# Impairment of Retinal Increment Thresholds in Huntington's Disease

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**We have investigated detection thresholds for a foveal blue test light using a Maxwellian view system in 61 normal subjects, 19 patients with Huntington's chorea, 14 patients with Tourette's syndrome, and 20 patients with schizophrenia. Ten measurements were made: The blue test light (1 degree diameter, 500 msec duration) was presented either superimposed on a yellow adaptation field (5 degree diameter) or 500 msec after switching off this field (transient tritanopia effect). In both cases five different background intensities were presented. The only abnormality found was in patients with Huntington's chorea. During adaptation these patients' thresholds are significantly higher than normal ($p < 0.005$). No change was found in the transient tritanopia effect. Huntington's disease causes degeneration of several different transmitter systems in the brain. Increment threshold testing allows for noninvasive investigation of patients and confirms the involvement of the retina in the degenerative process in Huntington's chorea.**

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Degenerative diseases affecting cerebral neurotransmission are also likely to impair the function of retinal neurons, which ontogenetically are part of the brain. By means of psychophysical as well as electrophysiological techniques retinal function and dysfunction can be assessed. Thus functional processes within the brain can be assessed by noninvasive methods. Parkinson's disease is the best known degenerative condition with involvement of retinal dopaminergic neurons that is not severe enough to produce subjective visual complaints [1].

In the present study we have used increment threshold measurements to test the function of the so-called cone-triad in the outer plexiform layer of the retina [2, 3]. Two transmitters, glutamate and gamma amino acid (GABA), are involved in the signal processing within this triad. Glutamate has consistently been found in rod as well as in cone pedicles and appears to be the major transmitter of the vertical pathway, e.g., the majority of bipolar and ganglion cells [4, 5]. The GABAergic function of horizontal cells has only recently become clearer. This delayed discovery was due to the following several unusual features: Horizontal cells are engaged in the invaginating synapses in photoreceptor pedicles. Physiologically they are nonspiking neurons and, at least in nonmammalian vertebrates, they have an unusual non–calcium-triggered, but voltage-dependent, transmitter release. It is thought very likely that GABA released from horizontal cells provides a negative feedback at the cone pedicles [6]. However, GABA is not only confined to the cone triad but, next to glycine, which is found in 45% of all amacrine cells, is also a common transmitter of amacrine cells in the cat retina [7]. Also, a small portion of bipolar cells have been shown to use GABA as their transmitter. Thus vertical and lateral retinal signal transmission could change in conditions that affect GABA metabolism.

To assess this, as a first step, we measured the increment threshold of a blue test light during adaptation to a yellow background and then monitored the paradoxical threshold increase of the blue test light after turning off the yellow adaptation light. This phenomenon was first observed by Stiles [8]. Mollon and Polden [9] studied it extensively and named it transient tritanopia (TT); after switching off a strong yellow adapting light, the threshold of a blue test light rises initially by about 1 log unit and then decreases exponentially over the following seconds. This is a paradoxical phenomenon because at the offset of the adapting light one would expect the threshold to fall immediately as in dark adaptation curves, without an initial

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transient rise of the threshold [10]. Although the threshold for blue light is raised in TT, adaptation of the blue sensitive cones cannot be responsible for this effect because the wavelength of the yellow adapting light (575 nm) is too long to be detected by the blue sensitive cones; thus neural interactions must be involved.

In our investigation, patients with Huntington's disease, but neither Gilles de la Tourette syndrome (GTS) nor schizophrenic patients, showed an abnormal increment threshold increase but normal TT.

## Patients and Methods

We have investigated 61 normal subjects (mean age, 33.7 yr), 19 patients with Huntington's disease (mean age, 43.1 yr), 20 newly diagnosed untreated schizophrenic patients (mean age, 26.6 yr), and 14 GTS patients (mean age, 40.9 yr). Visual acuity was normal in each patient.

The mean duration of the disease in the Huntington group was 8.75 years. The psychotic patients were diagnosed as schizophrenics according to the ICD 9 and the DSM III-R (*Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised). The severity of the schizophrenic symptomatology was rated by the Brief Psychiatric Rating Scale (BPRS). The BPRS total score (mean, 58; SD, 8) represented an acute, severe schizophrenic symptomatology. The mean severity of the GTS patients was 10 to 66 points on the Tourette syndrome global scale (mean, 37 ± 17 points). The age distribution of normals and Huntington patients is depicted in Figure 1.

