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# Correlation between morphological and functional retinal impairment in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis and Alzheimer's disease

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## Abstract

In this article the correlations between the morphological evaluation of the nerve fiber layer (NFL) thickness (by OCT) and retinal functional assessment (by Pattern ERG recordings) performed in patients affected by ocular hypertension (OHT), glaucoma (OAG), demyelinating optic neuritis (MSON), and Alzheimer's disease (AD) are reported.

In OHT eyes with ocular hypertension we observed that the inter-individual variation in NFL thickness is correlated with the variability of the PERG responses (the thinner the layer, the worse the visual function).

In our OAG, MSON and AD eyes we observed a significant reduction in NFL thickness when compared with controls. In OHT, OAG, MSON and AD eyes abnormal PERG responses with delayed implicit times and reduced amplitudes were found. The impairment in the PERG parameters was significantly correlated to the reduction in NFL thickness.

Our results suggest that in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis, and Alzheimer's Disease there is a reduction of NFL thickness evaluated "in vivo" by OCT, and this morphological involvement is correlated with electrophysiological responses assumed to be originating from the innermost retinal layers.

**Keywords:** Ocular hypertension; Glaucoma; Multiple sclerosis; Alzheimer's disease; Pattern Electroretinogram; retinal ganglion cells; Optical Coherence Tomography

## Introduction

A depletion of optic nerve ganglion cells and their axons has been observed histologically or with other methods of retinal fiber assessment in several pathologies such as glaucoma, demyelinating optic neuritis, and Alzheimer's Disease.[1–9]

An objective method of quantifying "in vivo" the optic nerve axons and retinal thickness has been proposed. This method consists of a new non-invasive technology allowing cross-sectional imaging of the eye by Optical Coherence Tomography (OCT), and so far has been widely employed in assessing nerve fiber layer (NFL) thickness in ocular hypertension[16] or glaucoma, in demyelinating optic neuritis and in Alzheimer's disease.[10–15,17–19]

The bioelectrical activity of ganglion cells and their fibers can be objectively assessed by recording electroretinographic signals in response to patterned stimuli (PERG).[20–24]

In this review the correlations between morphological (OCT) and functional (PERG) parameters in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis, and Alzheimer's disease are reported.

## Subjects and methods

According to the inclusion criteria (see above) we enrolled:

- Thirty-two patients (age range 29–64 years, mean 48 ± 9 years) affected by ocular hypertension (IOP >23 mmHg and <28 mmHg) with normal automatic full threshold perimetry (24/2 Humphrey, Mean Defect <2 dB), and none of the following papillary signs on conventional color stereo-slides: rim notch(es), peripapillary splinter haemorrhages, increased vertical-to-horizontal cup/disk ratio, cup/disk asymmetry between the two eyes <0.2 (OHT eyes).[16]

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- Thirty glaucoma patients (mean age 47.1 ± 7.15 years, refractive error between ±2 sf) with mean deviation of computerized static perimetry (24/2 Humphrey) between −5 and −28 dB and IOP <21 mmHg in pharmacological treatment (OAG eyes).[17]
- Fourteen patients (six males and eight females; mean age: 34.07 ± 5.8 years) with a diagnosis of definite multiple sclerosis, according to the criteria previously proposed by Poser *et al.*, and previously affected by optic neuritis (ON).[25] Since it has been observed that the retrograde degeneration process may fully develop in a life-span of six months, they were examined at least twelve months after the last ON episode (MSON eyes).[18,26]
- Seventeen subjects (mean age 70.37 ± 6.1 years) were selected from a group of forty patients with diagnosis of Alzheimer's Disease (AD eyes).[19] The diagnosis was performed using the established criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[27] For this study we included patients with a mild severity of cognitive impairment, according to criteria described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III).[28]

General inclusion criteria for patients and their age-matched controls were: no evidence of vascular dementia, no history of alcohol abuse, no psychiatric disorders, no dismetabolic diseases, no arterial hypertension, no other neurological diseases, no psychotropic therapy. Ocular inclusion criteria were: best corrected visual acuity >8/10 with refractive error between ±3 sf, intraocular pressure <18 mmHg, absence of previous history of optic media opacity, cataract or early lens opacity, retinal detachment, early age-related macular degeneration, or other macular degeneration, retinal vascular diseases.

