DRUGS AND CEREBRAL FUNCTION

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Chapter 6

Pupillography as a Tool in the Assessment of CNS Functions and Drug Effects

GAD HAKEREM*

When I looked over the program for this symposium on Cerebral Functions, I was surprised to find that none of the sections seemed to deal specifically with the electrophysiology of the cortex as an indicator of its function.

I have taken the liberty to include in my paper some discussion of data obtained from recordings of the evoked cortical potentials. These data have direct relevance to the data obtained by recording of the pupil motility. It is actually because of this close relationship between data obtained from scalp electrodes and from the pupil that I dare state that the motility of the pupils does indeed reflect cortical functions.

We have come to regard the pupil of the eye as an extremely precise indicator of cerebral functions, so much so that we think of it as a "permanently implanted electrode in man." Actually this concept is not new, the pupil has been described in the literature as "the window to the soul" or as "the finest anesthesiometer of the brain." The state of the pupil opening as an indicator of disease and emotions has long been known to physicians and psychiatrists. The question then arises whether the anecdotal and observational reports in the literature are based on verifiable facts and to what extent modern recording devices can help us to make use of this "window to the soul."

Let me briefly review the rationale for pupillographic studies and then discuss some of the techniques by which measurements of the pupil motility can be obtained.

The iris consists essentially of two groups of antagonistic smooth muscles, which are innervated by separate divisions of the autonomic nervous system. A group of radially located muscles is innervated by the peripheral sympathetic system via the cervical sympathetic chain. Impulses over this pathway contract the muscle and thereby dilate the pupil. A sphincter muscle forms the actual hole, called the pupil. This muscle is innervated from the Edinger-Westphal nucleus of the oculomotor center. Studies by Laties (1969) have shown that the innervation to the sphincter muscle is predominantly cholinergic.

* Assisted by Stephen Levine.
Lowenstein and Loewenfeld (12) have given a good review on the present state of knowledge on this complex innervation system.

The pupillary dilation, with which we will be mainly concerned in this paper, has at least two neural and two humoral components.

One of the neuronal components is the sympathetic activation from the hypothalamic area via the cervical sympathetic chain to the radial dilator muscles. Activation of this pathway results in a rapid, extensive pupillary dilation. The other neuronal component consists of impulses from cortex, thalamus, hypothalamus, and probably many other areas which have been shown to exert inhibitory influences in the tonic parasympathetic activity of the Edinger-Westphal nucleus. This results in a slower, less extensive dilation of the pupil. Lowenstein has called this activity "supranuclear inhibition." Studies with sympathectomized animals and Horner's syndrome patients allow us to differentiate between the dynamics of these two systems.

I will not go into the humoral elements acting on the pupil except to state that both adrenergic and cholinergic substances applied systemically and topically affect the pupillary diameter and motility.

Several recent studies have reported pupillary diameter changes to electrical stimulations of discrete areas of the brain. Ward and Reed found that electrical stimulation to parts of the frontal cortex reliably produced consensual pupillary dilation. Naquet (15) and his co-workers have shown a high correlation between cortical synchronization and pupil constriction and cortical desynchronization and pupil dilation respectively. Naquet pointed out that this correlation held whether the desynchronization was spontaneous or induced by reticular or sciatic stimulation. Delgado (1) summarized some of the stimulation work and stated that the dilation of the pupil is evoked by stimulation of cortical areas around the orbital cortex, temporal tip, cingulate gyrus, insula, rhinal fissure, and hippocampal gyrus, in addition to such deep structures as the basal telencephalon, hypothalamus, septum, midline group of thalamic nuclei, and some others.

Based on the knowledge that pupillary dilation is somehow tied into such an impressive number of major areas of the brain, it is not surprising that recent interest in the pupil has centered around its use as an indicator of the functional state of the brain. Though some people feel that the complexity of the interconnections make any meaningful interpretation of the data close to impossible, we feel that much can be learned about the functions by intelligent and creative experimental designs and procedures.

Over the centuries many efforts have been made to obtain objectives and reliable measurements of sequential changes in pupil diameter. Lups and magnification systems have been designed to closely observe pupil changes. Ballarminof in 1885 developed a system by which the pupil diameter was recorded on photosensitive brom silver paper. In 1922 Lowenstein started to
develop a cinephotographic method which photographed the pupil under dim blue light. Later, infrared sensitive film was used and it became possible to photograph the pupil in darkness. Several devices used the photocurrent produced by the visible and infrared light reflected from the iris on photosensitive cells. Since the outer diameter of the iris does not change, any change in reflectance can be attributed to the changes in iris area. This then is inversely related to pupil diameter.

