger amplitudes were seen for the least likely events. The same paradigm was employed by Bock (1976), who recorded pupillary and ERP data from monozygotic and dizygotic twin pairs, and from non-twin siblings.

A somewhat different approach was employed by Steinhauer and Zubin (1982), who used an auditory oddball procedure to record pupil diameter and ERPs from multiple scalp locations. The "oddball" in the typical experiment refers to the fact that two stimuli are presented with unequal probabilities. Unlike the tasks of Friedman et al. (1973) and Bock (1976), in which guessing was involved, the oddball task requires the subject to identify stimuli by either silently counting one of the stimuli, or by providing discriminative reactions (e.g., a finger press) to one or both stimuli. It explicitly differs from the guessing paradigm both behaviorally and physiologically. Maximum P300 amplitudes are seen at vertex (Cz) during guessing paradigms, but are found at the midline parietal location (Pz) for post-hoc identification tasks such as the oddball paradigm. The guessing paradigm tends to produce larger pupillary dilations and P300 amplitudes than the oddball task, but at the cost of long intertrial intervals in order to provide prestimulus guesses and post-stimulus reports by the subject. Thus, a limited number of individual trials (2-4/minute) can be obtained during test sessions, and this was problematic in our experiences testing schizophrenic patients. The guessing procedure could take several hours, and was especially fatiguing for patients. The oddball procedure, using continuous stimulus presentation at short intervals (e.g., 1-3 sec intertrial intervals), greatly increases the number of trials recorded during a single session, and therefore results in less fatigue when employed with patients.

However, we did not wish to relinquish comparisons employed in the guessing task between "certain" and "uncertain" stimuli. In the ERP (Tueting et al., 1970) and pupillary tasks (Friedman et al. 1973; Bock, 1976), subjects were recorded both during active guessing, and separately on blocks in which there was no guessing, but instead each stimulus was told to the
subject before the trial began, and thus the subjects were "certain." In the certain condition, there are primarily sensory components of the ERP present (e.g., N100, P200) and the pupil shows rapid habituation, with virtually no dilation (see Figure 1, "Certain" conditions). P300 and the dilation response immediately emerge whenever guessing is reinstated. The difficulty in adopting the oddball paradigm was to incorporate the notion of "certainty" within the presentation of rare and frequent stimulus events. This was ultimately accomplished by the simple procedure of allowing only one rare stimulus (e.g., a high tone) to occur at a time, without repetition. Furthermore, subjects were explicitly informed of this proviso -- that two rare tones could not occur in a row. Consequently, even chronically hospitalized patients found it easy to answer the question "If you hear a high (rare) tone, what will the next sound be?" with the answer "a low." Thus, after every rare tone, the frequent tone could be predicted to occur with great certainty (that is, a conditional probability of 1.0), while after any frequent tone, the subject was unsure whether the next sound would be one of the task-relevant rares or irrelevant frequents. Average pupillary waveforms to these conditions indicated an inverse monotonic relationship with conditional event probability: the largest dilation occurred to the rare event, the least dilation to the predictable frequent tone, and an intermediate dilation to the unpredictable frequent tone (Steinhauer & Zubin, 1982; also Clark & Niemi, 1985). Data from a recent sample of 19 normal control subjects, recorded in darkness, are shown in Figure 2. A similar relationship was observed for conditional probability with P300 amplitude (Steinhauer & Zubin, 1982) and with post-stimulus cardiac acceleration (Steinhauer, Jennings, van Kammen, & Zubin, in press), with parallel findings when reaction times, rather than counting, were recorded to each stimulus presentation (Steinhauer, 1985). In Figure 2, the high probability events (p = 0.67 and p = 1.00) show greater dilation in the Choice Reaction task than for the Counting task. This is related to the fact that during Choice RT, every stimulus is relevant. Note, however, that for rare

