The Role of Perimetry in the Diagnosis of Neuro-Ophthalmic Disorders and Its Implications to Neural Plasticity of Visual Perception

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I. ABBREVIATIONS

AMD: Age-related macular degeneration
BI: Barthel Index
BOLD: Blood oxygenation level-dependent
CDMS: Clinically definite multiple sclerosis
CF: Counting fingers
CFF: Critical fusional frequency
CIS: Clinically isolated syndrome
CRAO: Central retinal artery occlusion
DTI: Diffusion tensor imaging
DWI: Diffusion-weighted images
ECC: Eccentricity
EDSS: Extended Disability Status Score
EPI: Echo-planar imaging
EEG: Electroencephalogram
ETDRS: Early Treatment Diabetic Retinopathy Study
FDP: Frequency-doubling perimetry
fMRI: Functional magnetic resonance imaging
GBM: Glioblastoma multiforme
GVF: Goldmann visual field
HM: Hand motion
HRP: High-pass resolution perimetry
HRT: Heidelberg Retina Tomograph
HVF: Humphrey visual field
IN: Inferior-nasal visual field quadrant
ISI: Interstimulus interval
LHON: Leber’s hereditary optic neuropathy
MD: Mean deviation
MEG: Magnetoecephalogram
mfVEP: Multifocal visual-evoked potential
MPG: Motion probing gradient
MPRAGE: multiplanar rapidly acquired gradient echo sequence
MRI: Magnetic resonance imaging
MRS: Modified Rankin Scale
MS: Multiple sclerosis
MSFC: Multiple Sclerosis Functional Composite
NAION: Nonarteritic anterior ischemic optic neuropathy
OCT: Optical coherence tomography
PERG: Pattern electroretinogram
PERG N95: Pattern electroretinogram negative wave at 95ms
PROPELLER sequence: Periodically rotated overlapping parallel lines with enhanced reconstruction
PSD: Pattern standard deviation
RAPD: Relative afferent papillary defect
RGC: Retinal ganglion cell
RNFL: Retinal nerve fiber layer
ROT: Retrobulbar optic neuritis
SITA: Swedish Interactive Thresholding Algorithm
SLO: Scanning laser ophthalmoscopy
SLP: Scanning laser polarimetry
ST: Superior-temporal visual field quadrant
SWAP: Short wavelength automated perimetry
T: Tesla
T1W: T1-weighted sequence
T2W: T2-weighted sequence
VA: Visual acuity
VEP: Visual-evoked potential
VF: Visual field
3DAC: Three-dimensional anisotropy contrast
II. INTRODUCTION and BACKGROUND

*the visual field is an „island of vision in the sea of darkness”*

by Traquair

Visual field defect is one of the most important and sensitive sign of an afferent visual pathway injury. These defects may be accompanied by other visual dysfunctions such as decreased visual acuity, color vision, contrast sensitivity and may cause a relative afferent pupillary defect. However, the visual field loss may be the only detectable sign of dysfunction on physical examination.

Formal visual field testing is commonly ordered in patients with neuro-ophthalmic disorders such as optic neuropathies or intracranial lesions involving the visual pathways. However, performing visual field tests may be a challenge in patients confined to a wheelchair, those who are unable to communicate, those with cognitive disorders, or patients with severely decreased vision. Manual Goldmann kinetic perimetry is classically considered to be the gold standard perimetry technique in patients with neurological disorders or very poor vision. The technique is easy for the patient, fixation is continuously monitored by a technician, the test can be shortened depending on the patient’s alertness, and the technician is able to stimulate a sleepy or poorly cooperative patient as needed. However, not all centers have trained personnel capable of performing reliable GVF testing. Thus, there is a need for a faster, less technician dependent, standardized and commercially available test in neuro-ophthalmic practice. This is why in Study A we tested a new generation of perimetry strategy: SITA Fast in these patient populations in a large neuro-ophthalmic university referral center.

It is clinically known that following injury to the motor system such as cerebral infarction, there is potential to partial or even complete recovery. It has recently been established that at least some of this recovery is due to cortical functional reorganization during which time other areas take over function of the injured one.

As an analogy to the motor and certain sensory systems, visual field improvement that is seen following homonymous hemianopia may also be due to brain plasticity. However, much less is known about diseases affecting the anterior afferent visual pathway such as optic neuritis or ischemic optic neuropathy. We do know from clinical experience
that in demyelinating optic neuritis there is potential to normal or near normal recovery of visual function. Few studies tested the hypothesis that there is also plasticity within the visual system following optic neuritis that may be responsible for the observed clinical improvement. These studies suggested that optic neuritis incites extra-occipital baseline activation which likely represents an adaptive reorganization of the cerebral cortex to an abnormal input.

However, there are still several unanswered questions, for example why is there improvement of visual function following optic neuritis in certain patients and not others. Furthermore, why large percentage of patients following optic neuritis recover and there is usually no clinically significant improvement following ischemic optic neuropathy. To be able to answer these questions we first need to describe what determines recovery. Therefore, our goal was to develop and validate a clinically useful fMRI-perimetry method that would allow simultaneous mapping of visual field deficits and assess the neural reorganization processes underlying spontaneous and treatment induced visual field recovery.

1. History of Perimetry

To assess the extent of visual field loss several perimetry methods have evolved from the mid-19th century onwards (1). First manual kinetic then automated static perimetry developed.

In 1856, von Graefe introduced campimetry which is a flat surface kinetic perimetry for mapping of the central visual field. He used a chalk board and a piece of chalk and asked the patient to respond when they saw a light target. In about 1857 Aubert and Förster introduced the arc perimeter for the assessment of the entire visual field (2). In 1889, Bjerrum and his student Rønne reintroduced quantitative isopter campimetry, so called tangent screen, and described the prototypic scotoma of glaucoma, the arcuate defect which breaks out from the blind spot (3).

In 1945, Goldmann (4,5) invented the bowl perimeter which became the standard of perimetry in the ensuing years. This device allowed testing conditions to be standardized by exquisitely controlling the background and stimulus luminance. The machine is
equipped with a single light source, set of mirrors, neutral density filters which allows measurement of differential light sensitivity. It is still the gold standard for detecting neuro-ophthalmic visual field defects as it is customizable and allows improvisation of strategies in real time to be able to most accurately map the shape of visual field defect. The technique is easy for the patient, fixation is continuously monitored by a technician, the test can be shortened depending on the patient's alertness, and the technician is able to stimulate a sleepy or poorly cooperative patient as needed. The disadvantage of Goldmann perimetry that it requires a well-trained perimetrist and not all centers have trained personnel capable of performing reliable GVF testing, usually long testing time, and it is relatively insensitive to shallow defects compared with static automated testing, (6,7,8).

2. Automated Perimetry

In the 1970s, the current differential light sensitivity automated perimetry was established based upon the work of Fankhouser et al. (9), Lynn (10), Heijl (11,12) and Krakau (13). The first equipments were essentially automated Goldmann perimeters. They used Goldmann size III stimulus (measure 4 mm², i.e. 0.43° of visual angle). Test locations were standardized with a 6°-spaced grid using a 4dB/2dB staircase test bracketing procedure over a four log unit range. Most automated perimeters are superior to GVF in terms of sensitivity and quantification of the visual field defects (6,14-18). Automated perimetry has become the standard for visual field testing in glaucoma patients, and it is now widely available (6,14). However, few studies have evaluated automated perimetry in patients with neuro-ophthalmic diseases, and fewer still have compared GVF with automated perimetry in this group of patients (6,15-22). Most studies used the full-threshold Humphrey field analyzer, which is now the most common automated perimeter in the United States, and documented its usefulness in the quantification of neuro-ophthalmic visual field defects (20,22). They also confirmed, however, that most automated perimetry testing (especially that which uses the full-threshold Humphrey field analyzer) requires a higher level of understanding and greater concentration by the patient, often limiting its use in neurologically impaired individuals (6,16,19-20,22).
2.1. Humphrey perimeter

The most commonly used automated perimeter in the United States which has become the standard is marketed by Humphrey (San Leandro, CA). It requires minimal technician training and is often more sensitive than Goldmann perimetry for detection of early and shallow visual field defects (15). The full-threshold 30-2 strategy tests light sensitivity at the fovea and 76 other locations at 6º spacing of stimuli throughout the central 30º visual field. The testing conditions are reproducible and quantification is very good, although due to the fairly large spacing of stimuli defect-shape rendering is coarse. At the beginning, the test determines the threshold for light detection at each of four “seed points”, one in each quadrant. It uses the seed points’ threshold to determine light sensitivity of adjacent points using the 4dB/2dB staircase procedure. This means that light intensity is dimmed in 4-dB steps until the threshold is reached then it is increased in 2-dB steps until the threshold is crossed again. Thus, there is a risk of artifactually low or high thresholds as the threshold value at each seed point is used to determine the threshold value in each quadrant depending on the thresholds’ of the seed points. The test strategy was developed on normal individuals resulting in marked test-retest variability in patients with preexisting optic nerve disease. Other disadvantage of the test is long testing time and high variability of peripheral points. Variability and testing time can be reduced by using the 24-2 rather than the 30-2 strategy. The former tests the central 54 of the 76 locations tested with the 30-2 strategy. Khoury et al showed that the 24-2 strategy shortens testing time by approximately 30% and also decreases variability (23). FASTPAC is a strategy which uses one rather than two threshold crossings and 3-dB steps to reach the threshold. This resulted in reduce testing time by 30-40% but decreased sensitivity and increased variability (24).Variability could be further reduced by increasing stimulus size. Goldmann sizes I, III and V measure 0.25 mm², 4 mm², and 64 mm², respectively (0.11º, 0.43º, and 1.72º of visual angle, respectively). Wall used frequency-of-seeing curves to elegantly show in patients with glaucomatous visual field defect that variability with HVF could be reduced by using size V stimuli (1). He plotted the frequency-of-seeing curve in a normal subject (Figure 1) and in a patient with 12-20 dB loss from glaucoma (Figure 2). The larger stimulus likely raises the signal-to-noise ratio and results in lower variability. Steep slope signifies low variability. In addition, variability can cause problems in the determination of
progression of visual field deficits. He also evaluated short- and long-term variability (by doing five tests over the course of 1 day and on 5 different days 1 week apart) for the 30-2 strategy in 17 patients with resolved optic neuritis (25). He found significant variability in visual field sensitivity both short and long term (Figure 3). One patient’s results varied from a partial quadrant defect to a hemianopic defect within a day. These changes likely represent true test-retest variability rather than progression as the optic neuritis in the 17 patients had already resolved. Even though, the test is automated continuous visual field supervision is necessary, esp. in patients with less formal education and advanced age (26).

**Figure 1.** Frequency-of-seeing curve in a normal subject. Stimulus location is indicated by the arrow in the inset. The curve is created by intensively testing each location repeatedly with a range of stimuli. The frequency at which a stimulus is seen (in percent) is graphed against the stimulus intensity.
**Figure 2.** Frequency-of-seeing curves in a patient with 10–20 dB loss from glaucoma. Stimulus location is indicated by the left arrow in the inset. **A.** Stimulus size III. Note the shallow slope of the curve, signifying high variability. **B.** Stimulus size V. Note the steep slope of the curve, signifying low variability.

**Figure 3.** Repeated visual field testing in two patients with optic neuritis. The left half of the figure shows the results of testing a single patient who displayed consistency. The right half of the figure shows the results of testing a single patient who displayed variability. Same day columns display the results of testing every two hours during the same day. Different days columns display the results of testing on different days matched for time of day.
Short-wavelength automated perimetry (SWAP) is like the standard Humphrey perimetry, but it uses blue targets on a yellow background instead of white targets on a white background. Both full-threshold and FASTPAC strategies can be used for SWAP. The disadvantage is that variable amount of loss of sensitivity occurs as a result of variable ocular media absorption of the blue target light. It appears to be a sensitive measure of retinal nerve fiber layer (RNFL) defects even in patients in whom the results of conventional perimetry were nearly normal such as in patients with multiple sclerosis (27). However, variability seems to be double than with standard perimetry (28) and testing time is increased by 15%.