Informed consent was received from all subjects involved in the study. The research followed the tenets of the Declaration of Helsinki and the protocol was approved by the local Ethical Committee.

## OCT examination

OCT (Humprey, Dublin, CA) was used with a fiber optic delivery system coupled with a slit-biomicroscope. This system provides the operator with a video-camera view of the scanning probe beam on the fundus and OCT imaging acquired in real time on a computer monitor. After dilatation with 1% tropicamide, each eye was scanned three times using a circle size of 3.4 mm (1.7 mm radius). Near-infrared light (840 nm wavelength) was used. Throughout scanning, the patient kept each eye constantly fixed on an internal target provided by the equipment. The measurements were obtained from three non-consecutive scans (i.e., the patient was allowed to rest for a few seconds before being re-positioned to proceed to the following scan). As previously reported, the OCT software provides an automated computer algorithm that identifies the anterior and posterior borders of the retina.[11] This has been claimed to offer the possibility of calculating both NFL and total retinal thickness.[11] The software allows the mapping of the thickness data according to both quadrant-by-quadrant and clock hour analyses. Retinal thickness was determined by computer as the distance between the first reflection at the vitreoretinal interface and the anterior boundary of the second reflective layer, corresponding to the retinal pigment epithelium and the choriocapillaris. As discussed elsewhere, NFL thickness was automatically assessed by the computer assuming the correlation with the highly reflective red layer at the vitreoretinal interface.[11] The posterior margin of the NFL is automatically located by the software, starting within the photoreceptor layer (posteriorly) and searching forward in the image.[11]

We considered the average values of three different measurements per quadrant (superior, inferior, nasal and temporal): the overall data obtained in all quadrants (12 values averaged) were identified as NFL Overall.

## PERG recordings

According to previously published studies PERG recordings were performed using the following method.[16–19,29–33] The subjects under examination were seated in a semi-dark, acoustically isolated room in front of the display surrounded by a uniform field of luminance of 5 cd/m$^2$. Prior to the experiment, each subject was adapted to the ambient room light for 10 min and the pupil diameter was about 5 mm. Mydriatic or miotic drugs were never used. Stimulation was monocular after occlusion of the other eye. Visual stimuli were checkerboard patterns (contrast 80%, mean luminance 110 cd/m$^2$) generated on a TV monitor and reversed in contrast at the rate of 2 reversals/s. The check edges subtended 15 minutes of visual angle. The screen of the monitor subtended 18°.

The bioelectrical signal was recorded by a small Ag/AgCl skin electrode placed over the lower eyelid. PERGs were derived bipolarly between the stimulated (active electrode) and the patched (reference electrode) eye using the method previously described.[34] As the recording protocol was extensive, the use of skin electrodes with an interocular recording represented a good compromise between signal-to-noise ratio and signal stability. A discussion on PERG using skin electrodes and its relationship to the responses obtained by corneal electrodes can be found elsewhere.[35,36] The ground electrode was in Fpz. The interelectrode resistance was lower than 3 KOhms. The signal was amplified (gain 50000), filtered (band pass 1–30 Hz) and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 msec. The transient PERG response is characterized by a number of waves with three subsequent peaks, of negative, positive, negative polarity, respectively. In normal subjects, these

peaks have the following implicit times: 35, 50 and 95 msec (N35, P50, N95).

Since an intraindividual PERG variability, related to inattention or optical defocus, has been described in AD patients,[37] the recording session was continuously monitored (with an infrared videocamera) to check whether the patient tested maintained a stable fixation over a small, red target (0.5°) placed in the center of the stimulus field. The refraction of all subjects was corrected for viewing distance.

We accepted PERG signals with signal-to-noise ratio >2. The noise was measured by recording the bioelectrical signals (200 averaged events), while the monitor was screened by a cardboard. A retinal noise (peak-to-peak measure) <0.1 microvolt (mean 0.086 microvolt) was observed in all subjects tested. For all PERG recordings, the implicit time and the peak-to peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors.

### Statistical analyses

The data are reported as mean values ±1 standard deviation. The differences between controls and patients were statistically evaluated by ANOVA. In order to assess whether a correlation exists between NFL thickness and electrophysiological parameters, linear regression analysis (Pearson's test) was adopted. In both statistical analyses, a P value less than 0.01 was considered significant.

OCT scans were performed by one observer. Test-retest variability was maintained within the 5% limit. In case of a variability >5%, a new set of three independent scans was repeated until proper values were recorded.