![Figure 2. Average pupillary responses in 19 normal subjects. An infrequent high-pitched tone occurred one-third of the time after low-pitched tones \(T/nt, p = .33\). On the other two-thirds of trials following a low tone, another low tone occurred \(Nt/nt, p = .67\). After every high tone, only the low-pitched tone occurred \(NT/t, p = 1.00\). Pupillary dilation was inversely related to these conditional probabilities both when the subjects counted only the high tones (Counting) and when the subjects made a different motor response to each high or low tone (Choice Reaction).](image-url)
tones ($p = 0.33$), the dilations are similar across tasks. (Results for psychiatric patients are noted below.) Tonic diameters tend to decrease across experimental periods, reflecting habituation to the general test situation. Since the Counting task was always conducted first, it was not surprising to find that initial diameters were larger during the Counting than Choice Reaction task, which occurred later in the session. However, the lack of differences in dilation reinforce the notion that the amplitude of dilation is not strongly dependent on initial diameter, at least in the dark-adapted pupil.

While the majority of the studies incorporating both pupillary and ERP recording suggest strong parallels between the dilation and P300 responses, it would be erroneous to assume that the same process is always being manifest in the pupil and ERP. One class of exceptions will be noted. P300 has been related to information delivery (Sutton et al., 1965), and loss of information, or equivocation, has been hypothesized as reducing P300 amplitude (Ruchkin & Sutton, 1978). Adams and Benson (1973) reported that decreasing differences in loudness led to P300 reduction. Ruchkin and Sutton (1978) later interpreted the Adams and Benson study as follows: as the similarity between stimuli increased, and judgements of differences were made with less confidence, P300 decrement reflected loss of information, or in information theory terms, equivocation. In contrast, Kahneman & Beatty (1967) demonstrated that pupillary diameter increased, rather than decreased, as frequency differences between discriminative stimuli were reduced. The explanation for the dissociation between pupillary and ERP measures in these discrimination tasks is that in addition to processing of information, the pupil is also sensitive to effort, and the effort of making a difficult discrimination produces its own dilatation. This is presumably the source of the response in the Kahneman and Beatty (1967) experiment. Thus, it should be possible to demonstrate simultaneous dissociation of pupillary dilation and P300 amplitude in an auditory discrimination paradigm in which either frequency or intensity of stimuli are varied.

The activation of pupillary dilation as a prototypical component of the orienting reaction (Sokolov, 1963) has also led to some confusion in the interpretation of P300 mechanisms. Part of this confusion emanates from the fact that, as noted above, both pupillary diameter and P300 amplitude often covary in the same way in many studies. Combining these notions, Friedman (1978) suggested that since pupillary dilation was considered an aspect of orientation, and P300 and the dilation response were linked in several experiments, then a major aspect of P300 elicitation could be considered to be orienting activity. Subsequently, there have been a variety of discussions relating orienting and P300 activity (e.g., Donchin, Heffley, Hillyard, Loveless, Maltzman, Öhman, Rösler, Ruchkin, & Siddle, 1984) and interpretations of orienting as a primary basis of P300 have prospered. Without detracting from those discussions, it seems worth noting that there has been an unquestioned assumption that all signs of pupillary dilation in the tasks cited reflect orienting activity. Yet even the first association of pupil and P300 by Friedman and colleagues (1973) argues against this notion, since it was possible to eliminate dilation (and P300) merely by telling the subject which stimulus would be presented, yet dilation was elicited immediately when guessing was undertaken once again. In addition, the persistence, rather than habituation, of the dilation during task activity can be demonstrated. We (with David Friedman) once attempted to fatigue the pupil by continuing the guessing task for several hours: even after hundreds of trials, the subject (SRS) still showed dilation.

In dealing with the complexities of stimulus qualities which affect pupil diameter, it is worthwhile to take a brief look at one of the major controversies in pupillary research -- the statements of Hess and colleagues (Hess & Polt, 1960; Hess, 1964) that positive affect is
associated with dilation, while negative affect results in constriction. There have been many critical reviews of this research (e.g., Janisse, 1977), as well as attempts by Hess and his students to justify the work (Hess, Beaver, & Shrout, 1975). Two of the problems involved in using complex visual stimuli, which have usually been overlooked, will be mentioned.