2.2. Octopus perimeter

Octopus perimeter (Interzeag Inc. Schlieven, Switzerland) like Humphrey uses a differential light-sensitivity test with a bracketing of threshold strategy. The Octopus 123 automated perimeter’s G1x program has four stages allowing the examination to be stopped after 16, 32, 45 or 59 locations have been tested. Sugimoto et al. found that G1 stage, which evaluates 16 points, tended to underestimate visual field damage but G2 stage (32 test locations) may be adequate for screening (29). There is also a shorter version of the standard Octopus strategy: tendency-oriented perimetry which uses results from adjacent locations to establish threshold values for adjacent points (30). There is reduction of testing time from about 12 minutes with the standard Octopus 32 program to less than 3 minutes with tendency-oriented perimetry.

2.3. Swedish Interactive Thresholding Algorithm

As previously mentioned, the above described methods have several shortcomings, the two most important are high test-retest variability and insensitivity. Patients with neuro-ophthalmic disorders are often neurologically disabled or have poor visual acuity comprising a very difficult group of patients for clinical assessment. In these patients visual fatigue is a major limiting factor of test taking. Thus, the recently introduced Swedish Interactive Thresholding Algorithm (SITA) offers the benefit of shorter test time without affecting variability for neuro-ophthalmic patients. The algorithm for determining threshold has been created by Bengtsson and Heijl (31). The SITA strategy is
available on the standard Humphrey perimeter, although it differs from the full-threshold strategy in at least three ways. First, it eliminates catch trials designed to detect false-positive answers. Second, it uses two maximum likelihood visual field models (normal and glaucoma for patients of similar age) as probability distribution models. The chance of obtaining either set of data is determined by continuously updating estimates of threshold (staircase procedure) on the basis of patient responses. Using a predefined “error-related factor” the likelihood that a point is abnormal is calculated (31,32). As the test progresses, the models are updated until the threshold is estimated with the given level of confidence (Figure 4). The slope of the frequency-of-seeing curves which determines variability increases with threshold. Third, the time between stimulus presentations are automatically adjusted in response to the reaction time of the patient. These characteristics result in approximately 50% reduction in testing time: from 12 minutes (full-threshold, 30-2 test) to 6 minutes (SITA-standard, 30-2) and 4.5 minutes (SITA-standard, 24-2).

Figure 4. Visual field models for normal and glaucoma results and their change throughout the perimetry test using SITA. As the test continues, the maximum likelihood model is updated.
based on the results at the tested location and surrounding correlated locations. In this example, the glaucoma model gradually becomes the most likely model by the end of the test.

There is **lower test-retest variability** with SITA than full-threshold and FASTPAC strategies, and visual field defects are similar (Figure 5). There is also **decrease in intersubject variability** resulting in smaller depression of threshold reaching statistical significance which may make SITA actually **better** than other strategies for detecting progression (34). Therefore, the probability plots from SITA cannot be compared directly with those from full-threshold testing. However, the magnitude of visual field defects in dB maybe directly compared (36). Shirato et al. used the 30-2 full-threshold and SITA strategies in 38 normal and 80 open-angle glaucoma patients, and found that the mean sensitivities were slightly higher with SITA in both groups (37). Wall et al. also found increased sensitivities in patients with other than glaucomatous optic neuropathies and hemianopias(38). He concluded that **visual fatigue** was responsible for the increased threshold values in 25% of patients with optic neuropathies and 40% of patients with hemianopias.

Bengtsson and Heijl created another algorithm with even shorter testing time: **SITA Fast** which reduces testing time by an additional 34% (35). It is based on the same algorithms, and it has good reproducibility, even though it may be slightly less sensitive than SITA standard in glaucoma patients (39-41). SITA Fast's shorter test time and flexibility of test parameters would be expected to reduce visual fatigue, thereby improving cooperation in patients with neurogenic visual field defects. Indeed, based on the patient's response, the SITA strategy continuously updates threshold values during the test, and it automatically adjusts the time between stimulus presentations in response to the reaction time of the patient.
Figure 5. Gray-scale and probability plot results from a healthy patient (top left) and three patients with optic neuritis: one with consistent results (top right) and two with variable results (bottom left and right). Each patient was tested at five different times on the same day (left column) and different days (right column). Note that one patient’s fields (lower left) vary from normal to a dense scotoma on different days and that a second (lower right) varies from normal to a nearly complete hemianopia.

2.4. Alternative Perimetric Methods

Several other methods have been developed for selective evaluation of particular pathways of the afferent visual system such as high-pass resolution perimetry (HRP), frequency-doubling perimetry (FDP), motion perimetry, scanning laser ophthalmoscope (SLO), microperimetry, pupil campimetry, and automated kinetic perimetry (Tübingen computer campimeter) (6).
3. Neuro-Ophthalmic Imaging Techniques

3.1. Magnetic Resonance Imaging Methods

The main advantage of higher field magnetic resonance imaging (MRI) systems such as 3.0 Tesla (T) and above is the significantly superior signal-to-noise ratio compared with conventional 1.5 T systems. The higher field systems are more sensitive for molecular motion, allowing for diffusion contrast to be acquired using smaller b-values than on a 1.5 T system. The major disadvantage of the high-field systems is their high susceptibility effects. This property causes serious geometric distortion of images (field inhomogeneity), especially using certain sequences such as echo-planar imaging (EPI) for diffusion tensor imaging (DTI).

3.1.i. Diffusion Tensor Imaging

Diffusion tensor imaging is a technique for analyzing fiber tract physiology, in which diffusion anisotropy is quantitatively measured as the incoherent directional distribution of free water diffusibility on each voxel as a diffusion ellipsoid (42). To perform tensor analysis, multiple diffusion-weighted images (DWI), with a minimum of seven differential motion probing gradient (MPG) pulses, i.e. six directional and zero gradient, must be obtained, so called full tensor analysis. Diffusion ellipsoid is the three dimensional expression of molecular diffusion (Figure 6), distribution of particles at time t, all of which are initially located at the origin. To define the ellipsoid, the direction of the principal axes (Eigenvector: \( \mathbf{I}_\lambda \)) and magnitude (Eigenvalue: \( \lambda \)) at each principal axis need to be given. The principal Eigenvector direction represents the direction of axon fibers, whereas the \( x, y, z \) represent the axes of observation. Diffusion ellipsoid closely resembles axonal fibers, and fiber tract map can be created to display the axonal network when the shape and orientation of ellipsoids are similar between neighboring voxels. In the 1.5 T MRI systems the relatively higher b-value necessary for Eigenvalue determination makes it impossible to obtain stable numeric data. Therefore, repeated measurements with identical MPG are often required making DTI studies further cumbersome. DTI of the anterior visual pathways (optic nerves and chiasm) is a representative example of these limitations due to the proximity of these structures to air sinuses and pulsating...
cerebrospinal fluid. Ueki et al. described diffusion trace value analysis for non-invasive assessment of retinal ganglion cell (RGC) axonal degeneration at multiple anatomic levels along the human visual pathway in ten patients with unilateral chronic optic neuropathy of varying cause, and 16 age-matched normal subjects (43). Diffusion trace value is a tensor invariant that is considered to be a sensitive index for pathologic changes in axons. Diffusion trace analysis is a technique that is capable of reducing the number of necessary DWIs, and also reducing the requisite b-value (Figure 7). These authors analyzed trace at nine anatomic sites (region of interest) using a 3.0 Tesla magnetic resonance imaging system (General Electric Signa 3.0 Tesla). They obtained coronal DWIs on a PROPELLER sequence (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction) (44). Region of interest (ROI) determination was performed based on three-dimensional anisotropy contrast (3DAC) images as 3DAC vector contrast imaging is known to provide exceptionally clear contrast among brain structures, especially between gray and white matter. 3DAC images can be constructed by processing three principal images of seven images, a series obtained for Eigenvalue determination. They found that trace values of the optic nerve and uncrossed chiasmal fibers ipsilateral to the affected eye, the crossed chiasmal fibers, and optic tracts bilaterally were significantly higher than those of the corresponding sites in normal subjects indicating a degenerative process of retinal ganglion cell (RGC) axons (in anterograde and retrograde direction). On the other hand trace values of the optic nerve, uncrossed chiasmal fibers ipsilateral to the patient’s unaffected side, and the optic radiations bilaterally were not significantly different from the corresponding anatomic regions of normal subjects. Of note, mean trace value of optic nerve contralateral to the affected side in retrobulbar optic neuritis (ROT) is slightly higher in patients than in normal subject, suggesting subclinical involvement of the unaffected side. This latter result is consistent with findings of others obtained by OCT (45). However, due to the small number of subjects with ROT these results did not drive statistical significance. Acute cerebral infarction causes reduced diffusion anisotropy (46), which can produce a fiber-tracking defect. Several studies have evaluated axonal dysfunction after fiber tract mapping (47,48). However, this technique requires further refinement before it can be reliably used to quantitatively evaluate axonal dysfunction and its consequences.
FIGURE 6. Diffusion ellipsoid. In three dimensions, ellipsoid expression can provide “intuitive” impression of physical realism of molecular diffusion. Here, ellipsoid can be seen as a three-dimensional distribution of particles at time $t$, all of which are initially located at the origin. To define ellipsoid, the direction of the principal axes and magnitude at each principal axis need to be given. The former corresponds to Eigenvector, $|\lambda_1>$, whereas the latter to Eigenvalue, $\lambda$. The principle Eigenvector, $|\lambda_1>$, direction represents the direction of axon fibers. Whereas $(x, y, z)$ represent the axes of observation (laboratory axes), $(|\lambda_1>, |\lambda_2>, |\lambda_3>)$ represent Eigenvalue (principal) axes. Trace value is indifferent to observation axes.

3.1.ii. fMRI

Functional magnetic resonance imaging is a non-invasive technique with excellent special resolution used to investigate central nervous system function. fMRI indirectly monitors modulated local blood oxygenation levels associated with neural activity (49). In the case of metabolic change after acute stroke there is widespread cortical hyperexcitability in regions structurally connected to the lesion in both hemispheres. This hyperexcitability is due to downregulation of GABA receptor subunit and a decrease in
GABAergic inhibition with resultant increased diffuse blood oxygenation level-dependent (BOLD) signals (50).

**Figure 7.** Coronal three-dimensional anisotropy contrast (3DAC) images showing, as indicated by arrows, optic nerves (Top left), optic chiasm (Top right), optic tracts (Bottom left), and optic radiations (Bottom right) in a normal subject. Hue for the three orthogonal directions represents fiber orientation: right-left, red; anteroposterior, green; superior-inferior, blue. The visual pathway on these 3DAC images is identifiable as primarily green in color, indicating an anteroposterior orientation. The exception is the crossed chiasmal fibers, which are reddish in color (arrows).

