CHARACTERISTICS OF PUPILLARY REACTIVITY IN PSYCHIATRIC PATIENTS AND NORMAL CONTROLS

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The value of the pupillary reaction as a diagnostic indicator has long been recognized in neurology and ophthalmology. Granger (1953, p. 17), in his review of the literature on personality and visual perception, wrote: "It would not be surprising in view of the multiple connections of the pupillary pathways, if they were also found to be of considerable value for the study of personality and its functional disorders."

Behr (1924), in his textbook on the pupil, noted that the largeness of the area that the pathways traverse, and their interconnections with many upper and lower parts of the brain, would lead one to believe that there is scarcely any nervous function which has no effect, direct or indirect, on pupillary behavior.

In the context of psychopathology, the study of pupillary responses has a lengthy history. Abnormal reactions of the pupil to light and other sensory stimuli have been reported by many observers. Specific attention was given to such reactions after the Argyll–Robertson pupil had been established as a necessary symptom in the diagnosis of general paresis.

Kraepelin described at length his observations on pupillary unrest, speculating that the presence or absence of oscillatory movements of the pupil might be a prognostic indicator.

Reliable correlations between organic neurological disturbances and pupil-

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lary reactions have tempted investigators to search for similar relations between pupillary reactions and mental illness.

Summaries of the pertinent literature were presented by Bumke in 1904 and Bach in 1908. The problem with these early reports was their contradictory nature. Bumke, for example, claimed that dilation of the patient's pupil, in response to a painful stimulus, signified a favorable prognosis, while the absence of dilation indicated a poor prognosis. Oswald, writing in 1905, reported that he could not confirm Bumke's findings.

In 1907, Adolf Westphal published an important paper in which he described a specific pupillary phenomenon found in catatonic patients. These patients had dilated pupils which did not react to light. This condition could disappear suddenly and the pupil would react normally. Minutes later, the dilated, non-reacting pupil would reappear. He called this phenomenon the “catatonic pupil” or “spasmus mobilis.” Westphal's observations were confirmed later by Koester (1927) and by Levine and Schilder (1942). We ourselves have seen only one patient with this phenomenon.

Lowenstein and Westphal (1933) described four types of pupillary response to light stimuli, one of which was most common among psychiatric patients, namely, a sluggish contraction to light onset and slow refraction following stimulus cessation.

More recently, Rubin (1964) attempted to test the theory that psychiatric patients are either deficient or overactive in the sympathetic or parasympathetic branches of the autonomic nervous system. With pupillographic methods, by presenting strong light stimuli and observing the characteristics of constriction and the recovery from such stimuli, Rubin found that all of his psychotic subjects showed impairment (excess or deficiency) in either constriction or dilation, or both, when compared to normal controls. Rubin tried to account for these observations by postulating neurohumoral deficiencies of some biogenic amines or an enzyme disorder. Stroebel, McCawley, and Glueck (1966) felt that the differences between patients and normals found by Rubin could be ascribed to differences in age rather than to psychopathology.

In 1964, we reported differences in the pupillary reactions of acute patients, chronic patients, and normal controls (Hakerem, Sutton, & Zubin, 1964). The acute patients were found to have pupils of smaller initial diameter than either the chronic patients or the normal controls. An analysis of the pupillary reactions to light showed that the patients tended to reach maximum contraction in less time than the normals, that is, they contracted faster.

Our laboratory has been concerned with the study of pupillary reaction of both psychiatric patients and normal subjects since 1956. We have used a wide range of stimulus variables and experimental conditions in investigating the pupillary response.

There are several reasons for using the pupillary reaction as an indicator in
the study of psychopathology. One reason is the aforementioned fact that a substantial literature has accumulated showing that pupillary motility is related to a variety of specifiable variables. Second, the pupil is easily accessible and can be measured with a high degree of accuracy and with no discomfort to the subject. Third, the pupillary reflex is involuntary and, thus, an objective indicator, provided, of course, that it is possible to determine and analyze the factors that produce this response, with regard to both the stimulus characteristics and the neural centers regulating the flow of impulses to the pupillary muscle systems.