The first consideration involves so-called control slides, which are typically presented before each stimulus slide. The notion in several studies was that the control and stimulus slides should be matched for brightness, so that no differential constriction to the slides could occur, and differences could only be attributable to the content of the target stimulus slide. This approach, however, takes a naive view of the physiology of the optic system, including the afferent pathway even at the level of the retina. When stimuli of either different wavelengths or different intensities strike similar regions of the retina, they differentially stimulate receptors, which evoke pupillary constrictions. This was exquisitely demonstrated over two decades ago by Kohn and Clynes (1969): even matching for overall brightness did not eliminate sensory-related constrictions to the onset of different hues.

A second source of confounding is related to the pupillary constriction produced by the initial presentation of stimuli. This portion of the response was usually ignored by researchers employing pictures, who looked at average diameters over periods as long as ten seconds, rather than the specific dynamic responses to the pictures used. One exception to this was a study by Libby, Lacey and Lacey (1973), whose data clearly showed the initial constriction resulting from stimulus presentations. In their study, pupillary dilation was most often seen to interesting pictures, and although several individuals were reported to show constriction, the unpleasant stimuli overall yielded larger dilations than pleasant stimuli -- a finding totally at odds with the Hess formulation.

Our own research using complex pictorial stimuli was related to investigations of emotionality in neuropsychiatric patients: patients with right hemisphere lesions have been reported to show reduced skin conductance responses to emotionally-laden images than patients with left hemisphere lesions (Morrow, Vruntaki, Kim, & Boller, 1981). We decided to examine pupillary reactions to the same stimuli in 12 volunteer subjects. We presented a series of 27 slides, each preceded by a standard control slide, and recorded 10 seconds of data at 50 msec intervals (Steinhauer, Boller, Zubin, and Pearlman, 1983). Subsequently, it was possible to measure initial diameter, the point of maximum initial constriction which invariably followed slide onset, and subsequent maximum dilation. After each trial, the subject was asked to rate the slide on a five interval scale from very aversive to very pleasant. This in itself was unusual, since most previous studies had merely required subjects to look passively at stimuli and provide no judgements. In addition, a consensus judgement by laboratory staff was made for each stimulus. Responses were examined through a variety of techniques, including absolute maximum diameter, as well as maximum diameter after covarying out initial diameter or extent of constriction. Responses were analyzed first according to subjects' evaluations, and then according to the consensus evaluations. In all cases, the results were similar: the largest dilations were evoked by stimuli reported as most aversive or most pleasant, with smaller dilations to mildly unpleasant or pleasant stimuli, and the least dilation to neutral pictures. Thus, our own findings indicate that the level of emotional stimulation or interest, regardless of valence, is related to the pupillary dilation response, but the confounding effect of initial physiological reactions to visual stimuli must be carefully eliminated.

One of the more intriguing aspects of psychophysiological data is that there is clear evidence that familial similarity can be observed in tonic activity as well as in time-varying measures of
cognitive activity (Boomsma & Gabrielli, 1985). Thus, Bock (1976), Surwillo (1980), and Polich and Burns (1987) have reported on event-related potential similarity in twins, and we have also noted high correlations for P300 amplitude even in non-twin siblings (Steinhauer, Hill, & Zubin, 1986).

Patterns of pupillary dilation have also been examined among twin pairs in Hakerem's laboratory. Bock recorded pupillary dilation, comparing identical twins, fraternal twins, and non-twin siblings during a guessing task. Both objective numerical analyses of similarity, as well as judges' blind matching of pairs, indicated greater similarity of the pupil and ERP data for identical twins than for fraternal twins or non-twin siblings. A more recent dissertation (Gaudreau, 1991) used a forced-choice procedure for matching pupillary waveforms, demonstrating significantly high rates of matching identical twin pairs across two different tasks. Studies of psychiatric patients and their relatives have also been carried out, and are described in the next section.