### 3.2. Optical Coherence Tomography

Optical coherence tomography (Carl Zeiss Meditec, Inc., Dublin, CA) uses near infrared light to measure the thickness of different ocular structures, such as the retinal nerve fiber layer and macula (51). Thus, OCT has been shown to capture retinal ganglion cell axon loss in anterior visual pathway disorders, like in glaucoma, traumatic optic neuropathy, optic neuritis and chiasmal lesions. The RNFL thickness correlates well with
automated perimetry results in glaucoma patients (52-57). The third generation of commercially available OCT (OCT-3) has high levels of reproducibility (test-retest and interobserver reliability) in normal subjects (58). OCT provides invaluable information on anatomy of unmyelinated axons within the central nervous system, i.e. ganglion cell axons. It has been shown by Fisher et al that RNFL thickness is a strong structural biomarker for axonal loss in multiple sclerosis (MS) (45) and correlate well with scores for low-contrast letter acuity and contrast sensitivity. They found for every 1-line change in low-contrast letter acuity and in contrast sensitivity scores, RNFL thickness differences of 4µm, accounting for age. In addition, Pro et al longitudinally (at presentation, at 1 and 3 months) evaluated changes of the optic disc and peripapillary retinal nerve fiber layer as measured by OCT (StratusOCT-3) and scanning laser ophthalmoscopy (HRT-2) in eight consecutive patients who presented with acute retrobulbar optic neuritis (59). They also correlated these findings with presentation MRI of the affected optic nerve. There was a non-significant trend to increased total, superior and nasal RNFL thickness in affected compared with unaffected eyes in these patients. Even in these cases of retrobulbar optic neuritis where optic disc swelling is not seen clinically, the authors observed RNFL thickening and optic disc swelling (demonstrated by decreased mean cup-to-disc ratio and smaller cup area by HRT) in the affected compared with the unaffected eye. Optic nerve lesion on MRI did not correlate with RNFL thickening and decrease of the physiologic cup. At follow-up, even though visual function recovered, there was temporal RNFL thinning indicative of residual injury. Trip et al used optic neuritis as a model of multiple sclerosis relapse where axonal loss is the likely cause of persistent disability (60). OCT noninvasively quantifies primary axonal loss of the retinal nerve fiber layer and secondary retinal ganglion cell loss in the macula following acute optic neuritis. They studied twenty-five patients who had a previous single episode of optic neuritis with a selection bias to those with incomplete recovery and fifteen control subjects. They found highly significant reductions in RNFL thickness and macular volume in affected patients’ eyes compared with clinically unaffected fellow eyes and control eyes. They also found significant correlations among RNFL thickness, logMAR visual acuity, automated visual field mean deviation in dB (HVF, 30-2 program), color vision (Farnsworth-Munsell 100-Hue test, 61) and visual-evoked potential amplitude. The visual field data were divided into four sectors
based on the relationship of the central field and the optic disc, as derived from a previously published optic disc visual field map (62). The importance of this is that these four visual field quadrants corresponded to the RNFL quadrant obtained by OCT. The Farnsworth-Munsell 100-Hue test was scored as square root of the error score because this follows a normal distribution. They found that decreased macular volume in affected eyes is associated with impaired color vision. Axons originating in the macula pass in the papillomacular bundle to the temporal side of the optic disc. The authors found that macular volume was related to the thickness of the temporal RNFL quadrant. Reductions in the superior and inferior RNFL quadrants were significantly associated with the corresponding superior and inferior visual field sector performance, respectively. However, lack of association of temporal field defects with temporal RNFL thickness was found in a large study of glaucoma patients (63). The RNFL nasally and temporally are thinner than superiorly and inferiorly in histological studies (64) and are responsible only for a relatively small area of the central visual field. Thus, it is possible that the OCT device is not sensitive enough to detect change in these thinner sectors. In addition, the number of visual field test points in the nasal and temporal sectors of the automated program is far fewer than in the superior and inferior sectors. Thus, reduced sampling could result in greater noise in the visual field measure and contribute to the lack of correlation in these sectors. Also, there was a trend towards association of PERG N95 amplitude and RNFL thickness and macular volume. The authors concluded that OCT could be used in trials of experimental treatments that aim to protect optic nerves from axonal loss.

A recent, prospective case-controlled study from the University of Alabama (65) used scanning laser polarimetry (GDx-VCC) and optical coherence tomography (StratusOCT) to evaluate correlation between RNFL thickness and visual field sensitivities in twenty-one patients with nonarteritic anterior ischemic optic neuropathy. Sensitivities from global, hemifields and regional locations of the VF pertinent to the RNFL distribution were obtained. Commensurate to other investigators of neuro-ophthalmic disorders, correlations of all three HVF sensitivities with RNFL thickness were greater when RNFL was measured with OCT than SLP, except the nasal and inferonasal sectors. Interestingly, in nonarteritic anterior ischemic optic neuropathy (NAION) with altitudinal VF defect, both instrument showed decreased RNFL thickness even in sectors of the optic disc that
corresponded to relatively unaffected hemifield, suggesting damage beyond the extent estimated by VF methods.

Mehta and Plant reported two patients with congenital/longstanding occipital lobe lesions with resultant asymptomatic hemianopia (66). The differentiation between a congenital or very long standing and acquired occipital lobe lesion is by demonstration of trans-synaptic degeneration in the former. Trans-synaptic degeneration usually produce very subtle findings on clinical examination, such as band or bow tie atrophy (67,) in the contralateral eye to the injured side, and mild temporal pallor in the ipsilateral eye to the injury. Thus, right homonymous hemianopia (damage in the left hemisphere) results in band atrophy in the right eye and mild temporal pallor in the left eye. The decrease in RNFL thickness corresponded to the visual field defects. They concluded that OCT is an excellent technique to assess the degree of secondary trans-synaptic degeneration in patients with retrochiasmal visual pathway disorders by measuring RNFL thickness. Previously, Kanamori et al. has shown OCT to be superior to scanning laser ophthalmoscopy in the demonstration of band atrophy secondary to chiasmal lesions (68).

Barboni and Carelli also used StratusOCT 3 to examine thirty-eight patients with Leber’s hereditary optic neuropathy (LHON) and compared with seventy-five age-matched controls in a cross-sectional study (69). Patients with LHON were classified into two groups: early (E-LHON, n = 8) if onset of LHON was within six months and atrophic (A-LHON, n = 30) if duration of LHON was longer than six months. They used fast RNFL thickness (3.4mm around the optic disc) scan acquisition protocol. In E-LHON, they found thicker RNFL in the 360º average measurement. This increase involved all quadrants except the temporal. As expected in A-LHON, there was thinning of the RNFL. However, in the subgroups of A-LHON with visual recovery, RNFL was significantly thicker in all measurements, except the temporal quadrant, compared with A-LHON without visual recovery. The temporal fibers (papillomacular bundle) are the first and most severely affected and the nasal fibers seem to be partially spared in the late stage of the disease.
4. Electrohysiologic Methods

4.1. Visual-Evoked Potential

Multifocal VEP (mfVEP) has the advantage of detecting focal VEP responses from the visual field (70). The previously noted association of VEP amplitude with visual acuity (71) suggests that both measures are likely to be influenced by optic nerve axonal integrity, although temporal dispersion caused by persistent demyelination may also contribute to a reduction in these measures. Thus, VEP amplitude is more of a measure of axonal loss than demyelination. We know from primate studies that optic nerve transection leads to retrograde degeneration of retinal ganglion cells (72). Trip et al found in they OCT study that both RNFL thickness and macular volume were associated with whole-field and central-field VEP amplitude in eyes with history of a single attack of optic neuritis, at least one year after onset (60). The extent of conduction block is secondary to persistent demyelination.

A recent report form the University of Keio investigated the concordance between subjective perimetric visual field as assessed by Goldmann and Humphrey perimeters and objective visual fields evaluated by mfVEP in ten patients with hemianopsia (73). They obtained mfVEP by using the VERIS Scientific System (Electro-Diagnostic Imaging, San Francisco, California, USA). Each of the black-and-white segments of the checkerboard stimulus was alternated according to a binary m sequence. The first slices of the second-order kernels were extracted and analyzed. In half the cases, in all of which the lesion was located in the occipital lobe, the results of the subjective and objective perimetry were discordant. In these cases the results of mfVEP were within normal limits in areas where there was a scotomatous defect by HVF. Most importantly, these discordant results seemed to predict recovery, as two of these cases had entirely normal subjective visual field results at follow-up. The lesions of the concordant cases were located outside the occipital lobe (for example pituitary adenoma related).
4.2. Electroretinogram

The PERG N95 component is likely to be of ganglion cell origin (74). This is probably why Trip et al. observed a trend for an association between PERG N95 and RNFL thickness as well as macular volume in their OCT study (60).

5. Plastic Brain Processes

5.1. Motor and Sensory Systems

It is clinically known that following injury to the motor system, such as cerebral infarction, there is potential to partial or even complete recovery. Cortical remapping also has been observed in the somatosensory system after digit or limb amputation (75-77). It is thought that this remapping of cortical function reflects unmasking of latent lateral connections in the cortex that are nonfunctional as long as normal afferent signals are present.

Both anatomical and functional MRI provides high spatial resolution. The blood oxygenation level-dependent (BOLD) fMRI signals appear correlated mainly with synaptic activity (78). In comparison, EEG (electro-encephalogram) and MEG (magneto-encephalogram) have excellent temporal resolution, and signals obtained by these methods also correlate with synaptic activity (79). However, there are several pitfalls in directly seeding fMRI BOLD data into EEG/MEG source models. For example, fMRI EPI data maybe spatially distorted or misaligned with anatomical MRI, producing wrong orientations when assigned to 3D gray matter reconstruction (80).

When comparing task-related brain activation in the acute and chronic phases of motor recovery after stroke, positron emission tomography (PET) (81,82) and fMRI (83,84) data demonstrate greater and more widespread brain activation in the early stages than in the later stages. Motor recovery was inversely correlated with cortical activation, i.e. with better recovery there is less widespread cortical activation (83,85).

5.2. Visual System

By analogy from the above systems, there should be at least some cortical or even subcortical plasticity within the visual system. In a recent retrospective study from Emory
University the investigators reported improvement in about 50% of patients following homonymous hemianopia (86). To our knowledge, at least some of this recovery is due to cortical reorganization during which other functionally capable areas take over function of the injured cortex. However, there are several unanswered questions, for example, why is there improvement of visual function following optic neuritis in certain patients and not others; why large percentage of patients following optic neuritis recover and there is usually no clinically significant improvement following ischemic optic neuropathy. Thus, it is unclear what determines recovery and what the course of cortical adaptation is. We need to answer these questions before visual cortical reorganization for the benefit of our patients could be altered.

5.2.i. Retinopathy

Sunness et al. reported on the retinotopic mapping of the visual cortex in a patient with bilateral central scotomas from atrophic macular degeneration (87). It is known that some patients with age-related macular degeneration (AMD) are able to use the remaining seeing retina and develop a stable eccentric preferred retinal locus. However, there is significant variability among patients in terms of their ability to use an eccentric retina. Scanning laser ophthalmoscope macular microperimetry suggests that the improvement in vision is related to being able to move the object of interest out of the scotoma onto the seeing retina. The authors were interested in seeing if loss of neural input from the damaged retina to the cortex may result in cortical remapping. This would mean that regions of cortex that normally are innervated by the damaged retina are recruited to respond to stimuli falling on undamaged retinal areas. They used SLO and microperimetry to define the site and stability of fixation and the scotoma. The fixation cross was placed at the superior edge of the atrophy, nearest the fovea. Fixation stability was reported to be excellent during testing. They suggest techniques to stabilize fixation for patient with central scotomas including the fovea, such as training in SLO and eye tracking in the MRI scanner. The patient and a healthy control underwent fMRI retinotopic eccentricity mapping (at the same statistical threshold). They used an expanding annulus stimulus containing black and white checks that reversed contrast at 8 Hz (Figure 8). A small annulus (inner radius: 0.3° visual angle; outer radius: 1.3°) appeared in the fovea and
expanded smoothly and continuously outward at a rate of 1 cycle per minute. The most peripheral sizes of the annulus were 8.3° (inner radius) and 9.3° (outer radius) horizontally. The patient viewed the stimulus monocularly with the other eye covered by an eye patch. Two runs were carried out for each eye (a single run was 8 minutes of duration). The high-resolution anatomical volume was segmented at the gray-white boundary and then computationally inflated, cut and flattened to allow visualization of the calcarine sulcus and neighboring areas. They found loss of activity in the ventral visual cortex, which corresponds to the inferior retina containing the scotoma, whereas the representation in the dorsal cortex, corresponding to the undamaged superior retina, was intact.
Figure 8. Scanning laser ophthalmoscope fundus image and fixation map of right (1a) and left (1b) eyes. The cross just above the atrophy shows the fixation site (arrows). The area of geographic atrophy had an associated dense scotoma, with borders indicated by the thick blue line. Fixation is just at the foveal margin of the atrophy. The small dots show the variation in fixation position during the testing. The close clustering of points indicates stable fixation.

2. Retinotopic mapping using fMRI. 2a, Expanding annular stimulus. 2b, Pseudocolor representation of the timing of stimulation of the visual field used to visualize the cortical eccentricity map. 2c, Results of a single retinotopic mapping run in a healthy adult control subject, showing the large representation of the most central region (orange) and the smaller representations of the more peripheral areas (blue). 2d, Retinotopic map for patient with geographic atrophy, showing intact dorsal cortical activity (orange) and the silent ventral cortex (arrow).

5.2.ii. Optic neuropathy

In regards to cortical recruitment, the least is known about diseases affecting the anterior afférent visual pathway. It is known from clinical experience that following
demyelinating optic neuritis there is potential to normal or near normal recovery of visual function. Werring et al reported in a single functional magnetic resonance study that there is functional reorganization of the cerebral response to simple visual stimuli after optic neuritis (88,89). The authors concluded that this recruitment is likely to represent an adaptive response to a persistently abnormal input, and is at least partly responsible for the recovery following demyelinating optic neuritis in a small cohort of patients. Axonal loss, as measured by OCT, especially peripapillary retinal nerve fiber layer thickness, contributes to optic nerve atrophy following a single attack of optic neuritis (60). This RNFL thickness has been proven to be a structural biomarker of axonal loss and shown to correlate well with scores for low-contrast letter acuity and contrast sensitivity following optic neuritis (45). Optic nerve diffusion tensor magnetic resonance imaging (DTI) provides another measure of the structural integrity of axons. Furthermore, axonal loss due to demyelinating brain lesions is likely to give rise to the global MRI measure of brain atrophy which thought to be responsible for disability in multiple sclerosis.

