Pupillary Reactions to Single Light Pulses in Psychiatric Patients and Normals

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A substantial literature has been accumulating, wherein pupillary motility is found to relate to a variety of specifiable variables (5, 13, 10). In terms of physiological mechanisms and the responses of the pupil to discrete light and other sensory stimuli, and variations in reactivity associated with organic and functional disorders, there is much evidence to support the study of pupillary functions as manifestations of autonomic balance, neural activity, and information processing.

The anatomic pathways of the pupillary light reflex consist of both sympathetic and parasympathetic representations (13, 17). Fibers from the retina bifurcate before the lateral geniculate, then synapse in the pre-geniculate nucleus, and proceed via the pretectal area and Sylvian aqueduct to the Westphal-Edinger nucleus in the third nerve nucleus on both hemispheres. Decussation is fifty percent. The Westphal-Edinger nucleus sends out efferent fibers via the ciliary ganglion to the sphincter muscle of the iris. This parasympathetic component is opposed by two dilatory mechanisms. One is the excitation of the radial iris muscles via the cervical sympathetic chain, originating in the vegetative centers of the midbrain. The other is an inhibitory mechanism which acts on the Westphal-Edinger nucleus, the neural activity of which seems to originate in a number of centers, such as the posterior hypothalamus, reticular formation, frontal cortex, areas four and eight. While the dilation effected by the activation of the iris dilator muscle is rather rapid, the dilation due to the inhibition of the Westphal-Edinger is relatively slow. Study of the temporal characteristics of the response permits a differentiation between the two. Many relationships between pupillary motility and localization of specific lesions in the central nervous system, and both afferent and efferent pathways, have been dealt with by Lowenstein and Lowenfeld (13).

Reliable correlations with organic disturbances have tempted investigators to search for similar relations between pupillary responses and mental illness.
In fact, at the turn of this century many psychiatrists suspected such relationships. The summaries of the pertinent literature by Bumke (2) and by Bach (1) are examples. The major problem, however, was the contradictory nature of early reports. Bumke claimed that dilation of the patient's pupil, in response to a painful stimulus, signified a favorable prognosis, while absence of the dilation indicated a poor prognosis. Oswald (16), another German psychiatrist, claimed the opposite. In 1907, Westphal described a specific form of responsivity, which he called the "catatonic pupil", because of its high incidence in catatonic patients (20). Lowenstein and Westphal (14) described four types of response to light stimuli, one of which was most common among psychiatric patients; this was characterized by sluggish contraction to light onset, and slow redilation following stimulus cessation. Levine and Schilder (9) and May (15) have also reported on abnormal reactions in psychiatric patients, to stimulation by light and non-visual stimuli. More recently, Rubin (18, 19) has described some seven patterns of adrenergic-cholinergic imbalances, on the basis of pupillary reactions to light and darkness, both at rest and under stress. Compared to the reactions of normals, patients appear to react either excessively or insufficiently, or both, to appropriate stimulation.

In a previous report from our laboratory (7) we attempted to distinguish between the pupillary reactions of acute and chronic patients and normal controls using cycles of one second light and three seconds darkness. Acute patients were found to have smaller initial diameters than did either the chronic patients or the controls. The pupillary reaction to light showed only that patients tended to reach maximum contraction in less time than did normals.

The present report is based on data obtained with more precise and sophisticated methods of recording and analysis. Measurements were obtained with an infrared scanning device, developed by Lowenstein and Lowenfeld, which measures the pupil diameter electronically sixty times per second. The diameter is
converted into a proportional voltage which in turn is stored on magnetic tape. Averaging procedures were used in order to overcome the problem of randomly occurring changes in the neural activity in centers relating to pupillary innervation.

Procedure

Subjects

Our sample consisted of eighty-two subjects, of whom fifty-one were recent admissions to the Brooklyn State Hospital. Most patients were diagnosed as schizophrenic in preliminary examinations by the hospital staff. They were free of neurological or ophthalmological pathology, and had received no psychoactive medication for at least ten days prior to our test. Thirty-one normal volunteers served as controls. All subjects ranged in age between eighteen and forty-five years, the range during which the effect of age on pupillary reactivity is minimal.

Method

Subjects were seated in a ventilated dark booth, and adapted for ten minutes. A headrest device, with a biteboard, permitted the subjects to maintain a fixed position relative to the scanning apparatus during the measurements, and to move out of that position between trials. An intercom was used to convey instructions to the subject.

The stimulus, a thirty millisecond light, was presented to the subject's left eye via a Ganzfeld, at an intensity of 0.3 millilamberts. Three seconds after light onset, a soft "beep" informed the subject that the trial was over and that he could remove his head from the biteboard and relax. After a thirty second intertrial interval, another auditory signal informed the subject to position himself and fixate a red spot in preparation for the next stimulus. Ten trials were given in this manner.

Both pupillary responses and stimulus intensity were monitored on an
oscilloscope. A calibration pulse was inserted into the response curve in each trial and averaged with all the responses; this allowed us to determine the absolute diameter of the pupil and to check the correctness of our averaging procedure. Recorded response curves were fed into the computer of average transients, and the normalized curves were plotted with an X-Y plotter.