We have measured the threshold of a blue test light (1 degree diameter, 500 msec duration), first superimposed on a yellow adapting background and then after switching off the yellow adapting light. The apparatus (Nidek, Japan; Retinal Function Test Instrument) presents stimuli in a Maxwellian view with an artificial pupil of 1.5-mm diameter. The major advantage of this method is that the light beam is smaller than the natural pupil and the retinal illuminance is kept constant without the need for artificial pupil dilatation; the major disadvantage is that the patient is required to look through a small aperture of an optical system and not at a distant visual target. The standard version of the apparatus confines the diameter of the blue light to 1 degree; a larger diameter of 3 degrees or more might turn out to be more sensitive due to the 0.5 degrees of scotoma for blue perception at the fovea. The apparatus has been calibrated in microwatts (see figures). Only one eye can be tested at a time.

Observers were dark adapted for 10 minutes. The investigation started with a 2-minute presentation of the yellow background light in order to adapt the observer's eye to the given intensity level of long wavelength light. Thresholds were determined using a staircase procedure. The investigator increased or decreased the blue light intensity in steps of 0.1 log units according to the observers' answers. This procedure was repeated five times and thresholds were determined by starting well above and below the threshold. Ascending and descending thresholds did not differ by more than 0.2 steps and therefore threshold was defined by their mean values. Increment thresholds have been determined for a defined background light intensity. After adaptation to the background light for a further 2 minutes, blue thresholds were measured 500 msec after the background was switched off. Further measurements at a given adaptation level at each luminance were done after 5 seconds of readaptation. An overall time limit was not imposed; during the experiment the patients were continuously monitored and reinforced by the investigating physician. With eye or head movements the visual image disappeared. In this case the ongoing trial was terminated and repeated.

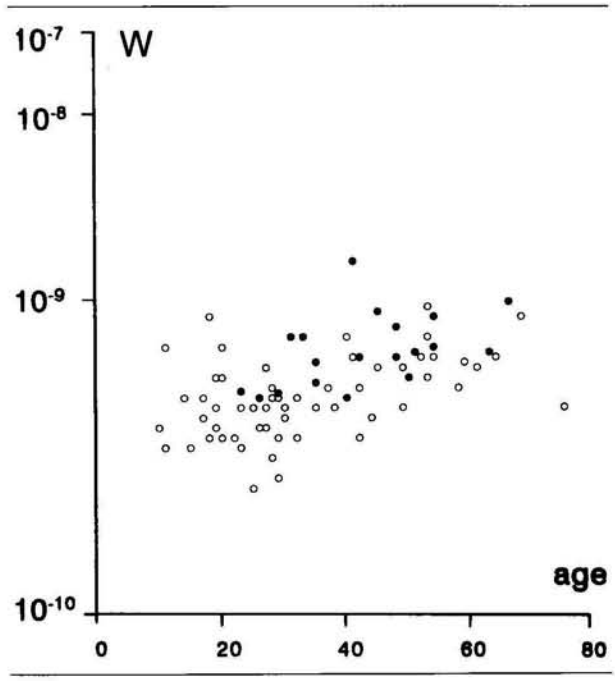


*Fig 1. Increment thresholds for blue test light during adaptation with $1.9 * 10^{-7}$ W yellow adaptation light. Thresholds of the choreatic patients (closed dots) are significantly increased ($p \leq 0.001$) when compared with normals.*

While previous investigations concentrated on the time course of transient tritanopia [10], we confined our measurement to a test stimulus duration of 500 msec, beginning 500 msec and ending 1 second after switching off the adapting light, but investigated five different levels of adaptation intensities ($1.2 * 10^{-9}$, $9.7 * 10^{-9}$, $1.4 * 10^{-8}$, $1.9 * 10^{-7}$, $1.4 * 10^{-6}$ W).

Each intensity level was measured during and after adaptation in patients and normals. In order to account for the age dependency of the data in three different patient groups with different age distribution we chose for statistical analysis a two-dimensional linear regression model with age and disease as independent parameters and the thresholds a dependent parameter [11, 12]. We tested increment thresholds and TT in each of the patient groups against the normal group:

$$Value_i = \gamma + \alpha Code_i + \beta Age_i + \epsilon_i \qquad (*)$$

The model error $\epsilon_i$ was assumed to be data independent and normally distributed. Code was set to 0, if the subject was healthy, otherwise to 1. An $F$ test ($p < 0.0001$ in each test) showed that the model (*) is able to explain the data. The zero-hypothesis $H_{code}$ was taken as $\alpha = 0$; the $t$ test was used.

In the Huntington group we could show that in the three upper intensity levels $H_{code}$ can be rejected ($p < 0.001$) in the increment threshold but not in the TT case ($p > 0.3$).

## Results

We have measured increment thresholds and TT at five different levels of light adaptation intensity in normals and three different subgroups of patients. At the two lowest levels no difference between normals and patients could be detected. The three upper intensity levels (labeled low, mean, and high intensity) disclosed a disease-related abnormality, details of which are presented below.