In 1956, Lowenstein and Loewenfeld developed an infrared scanning device which allowed direct electronic measurement of pupil diameter. This instrument uses a mechanical scanner which scans the eye with twelve lines of infrared light at the rate of 60 rasters per second. On each scan the infrared light spot is either reflected by the iris and sclera or absorbed in the area of the pupil opening. The reflected or nonreflected part of the scan is then directed to an infrared sensitive photomultiplier. Since the speed of the scan is calibrated, the width of the resulting square wave is proportional to the length of the sector of the pupil. Naturally, the largest sector in each raster corresponds to the pupil diameter. The level of a dc output is then made proportional to the pupil diameter at any moment in time.

Several more-recently developed devices use infrared sensitive vidicons in a television-like system (2). Except for the rather slow decay time of the presently available vidicons, these systems are very efficient. They can be made very compact. The electronics are reliable solid state circuits.

In our own laboratory we use the Lowenstein pupillograph as a basic measuring device, to which we have added a data recording and analyzing

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**Figure 6-1.** Schematic block diagram of measuring, recording, and data analysis system.
system (3). The pupil, like other parts of the brain, is a very noisy organ. There are constant diameter changes in the pupil even at rest or when no discernible stimulus is applied. This is called "pupillary unrest" and many efforts to determine regularity in these movements have failed. Thompson (18) has traced the history of this so-called Hippus and found that it has something to do with horses but nothing to do with the eye. The term is probably a misnomer or a misunderstanding which has been carried through medical history. For all practical purposes, the unrest is random. We have therefore used average response curve techniques to pull the signal, that is, the response to our stimuli, out of the biological noise. These methods are very powerful and we have been able to detect reliable changes in pupil diameter of the order of .02 mm. Figure 6-1 shows a schematic block diagram of our measuring recording and data analysis system. The dc output of the pupillograph is recorded on magnetic tape. Appropriate identification and calibration pulses are added to each trial. After completion of the experiment, a tape search system identifies the code of each trial and then feeds the data into the Computer of Average Transients (CAT) The summed curves are then read out through a passive network which essentially divides each data point by N and thereby produces a true average (3).

Let us now look at some of our experiments. We have been interested in pupil motility related to rather complete conceptual events. Hess (5, 6) has recently stated that the "emotionality" of a subject and his "true" responses to specific stimulus situations can be gauged by the extent of his pupillary dilation or constrictions. Kahneman (7, 8) has reported pupillary responses to mental activity of varying difficulty, relating the amplitude of the dilation to the degree of difficulty. The phenomenon of pupillary dilation as a response to startle, fear, excitement, and interest has been described in the literature for well over one hundred years.

Our efforts were in part inspired by the work of Sutton and his co-workers (17) in our laboratories. Sutton had shown that the amplitude of the late so-called P3 component of the evoked cortical potential, as recorded from scalp, was related to such attributes of the stimulus as the certainty of its occurrence, or the value a subject might attribute to the stimulus. In Sutton's experiments the subject had to guess whether stimulus would be light or sound (uncertain). In the control experiment, the subjects were told what the stimulus would be (certain). In all subjects there was a difference between curves at 300 msec. The recordings were obtained from electrodes attached over the vertex, thus there is no doubt that they reflect cortical activity. We elaborated somewhat on Sutton's experimental design to take into consideration the somewhat slower response characteristics of the pupillary muscles. In these experiments we used a guessing situation as our experimental paradigm. We assumed that in such a guessing situation, the subject would try his best to
come up with as many right guesses as possible. It is interesting to note that none of our subjects ever used a "safe" guessing strategy. They all took certain risks.

Figure 6-2 shows the stimulus situation which we presented the subjects, all normal adults. The stimuli were clicks of 50 msec duration and about 50 dB above threshold.

There was a single click, a double click, two clicks separated by 50 msec, and a triple click (a double click followed by a third click 1000 msec later). The subject was asked to guess whether the next stimulus constellation would be a triple click (yes) or a double or a single click (no). If the subject hears the single click, he has all the information about the stimulus constellation, namely that it is a single click.

In the double click constellation the subject cannot be sure whether it was a double or triple click until the 1000 msec have passed. Then, by the presence or the absence of the third click his uncertainty of the situation will be resolved. This means that the first two clicks contain only 50 per cent of the information. In a control situation the subject was informed before the stimuli were presented what constellation would appear. Thus the subjects were certain about the characteristics of the stimuli.

Averaged response curves were obtained from five subjects. In all subjects the dilation in the guess situation (uncertain) is larger than in the told or certain condition. Also in the certain condition there is no double dilation, even when the triple click is present. This seems to indicate that the dilation is related to the uncertainty of the situation and not to the occurrence of the stimulus per se. The curves also are highly characteristic for each of the subjects. This intra-individual reliability of the data and its inter-individual

![Figure 6-2. Stimulus constellation.](image-url)
difference was one of the striking findings in our work. We superimposed all
the curves from the five subjects to show the differences.