IV. Psychopathology and Pupillary Motility

As noted at the beginning of this chapter, pupillary abnormalities in psychiatric patients were well documented as early as the beginning of this century. With the advent of averaging techniques, it was possible to examine reactions of psychiatric patients with greater precision. In addition to the work of Rubin, already mentioned, Hakerem and colleagues in New York conducted a number of initial studies which indicated decreased light reactions and abnormal response latencies in schizophrenics (Hakerem & Lidsky, 1969; Hakerem, Sutton, & Zubin, 1964; Lidsky, Hakerem, & Sutton, 1971), as well as difficulties in integrating irregular sequences of light pulses (Hakerem & Lidsky, 1975).

At the Pittsburgh laboratories, we have studied the pupillary constriction to light in schizophrenics and normals, examining intra-session variability and retest stability. In addition to replicating the widely reported finding of decreased constriction in schizophrenics, we have been able to study aspects of the response related to clinical state. In collaboration with Drs. Daniel P. van Kammen and Jeffrey L. Peters, twenty patients from the Schizophrenia Research Unit at the Highland Drive VA Medical Center in Pittsburgh were followed during initial neuroleptic treatment and subsequent (double-blind) drug free withdrawal. Weekly recording of the pupillary light reaction was carried out for durations of up to six months. Stabilization on haloperidol resulted in a significantly larger extent of constriction (though small in amplitude of increase) than during a subsequent drug-free period in patients. Thus, neuroleptic treatment appeared to normalize the response slightly, but generally still kept the response measure below the mean for normals. During the drug free period, the extent of constriction, already smaller in patients than normals, was found to be reduced even further, to a significant degree, as patients' psychosis ratings rose.

In addition, response characteristics were examined during haloperidol stabilization, prior to the subsequent drug-free phase. Compared to controls, schizophrenics tended to cease the active constriction process earlier after visual stimulation. Patients were grouped according to those who remained stable in the subsequent drug-free period vs. those who would eventually relapse during the drug-free stage. The patients who would remain stable were observed to have reached the end of the constriction process significantly later -- more like the normal response. This suggests that while amplitude of constriction may remain reduced, the latency to the end of constriction while under haloperidol treatment may predict the likelihood of relapse after
withdrawal of medication.

Indicators of vulnerability to schizophrenia. A consortium of researchers, led by Joseph Zubin, with the collaboration of Bonnie Spring and Samuel Sutton, among others, worked on a conceptual framework and series of experimental approaches for dealing with the etiology of schizophrenia exemplified in the work on vulnerability (Zubin, Magaziner & Steinhauer, 1983; Zubin & Spring, 1977; Zubin & Steinhauer, 1981; Zubin, Steinhauer, Day & van Kammen, 1985). It postulates that the etiology of schizophrenia emerges from the interaction between the genetic and other biological sources and the environmental factors which influence the development of the disorder. It is further postulated that schizophrenia, instead of being a chronically manifest disorder, is episodic in nature, but that the vulnerability to the disorder persists. A structure for interpreting the relationship of specific "markers" to schizophrenia has been developed (Zubin & Steinhauer, 1981) which is also applicable to other psychiatric disorders. Areas of research interest have included both psychosocial and neurophysiological aspects of schizophrenia, with the latter most relevant to the present discussion.

In contrast to a substantial literature dealing with pupillary light reactions in schizophrenics (and some discussion of the orienting response), there have been few studies of patients involving task-related dilation. Straube (1982) reported that schizophrenics exhibited larger dilations than controls during performance of the digit span task, which could be interpreted as an indication that patients employed greater effort than did controls. This represents an important finding which needs to be replicated. In our own laboratories, and on different tasks, we have observed decreased dilation amplitudes among schizophrenics compared to controls (Steinhauer, Hakerem, & Spring, 1979; Steinhauer & Zubin, 1982).