Much work has been done to determine the effect of stimulus characteristics on the pupillary response. Most of the work has involved visual stimuli, and the general findings are that the pupillary reactions to visual stimuli are similar to, if not identical with, the experimental responses reported by the subjects in psychophysical experiments (Bartley, 1943).

The neural pathways and centers controlling the pupillary reflex are also fairly well known. A brief summary of these pathways might be in order here.

Fibers from the retina bifurcate before the lateral geniculate, then synapse in the preganglionic nucleus, and proceed via the pretectal area and Sylvian aqueduct to the Edinger–Westphal nucleus in the third nerve nucleus on both hemispheres. Approximately 50% decussation occurs, thus producing a consensual response. The Edinger–Westphal nucleus sends out efferent fibers via the ciliary ganglion to the sphincter muscles of the iris that produce pupillary constriction. This parasympathetic component is opposed by two dilatory mechanisms. One is the excitation of the radial iris muscle, which originates in the vegetative centers of the midbrain and descends via the cervical sympathetic chain. The other is an inhibitory mechanism that acts on the Edinger–Westphal nucleus. It probably receives its neural activity from several midbrain centers such as the posterior hypothalamus, and the reticular formation, from area four, and eight, and from the frontal cortex.

While the dilation effected by the activation of the iris dilator is rather rapid and extensive, the dilation due to the inhibition of the Edinger–Westphal nucleus is relatively slow and small. Study of the temporal characteristics of the response permits differentiation of the two. A number of relationships between pupillary motility and localization of specific lesions in the central nervous system, in both the afferent and efferent pathways, have been discussed by Lowenstein and Loewenfeld (1950).

The techniques for measuring the pupil diameter also have a long history, dating back to the ancient Greeks. It can be stated that, in general, these techniques have kept in step with the technological advances in other areas. We have gone from direct observations to photographic procedures of different kinds to mechanical and electronic infrared scanning devices. A detailed description of these techniques has been given elsewhere (Hakerem, 1967).
We would like to report now on two studies that have recently emerged from our laboratories and that are characteristic of our research activities.

The apparatus in these experiments consisted of an electronic pupillograph and of electronic programming and data processing units. The scanner unit of the pupillograph was placed in a lightproof room, so that complete control of light conditions could be maintained. The outputs from the pupillograph were DC voltages equivalent to (1) the pupillary diameter, and (2) the rate of pupillary diameter changes. These were recorded on magnetic tape by a seven-channel tape unit. The tape was subsequently fed into a computer of average transients (CAT), and the resulting curves were plotted by a Moseley X–Y plotter.

The recording and data processing systems permitted the sorting of responses on the tape according to specific experimental conditions, as well as the elimination from the averaging process of those trials during which an eyeblink or other artifact had produced spurious voltage changes.

A Sylvania glow modulator tube was used to generate the light stimuli. The light output was monitored by a phototube and displayed on an oscilloscope. Light stimuli were presented by a “Ganzfeld” system placed over the left eye of the subject. All recordings were made from the consensual pupil. More detailed descriptions of the equipment have been published elsewhere (Hakerem, 1967).

In a series of investigations into the limits of the ability of the pupillary system to replicate the temporal sequences of flickering light, we have observed a substantially delayed, yet orderly, sequence of dilation and contraction, which could be related to the stimulus pattern. The output pattern of contraction and dilation ran its full course, even subsequent to the cessation of a particular light–dark sequence (Hakerem & Lidsky, 1969). Although we do not have a ready explanation for such events, we have discounted the conditioned-response interpretation, on the basis of the results of lengthy study on pupillary conditioning in our laboratory (Kugelmass, Hakerem, & Mantgiaris, 1969).

Several experimental designs were developed in order to identify the specific response to each individual stimulus in a flickering light pattern.

A sequence of light stimuli of different durations, separated by variable dark periods, was presented. In Figure 1, the pupillary reactions to a stimulus pattern consisting of 250 msec of light, 250 msec of dark, 150 msec of light, and 150 msec of dark are presented as an example.