In the recording session, PERGs were recorded at least twice and the resulting waveforms were superimposed to check the repeatability of the results. The test-retest variability of PERG parameters proved to be <5%.

## Results

Examples of NFL assessment and relative PERG recordings are reported in Figure 1.

The mean data of NFL thickness and PERG parameters are reported in Table 1.

The correlation between NFL thickness and PERG parameters are reported in Table 2.

### OHT eyes

In OHT patients we evaluated the variability of the electrophysiological data as a function of nerve fiber thickness. PERG recordings gave the following results (95% confidence limits): PERG P50 latency = 59.3–63 msec; PERG P50-N95 amplitude = 0.74–1.15 μV. The thickness of the nerve fiber layer, measured across the 360° section along the optic disc (NFLO), ranged between 113 and 169 μ (mean ± S.D. = 145

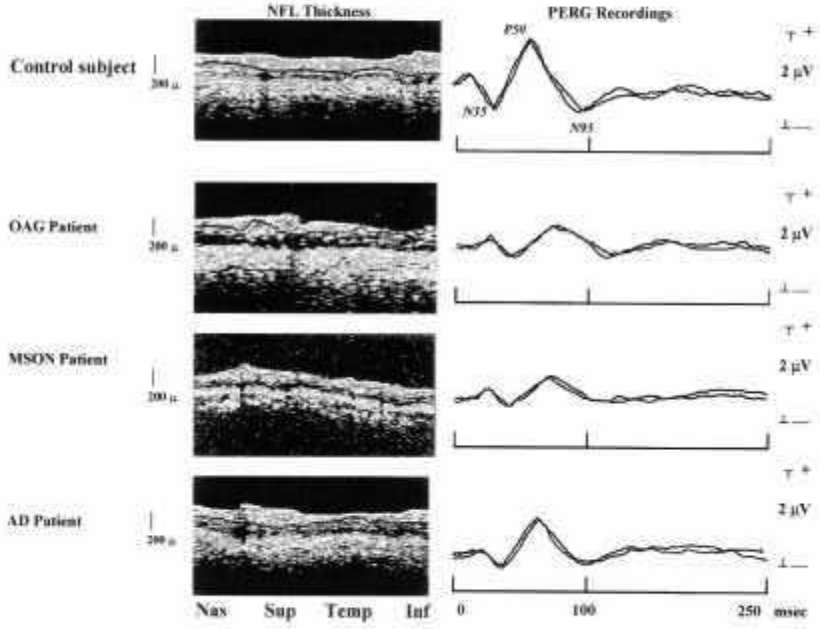


*Figure 1.* **Left**: Circular Optical Coherence Tomography (OCT) taken in cylindrical section of tissue surrounding the optic disc. The anterior most red reflection indicates the nerve fiber layer (NFL); **Right**: Transient PERG recordings obtained in response to high contrast (80%) 15′ checks of visual stimuli. In comparison with the control subject, in OAG, MSON and AD patients OCT shows a marked decrease of NFL reflection (smaller NFL thickness) in each quadrant; PERG recordings show delayed implicit times and reduced amplitudes.

*Table 1.* Mean values and one (±) standard deviation of morphological (NFL thickness) and electrophysiological (PERG) parameters in glaucoma (OAG), Optic Neuritis in Multiple Sclerosis (MSON), Alzheimer's Disease (AD) patients and in relative age-matched controls. Statistics: Analysis of Variance with respect to Controls, * = $P < 0.01$.

| Group | NFL Overall (μm) | NFL Temporal (μm) | PERG P50 Implicit Time (ms) | PERG P50-N95 Amplitude (microvolt) |
|---|---|---|---|---|
| OAG (N = 30) | 51.5 ± 25.7* | 40.0 ± 19.7* | 64.00 ± 4.11* | 0.71 ± 0.19* |
| Controls (N = 14) | 119.57 ± 11.0 | 84.9 ± 6.67 | 56.92 ± 4.04 | 1.71 ± 0.17 |
| MSON (N = 14) | 59.79 ± 10.8* | 41.54 ± 15.5* | 65.93 ± 7.14* | 0.91 ± 0.41* |
| Controls (N = 14) | 111.11 ± 11.4 | 83.64 ± 11.87 | 57.72 ± 5.08 | 1.81 ± 0.22 |
| AD (N = 17) | 59.5 ± 16.7* | 37.9 ± 17.60 * | 70.47 ± 4.93* | 0.78 ± 0.25* |
| Controls (N = 14) | 99.9 ± 8.95 | 85.6 ± 8.21 | 60.79 ± 2.83 | 1.54 ± 0.16 |