Figure 1 depicts the blue light increment thresholds measured during yellow adaptation at the mean adaptation level of $1.9 * 10^{-7}$ W. Whereas no significant difference between normals and psychotic and GTS patients could be detected, a relative threshold increase was found between normals (open dots) and choreatic patients (closed dots) ($p < 0.001$). Blue light thresholds following yellow light adaptation revealed no significant threshold differences at any adaptation level and any patient group, hence the results are not shown here. Only the psychotic patients showed some just significant ($p < 0.05$) results, which were inconsistently distributed across light intensities and increment threshold and TT. We refer these results to the particular difficulties arising when performing psychophysical tests in this subgroup of patients.

Figure 2 and Figure 3 demonstrate that the separation between Huntington's disease and normals holds true also for the next lower and next higher adaptation levels. One patient was on clozapine, 1 on tiapride, and 3 were on sulpiride. In order to exclude drug effects we have repeated the statistics excluding these patients. Because we got essentially the same $p$ values the results are not due to drug effects.

Figure 4 demonstrates the essentially normal results in psychotic and in GTS patients at the most interesting background illumination level of $1.9 * 10^{-7}$ W.

## Discussion

To our knowledge this is the first study of retinal function in Huntington's disease. This is a degenerative disorder that affects GABA, GABA + metenkephalin, GABA + substance P, and glutamate. Other transmitters may also be involved, but this question is not yet settled [13]. Increment thresholds have been investigated mainly in retinal disorders such as diabetic retinopathy or retinitis pigmentosa to detect retinal damage earlier than by other methods [10, 14, 15]. In this investigation we have studied increment threshold and transient tritanopia in three different neurological or psychiatric disorders primarily affecting the brain. While Gilles de la Tourette and schizophrenic patients did not differ from the normal popula-

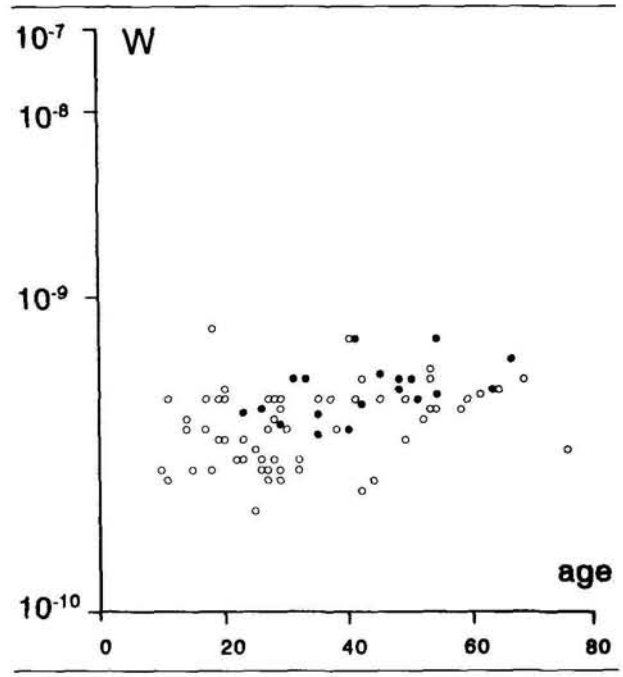


*Fig 2. Increment thresholds for blue test light at the illumination level of $1.4 * 10^{-8}$ W for the yellow adaptation light. A significant difference* ($p < 0.005$) *between normals and choreatic patients is present also with this adaptation level.*

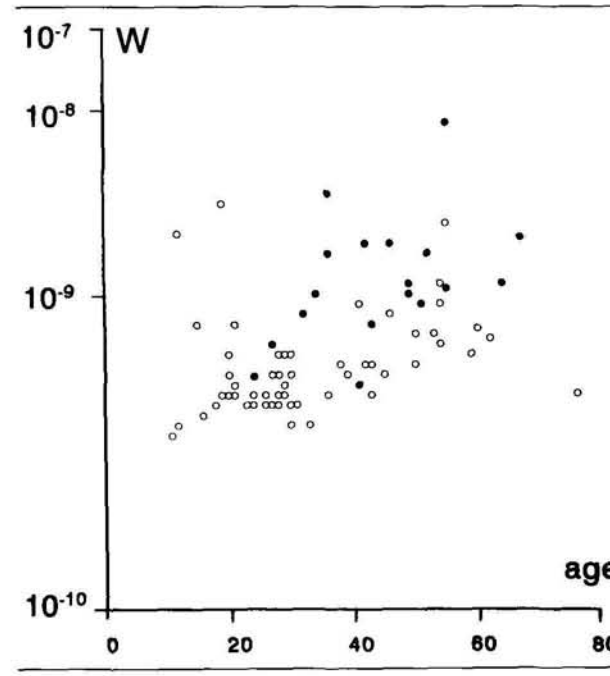


*Fig 3. Increment thresholds for blue test light increase with the higher adaptation level of $1.4 * 10^{-6}$ W for the yellow background. The separation between the Huntington group and the normals is still evident* ($p < 0.001$), *whereas no difference exists with the transient tritanopia effect not shown here.*