In the New York Vulnerability project (Steinhauer et al., 1979), we recorded pupillary diameter and event-related potentials in 12 inpatient schizophrenic patients and 12 of their brothers, and in 15 control subjects during a task in which the subject guessed whether a sound or light would be presented on each trial, similar to the paradigm originally employed by Levit et al. (1973). The schizophrenic patients showed decreased constriction to light as compared to controls, replicating previous studies. In addition, schizophrenics also showed greatly reduced dilations in response to unpredictable sounds, with no differences between correct and incorrect guesses. In contrast, controls and siblings showed vigorous dilations, which also differed following correct and incorrect guesses.

As noted earlier, pupillary and ERP (P300) amplitudes were found to be inversely related to the conditional probability of stimulus events during a counting task for normals. For inpatient schizophrenics, however, amplitudes were significantly smaller under all conditions, while responses for depressives tended to be intermediate (Steinhauer & Zubin, 1982; Steinhauer, 1985). Figure 3 illustrates grand means for a recent sample of 17 outpatient schizophrenics who were clinically stable at the time of testing. Note that while the amplitudes are greatly reduced compared to controls (Figure 2), there is still some pupillary motility, suggesting that while neuroleptic treatment in these patients may affect amplitude, it is unlikely to account for the failure to correctly differentiate between conditions.

In addition, the pattern of responses across conditions for patients suggested that schizophrenics responded more to a change in physical stimulus from trial to trial than to conditional probability of stimulus events, as was the case with normals. Specifically, more than half of the patients exhibited a pattern of greater responding to stimulus change, but less responding even to unpredictable stimulus repetitions of intermediate sequential probability (Steinhauer & Zubin, 1982). This is a pattern which was seen more recently among those
brothers of patients where the brothers met criteria for Axis II schizotypal personality disorder (see Figure 4), as described in greater detail below.

Figure 3. Pupillary responses of 17 outpatient schizophrenics during the Counting and Choice Reaction tasks.

Data have been analyzed on a group of 33 brothers of schizophrenics, including brothers of the outpatient schizophrenic group reported above. The pattern of responding to stimulus change rather than event probability, which first was described for inpatient schizophrenics (Steinhauer & Zubin, 1982) was observed for many of the schizophrenic outpatient probands, but was not seen initially in the averages for the sibling group. Moreover, siblings had significantly larger dilations than the patients for the Counting and Choice Reaction tasks. However, when the siblings were separated into groups according to Axis I and II diagnoses, the group of 5 brothers meeting criteria for schizotypal personality disorder showed the inverted pattern of responding -- that is, they were hyperresponsive to stimulus change rather than conditional probability.

Data for five brothers are presented in Figure 4. All of these siblings were affected with schizotypal personality disorder. There are clear dilations present to all conditions. However, a careful inspection indicates that for the two types of frequent low tones, the subjects did not make use of the predictability of events. Instead, the subjects show greater dilation to the predictable low tones which followed high tones (dotted line) than to the unpredictable low tones (dashed lines). It is this pattern which we have interpreted as reflecting an overreaction to stimulus change, rather than to sequential probability. Thus, the pattern of responding appears to be a promising measure not only in schizophrenics, but also in their siblings.

Cardiac changes have also been observed to vary with these probability changes in normals. Schizophrenics, compared to control subjects, showed reduced anticipatory deceleration as well as decreased post-stimulus acceleration during the counting task; patients also showed faster resting heart rate (Steinhauer, Jennings, van Kammen, & Zubin, in press).
Figure 4. Pupillary response of five brothers of schizophrenic probands in the Counting and Choice Reaction tasks. All of these subjects met criteria for a diagnosis of schizotypal personality disorder. Note the greater dilation to frequent low tones that are predictable (dotted line) than unpredictable (dashed line) in both tasks.

These studies suggest that pupillary deviations are observed in schizophrenics for tasks in the information processing domain, but are not merely a reflection of a lack of effort or lack of potential pupillary change due to physiological limitations. We believe that a pupillary study in which variations in effort, processing capacity, and information utilization are examined in the same patients will be of major importance in clarifying the contributions of each of these factors in the performance of schizophrenics.