*Table 2.* Linear regression and correlation between PERG parameters and Overall or Temporal Nerve Fiber Layers (NFL) evaluated in ocular hypertension (OHT), glaucoma (OAG), Optic Neuritis in Multiple Sclerosis (MSON), Alzheimer's Disease (AD) patients.

| vs | OHT | | OAG | | MSON | | AD | |
|---|---|---|---|---|---|---|---|---|
| | PERG P50 Implicit Time | PERG P50-N95 Amp | PERG P50 Implicit Time | PERG P50-N95 Amp | PERG P50 Implicit Time | PERG P50-N95 Amp | PERG P50 Implicit Time | PERG P50-N95 Amp |
| NFLO | r: −0.470 | r: 0.518 | r: −0.422 | r: 0.460 | r: −0.744 | r: 0.794 | r: −0.634 | r: 0.742 |
| | t: −2.916 | t: 3.318 | t: −2.546 | t: 2.835 | t: −3.866 | t: 4.531 | t: −3.180 | t: 4.288 |
| | P = 0.007 | P = 0.002 | P = 0.016 | P = 0.008 | P = 0.002 | P = 0.001 | P = 0.0062 | P = 0.0006 |
| NFLT | r: −0.404 | r: 0.493 | r: −0.447 | r: 0.349 | r: −0.635 | r: 0.607 | r: −0.749 | r: 0.775 |
| | t: −2.420 | t: 3.102 | t: −2.738 | t: 2.109 | t: −2.849 | t: 2.652 | t: −3.349 | t: 3.288 |
| | P = 0.022 | P = 0.004 | P = 0.010 | P = 0.043 | P = 0.010 | P = 0.020 | P = 0.0004 | P = 0.0004 |

± 16). The NFL Overall and Temporal values of each patient showed a significant correlation with PERG P50 implicit time and PERG P50-N95 amplitude.

### OAG eyes

In OAG eyes, we observed NFL Overall thickness within 12.9 and 109.3. (mean 51.5 ± 25.7) microns; this was significantly ($P < 0.01$) reduced when compared with controls; NFL Temporal thickness was within 10.0 and 84.0 (mean: 40.0 ± 19.7) microns and therefore significantly ($P < 0.01$) reduced when compared with controls. NFL thickness was not correlated ($P > 0.01$) with IOP values or with age.

OAG eyes showed PERG P50 implicit time significantly ($P < 0.01$) delayed and PERG P50-N95 amplitudes significantly ($P < 0.01$) reduced with respect to control eyes. In OAG eyes, the NFL Overall and NFL Temporal values were significantly correlated ($P < 0.01$) to PERG parameters (P50 implicit time and P50-N95 amplitude).

### MSON eyes

In control eyes we found an NFL thickness within 92.5 and 127.4 (mean: 111.11 ± 11.42) microns in the NFL Overall evaluation and within 68.9 and 106.5 (mean: 83.64 ± 11.87) microns in the NFL Temporal evaluation. In MSON eyes we observed NFL thickness within 35.58 and 77.10 (mean 59.79 ± 10.80) microns in the NFL Overall evaluation and within 15.30 and 63.30 (mean: 41.54 ± 15.55) microns in the NFL Temporal evaluation. We observed a significant ($P < 0.01$) reduction of NFL thickness values in MSON eyes when compared to controls.

In MSON eyes PERG P50 implicit time was significantly ($P < 0.01$) delayed with respect to control eyes and the PERG P50-N95 amplitudes were significantly ($P < 0.01$) reduced with respect to controls. NFL Overall and NFL Temporal values were significantly correlated ($P < 0.01$) to PERG P50 implicit time and PERG P50-N95 amplitude in MSON eyes.

### AD eyes

NFL Overall thickness was within 86.7 and 111.7 μm (mean: 99.9 ± 8.95 μm) in control eyes and within 29.5 and 105.4 μm (mean: 59.5 ± 16.70 μm) in AD eyes. In AD eyes NFL thickness evaluated in the separate quadrants (Inferior, Superior, Nasal, and Temporal) or in the Overall evaluation was significantly ($p < 0.01$) reduced when compared with that of control subjects.