5.2.iii. Retrochiasmal afferent visual pathway injury
Slotnick et al. performed retinotopic mapping with fMRI of a patient with a right homonymous quadrantanopia (90). They did so to be able to differentiate between the two cortically based models of homonymous quadrantanopia in their patient. According to the Holmes’ model (91,92) a V1-based lesion would give rise to either a superior or inferior visual field defect depending on whether the lower (dorsal) or upper (ventral) lip of the calcarine fissure is involved, respectively. However, such a lesion would require perfectly clean borders along the horizontal meridian (base of the calcarine fissure) that is why an alternative model was created by Horton and Hoyt (93,94) based upon evidence form structural MRI. In agreement with this model an early extrastriate lesion (for example. V2, VP, V3, and V4v), each of which have representation of a single quadrant in the visual field, may at least in some cases, give rise to such quadrantanopia. Their patient was a 51 year-old Caucasian woman, initially presenting with a right homonymous hemianopia due to a cerebral infarct to the left inferior occipital lobe (Figure. 9). Anatomical and functional imaging was conducted using a 1.5 T Phillips Gyroscan ACS-NT scanner. The patient lay supine and viewed the stimulus display through a mirror, which was located at
the superior end of the magnet bore. T1-weighted anatomic data were acquired with a multiplanar rapidly acquired gradient echo sequence (MPRAGE) (12.4 min acquisition time, birdcage head coil, 8.1 ms repetition, 3.7 ms echo time, 8° flip angle, 256 x 256 mm field of view, 256 x 256 acquisition matrix, 256 slices, 1mm slice thickness, no gap, i.e. 1 mm isotropic resolution). T2-weighted functional data were acquired with an echo planar sequence, using a circular surface head coil centered on the inion to maximize signal in the occipital region (3 sec time of repetition, 40 ms echo time, 90° flip angle, foot to head phase encoding, 192 x 192 mm field of view, 64 x 64 acquisition matrix, 33 slices, 3 mm slice thickness, no gap, i.e. 3 mm isotropic resolution). All functional slices were oriented perpendicular to the calcarine sulcus. FMRI preprocessing included the following: slice-time and motion correction, spatial low pass filtering at 16 cycles/image matrix and temporal bandpass filtering between 3-32 cycles/run lengths. For retinotopic mapping they used a flickering checkerboard stimulus wedge with 30° polar angle width, extended 6.8° of visual angle from fixation. The wedge comprised of squares scaled by the human cortical magnification factor, reversed in contrast 8.3 times/sec and rotated about the fixation point in the counterclockwise direction, taking 72 sec to complete a single cycle (95). The retinotopic mapping run consisted of eight cycles (with additional 6 sec to complete stimulation of the right visual field and 15 sec fixation period at the end to allow the hemodynamic response to return to baseline, taking a total of 8 min 42 sec. For a given position in the visual field, this resulted in 6 sec of stimulation, 66 sec of no stimulation, and so on in a square wave protocol with eight peaks. The associated hemodynamic model was then constructed by convolving this protocol with a canonical impulse response function of the form: \((t - \delta/\tau)\delta e^{-(t-\delta/\tau)}\), where independent variable \(t = \text{time}\), and the constants \(\delta = 2.5\) and \(\tau = 1.25\). Each hemodynamic response model was then correlated with the activity time course associated with each voxel, and those voxels that reached a threshold value of 0.25 were painted the color associated with that stimulus position. The correlation threshold was selected (p < 0.05, Bonferroni corrected for multiple comparisons) to ensure that the retinotopic activity reported was not due to type 1 error. The authors found no retinotopic activity in the left anterior extrastriate areas (VP and V4v) but normal activity in the left V1v and V2v, corresponding to the impaired right superior quadrantic field defects. Thus, these results give support to the Horton and Hoyt
model of extrastriate cortical lesion being responsible for quadrantanopias. However, this does not mean that all homonymous quadrantanopia is due to an extrastriate lesion.

Yoshida et al. described the longitudinal results of DTI and fMRI (two and nine days, four weeks and 1 year after onset) of a 68-year-old man who developed right homonymous hemianopic paracentral scotomas from acute infarction of the left extrastriate area (96). Initially, DTI showed complete interruption of the posterior optic radiation. This interruption lessened with time and disappeared by one year after onset confirming structural recovery of the retrochiasmal visual pathway. Also, as the visual field defect became smaller, fMRI demonstrated progressively larger areas of cortical activation of the affected left hemisphere confirming functional recovery of the same pathway. In addition, there was progressive decrease in the activation of the unaffected right hemisphere associated with recovery. This was a binocular vision investigation in which the subject’s task was to fix on the central dot during the rest and activation phases. Each experimental run consisted of the acquisition 120 volumes, with volume acquisition of three seconds and a total run time of six minutes.

**Figure 9.** (a) A visual field perimetry map of the patient’s homonymous quadrantanopia, restricted to the upper right quadrant of the visual field in both eyes. Dark regions indicate poor or absent ability to detect visual stimuli at those visual field locations. The axes intersection represents the fixation point, and tick marks on the horizontal and vertical meridian are separated by 108 of

(b) An axial slice through the patient’s MRI at the level of the ventral extrastriate cortex (the left hemisphere is on the left, L, and anterior is toward the top).
visual angle. The small dark circular regions in each eye, just below the horizontal meridia, represent the blind spot in each eye; these are normal under monocular viewing conditions. The white dotted arrow indicates the ventral extrastriate lesion caused by a stroke.

The 120 volumes were divided into 15 blocks of 8 volumes. This corresponded to five iterations of three phases: rest, Activation 1 and Activation 2 phases. Each phase contained 8 volumes with duration of 24 seconds. Three types of stimuli were presented: in the resting phase (first block), a central fixation point was projected on a front-projection screen (grey background with the same mean luminance as the checkerboard) viewed via an adjustable mirror angled at 45º to the line of sight. In Activation 1 and 2 phases (second and third blocks) a horizontal wedge-shaped checkerboard reversing at 8 Hz with 30º of polar angle was projected on the right visual field and a round, centrally positioned checkerboard subtending 15º of visual angle was projected onto the central fixation point. Each square of the checkerboard subtended a visual angle of 0.75º in height and width. The mean luminance of the checkerboard projection screen was 75 candela /m² and its contrast was close to 90%. The activated visual areas of the healthy right hemisphere were most widespread 2 days after ictus. Therefore, the affected left hemisphere recruits more cortical regions to the healthy right hemisphere during the acute phase. This is in accordance with the findings seen in patients following stroke affecting the motor system (83,84).

5.2.iii. Amblyopia

Bonhomme et al. described decreased cortical activation in response to a motion stimulus in anisometropic amblyopic eyes using fMRI (97). They examined whether interocular differences in activation are detectable in motion-sensitive cortical areas in these patients. They performed fMRI at 1.5 T on 4 control subjects, 1 with monocular suppression (form fruste of amblyopia) and 2 with anisometropic amblyopia. The experimental stimulus consisted of expanding and contracting concentric rings, whereas the control condition consisted of stationary concentric rings. Activation was determined by contrasting the two conditions for each eye. They observed significant fMRI activation
in V3a and V5 in the controls and the patient with monocular suppression. In contrast, the anisometropes exhibited decreased extrastriate activation in their amblyopic eyes compared with the fellow eye. These results seem to support the hypothesis that extrastriate cortex is affected in anisometric amblyopia suggestive of a magnocellular defect.
III. OBJECTIVES

- The first objective (Study A) is to assess the potential role of Swedish Interactive Thresholding Algorithm (SITA) Fast automated static perimetry, compared with that of Goldmann manual kinetic perimetry (GVF), for reliably detecting visual field defects in neuro-ophthalmic practice.

- The second objective (Study B) is to describe a novel objective perimetry technique: functional magnetic resonance perimetry (fMRI-perimetry) developed by us on a neuro-ophthalmology patient.

- The third objective (Study B) is to correlate standard automated perimetry with fMRI-perimetry findings in a patient with recurrent optic neuritis.
IV. MATERIALS, METHODS and DESIGN

STUDY A.

1. Patients

In Study A we prospectively evaluated 64 consecutive patients seen with either severe neurological impairment (n=50 eyes) or severe vision loss (n=50 eyes) in the Neuro-Ophthalmology Unit at Emory University (Atlanta, Ga) between September 2000 and April 2001 (Table 1 and Table 2). Severe neurological impairment was defined by a score of 3 or 4 on the Modified Rankin Scale (MRS) (MRS 3 = moderate disability: requires some help, but able to walk without assistance; MRS 4 = patient unable to walk: requires permanent help) (98). Severe vision loss was defined by a visual acuity of 20/200 or worse in at least one eye. The following patient inclusion criteria were applied: age 18 years or older, ability to understand instructions, motor ability to carry out a visual field examination (patient able to sit upright for at least half an hour and to press a button in response to visual stimulation). Patients not willing to have both GVF and SITA Fast perimetry on the same day were excluded.

2. Visual field testing

Visual field examinations were performed using the GVF and the Humphrey automated static perimeter with the SITA Fast algorithm. Both tests on both eyes were always performed on the same day, with the GVF examination performed first. The GVF was performed by the same skilled technician. Patients were seated before the Goldmann perimeter with the left eye occluded first. Each patient's near refraction, with additional diopters adjusted for age, was provided. The machine was calibrated according to the manufacturer's instructions, and the background-target luminosity ratio was set at 1:33. The blind spot was mapped using the I2e or I4e test object (depending on the patient's visual acuity) at a distance of 300 mm to ensure patient reliability. Relative defects in the visual field were detected by using standard test objects such as V4e, I4e, I2e, I1e, with additional isopters plotted as indicated. To mark the peripheral edge of an isopter, the test object was
moved at a rate of 2° to 3° per second from the far periphery toward fixation until it was
seen.

For scotoma testing, the test object was presented inside the region of field loss and
moved radially in a straight line until it was seen. The left eye was then tested in the same
fashion. SITA Fast perimetry was obtained for all patients after at least 1 hour of rest. We
used a Humphrey 740 perimeter with the standard settings of a size III (4 mm²) test object
at a distance of 333 mm, with a 200-millisecond stimulus duration, and a bowl illumination
of 31.5 apostilb (asb) as previously described (31, 35). To perform the fastest test, we
chose the 24-2 strategy (exploring the central 24°) rather than the 30-2 strategy. Each
patient's fixation and position were checked every 1 to 2 minutes on the video eye monitor,
with adjustments made as necessary. The right eye was tested prior to the left eye.
3. Reliability of visual fields

The GVF was considered unreliable if the technician performing the test assessed the patient's cooperation and fixation to be too poor to plot an adequate field, or if the blind spot could not be plotted. A SITA Fast visual field was considered unreliable if fixation losses were 50% or more. We did not use false-positive and false-negative catch trials.