Several questions are raised in reviewing the pupillary and other psychophysiological data from schizophrenic patients. (For a full review of pupillary reactions in schizophrenia, see Zahn, Frith, & Steinhauer, 1991.) Schizophrenics show diminished response amplitudes for a wide variety of psychophysiological responses (Spohn & Patterson, 1979; Zahn, 1986). For example, the finding of a decreased amplitude for the P300 component of the ERP in schizophrenics is one of the most robust findings in the literature (cf. Roth, Tecce, Pfefferbaum, Rosenbloom, & Callaway, 1984; Zahn, 1986; Zubin, Sutton, & Steinhauer, 1986). It is not clear whether these indicators in schizophrenics point to a lack of capacity specific to information processing demands, or whether they signify more basic, general non-responsiveness of physiological systems. What has often been overlooked is the question of whether or not the mechanics of the response system appear to be intact; it is possible to test the integrity of responses, independent of reactions elicited during information processing tasks. For example, the decreased pupillary constriction of schizophrenics in response to light has been reported even in patients who showed a normal constriction of the pupil during visual accommodation (Okada, Kase, & Shintomi, 1978). Changes in bodily position (e.g., going from a sitting to standing position) will normally increase heart rate, but this has not yet been examined in cardiac studies of schizophrenics who at other times were also performing tasks. Even the P300 response, which usually is evoked
during tasks (Donchin, 1979; Sutton, 1979; Sutton et al., 1965) can be elicited without a task demand: Roth, Dorato, and Kopell (1984) have shown that very loud auditory stimuli evoke what appears to be a true, though involuntary, P300 response at the scalp. Thus, the integrity of physiological underpinnings of the pupillary dilation or "P300" systems could be tested even in patients who fail to show a large response during typical information processing tasks. Experiments are needed to determine whether some of the findings observed in schizophrenics may be attributed to either a general lack of ability to mobilize sufficient effort in approaching tasks, or to deficits primarily in processing capacity.

Further puzzles are suggested by findings of deviant response patterns in siblings of the patients. Are there only single measures which are likely to be markers, or are there patterns of indicators which characterize identifiable subgroups? Do those indicators which the siblings share with their proband brothers show an association of response deviance with history of psychopathology, or only to history of schizophrenia spectrum disorder, or is there familial association without regard to personal history?

It has also been suggested that schizophrenics may respond more than controls to tasks requiring physical or general mental effort. Do patients consistently show more of a pupillary dilation (and/or concomitant cardiac changes) during physical tasks, or during tasks requiring effort, such as the digit span (as indicated by the data of Straube, 1980)? If this were to be clearly established, it would suggest that patients are not merely unwilling to take part in tasks, but in fact may utilize more effort in performance of tasks. Deviations observed during tasks involving easily encoded stimuli, but which represent the possibility of more complex utilization according to probability (the counting and choice RT tasks) would then be assumed to represent a difficulty with a later stage in the sequence of information processing operations. If pupillary dilation in patients occurs during presentation of short digit strings, but shows a decrease in diameter when moderate string lengths are used, it would imply that the available capacity for storing information is decreased in the patients.

What is the nature of the mechanisms which are responsible for these effects? The bases for many of the response deviations observed in schizophrenia tend to be unknown. Even for the normal subject's pupillary dilation response, for example, the relative contributions of the sympathetic and parasympathetic components of the autonomic nervous system (ANS) are unclear, since dilation may result from sympathetic activation as well as reciprocal parasympathetic inhibition. Similarly, the reduced light reaction in patients could involve portions of decreased parasympathetic activity as well as increased sympathetic inhibition. A concern with determining the contributions of these systems, and review of the normal literature, has led to a series of hypotheses regarding autonomic contributions to pupillary dynamics during information processing tasks.