AD eyes showed PERG P50 implicit time was significantly ($p < 0.01$) delayed compared with that of control eyes; PERG P50-N95 amplitudes were significantly ($p < 0.01$) reduced compared to control eyes. In AD eyes NFL Overall and NFL Temporal values were significantly correlated ($p < 0.01$) to PERG P50 implicit time and PERG P50-N95 amplitude.

In control eyes, no significant correlation between PERG parameters and NFL thickness was observed.

## Discussion

We studied the correlation between the NFL thickness and retinal function in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis, and Alzheimer's Disease.

In 32 patients with ocular hypertension we observed that the inter-individual variation in NFL thickness is associated with the variability of PERG responses (the thinner the layer, the worse the visual function).[16]

In our 30 OAG patients we observed a significant reduction in NFL thickness. The OCT readings are comparable to those previously observed in normal and glaucomatous eyes by several authors.[15,38–41]

We observed a significant reduction in NFL thickness in 14 patients with MS and this is in agreement to previous studies performed using different methods of retinal fiber assessment.[42–45] This finding could be considered the expression of a loss of those axons that form the head of the optic nerve. A high frequency of transected axons in the lesioned brain area in MS patients was observed in a recent neuropathologic study.[46] It is likely that a similar degree of axonal involvement may develop in the optic nerve affected by the inflammatory process. A retrograde degeneration could then initiate in the damaged ganglion cell fibers leading to the morphological changes that we have observed.

In 17 Alzheimer's Disease patients our OCT results show an NFL reduced thickness in each quadrant examined, indicating an involvement of the neuroretinal tissue. These data confirm previous observations obtained by histological studies or by other methods of evaluating the NFL in vivo.[9,47–51] The loss of ganglion cells and their fibers observed in AD patients could be ascribed to a neurodegenerative process involving the neuroretinal structures.

According to several studies revealing a retinal dysfunction in patients affected by ocular hypertension,[20,52–58] glaucoma,[29,30,33,59–64] demyelinating optic neuritis,[65–71] and Alzheimer's Disease,[17,72,73] we observed, in the same categories of patients, abnormal PERG responses with delayed implicit times and reduced amplitudes. In our patients the impairment in PERG parameters was significantly correlated to the reduction in NFL thickness.

Although studies performed in animal models have shown that PERGs reflect the bioelectrical activity of the innermost retinal layers (ganglion cells and their fibers), the existence of similar evidence in humans is still controversial.[20–24]

In fact, a shortening of P50 implicit time has been observed in pathologies in which there is a primary retinal ganglion cell dysfunction such as dominant optic atrophy, optic nerve compression and surgical optic nerve section.[74–76] These human data are supported by a recent paper by Viswanathan *et al.*, in which a shortening of the P50 implicit time has been observed after inducing experimental glaucoma or TTX treatment in monkey eyes.[77] Therefore, these studies suggest that in the presence of a "pure" retinal ganglion cell dysfunction there is a shortening and not a delay of the P50 component. On the basis of these studies, we believe that the delay in the P50 component observed in our ocular hypertension, glaucoma, demyelinating optic neuritis, and Alzheimer's Disease patients cannot be exclusively ascribed to a "pure" ganglion cell dysfunction.[74–77]

A possible dysfunction of pre-ganglionic elements could explain the delay in P50 implicit time observed in our patients, and this is supported by data obtained in glaucoma or in multiple sclerosis in which the delay of the P50 implicit time could be ascribed to a dysfunction of both ganglionic and preganglionic elements.[78,79]

Nevertheless, the significant correlation between the delay in P50 implicit time and the reduced NFL thickness observed in our AD patients, lead us to believe that a contribution of the inner retinal neurons to the P50 component cannot be entirely excluded. On the contrary, the correlation between the reduction in P50-N95 amplitude and the reduced NFL thickness can be explained, in agreement with Viswanathan *et al.*, by the hypothesis that the N95 component depends exclusively on ganglion cell function.[77]

In conclusion, our results suggest that in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis and Alzheimer's Disease, there is a reduction of NFL thickness evaluated "in vivo" by OCT, and this morphological involvement is related to a retinal dysfunction as revealed by abnormal PERG responses.

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