Table 1. (Continued)

<table>
<thead>
<tr>
<th>Visual Field Defect</th>
<th>GVF</th>
<th>SITA Fast Visual Field</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reliability</td>
<td>Time, min</td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td>OD/OS</td>
<td>OD OS</td>
<td>OD/OS</td>
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<tr>
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<td>Y/Y</td>
<td>9 8</td>
<td>Y/Y</td>
</tr>
<tr>
<td>OU: full</td>
<td>Y/Y</td>
<td>6 7</td>
<td>Y/Y</td>
</tr>
<tr>
<td>OU: L homonymous hemianopia</td>
<td>Y/Y</td>
<td>5 5</td>
<td>Y/Y</td>
</tr>
<tr>
<td>OU: R inferior homonymous quadrantoplia</td>
<td>Y/Y</td>
<td>6 5</td>
<td>Y/N</td>
</tr>
<tr>
<td>OU: full</td>
<td>Y/N</td>
<td>15 12</td>
<td>N/N</td>
</tr>
<tr>
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<td>7 7</td>
<td>Y/N</td>
</tr>
<tr>
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<td>8 8</td>
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</tr>
<tr>
<td>OU: full</td>
<td>Y/Y</td>
<td>8 10</td>
<td>N/N</td>
</tr>
<tr>
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<td>10 8</td>
<td>N/N</td>
</tr>
<tr>
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<td>10 5</td>
<td>N/N</td>
</tr>
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<td>6 8</td>
<td>Y/N</td>
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<td>Y/Y</td>
<td>5 6</td>
<td>Y/Y</td>
</tr>
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<td>5 9</td>
<td>Y/Y</td>
</tr>
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<td>5 6</td>
<td>Y/Y</td>
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<tr>
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<td>6 10</td>
<td>Y/Y</td>
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<td>6 8</td>
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<td>4 5</td>
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<td>10 11</td>
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<tr>
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<td>9 6</td>
<td>Y/Y</td>
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<td>Y/Y</td>
<td>7 9</td>
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<td>N/N</td>
<td>7 6</td>
<td>Y/N</td>
</tr>
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</table>

4. Comparison of GVF and SITA Fast visual fields

The 3 investigators made an independent subjective assessment of the pattern configuration, extent and depth of the visual field defects on the hand-drawn Goldmann chart, and on the pattern SD and the graytone printout from the SITA Fast perimeter. Direct comparison was made between the central 24° of the GVF as assessed by putting a template over that area, and with the pattern SD and the graytone printout from SITA Fast (Figure 10).
Table 2. Demographics and Visual Field Results of Patients With Severely Decreased Vision in at Least 1 Eye

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/sex</th>
<th>Disease/Withdraw</th>
<th>Visual Acuity</th>
<th>Neurological Status</th>
<th>Examination</th>
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<td>100</td>
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<td>CM OD</td>
<td>OD 20/200</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>33/F</td>
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</tr>
<tr>
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</tr>
<tr>
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<tr>
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<td>51/F†</td>
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</tr>
<tr>
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<td>32/F</td>
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<tr>
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<td>Maculopathy OS</td>
<td>OD 20/200</td>
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*Severely decreased vision indicates a visual acuity of 20/200 or worse, MRS indicates Modified Rankin Scale; BI, Barthel Index; GFVF, Godmann visual field; SITA, Swedish Interactive Thresholding Algorithm; AION, anterior ischemic optic neuropathy; L, left; ON, optic neuropathy; R, right; HM, blind motions; N, normal; AMD, age-related macular degeneration; PDR, proliferative diabetic retinopathy; CRVO, central retinal vein occlusion; GF, counting fingers; NLP, no light perception; CRAO, central retinal artery occlusion; CSMF, clinically significant macular edema.

†Indicates that the patient underwent SITA Fast perimetry.
<table>
<thead>
<tr>
<th>Visual Field Defect</th>
<th>GVF</th>
<th>Reliability</th>
<th>Time, min</th>
<th>IFTA Fast魏中 Fast Reliability</th>
<th>Groups</th>
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<tr>
<td>CD: inferior altitudinal defect, central scotoma</td>
<td>6</td>
<td>Y</td>
<td>6</td>
<td>Y</td>
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</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>OU: R homonymous hemianopia</td>
<td>7</td>
<td>Y</td>
<td>10</td>
<td>Y</td>
<td>I</td>
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<td>Y</td>
<td>10</td>
<td>Y</td>
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</tr>
<tr>
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<td>15</td>
<td>10</td>
<td>Y/Y</td>
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<td>CS: superior superior nasal defect</td>
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<td>6</td>
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<td>CS: superior nasal defect, inferior central scotoma</td>
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<td>CS: superior nasal defect, inferior central scotoma</td>
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</table>
| OD: superio...
Goldmann perimetry was then compared with the pattern deviation and the graytone printout from the SITA Fast. The black spots on the pattern deviation and the dark areas on the graytone printout of the SITA Fast correspond to areas with decreased sensitivity. In this example, there was a relatively good correlation between the GVF and SITA Fast, and these eyes were classified as group II.

The results of the visual field comparison were classified into 1 of 9 groups, as previously suggested by others (Table 3) (17,20).

**Figure 10.** Comparison of Goldmann manual kinetic perimetry (GVF) (A) and Swedish Interactive Thresholding Algorithm (SITA) Fast perimetry (B) visual fields. The central 24º of the GVF were assessed by putting a template over that area (dashed line). Goldmann perimetry was then compared with the pattern deviation and the greytone printout from the SITA Fast. The black spots on the pattern deviation and the dark areas on the greytone printout on the SITA Fast correspond to areas with decreased sensitivity. In this example, there was a relatively good correlation between the GVF and SITA Fast, and these eyes were classified as group II.
5. Other outcome measures

The testing time required for each visual field strategy in each eye was compared using the $\chi^2$ test. The patient's functional status was assessed with the MRS and the Barthel Index (98), on the day of the visual field tests. Patient preference was evaluated by asking the patient which visual field test they would rather have on their follow-up examination.

STUDY B.

6. Optic neuritis pilot study

This is an interventional case report of a patient with recurrent optic neuritis seen at Semmelweis University, Department of Ophthalmology, Neuro-Ophthalmology Unit.

6.1. Patient and controls

Subjects were two healthy male volunteers and a twenty-eight-year-old right handed man with monocular visual field defect due to recurrent optic neuritis. He had three episodes of visual loss in the right eye. His first episode was in 1996 at which time he received high dose steroids intravenously and within about 6-8 weeks his vision essentially returned to normal. His second onset was in 2001 when he did not seek medical attention and had spontaneous recovery in 6-8 weeks. His third visual loss was on May 17, 2006.
when he presented with recurrent acute visual loss in the right eye and pain when looking to the right and down. Few days later he was examined by an ophthalmologist who recorded visual acuity of 0.1 O.D. and 1.0 O.S., CFF of 41 Hz O.D. and 42 Hz O.S., swollen optic nerve on funduscopy with nasal depression and enlarged blind spot on Goldmann perimetry O.D. His left eye examination was entirely normal. MRI of the brain without contrast was reportedly negative. He denied ever having any other symptoms, such as paresthesias, paresis or urinary retention. Few weeks after his latest complaint he was admitted to a hospital by a neurologist and received a modified regimen of what is recommended by the Optic Neuritis Treatment Trial of intravenous methylprednisolone, which is the present standard of care for patients with presumed demyelinating optic neuritis. His social history was negative for smoking, alcohol consumption, cat scratch or tick bite. He was taking no medications, except tapering dose of oral steroids when I first saw him on July 7, 2006. His best corrected visual acuity was 0.8 O.D. and 1.0 O.S. His color vision on the Ishihara color plates was 9/10 slow O.D. and 10/10 brisk O.S. (Table 4). He had a large relative afferent papillary defect on the right. The rest of his neurological examination was negative, including his other cranial nerves, sensory, cerebellar and motor exam. On funduscopy, he no longer had optic nerve swelling but temporal pallor with nerve fiber layer loss in the right eye with significant hard exudates on the posterior pole in a macular star configuration (Figure 11).

![Figure 11](image)

**Figure 11.** The patient’s fundus appearance shows optic disc pallor and macular star in the right eye (O.D.) and normal findings in the left eye (O.S.).
Table 4. Clinical and MRI data of the pilot patient.

<table>
<thead>
<tr>
<th></th>
<th>1st visit</th>
<th></th>
<th>2nd visit</th>
<th></th>
<th>3rd visit</th>
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<td>ETDRS</td>
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<td>70</td>
<td>o.s.</td>
<td>70</td>
<td>o.s.</td>
<td>70</td>
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<td>20/20-</td>
<td>20/20</td>
<td>20/30</td>
<td>20/20</td>
<td>20/20-</td>
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<tr>
<td>Pelli-Robson CS</td>
<td>2.25</td>
<td>1.70</td>
<td>2.25</td>
<td>1.65</td>
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<td>1.70</td>
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<td>not assessed</td>
<td>Not assessed</td>
<td>10/10</td>
<td>9/10 slow</td>
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<td>Absent</td>
<td>present</td>
<td>absent</td>
<td>present</td>
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<td>VF</td>
<td>GVF: full</td>
<td>inf-nas, ↑ blind spot</td>
<td>Full</td>
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<td>SITA: full</td>
<td>concentric scotoma</td>
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<td>Not assessed</td>
<td>Not assessed</td>
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<tr>
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<td>temporal pallor</td>
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<td>temporal pallor</td>
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<td>Absent</td>
<td>macular star</td>
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<td>absent</td>
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<td>Negative with contrast</td>
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<td>absent</td>
<td>absent</td>
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<tr>
<td>MRI</td>
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<td>Negative with contrast</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
</tr>
</tbody>
</table>

**ETDRS**: Early Treatment Diabetic Retinopathy Study charts have 5 letters per line; scores are expressed herein as number of letters identified correctly, range 0-70 (0 lines < 20/250 Snellen equivalent, 15 lines = 20/12.5 Snellen equivalent); MD: mean deviation in dB; PSD: pattern standard deviation in dB.

**Snellen VA**: visual acuity; **CS**: contrast sensitivity; **MRI**: magnetic resonance imaging.

**Pelli-Robson** contrast sensitivity charts at 1 m: as used in the Optic Neuritis Treatment Trial consist of 16 groups of 3 large (~20/680 equivalent) letters (lines); scores are expressed herein as log contrast, range: 0.00-2.25 (0.00 = 1 line/3 letters correct, 2.25 = 16 lines/48 letters correct).

Color vision is evaluated by Ishihara color plates of 10; **RAPD**: relative afferent pupillary defect; **VF**: visual field as assessed by GVF or SITA Standard 24-2 on the Humphrey visual field automated perimeter; **EOM**: extra-ocular movement;

His fundus on the left was unremarkable with a cup-to-disc ratio of 0.1. The diagnosis of recurrent optic neuritis and neuroretinitis O.D. was made. The most likely differential diagnoses responsible for his visual loss were demyelinating or inflammatory-infectious processes. The latter one could be caused by sarcoidosis, Bartonella henselae, Borrelia burgdorferi and less likely Chlamydia or toxoplasma. To exclude a demyelinating process anywhere else in the central nervous system, we obtained an MRI of the brain with contrast. We also requested laboratory tests for ACE, Bartonella henselae, Borrelia burgdorferi, toxoplasma and Chlamydia titers. His laboratory tests were negative, thus, the patient was diagnosed with clinically isolated syndrome (CIS) with low risk for the...
development of clinically definite multiple sclerosis (CDMS), as defined by his negative MRI with no disease burden. The patient’s functional status was recorded as assessed by the Extended Disability Status Score (EDSS) (99) and MS Functional Composite (MSFC) (100).

He had electrophysiology testing on July 3, 2006, with pattern VEP but unfortunately his multifocal VEP was uninformative due to technical difficulties. In January, 2007 he had a pattern ERG. At another institution the patient was ordered cervical and thoracic MRI without contrast, which was reportedly negative. His repeat neuro-ophthalmic exam on September 26, 2006 revealed visual acuity of 1.0-² O.D. and 1.0 O.S., 9.5/10 O.D. and 10/10 O.S. on Ishihara color plates. He continued to have a large relative afferent papillary defect with CFF: 37/47 Hz and temporal pallor with retinal nerve fiber layer loss in the right eye. His Goldmann perimetry in his effected right eye n September, 2006 showed severe temporal and inferior depression with the V4e isopter but severe concentric visual field loss with the I4e isopter (Figure 12).

Figure 12. Goldmann visual field results of the left (on the left) and the right (on the right) eye.

6.2. Main Outcome Measures

We chose the following primary outcome measures: fMRI-perimetry, automated perimetry with the 24-2 SITA Standard (MD) protocol and visual function test results: low-contrast letter acuity (Sloan Charts, 2.5% and 1.25 % contrast levels at 2 m), contrast
sensitivity (Pelli-Robson chart at 1 m). These tests were performed mono- and binocularly, as previously described by Balcer et al (45).

The secondary outcome measures were the following: retinal nerve fiber layer thickness (RNFL), macular volume and thickness, cup-to-disc ratio, visual acuity (retroilluminated Early Treatment Diabetic Retinopathy charts at 3.2 m), color vision test, pattern and mfVEP amplitude and latency.

The following inclusion criteria were applied: diagnosis of unilateral optic neuritis, visual field defect involving the central 24 degrees, patient willing and able to perform reliable fMRI testing and automated perimetry. We considered the pilot patient to be an excellent candidate for fMRI after performing reliable SITA Standard perimetry six times in his affected eye within one hour with only one fixation loss in all of these exams. In addition, he had 0 % false positive errors and only once 1%.

Exclusion criteria were the following: the patient is unable or unwilling to perform the clinical and experimental testings.

Standard brain MRI for evaluation of disease burden was done.