The ECP (17) data show a similar trend. We wondered whether this intra-
individual consistency of the data, even over periods of several weeks, was de-
termined by the subject's specific strategy in the stimulus situation, by the
value system of the subject, or whether this was the reflection of a specific
"neuronal hook-up." We attempted to study this question by using identical
twins as subjects. We have tested so far only three pairs of twins, but the data
show a high similarity between twins. If I might be allowed to speculate, I
would tend to prefer the "neuronal hook-up" hypothesis.

In order to determine whether the larger dilation in the uncertain condi-
tion was the consequence of a higher level of vigilance, or attention, or in
physiological terms, higher arousal level, we added a "report" condition to
our design. In this condition the subject was asked to report after the trial
what he had heard. The data from all subjects show that there is still a differ-
ence in amplitude between the guess and the report condition, indicating that
although the higher attention produced a larger dilation, this "attention"
alone did not account for the total amplitude in the uncertain condition.

Figure 6-3 shows the trials averaged according to trials guessed correctly
(rights) and trials guessed incorrectly (wrongs). The curves are identical up
to the peak of the dilation about 1200 msec after the information has been
given to the subject by the occurrence or nonoccurrence of the third click.
The slope of the descending curves differentiate clearly between the "rights"
and the "wrongs." These data too show the very high intra-individual reliabil-
ity. We might then relate the characteristics of these curves, their slopes, am-
plitudes, and latencies to the contributions of specific areas or pool of neurons
through either increased or decreased impingement on the pupillomotor nu-
clei.

We make no claim of knowing the nature or locus of these contributions.
What we have shown here is a method by which rather complex sequential
events in the nervous system relating to conceptual and cognitive aspects of
human functioning can be analyzed.

I would like to discuss briefly some data we have obtained in our studies with
psychiatric patients. All the patients in this study were originally diagnosed as
schizophrenics and had not received chemotherapy for at least two weeks.
They were presented, after dark adaptation, with a series of 30-msec light
flashes (.3 ml intensity via a Ganzfeld) at 30-sec. intervals.

Response curves were superimposed at stimulus onset to compare extent of
pupillary contraction. I should point out that in this study we did not find dif-
fferences between the dark-adapted diameter of the pupil of the patients and
the controls as we had reported previously. Even without statistical analysis
we saw that these curves neatly separated the patients and the controls. Figure
Figure 6-3. Averaged response curves of trials where the guess was correct or incorrect.
6-4 shows these data plotted as cumulative percentage curves. A cutoff point at 1.7 mm extent of contraction shows about 15 per cent overlap at each end.

Knopp (9) has repeated some of these experiments and essentially confirmed these findings.

Knopp has also done some interesting studies of the effect of trifluoperazine on the pupillary light response in schizophrenic patients. He reported a high correlation between extrapyramidal side effects and changes in the pupil constriction response. There were, however, large individual differences among the patients with respect to drug tolerance, relief of psychotic symptomatology, and change in the pupillary response. Knopp feels, as a clinician, that the pupillary response changes are good indications for monitoring individual patient's drug treatment. Though his data are suggestive, they do not yet warrant generalization.

Knopp also reports some interesting findings in studies of two patients with Gilles de La Tourette disease. Pupillary changes correlated well with the disappearance of the clinical symptoms during treatment with haloperidol. Knopp is now testing psychotic patients under treatment with haloperidol as well as patients with Parkinson's disease who are under treatment with L-Dopa.

Laub effectiveness of different reagents in altering the reactive state was assessed.

We already tested procedures for assessing changes in this reaction for the sympathetic system and for such a change in such a given direction.

I hope to report on some of the functional changes.

1. Del
2. Gre
3. Ha
4. Ha
5. He
6. He
7. Ka
8. Ka
9. Kn
10. La
11. Lo
12. Lo

Figure 6-4. Cumulative percent graphs of extent of pupillary condition to single light flashes. The graphs for patients and controls are clearly separated.
Lauber (10) in Germany has studied the effects of a number of psycho-effective drugs on the pupil diameter in normal subjects. His data show different responses in pupil diameter to these drugs. More insight as to the effective loci of these drugs might be gained from studies of not only the static reactivity of the pupil, that is the diameter, but from the dynamic reactivity changes of the type I have described earlier.

We are now embarking on a project to follow psychotic patients with weekly testing sessions through their chemotherapy. We are going to use the procedures I outlined earlier. We hope to obtain data on their information processing characteristics and possible changes under proper treatment.

I should not close my presentation without mentioning Rubin's work (16) in this context. Rubin feels that psychotic patients show in their pupillary reaction either an overactivity or underactivity (or both) in either of the two sympathetic or parasympathetic systems. His 1962 paper seems to confirm such a distribution. Rubin is now engaged in a study in which the patients are given drug treatment according to the type of aberration in their pupillary reactivity. We have to wait for the results of this interesting approach.

I hope I have demonstrated to you the wide range of scientific applicability of the tool of pupillography to the study of brain functions and psychopharmacology.

REFERENCES