V. Delineating Separate Autonomic Contributions to Pupillary Dynamics During Cognitive Processing

There has been only limited clarification of the mechanisms which are reflected in changes in pupillary diameter during performance of cognitive tasks, either from the conceptual or neurophysiological point of view. A model has been developed which proposes to evaluate the relative contributions of the two separate autonomic nervous system components in the expression of information-related changes in the pupillary system (Steinhauer, in preparation). This discussion summarizes the model, and methods for testing its validity.
A survey of the literature has indicated a number of trends which suggest that it may be possible to dissect out the components of the ANS which are active in pupillary dilation and constriction in normals. Relevant facts include the following:

1) During a variety of cognitive processing tasks, when conducted in darkness with or without a required motor response, maximum pupillary dilation occurs with a peak latency of approximately 1200 msec. This response is also related to similar changes in P300 (Friedman et al., 1973; Hakerem, 1974; Steinhauer & Zubin, 1982). Both types of changes occur even for responses emitted following stimulus absence, when that absence conveys information to the subject (Levine, 1969; Steinhauer, 1982; Sutton et al., 1967).

2) In animal preparations, there is relatively little parasympathetic tone in darkness (Loewenfeld, 1958), so that most reflex dilatation in darkness has been attributed to sympathetic activity.

3) During tasks involving a clear motor-response component, carried out in the light, dilations tend to occur with an earlier peak (600-900 msec (Richer et al., 1983)). Using high potential rates of stimulation, Beatty (1989) has also demonstrated that an irrelevant stimulus in an attended channel produces an extremely small (approximately .01 mm) dilation with a peak latency of approximately 600 msec.

4) An auditory stimulus produces a dilation with a long latency (i.e., 1200 msec) in darkness. As ambient light increases, an additional, earlier dilation can be seen. Shiga & Ohkubo (1979) observed only the long-latency peak during dark recording, but when they increased room illumination so that the initial diameter of the pupil was less than 4 mm in diameter, an earlier peak (700 msec) also appeared.

5) The pupillary light reflex can be diminished by psychosensory stimulation (Loewenfeld, 1958). We observed that even during a guessing task, resulting in a cognitive load, the light reaction (which reached minimum diameter at 800 msec) was reduced compared to conditions in which no task was imposed (Steinhauer et al., 1979).

The above data can be interpreted as follows: the early dilation observed in tasks performed under light, and reduced light reactions for subjects under stress or while performing a task, reflect active inhibition of the parasympathetic efferent pathway (occurring maximally during 600-900 msec post-stimulus). This is probably due to descending cortical and ascending reticular inhibitory inputs to the Edinger-Westphal complex of the oculomotor nucleus (N. III).

The major component of dilation elicited during cognitive processing activities occurs later, with a peak latency greater than 1100 msec. This is probably a primary sympathetic component, which is mediated through hypothalamic pathways via the cervical sympathetic chain.

We suggest that the typical pupillary dilation response during cognitive activation is the result of these two separate components, depicted in Figure 5. The first, early dilation component is associated with inhibition of the central parasympathetic pathway, leading to relaxation of the pupillary sphincter muscles. The sphincter pupillae form a band of muscles arranged in circular orientation around the pupillary margin; contraction of the muscles results in pupillary constriction. Given the well known specificity of the parasympathetic system, the model assumes a relatively symmetrical onset and offset for this component. The second, later component is produced by direct sympathetic stimulation of the pupillary dilator muscles. The dilator pupillae are oriented in a radial fashion, so that contraction of the muscles enlarges the pupillary aperture. Once peak activity is reached, it is known that sympathetic activation takes longer to return to baseline (Loewenfeld, 1958; Lowenstein & Loewenfeld, 1962).
Figure 5. Hypothesized contributions of parasympathetic and sympathetic components of activation in the generation of pupillary dilation during cognitive tasks. In darkness (A), there is minimal early dilation resulting from inhibition of parasympathetic pathways, and consequent relaxation of the sphincter pupillae. The primary dilation occurs later through sympathetic activation of the dilator pupillae. In light (B), the greater tonic constriction of the sphincter muscles results in more extensive early dilation due to parasympathetic inhibition, which contributes to an additional early peak in the response.