Figure 1 represents an average response curve obtained by averaging sequential 2-sec time samples of pupillary changes. These samples were time-locked to the onset of one of the stimuli. The figure shows that a time lag of about 420 msec occurred between stimulus onset and pupil contraction. It should be noted that with near-threshold stimuli, we have observed contraction latencies as long as 480 msec. Of particular interest in this figure is the fact that
Figure 1. Pupillary reactions to a stimulus light pattern of 250 msec on, 250 msec off, 150 msec on, 150 msec off.

A pupillary reaction to a given light stimulus, such as number 1, occurred while the next stimulus, number 2, was being presented. Contraction to stimulus number 2 began during the next stimulus 1, and so forth. It was consistently observed that all the input information from the retina was precisely followed by the pupil, but with a delay of over 400 msec. In other words, input and output were out of phase by 420 msec, with no apparent degradation in information.

By sampling the end of a flickering cycle, we noted that the pupillary system could retain the information contained in a final 150-msec light pulse until after it had completed processing the 250-msec dark pulse, and could then finally execute the next appropriate response.

This phenomenon was demonstrated even more effectively by interspersing a 450-msec dark pulse after three succeeding 300-msec dark pulses. The use of such a "limp" stimulus permitted clear indentification of the first response in the sequence of four responses. The first response always provided the largest contraction, since it followed the "limp" interval, which occurred after every four light flashes. Figure 2 presents the average response curves of the pupillary reactions to light flashes of 30 msec duration each, separated by dark intervals of 300 msec and 450 msec. The first three dark intervals in this pattern

Figure 2. Pupillary reactions to a stimulus light pattern of 30 msec on, 300 msec off, with a 450-msec off period interspersed after each three 300-msec off periods.
are 300 msec long and the fourth dark interval is 450 msec long. The computer-averaged, 4-sec time samples were always locked to the first stimulus of the pattern.

It can be seen from this response curve that the constriction responses occur with a delay. The related output information (constriction) is retained even though two additional light pulses had been presented in the meantime. The observation that there is no degradation of the output information over this phase delay is in conflict with the prevailing assumption of a simple input–output reflex arc in the pupillary constriction reflex. In fact, it appears necessary to invoke the existence of some delay or storage mechanism in the response system.

We have investigated some of the parameters of this "following response," such as duration of dark and light periods, intensity of light stimulus, and duration of the "limp" stimulus. In this way we have been able to drive this response to its limits, that is, to the point where there is no longer a "following response," but a simple decrease in pupil diameter from the dark-adapted condition, as if the light appeared fused. Although we can offer no unique explanation for this "delayed response" phenomenon, it may be that the notion of "information input overload," as proposed by Miller (1963), would be most appropriate. Miller suggests that when the organism is faced with too much information input at a given moment, it can handle the situation in several ways: (1) by omitting the input; (2) by processing the information erroneously; (3) by filtering the information; or (4) by "queuing." Queuing is defined as a brief storing of the information during peak load periods and a subsequent releasing of it at a time when the channel is less busy. Our data seem to illustrate such a system.

We then hypothesized that, if the neural transmission system in psychiatric patients is deficient, as has been proposed by several authors (e.g., Marrazzi, 1957), then the "following response," which requires very exact and precise handling of the input, would be less accurate in patients than in normals. We conducted a number of experiments to test this hypothesis and, indeed, found the patients to have a less accurate response to a given light–dark pattern than the normal controls.

Figure 3 shows the pupillary reactions of normal subjects to a light–dark pattern (30 msec light, 200 msec dark, 30 msec light, 280 msec dark, 30 msec light, 360 msec dark, 30 msec light, 440 msec dark). Each of these curves is the average of 50 time samples from the continuing cycle of one subject. The reactions to the individual light stimuli in the cycle can easily be identified: Figure 4 shows the reactions of 19 psychotic subjects to the same stimulus problem. It is quite clear from a comparison of these two figures that the patients show little or no "following response," while the response is extensive in most of the controls. There are two patients in the sample who show adequate
Arousal]

Figure 3. Pupillary reactions of normal subjects (N = 15) to indicated light–dark pattern.