### 6.3. Visual Function Tests

Low-contrast letter acuity was obtained using Sloan letter charts (Precision Vision, LaSalle, IL), which requires identification of grey letters of progressively smaller size on a white, retroilluminated background at 2 m. We used 1.25% and 2.5% contrasts levels. Sloan charts are similar to the ETDRS charts in that they use five letters per line, and each Sloan chart corresponds to a different contrast level. The charts are scored based on the letters identified correctly. Bodis-Wollner et al. reported that these charts capture losses of contrast at smaller letter sizes in MS and other neurologic disorders (101) than high-contrast acuity charts. In addition, we measured contrast sensitivity with Pelli-Robson charts (Lombart Instrument Co., Norfolk, VA), which detect the minimum contrast level at which patients are able to perceive letters of a single large size at 1 m. This chart consists of 16 groups of 3 uppercase letters (triplets or lines) of single large size (~20/680 Snellen equivalent) (102). To measure high-contrast we used the Early Treatment Diabetic Retinopathy Study (ETDRS, Lighthouse Low-Vision Products, Long Island City, NY) charts at 3.2 m. All testing was performed for each eye separately and binocularly (103).
The summary scores for visual function tests were calculated for Sloan and ETDRS VA charts by number of letters identified correctly (maximum 70) and number of lines correct (letters correct/5). Snellen equivalents were also recorded for ETDRS VA measurements. Scores on the Pelli-Robson chart were recorded as log contrast sensitivity (maximum: 2.25 log, equal 48 letters) and number of lines correct (letters correct/3).

Prior to visual acuity testing the patient underwent refraction, which was performed for each eye at 6m.

6.4. fMRI Experimental Design

The fMRI experiments were performed at the Szentágothai Knowledge Center Magnetic Resonance Research Unit, Budapest, Hungary. Informed consent was obtained from the patient in accordance with the Declaration of Helsinki and the protocol was approved by the Internal Review Board of Semmelweis University, Budapest. We designed our experimental protocol (fMRI paradigm) for the functional assessment of anterior visual pathway disorders, by designing a monocular novel stimulus. The untested eye was patched during the experiment. The unaffected eye was used for intereye comparison.

We carried out fMRI testing three times: five, six and eight months after the patient’s third visual loss. This allowed us to longitudinally compare the results of retinotopic mapping.

MR data acquisition for the anatomical and functional MRI was carried out with an Achieva 3.0-T clinical MR scanner (Philips, Inc.). Functional data was coregistered with high resolution T1-weighter (T1W) anatomical scans acquired in the same session (anatomical acquisition) during all three experiments. We scanned the whole brain volume with 180 sagittal slices with 1 x 1 x 1 voxel resolution. This allowed individual coregistering of the data across experiments and for reconstruction of the cortical surface.

T2-weighted FLAIR functional data were acquired in an EPI sequence with 23 coronally oriented functional slices, 64 x 64 matrix, 3.44 x 3.44 x 3 mm voxel size (resolution), TR=1200 ms, volume of interest: 330 volumes, 4mm slice thickness, time-lag: 0-20 in an ascending non-interleaved manner (Ret23sl_QUAD_PNShi_inpl protocol), oriented perpendicularly to the calcarine sulcus. The information from the ipsilateral visual
field of both eyes is represented in the contralateral visual cortex, for example the right visual world is projected onto the left occipital cortex (Figure 13). Visual cortical retinotopy may be depicted on either an inflated or flattened (smoothed) view of the low and high order visual cortex (Figure 14).

![Figure 13. Retinotopic mapping. (by Gazzaniga, Ivry, Mangun, 2002)](image)

For all three fMRI quadrant mapping experiment multiple runs of standard retinotopic mapping stimuli were used, such as clockwise rotating wedges (Figure 15 A) and expanding and contracting rings consisting of black-and-white checkerboard patterns with 100 % contrast, reversing at 8 Hz (Figure 15 B). Subjects fixated on a stationary target: red dot in the bottom left corner while the contrast reversing checkerboard patterns were presented in the periphery. The stimuli were presented in two modes: normal mode, i.e. in the full quadrant and simulated scotoma mode, i.e. the outer 40% of the stimulus masked with a patch having the same luminance as the background. The wedge stimulus for retinotopy (80) was implemented using the standard traveling wave method with a slowly rotating phase reversing wedge (30º wide) extending from the center of gaze to 20º eccentricity. The wedge rotated 90º clockwise about the fixation dot in each of the 12 cycles (=1 run), and each cycle was 28.8 s in duration. Eccentricity was mapped in a similar fashion by measuring the phase of the response to a slowly expanding or
contracting stimulus annulus (width 1.5, corresponding to a duty cycle of 25%). Retinotopic mapping run with the expanding rings continually expanded outward from the fixation point, and consisted of 12 cycles, and each cycle duration was of 28.8 s.

![Image](image1)

**Figure 14.** The left half of the visual field is represented in the right occipital lobe. A) Left visual field. B) Right hemisphere inflated view and C) flattened view.

20° isopter stimulus and meridian mapping stimuli were presented in 10 cycles of 36 s with intermittent periods of no stimulation every ½ cycle (Figure 39). Quadrants of the visual field were mapped in a block-design manner with the phase reversing stimuli. For scotoma mapping the contrast reversing checkerboard pattern was presented in alternating ½ cycles of 36 s. We designed an fMRI-perimetry stimulus consisting of 1.66° diameter circular patches which were presented in a pseudo-random manner overlaid on a continually expanding contrast reversing checkerboard pattern with an interstimulus interval (ISI) of 2.4 s (Figure 39 F).

![Image](image2)

**Figure 15.** A) The wedge stimulus. B) The expanding or contracting stimulus.
The high resolution T1W anatomical data was preprocessed and analyzed with a dedicated software package: Brain Voyager QX, using standard analysis methods (linear correlations for the traveling wave retinotopy and GLM analysis for the quadrant mapping paradigms) (Figure 16). The Brain Voyager QX software was used for the surface-oriented data analysis. On the surface, the functional data were smoothed with a sigma = 1.5 mm Gaussian kernel (FWHM = 3.5 mm). Retinotopic maps were calculated by linear correlation of a design matrix containing stimulus timing information, convolved with the hemodynamic response function. Cross-correlation above 0.45 was applied (r range: 0.45-0.8). Extent of activation for each eye was determined separately. In the volunteers we used a set of normal stimuli and a set of stimuli overlaid with a simulated scotoma mimicking the extent of the visual field deficit of the patient. Stimuli were generated with Matlab (Mathworks, Inc.) and presented with a PC, running Windows XP and the Presentation software (Neurobehavioral Systems, Inc.) and projected onto a back projection screen with an LCD video projector (Epson 7250M, Epson Inc., Japan). The subjects viewed the projected (75 Hz DLP) stimuli on a 28° H x V screen fixed to the headcoil via a mirror. The characteristics of stimuli, such as visual angle and contrast were controlled. The fMRI data for all three retinotopic mapping experiments were collected with a single-loop surface coil (diameter = 14cm) centered under the occipital pole. The low-order visual areas could be detected and delineated robustly by the visual field sign analysis up to V3, both ventrally and dorsally. The decrease of MR detection sensitivity with distance form the surface coil may have prevented detection of V4 and V3A. One session was acquired per retinotopic stimulus (clockwise and counterclockwise rotating wedge, and contracting and expanding annulus). Motion correction was applied with Statistical Parametric Mapping (SPM) (110) and statistical parametric maps were created. The SPM maps, uncorrected for multiple comparisons and unsmoothed were thresholded at t = 3.12 (P < 0.001) before the projection onto the 3D anatomical model. The use of unsmoothed data was necessary to prevent displacing data sufficiently to induce a wrong assignment to the gyrus across the sulcus or the opposite bank. The selected threshold produced reasonable retinotopic activations, usually without showing large positive clusters.
In Experiment 1 (Figure 17), one or two checkerboard patterns (dark 4cd/m², light 40 cd/m²) were presented to the right eye in the superior-temporal then inferior-nasal visual field quadrant (RVF sessions), each repeated twice and followed by T1-weighted 180 anatomical slices. Following this, quadrantic mapping of the left eye in the superior-temporal then inferior-nasal visual field quadrants (LVF session) were performed, each repeated twice (2 runs). The patterns were repeatedly presented for 0.5 s with interstimulus interval (gray background and fixation point) of 1 s. Conditions were presented per block, each block lasting 28.8 sec. Each session (RVF and LVF) contained two 14-min runs. In addition to the RVF and LVF pattern onset sessions which represent the main sessions, a series of retinotopic fMRI experiments were also carried out to delineate the low-order visual areas on the cortical surface of the subject using phase encoded retinotopic stimuli (105-108).
In Experiment 2 (Figure 18), eccentricity of the right superior-temporal visual field quadrant was performed (RVF session) and repeated five times (5 runs), followed by T1-weighted FFE and multishot 3D TFE sequences. Eccentricity of the left superior-nasal quadrant (LVF session), i.e. the homonym quadrant mapped in RVF session, was mapped again five runs. The experiment was completed with T1-weighted FFE and T2-weighted FLAIR sequences. Perimetry parameters were the following: stimulus is a 1.66 deg diameter filled circle, radial distance changes in 1.63 deg steps starting at 0.8 deg from the fovea, measurements are done in 6 angles: 15, 27, 39, 51, 63, 75, ISI is 2 TRs (~2.4 sec), 10 measurements at each location. The visual field sign, derived from the eccentricity and polar angle fMRI phase maps, was used to delineate borders between the retinotopic areas (107, 109).

In Experiment 3, in addition and in conjunction with the standard retinotopic mapping stimuli such as in the previous experiments we presented meridian, isopter, and scotoma mapping stimuli to identify and delineate the primary visual cortex and to obtain full quadrant activation maps in all subjects. During fMRI-perimetry subjects were asked to report on in 2-AFC manner on the color of a 1.66° diameter circular patch pseudo-randomly overlaid on an expanding ring fMRI eccentricity mapping stimulus (Figure 19).
ON-itis pilot 2 (KCs)
quadrant mapping w/ perimetry (20061121)

KCs (right eye is affected)

RIGHT SUPERIOR QUADRANT IS TESTED

O.U.

03: 3DTFE 180 slices
04: ecc ST-01
05: ecc ST-02
07: ecc ST-03 O.D.
08: ecc ST-04
09: ecc ST-05
11: ecc ST-06 O.S.
12: ecc SN-01
13: ecc SN-02
14: ecc SN-03 O.S.
15: ecc SN-04
16: ecc SN-05
17: T1W FFE
18: T2W FLAIR

functionals: 330 vols 18 slices (TR 1.2 voxel size: 3.44x3.44x3.44, ascending non-interleaved)
protocol: Ret18sl_wfs_QUAD_PNShi_inpl

Figure 18. fMRI paradigm of Experiment 2.

Figure 19. fMRI-perimetry stimulus parameters.

6.5. Optical Coherence Tomography
We obtained optical coherence tomography for both eyes using OCT-3 with OCT 4.0 software (Carl Zeiss Meditec). OCT uses low-coherence interferometry to obtain cross-sectional tomograms of the retina with axial resolution of $\leq 10$ µm. A trained physician performed the fast RNFL thickness, fast macular and optic nerve protocol after the above visual function testings. The fast RNFL thickness protocol computes the average of 3 circumferential scans 360° around the optic disc producing 256 axial scans each of 3.4 µm
diameter. The patient eye was dilated with a mydriatic eye drop (1% tropicamide) to assure adequate imaging (5-mm diameter) as dilation has been shown to have little effect on OCT values and reproducibility. Appropriate scans were defined according to the users’ manual: signal strength of >/=7 (maximum 10) and uniform brightness across the scan circumference. We used internal fixation and patched the nontested eye for better fixation. Average peripapillary RNFL thickness values were obtained.

6.6. Electrophysiology

Pattern visual-evoked potentials (VEPs) were recorded to monocular stimuli using skin-surface electroencephalogram electrodes placed over the occiput, 5 cm above the inion and referred to a frontal electrode at Fz (frontal midline placement) as in the 10-20 System. The ground electrode was placed at Cz (central midline placement). Channels 1 and 2 recorded the right eye and, channel 3 and 4 the left eye visual-evoked potentials. The stimuli consisted of reversal of a checkerboard pattern in the central field small and large stimuli. The interelectrode impedance was less than 5 kΩ, and the gain was 10,000. The contrast was 93% and the pattern reversed at 0.9 Hz. The analysis time was 300 milliseconds. The filter was set at 1-50 Hz.