Results

Data were analyzed in terms of initial diameter at the moment of light onset, extent of contraction, and the 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.

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 millimeters; 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 our previously reported observations for acute patients and normals.

Much more striking, and in contrast to our former findings, were the observations of the extent of the pupil contraction to light. The median patient contraction was 1.40 millimeters, while for the controls it was 1.79 mm., a difference significant beyond the .001 level of confidence. These data are presented in Figure 1 in the form of a cumulative distribution, where the ordinate

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represents the percent of subjects in each group whose contraction exceeded a given value on the abscissa. Thus, by empirically selecting 1.70 millimeters as a cut-off line, we observed that a contraction of 1.70 mm. or less comprised
eighty-six percent of our patient sample, whereas a contraction greater than 1.70 mm. represented over eighty percent of the normals. From these data we may predict that a given normal will be correctly assigned to the normal group eighty percent of the time, and a given patient correctly assigned eighty-six percent of the time, on the basis of pupillary responses to light. Male-female differences and differences attributable to age revealed no statistical differences.

Since the distinctive amplitudes of contraction might be erroneously interpreted as a function of differences in initial diameter -- that is, the larger the initial diameter, the larger the scope for contraction -- a subsample of twenty-one subjects was selected from each of the patient and normal groups to yield matched pairs in terms of initial diameter. Thus the median initial diameter was the same for both groups. The data for this subsample, again in the form of a cumulative frequency plot, are virtually identical with the total group shown in the previous figure. Figure 2 shows the difference between the matched normal and patient groups, which confirms our findings of the difference between

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schizophrenics and normals effect when the effect of initial diameter is ruled out. The consistency of these findings would seem to be a reflection of some underlying mechanisms.

Discussion

Such striking evidence as we have presented may raise the suspicion that a factor unrelated to the assumed characteristics of our groups has been operating. Kety's critique (8) of the biochemical theories in schizophrenia is indicative of the care required in the interpretation of patient-normal differences. We have, therefore, searched for possible artifacts.
Recent reports have suggested that the long term intake of phenothiazines may produce ocular deposits in the cornea and lens, in about twenty three percent of chronic psychiatric patients (3). Since some of our patients received phenothiazines until as little as ten days prior to being tested we must contend with the possibility that slight ocular deposits have occurred, and therefore less light reached the patient's retina -- consequently reducing the amplitude of the contraction to light.

From other studies in our laboratory on the effects of light intensity on the pupillary contraction response, we have inferred that the median difference in contraction between the patients and normals was of the order of a stimulus intensity difference of one log unit. The melanosis argument is opposed by several factors. Five of our patients, who showed the reduced contraction response, were examined by an ophthalmologist with the slit lamp, and no opacities were found. Furthermore, the long term dosage of 300 milligrams or more of phenothiazines daily, on which the melanosis reports were based, was rarely attained in our recent admissions. Another argument against the melanosis artifact explanation is the finding by Granger (6) which showed differences in visual threshold between patients and normals of about 0.5 log units. Granger's data were obtained in the early 1950's, predating the extensive use of pharmacotherapy.

A further possibility which has yet to be completely excluded, is the tendency for phenothiazines to lodge in the tissue of the retina to a greater extent than in any other brain structure (4). Small effects might thereby reduce the efficiency of the light processing characteristics of the neural elements in the retina, so that our results would be generated by drug effects rather than by a characteristic of psychiatric disorder.

In summary of our findings, we have established that:
1. There is a smaller initial diameter in the patient group. While this is a small effect, it has been found reliably in two studies.

2. There is less contraction of the pupil to light in the patient group. This is a large effect, which dramatically differentiates patients from normals. However, this effect has been prominent only in the most recent study.

On the basis of our knowledge of the pupil's neural pathways, it may be said that finding 1, above, is consistent with the interpretation of reduced sympathetic activity (smaller initial diameter). Finding 2, above, is consistent with either increased sympathetic activity (which contradicts the first statement), or reduced parasympathetic reactivity to light in the patient sample, or the operation of the artifact of corneal opacities or retinal concentration of phenothiazines. The results based on our sample, which was matched for initial diameters, do not support the interpretation of reduced sympathetic activity, and in fact they are consistent with either reduced parasympathetic reactivity or the artifact hypothesis.

The arguments pertaining to the melanosis explanation have already been dealt with. The relevance of arousal level to our patient-normal discriminations may be emphasized, as a result of findings by Lowenfeld (11) with normal subjects under the influence of amphetamines. Although amphetamines are presumed to raise arousal level, Lowenfeld observed that initial diameter was not affected by the drugs, but that extent of contraction was in fact greatly reduced. This raises the possibility that under certain conditions the central and peripheral sympathetic activities may become uncoupled.

In conclusion, then, we have demonstrated some rather striking and consistent differences in the pupillary reaction to light between psychiatric patients and normal controls. That these differences may be the results of long lasting drug side effects seems to us unlikely, although our doubts have not been
completely dispelled. To untangle the components of contraction and dilation of the pupil, we are also using other sensory stimuli, such as sound which acts directly on the arousal centers and produces pupillary dilation, and phosphene stimulation to circumvent the optical apparatus in the production of contraction responses.
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