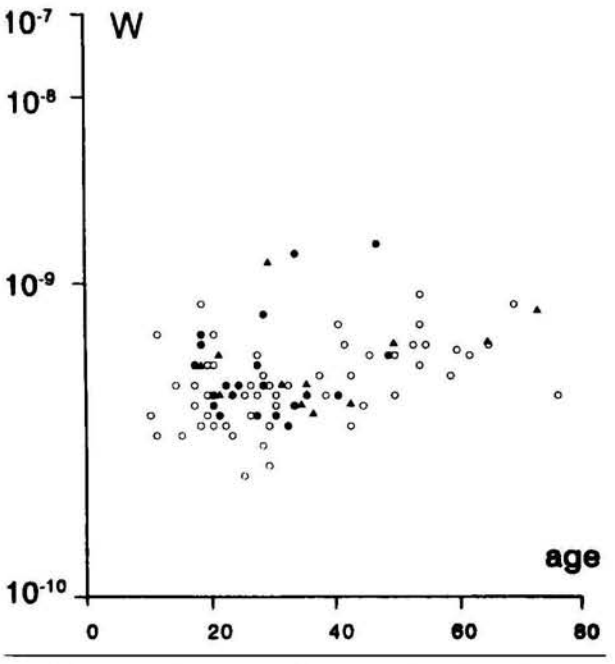


*Fig 4. Increment thresholds for blue test light with a yellow background illumination level of 1.9 * $10^{-7}$ W. There is no difference between normals* (open dots) *and psychotic* (closed dots) *and Gilles de la Tourette patients* (closed triangles) *in this nor in any other of our test conditions.*

tion, we found at three different luminance levels of the background light a significant increase of increment threshold in patients with Huntington's disease. Transient tritanopia itself did not give significant deviations in Huntington patients when compared with normals. However, in the light of increased increment thresholds in Huntington patients, one could expect a further increase in TT in parallel with the normals. Because this was not the case a further pathological process may possibly be involved.

The simplest explanation for the threshold increase in Huntington's disease may be that glutamate liberation from cones in darkness decreases. Light hyperpolarizes the cones and thereby reduces glutamate release still further. A reduction of dark would be equivalent to a weak background light and may thus be responsible for the observed threshold increase.

Involvement of GABA has been postulated as the physiological basis for TT [2]. H cells are hyperpolarized by yellow light that stimulates L and M cones. They have a sign-inverting input into blue cones. The H-cell to B-cone transmitter is thought to be GABA, which is released in darkness. Yellow light hyperpolarizes the middle and long wave cones in the surround and concurrently the horizontal cells, which stops the release of the transmitter GABA. This in turn depolarizes the B cone by decreasing its $Cl^-$ or $K^+$ conductance so that it can reach a more positive resting potential. Consequently the continuous activity of the ganglion cell is decreased. This in turn leads to an enhancement of blue receptor sensitivity to incoming blue light by enhancing the response gain. The loss in increment sensitivity for blue light as observed in Huntington's disease could in principle also be caused by a loss in GABAergic efficiency. However, their normal TT findings argue against a GABA deficit.

The decrease in blue light sensitivity, as observed in healthy observers after long wavelength adaptation, can be attributed to a rebound depolarization of the long wavelength cones and an even stronger transient depolarization of the horizontal cell, which in turn is suggested to release the hyperpolarizing transmitter onto the B cone's submembrane. The psychophysical correlate of the induced strong hyperpolarization of the B cone is seen in the phenomenon of transient tritanopia. Thus TT may be a more sensitive test than increment threshold testing when monitoring GABAergic function.

Psychophysical techniques can be designed in order to analyze the function of a certain type of cell. The best studied example again is the dopaminergic function of interplexiform retinal cells, which is monitored best by using gratings with high spatial and temporal frequency [16]. This spatiotemporal frequency domain is affected predominantly in Parkinson's disease, probably due to dopaminergic influence on the functional coupling of center and surround activity of bipolar and ganglion cells at an early retinal stage [17]. Dopaminergic dysfunction, which is probably involved in psychotic patients and in GTS patients is of minor importance in Huntington's disease [13]. Thus the normal results in these two groups of patients support the assumption that dopamine is not involved in the increment threshold increase. We thus feel safe to speculate that transient tritanopia may primarily monitor GABAergic function, whereas increment thresholds primarily give an estimate of glutaminergic function. Further studies are necessary to support these assumptions.

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