In Figure 5A, the dilation resulting from performance in a cognitive task has been modelled for recordings obtained in darkness. Dilation resulting from inhibition of parasympathetic centers is presumed to contribute a relatively small dilatory component, reaching a peak effect at 600 msec. The sympathetic component begins to increase somewhat later. The resulting waveform appears to be primarily sympathetic in nature, although a break at or slightly beyond 600 msec reflects the interaction of both components. Such waveforms are typically seen, for example, in guessing or oddball tasks recorded in darkness. For example, the data for control subjects performing the Counting task seem to exhibit a similar pattern in the .67 and 1.00 probability conditions (Figure 2).

During recording in bright ambient light conditions, the tonic pupil diameter would be decreased by parasympathetic stimulation. Thus, there should be a greater dilation produced by inhibition of this system. Consequently, in Figure 5B, the gain of the parasympathetic component has been increased, while the sympathetic component has been left constant. The resulting pupillograph indicates both the later (sympathetic) dilation as well as an earlier peak, which reaches a maximum diameter between 600 and 1000 msec. This model fits well with the findings of earlier peaks for pupillary data recorded under normal room illumination (Richer et al., 1983; Shiga & Ohkubo, 1979).
Moreover, we hypothesize that during performance of motor responses, the primary component of dilation associated with the motor response is parasympathetic inhibition having its effect in the early (600 msec) dilation. Richer et al. (1983) depict an early peak for averages time-locked to a motor response, which is entirely consistent with the present hypothesis. Consequently, the motor component should show only a minimum contribution to pupillary dilation responses recorded in darkness.

If we can demonstrate that these relations hold true across a variety of different tasks, then we will have established alternative procedures for testing the integrity of the separate sympathetic and parasympathetic components of the ANS. This would be especially useful in examining the role of separate pathways in patient populations.

Studies by Beatty, Richer, and colleagues (Beatty, 1982; Richer et al., 1983) have examined the contribution of motor responses in eliciting pupillary dilation, and we were inspired to investigate the effects of motor activity on the dilation produced during our own paradigms. We conducted a pilot experiment in which five subjects performed the counting task (Steinhauer & Zubin, 1982), with the addition that subjects were requested to clench their teeth when target tones occurred. We suspected that there might be different contributions in light and darkness, so the task was performed under both conditions of room lighting. For all subjects, we observed an extensive early dilation when the room was lit, but in darkness, we primarily observed only a later, lower amplitude dilation. We interpreted these findings as indicating differential activity contributing to the dilation response: a late sympathetic component in darkness, as well as an early dilation related to parasympathetic inhibition during the lighted room condition.

Several additional predictions emanate from the proposed model. If early dilations (600-900 msec peak) are related to parasympathetic inhibition, then this should be seen more clearly under all tasks in light, but less so (or not at all) in darkness, and the pupillary reaction to light should be inhibited during cognitive tasks such as the digit span. If motor activity results primarily in inhibition of the final parasympathetic pathway, then tasks involving motor responses should result in little early dilation activity when performed in darkness. Moreover, if some tasks primarily involving mental effort but no motor response (i.e., digit span) show little dilation when performed in darkness, then it would be possible to identify such tasks with activity involving the parasympathetic rather than the sympathetic components of the ANS; when both occur, it may be possible to estimate the change attributable to each component. Loewenfeld (personal communication) has pointed out that similar verification can be obtained by pharmacologically blocking post-synaptic activity of either the dilator or sphincter muscles of one iris, and by comparing the response of the treated eye to the untreated eye (using binocular pupillographic recording) to obtain a "pure" measure of the remaining autonomic component.

The investigation of the pupil as a window into the mechanisms of cognitive processes, and a reflection of vulnerability to psychopathology, is proceeding. In a conversation with Sutton about the meaning and basis of such measures -- why they should be so responsive, and what specific physiological changes they represented -- he once remarked: "Aside from the new technologies, it may still take another century to understand what is really going on." The path along which he directed us involves the search for psychological and physiological understanding, keeping in sight the wonder of what these measures represent for the complexities of physiological and mental function.
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