"following response," while two of the controls show a small response.
A second experiment which we would like to report deals with responses to single flashes of light in psychiatric patients and normals. In the interval between this conference and this volume, the experiment has been described in

Figure 4. Pupillary reactions of psychiatric patients (N = 19) to indicated light–dark pattern.
more detail elsewhere (Lidsky, Hakerem, & Sutton, 1971). However, in view of its special methodology and implications, it is also mentioned here. Serving as subjects were 51 patients newly admitted to Brooklyn State Hospital and 31 normal volunteers. Most patients were diagnosed as schizophrenic in preliminary examinations by the hospital staff. They were free of neurological or ophthalmological pathology, and they received no psychoactive medication for at least 10 days prior to testing. All subjects ranged in age from 18 to 45 years, the period during which the effect of age on pupillary reactivity is minimal.

Each subject was seated in a ventilated dark booth and dark-adapted for 10 min. A headrest device, with a biteboard, permitted the subject to maintain a fixed position relative to the scanning apparatus during the measurements, and to move out of that position between trials. Instructions were conveyed through an intercom.

The stimulus, a 30-msec light, was presented to the subject’s left eye via a Ganzfeld, at an intensity of 0.3 mL. Three sec after light onset, a soft “beep” informed the subject that the trial was over and that he could relax. After a 30-sec intertrial interval, another “beep” was a signal for the subject to position himself and to fixate a red spot in preparation for the next stimulus. Ten trials were given in this manner.

Intensity of the stimulus and the pupillary responses were monitored on a two-channel oscilloscope. A calibration pulse was inserted into the response curve of each trial and was subsequently averaged with all the responses; this method served to determine the absolute diameter of the pupil and acted as a check on the correctness of the averaging procedure. Recorded response curves were fed into a CAT computer, and the normalized curves were plotted with an X–Y plotter.

Data were analyzed in terms of initial diameter at the moment of light onset, extent of contraction, and speeds of contraction and redilation. The latter measures were obtained from the first derivatives of the contraction curves, which were computed simultaneously with the diameter records. Mann–Whitney U tests and rank order correlations were used for comparisons between the groups.

RESULTS

In this paper we concern ourselves primarily with the measures of initial diameter and extent of contraction. Initial diameter scores showed that the patients tended to have smaller pupils than did the normal controls. The median diameter for patients was 6.4 mm; for normals it was 6.9 mm. The difference is
significant at the .01 level. There was, however, considerable overlap between
the groups on this measure, and predictability of the individual response was
low. This tended to confirm previously reported observations for acute patients
and normals (Hakerem et al., 1964).

More striking, and in contrast to former findings, were the observations on
the extent of the pupil contraction to light. The median patient contraction
was 1.40 mm, while for the controls it was 1.79 mm, a difference significant
beyond the .001 level of confidence. These data are presented in Figure 5 in the
form of a cumulative distribution, where the ordinate represents the percentage
of subjects in each group whose contractions exceeded a given value on the
abscissa. Thus, by empirically selecting 1.70 mm as a cut-off line, we found
that a contraction of 1.70 mm or less comprised 86% of the patient sample,
whereas a contraction greater than 1.70 mm represented over 80% of the
normals. From these data it can be predicted that, on the basis of pupillary
response to light, a given normal will be correctly assigned to the normal group
80% of the time, and a given patient correctly assigned 86% of the time. Group-
ing by age and sex did not produce statistically significant pupillary differences.

One interpretation of these distinctive amplitudes of contraction is that
larger contraction responses occur where these are larger initial diameter—i.e.,
a larger pupil simply has more scope for contraction. To test this, a subsample
of 21 subjects was selected from both the patient and normal groups to yield
pairs matched for initial diameter. Thus, the median initial diameter was the
same for both groups. The data for this subsample, again in the form of a cumu-
lative percentage plot, are virtually identical with those for the total groups
shown in the previous figure. Figure 6 shows the difference between the
matched normal and patient groups, which confirms the findings of a difference
between schizophrenics and normals even when the effect of initial diameter
is ruled out. The consistency of these results would seem to be a reflection of
some underlying mechanisms.