The pattern elecroretinogram (ERG) was recorded on a Retiport 32 system. We used binocular stimulation of the central field, subtending 28° horizontally by 20° vertically, using ocular-surface (DTL) electrodes referred to skin-surface electrodes over the ipsilateral outer canthus. The stimuli were pattern reversal checkerboard with check sizes of 30’, and reversing 4.0 times per second. The contrast was set at 97%. The amplifier corner frequencies were 1 and 1,000 Hz. The sampling rate was three samples per millisecond, and the sweep duration was 170 milliseconds. Sweeps containing artifacts of more than 100 µV were automatically rejected. Filter for channel 1 and 2 were set at 5-50 Hz and for channel 3 and 4 5-100 Hz.
V. RESULTS

STUDY A.

1. Patients

A total of 64 patients were included in the study. There were 36 men and 28 women with a mean age of 53 years (range, 18-92 years). Patients were divided into 2 groups, depending on their neurological status and visual acuity. Twenty-five patients (17 men, 8 women; mean age, 51 years [range, 18-86 years]) with severe neurological impairment (MRS 3 or 4) were included in the first group (Table 1). All 25 patients were able to perform both visual field tests with both eyes, and all 50 eyes were included in the analysis. The mean MRS was 3.4 (range, 3-4), and the mean Barthel index was 52.4 (range, 25-85). Five patients with neurological deficits also had 8 eyes with poor visual acuity, ranging between 20/200 and hand motions. The other 42 eyes had a mean visual acuity of 20/30 (range, 20/20-20/100). Thirty-nine patients with severe vision loss (19 men, 20 women; mean age, 54 years [range, 18-92 years]) were included in the second group (Table 2). Among these 39 patients (representing 78 eyes), 3 patients had 1 eye with a visual acuity of no light perception, and 25 patients had 1 eye with a visual acuity better than 20/200. These 28 eyes were excluded from the study, and the analysis was performed on the remaining 50 eyes. Visual acuity was extremely poor (20/400 or worse) in 34 of 50 eyes.

Clinical characteristics of the patients and visual field description, reliability, test time, and categorization of the visual field comparison for each of the 100 eyes included in the study, are detailed in Table 1 and Table 2.

2. Reliability of visual fields

Visual field examinations with GVF were reliable in 77% of all eyes. Visual fields obtained with the SITA Fast strategy were also estimated to be reliable in 77% of all eyes. Among the 50 eyes of patients with severe neurological deficits, 32 (64%) had a reliable GVF, and 36 (72%) had a reliable SITA Fast visual field. Among the 50 eyes with severe vision loss, 45 (90%) had a reliable GVF, and 41 eyes (82%) had a reliable SITA Fast


visual field. In 16% of all eyes (7 [14%] of 50 eyes in patients with severe neurological deficits, and 9 [18%] of 50 eyes with severe vision loss), the GVF was reliable, but the SITA Fast was not. In 14% of all eyes, (11 [22%] of 50 eyes of patients with severe neurological deficits, and 3 [6%] of 50 eyes with severe vision loss), the SITA Fast was reliable, but the GVF was not. In 7 (14%) of 50 eyes of patients with neurological deficits, neither of the visual field tests were reliable.

3. Comparison of GVF and SITA Fast visual fields

The distribution of the results of the visual field comparisons is demonstrated in Figure 20. Overall, the 2 fields were similar (groups 1, 2, 3, and 4) in 75% of all eyes. Among the eyes of patients with neurological deficits, 35 (70%) of 50 eyes had similar visual field tests on both strategies (Figure 21). However, 11 (22%) of 50 eyes of patients with neurological deficits had normal visual fields (group 4) (Figure 20). Excluding these 11 healthy eyes from the analysis, 24 (61.5%) of 39 eyes of patients with neurological deficits had similar visual field defects with both tests. Among the eyes with vision loss, 40 (80%) of 50 had similar visual field defects on both fields (Figure 22).

![Figure 20. Distribution of the results of the visual field comparisons.](image-url)
A few eyes were classified in groups 5 and 6, in which both visual field tests were reliable, with one of the tests being abnormal and the other one being healthy. In 8% of all eyes (6 of 43 eyes of patients with neurological deficits, and 2 of 50 eyes with vision loss), GVF failed to show a defect demonstrated by SITA Fast (group 7) (Figure 23).

Figure 21. Similar visual field results (group I) in a patient with Parkinson disease and dyskinesia, who developed a right homonymous hemianopia after a left pallidotomy. The discrepancy between Goldmann manual kinetic perimetry (A) and Swedish Interactive Thresholding Algorithm Fast perimetry (B) is less than 5°.
Figure 22. Similar visual field results (group II) in a patient with poor vision. The discrepancy between Goldmann manual kinetic perimetry (GVF) (A) and Swedish Interactive Thresholding Algorithm (SITA) Fast perimetry (B) is more than 5°, but the 2 fields are very similar, with SITA Fast demonstrating a slightly larger defect than GVF in this patient with bilateral central scotomas.

In 9% of all eyes (3 of 43 eyes of patients with neurological deficits, and 6 of 50 eyes with vision loss), SITA Fast failed to show the visual field changes demonstrated by GVF (group 8). In 4 of these patients categorized as group 8, the visual field defect or the residual island of vision was located at the edge or outside of the central 24° explored by automated perimetry (Figure 24).
Figure 23. Visual field results in a patient in whom Goldmann manual kinetic perimetry (A) failed to show the right superior homonymous defect demonstrated by Swedish Interactive Thresholding Algorithm Fast perimetry (B) (group VII).

4. Test time

The mean ± SD test time on the GVF perimeter was 7.97 ± 3.2 minutes per eye (range, 3-22 minutes). It was 8.04 ± 3.57 minutes (range, 4-22 minutes) in the group of patients with neurological deficits, and 7.9 ± 2.7 minutes (range, 3-15 minutes) in the group of patients with poor vision. The mean ± SD test time on the SITA Fast perimeter was 5.43 ± 1.41 minutes per eye (range, 3.03-11.4 minutes). It was 5.44 ± 1.54 minutes (range, 3.05-10.52 minutes) in the group of patients with neurological deficits, and 5.79 ± 1.30 minutes (range, 3.40-11.73 minutes) in the group of patients with poor vision. The SITA Fast perimeter reduced the test time by 2.54 minutes (47%) compared with the GVF perimeter ($P<.001$). The amount of reduction of test time with the SITA Fast perimeter was similar in the group of patients with neurological deficits and in the group of patients with severe vision loss.
Figure 24. Visual field results in a patient with a left optic neuritis in whom Swedish Interactive Thresholding Algorithm (SITA) Fast perimetry (B) failed to show the residual island of vision demonstrated by Goldmann manual kinetic perimetry (A) (group VIII). The patient had a large scotoma involving fixation, and the residual temporal island of vision was located outside of the central 24° of the visual field tested with SITA Fast.

5. Patient preference

When asked which visual field test they would rather have on their follow-up examination, 58 (91%) of our 64 patients preferred GVF. The main reason given by the patients who preferred GVF was the difficulty of maintaining concentration during testing with the SITA Fast. Among the 6 patients who preferred SITA Fast, one had severe neurologic deficits, and 5 had severe vision loss. They all enjoyed the computerized aspect of the test.

STUDY B.

6. Outcome of fMRI Pilot Study

6.1. Clinical Outcome Measures

The patient’s visual functions in his unaffected eye were entirely normal. In his affected eye his high-contrast central visual acuity as assessed by both the Early Treatment Diabetic Retinopathy Study charts and the Snellen chart was normal, except during the
second visit when due to his macular star he had mildly decreased visual acuity to 20/25 (as previously summarized in Table 4). However, his contrast sensitivity as evaluated by the Pelli-Robson chart and expressed in log contrast was reduced from 2.25 to 1.65 at the second visit. This improved to 1.70 by the third visit. His color vision was measured by the Ishihara color plates and was reduced from 10/10 to 9/10 (slow). During all three visits he was observed to have a large right relative afferent papillary (RAPD) defect indicative of an optic neuropathy.

### 6.2. Electrophysiology

He had electrophysiologic testing on July 3, 2006, when his pattern VEP revealed normal latency and amplitude on both sides, though, amplitude was reduced on the right compared with the left (Table 5 A) (Figure 25). Unfortunately, his multifocal visual-evoked potential (mfVEP) was uninformative due to technical difficulties.

He had pattern electroretinogram (PERG) on February 8, 2007 that showed increased P50 and N95 latency in his diseased eye compared with his intact eye. Both his N35-to-P50 and P50-to-N95 amplitudes, particularly his P50-N95 amplitude, were decreased in his affected eye in comparison to his unaffected eye (Table 5 B) (Figure 26).

Table 5. A) Mean pattern evoked-visual potential (VEP) and B) mean pattern electroretinogram (ERG). N35, N75, N95, N135: negative wave at 35, 75, 95 and 135 ms, respectively; P50, 100: positive wave at 50 and 100 ms. O.D. right eye; O.S. left eye.

<table>
<thead>
<tr>
<th>A) Pattern VEP</th>
<th>B) Pattern ERG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean latency (ms)</strong></td>
<td><strong>Mean latency (ms)</strong></td>
</tr>
<tr>
<td>O.D.</td>
<td>N75</td>
</tr>
<tr>
<td>75.5</td>
<td>99</td>
</tr>
<tr>
<td>O.S.</td>
<td>72</td>
</tr>
<tr>
<td><strong>Mean amplitude (µV)</strong></td>
<td><strong>Mean amplitude (µV)</strong></td>
</tr>
<tr>
<td>O.D.</td>
<td>N75-P100</td>
</tr>
<tr>
<td>6.59</td>
<td>11.9</td>
</tr>
<tr>
<td>O.S.</td>
<td>11.8</td>
</tr>
</tbody>
</table>
Figure 25. Pattern visual-evoked potentials (VEP) of the pilot patient.

Figure 26. Pattern electroretinogram (P-ERG) of the pilot patient.
6.3. Perimetry

The patient’s initial Goldmann manual kinetic perimetry showed an inferior-nasal defect. By his second visit, he developed a concentric scotoma that was essentially unchanged during his third exam. In addition, on September 26, 2006, after his third physical examination, we performed Humphrey visual fields with the SITA-standard 24-2 protocol six times within sixty-five minutes (Table 6) (Figure 27). The reason for performing such serial examination was to evaluate visual fatigue, assess reliability and to teach the patient of appropriate fixation (learning effect) in order to see if he is an appropriate candidate for fMRI testing. His SITA Standard static perimetry showed circular scotoma present outside ~12° eccentricity and intact central visual field in the right eye and entirely normal visual function in the left eye. He had greatly reproducible results and excellent reliability indeces without any fixation loss. Therefore, he was considered a great candidate for fMRI which requires excellent fixation and cooperation for about 2 hours.

Table 6. Summary of six consecutive Humphrey visual fields (HVF) of the pilot patient depicting mean deviation (MD), pattern standard deviation (PSD) and test duration.

<table>
<thead>
<tr>
<th>HVF exams</th>
<th>MD (dB)</th>
<th>PSD (dB)</th>
<th>Test Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.D.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>-19.19</td>
<td>8.46</td>
<td>7.12</td>
</tr>
<tr>
<td>2nd (11min later)</td>
<td>-27.96</td>
<td>12.42</td>
<td>6.08</td>
</tr>
<tr>
<td>3rd (10 min later)</td>
<td>-28.20</td>
<td>11.86</td>
<td>6.05</td>
</tr>
<tr>
<td>4th (8 min later)</td>
<td>-27.86</td>
<td>12.03</td>
<td>6.14</td>
</tr>
<tr>
<td>5th (8 min later)</td>
<td>-28.72</td>
<td>11.63</td>
<td>6.25</td>
</tr>
<tr>
<td>6th (9 min later)</td>
<td>-28.03</td>
<td>12.50</td>
<td>5.36</td>
</tr>
<tr>
<td>Mean values</td>
<td>-26.66</td>
<td>11.48</td>
<td>6.17</td>
</tr>
<tr>
<td>HVF exam O.S.</td>
<td>+1.35</td>
<td>1.10</td>
<td>4.11</td>
</tr>
</tbody>
</table>
Figure 27. Grey-scale (on the left side of the panel) and pattern deviation plot (on the right side of the panel) representation of consecutive SITA Standard automated perimetry results of the pilot patient. These tests were obtained in succession within sixty-five minutes to test patient reliability determined by fixation loss, false positive and negative errors. This patient showed excellent reliability indices. The largest difference in the pattern deviation is seen between the first and second test.
6.4. fMRI-Perimetry

At the initial functional experiment (Experiment 1) we found selective loss of signal intensity in the retinotopic regions corresponding to the right eye visual field scotomas (Figure 28).