Figure 5. Cumulative distribution of percentage of
subjects with a given pupillary contraction to a 30-msec
light stimulus. Patients (N = 51); normals (N = 31).
Figure 6. Cumulative distribution of percentage of subjects with a given pupillary contraction to a 30-msec light stimulus. Patients ($N = 21$) and controls are matched for initial diameter.

DISCUSSION

These patient–normal differences may raise the suspicion that a factor unrelated to the assumed characteristics of our patient groups has been in operation. Kety’s critique (1959) of the biochemical theories of schizophrenia indicates the care required in the interpretation of patient–normal differences. It is, therefore, important to consider the possible roles of artifacts.

Long-term intake of phenothiazines produces ocular deposits in the cornea and lens, in about 23% of chronic psychiatric patients (Forrest & Snow, 1968). Since some of the patients we tested had received phenothiazines until as few as 10 days prior to being tested, it is possible that slight ocular deposits had occurred; such deposits can act as a filter, and, consequently, less light energy might have reached the patient’s retina. This, in turn, would naturally reduce the amplitude of the contraction (the melanosis-filter argument). From other studies in our laboratory on the effects of light intensity on the pupillary contraction response, we have inferred that the median difference between patients and normals in pupillary constriction response to a given light intensity is equivalent to the difference that would be obtained by reducing the intensity of the stimulus by about one log unit. Thus, for the patients it is as if there were a one-log-unit neutral density filter in front of the light source.

The melanosis-filter argument is, however, opposed by several factors. The five patients who showed the smallest contraction responses were examined by an ophthalmologist with the slit lamp, and no opacities were found. Also, the long-term daily dosage of 300 mg or more of phenothiazines, on which the melanosis reports were based, was rarely attained in our recently admitted
patients. Finally, the results obtained by Granger (1957), showing that visual thresholds of patients and normals differed by about 0.5 log units, would tend to support the genuine nature of the present findings. Granger’s data were obtained in the early 1950s, before the extensive use of pharmacotherapy.

Another possible artifact that has yet to be completely excluded is related to the tendency for phenothiazines to lodge in the tissue of the retina to a greater extent than in any other brain structure. Because of this tendency, even small drug dosages could reduce the efficiency of the light-processing characteristics of the neural elements in the retina, and, thus, it is possible that the present findings are generated by drug effects rather than by a specific characteristic of the psychiatric disorder.

The empirical findings, in any event, are as follows. (1) In the patient group there is a smaller initial pupil diameter. While this is a small effect, it is a reliable finding of two separate studies. (2) In patients there is less contraction of the pupil to light. This is a large effect, which, while prominent only in the present study, dramatically differentiates patients from normals. On the basis of the known neural pathways of the pupillary system, it may be said that the first finding is consistent with the interpretation of reduced sympathetic activity. The second finding is consistent either with increased sympathetic activity (contradicting the first statement), with reduced parasympathetic reactivity to light in the patient sample, or with the operation of one of the artifacts referred to previously. The interpretation of reduced sympathetic activity is not supported by the results of the subsample which was matched for initial diameters; in fact, those data are consistent with either reduced parasympathetic reactivity or the artifact hypothesis.

The relevance of arousal level to these patient–normal discriminations is emphasized by Loewenfeld’s findings (personal communication) with normal subjects under the influence of amphetamines. Although amphetamines are presumed to increase the arousal level, Loewenfeld observed that initial diameter was not affected by the drug, but that extent of contraction was, in fact, greatly reduced. This raises the possibility that, under certain conditions, the central and peripheral sympathetic activities can become uncoupled.

We may summarize by stating that some rather striking and consistent differences between psychiatric patients and normal controls have been demonstrated in their pupillary reactions to light. That these differences may be the results of long-lasting drug side-effects appears unlikely, although such doubts have not been completely dispelled. To untangle the components of contraction and dilation of the pupil, studies of other sensory stimuli are in progress.

In these studies, we use sound stimulation that acts directly on the arousal centers to produce pupillary dilation, and phosphene stimulation that circumvents the optical apparatus to produce contraction responses. Other extensions of the present approach to pupillography include pupillary and reaction time
correlates of arithmetic processing in retarded persons and normals (Lidsky), and simultaneous recordings of evoked potentials and pupillary responses in normals (Hakerem).

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