**Figure 28.** Loss of retinotopic activity corresponding to the visual field scotoma in the right eye, when compared with the left eye (Figure 29) the reduction in the corresponding visual field quadrants is apparent.
Left eye
(cross-correlation range: 0.45-0.8)

Figure 29. Normal retinotopic activity of the inferior-nasal and superior-temporal visual field quadrants.

In the affected right eye there was activity detected between fixation and 13° eccentricity in the superior-temporal (ST) quadrant within the central 20°. Moreover, the activity was reduced to between fixation and 11° in the inferior-nasal quadrant (IN) of the same central visual field. Eccentricity mapping was entirely normal in the unaffected left eye where also the ST and IN quadrants were mapped (Figure 29). Extent of activation with cross-correlation range of 0.45-0.8 the right and left occipital lobe also showed reduced activation in the right eye corresponding areas. There was reduced BOLD activity in the retinotopic representation of the affected right eye in both cerebral hemispheres (Figure 30).
**Left and right eye**

extent of activation (cross-correlation range: 0.45-0.8)

Figure 30. Retinotopic mapping of both visual cortices showing reduced activity corresponding to the right eye scotomas.

In **Experiment 2**, there was decreased psychometric performance of the affected right eye as depicted in Figure 31. When we presented performance and number of active voxels as a function of distance from the fovea that was equal till about 12º eccentricity in both eyes (Figure 32 A and B). However, there was a sudden drop from 12-20º in the affected right eye. In the unaffected left eye, more voxels were recruited for each distance than in the affected right eye (Figure 32 B). The extent of activation was higher in the healthy than the other eye across all correlation thresholds (Figure 33 A and B). The same was true for the amplitude of activation. The correlation between the two eyes (cross-correlation) regarding extent of activation was higher in the unaffected left eye across all correlation thresholds. Also, the amplitude of activation was higher in the left eye across all thresholds. Notably, higher eccentricities are more correlated to the stimulus design in the healthy than in the involved eye.
Results of perimetry
both the size and color of the dots represent performance

Figure 31. Results of fMRI-perimetry (psychophysical performance).
Performance as a function of distance from the fovea

- Performance values are collapsed across stimulus paths (angles)
- Performance drops to chance level at about 12° eccentricity

Figure 32. Performance (A) and total extent of BOLD activation (active voxels) (B) presented as a function of distance from the fovea. A similar pattern is visible on both plots: performance and neuronal activation has a steep decay at about the same eccentricity in the affected O.D.

We observed decreased amplitude of activation with distance from the fovea. In addition, neuronal activation is in general less even in the cortical areas receiving their input from the well performing region of the affected eye. The overall decreasing slope of activation is explained by cortical magnification, i.e. the difference in scaling between the standard perimetry space and the cortical space due to an overrepresentation of central visual field in the visual cortex.

In Experiment 3, like in the previous experiments the performance on the newly developed fMRI-perimetry very well correlated with the performance obtained by the SITA Standard static automated perimetry (Figure 34). In addition, we examined the activation patterns of simulated and pathological scotomas. There was marked difference observed in case of simulated scotoma as there was no significant BOLD activation in that part of V1 where the eliminated visual field was represented. However, in case of pathological scotoma there was gradual decrease of activation in V1 with increasing
eccentricity, and some remaining activation even in the part of V1 corresponding to the scotoma (Figure 40).

**Figure 33.** A) The healthy eye produces a more correlated activity than the other. High eccentricities are more correlated to the stimulus design in the healthy eye than in the other. **B)** On the healthy eye more voxels are recruited for each distant patch than in the other. The ratio of total activation drops as a function of distance. No voxels are recruited to the map on the affected eye after reaching 14° eccentricity.
Figure 34. fMRI-perimetry (upper row) and automated perimetry pattern deviation results of the left (on the left) and the right (on the right) eyes showing great resemblance.

Moreover, we tested BOLD activation in the normal and in the simulated scotoma mode in the V1 subregion (Figure 35) in the healthy volunteers. We found decreased activity in the outer V1 region in the scotoma mode correlating with the simulated scotoma (Figure 39 E).
Figure 35. BOLD activation responses to the scotoma mapping stimulus in healthy subjects. Normal mode stimulation responses are found on the left and simulated scotoma responses on the right. The inner functional region of interest (ROI) is depicted in the upper row and outer ROI in the lower row.

6.5. Optical Coherence Tomography

OCT appears to be comparable to both scanning laser polarimetry (GDx with variable compensation, Carl Zeiss Meditec) and confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II, Heidelberg Engineering GmbH, Heidelberg, Germany) in its ability to differentiate between healthy and glaucomatous eyes with visual field loss. However, OCT seems to be superior to these methods in the detection of RNFL loss in multiple sclerosis (MS) patients as GDx may be less sensitive for detecting RNFL loss in the temporal and nasal quadrants, and HRT gives only an indirect measure of the RNFL (112). This is why we used OCT in our patient with recurrent optic neuritis.

We observed decreased peripapillary retinal nerve fiber layer in all four quadrants (Figure 36) along with reduced macular thickness (Figure 37) in the affected right compared with the unaffected left eye due to axonal loss.
Figure 35. Mean values for overall average retinal nerve fiber layer thickness (360° around the disc) and for RNFL thickness in temporal, superior, nasal and inferior quadrants of the pilot patient.

In addition, as a result of secondary peripapillary retinal nerve fiber layer loss there was decreased optic nerve head rim area with resultant increase in cup size. The summary of these measurements is shown in Table 7.

Table 7. Summary of Optical Coherence Tomography Data.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Unaffected eye (O.S.)</th>
<th>Affected Eye (O.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL thickness mean (µm)</td>
<td>300</td>
<td>240</td>
</tr>
<tr>
<td>Macular thickness (µm)</td>
<td>246</td>
<td>207</td>
</tr>
<tr>
<td>c/d ratio</td>
<td>0.224</td>
<td>0.459</td>
</tr>
<tr>
<td>Rim area</td>
<td>1.832</td>
<td>1.522</td>
</tr>
<tr>
<td>Cup area</td>
<td>0.559</td>
<td>1.29</td>
</tr>
</tbody>
</table>
Figure 36. Macular thickness of the right (O.D.) and the left (O.S.) eye. There is reduced thickness in all quadrants around the fovea in the right eye.

Figure 37. Optic Nerve Head Optical Coherence Tomography Images. There is so called cupping demonstrated by increased cup-to-disc ratio in O.D.
VI. DISCUSSION and CONCLUSIONS

In the first part of my study (Study A) we evaluated the reliability of Goldmann perimetry, which is the traditional method used for the assessment of visual field defects in patients with severe neurological handicaps or severe vision loss compared with SITA Fast perimetry. There are multiple more sophisticated, reliable, sensitive, affordable, and easily performed automated perimetry programs, thus, GVF performed by a skilled technician has become less available. Although the full-threshold Humphrey analyzer has proven to be one of the most sensitive and reliable automated perimetry strategies for more than 20 years, it is still only rarely used by neurologists. Indeed, it does have drawbacks compared with GVF, such as prolonged test time, the rapid appearance and disappearance of the light stimulus, lack of human contact and reassurance, and continued testing despite detection of poor fixation (6). Previous studies (19,20) have shown that the full-threshold Humphrey analyzer cannot overcome many of the major obstacles to accurate visual field assessment, such as fixation losses, poor concentration, and patient fatigue, which are all common findings in neurologically disabled patients. The SITA family of automated perimetry uses the Humphrey perimeter with different algorithms, making the visual field testing process much shorter and easier for the patient (6,31,35). These automated perimetry programs have replaced the full-threshold Humphrey analyzer in most glaucoma centers and will soon be readily available and accessible in most ophthalmic and neuro-ophthalmic practices.

Our study shows that SITA Fast computerized static perimetry, a new rapid perimetric threshold test, can be used to identify and localize visual field defects in most patients with neuro-ophthalmic diseases. Previous studies (35,36) have shown that SITA Fast is reliable in healthy subjects and in glaucoma patients, in whom visual acuity is usually relatively well preserved. We evaluated only patients with either severe vision loss who may not be able to see the standard target used on the automated perimeter, or those with a neurologic deficit that may compromise their ability to perform a computer-driven test. We assumed from previous studies (16,19-20,22,36) that patients with good visual acuity or mild neurological deficits would not have trouble performing SITA Fast perimetry, and therefore, we excluded such patients from our study.
The overall reliability of visual field testing in our study seemed to be very good (77%) even in our disabled patient population. However, without an accepted established definition of a "reliable visual field test" for both GVF and SITA Fast perimetry, these results should be interpreted with caution. Our estimation of a "reliable" GVF was based on the technician's subjective assessment of the patient's cooperation. For SITA Fast perimetry, we used a very high rate of fixation loss (>50% rather than >20%) to establish that a visual field was not reliable. Sanabria et al (114) showed that fixation losses result not only from subjects looking around, but also from faulty initial localization of the blind spot and, therefore, that these losses may be the result of technical artifacts. Using our criteria, we observed similar reliabilities with both GVF and SITA Fast perimetry in the group of patients with poor visual acuity. For the SITA Fast strategy, we used the standard size III target provided by the Humphrey analyzer, which corresponds to a 4-mm² stimulus size (equivalent to a size III target on GVF). This target allowed reliable evaluation of the visual field of patients with visual acuities as poor as hand motions. Nevertheless, in 9 eyes with vision loss, and in 7 eyes of patients with neurological deficits, GVF was reliable, but SITA Fast was not, according to the high percentage of fixation losses. In this group of patients who had an unreliable SITA visual field, most patients with vision loss had visual acuities worse than 20/400 or were older than 72 years. It is likely that a larger stimulus (such as 64 mm², equivalent to the size V target on GVF) would have provided more useful information in these patients (115). However, we selected the "standard" stimulus size provided by the standard Humphrey package, as used by most community-based ophthalmologists, to simulate common referral conditions. We felt it would be too taxing on the patients who failed to perform a reliable SITA test to repeat perimetry with a larger stimulus on the same day. Most patients with neurological deficits who were not able to perform a reliable SITA Fast had either a cerebellar syndrome compromising their coordination and their fixation, or frontal or occipital lesions associated with spatial and cognitive disorders (Figure 38). Without the experience of the highly skilled technician who performed all GVFs, it is likely that most of these patients would not have been able to perform a reliable GVF. Nevertheless, in 22% of our patients with neurological deficits, SITA was more reliable and provided better visual field information than GVF (Figure 23).
This may be explained by the short examination time of the 24-2 SITA Fast perimetry, as well as the flexibility of the SITA Fast parameters (35).

Figure 38. Visual field results in a patient with bilateral occipital infarctions in whom Swedish Interactive Thresholding Algorithm Fast perimetry (B) failed to show the bilateral homonymous hemianopic defects demonstrated by Goldmann manual kinetic perimetry (A) (group VIII).

The results obtained with SITA Fast perimetry indicate a relatively good correlation with Goldmann perimetry in the detection, characterization, and quantification of visual field defects in this particular population. We found that 75% of all eyes with abnormal visual fields had similar visual field results with GVF and SITA Fast (70% of eyes in patients with neurological deficits, and 80% of eyes with severe vision loss). Only a few previous studies have compared GVF with automated perimetry in patients with neuro-ophthalmic disorders. Various automated perimetric strategies were used, including the Fieldmaster (18-19), the Octopus (17), and the Humphrey full-threshold analyzer (20-22). These studies showed that automated perimetry was comparable to GVF in detecting visual field abnormalities in neurologic diseases. For example, visual field defects were almost identical with automated perimetry and GVF in 84% of the 25 patients studied by McCrary and Feigon (16), and in 87% of the 69 eyes studied by Beck et al (20). The purpose of these...
studies was to evaluate the reliability of automated perimetry in identifying and quantifying visual field defects from neuro-ophthalmic diseases such as nonglaucomatous optic neuropathies and lesions involving the retrochiasmal visual pathways. None of these studies specifically addressed the issue of severely decreased vision in some patients with optic neuropathies, nor did they correlate their results to the degree of a neurological handicap. Most of these studies (16,18-20) used older-generation perimeters that are much slower and generate more visual fatigue than the SITA Fast algorithm used in our study.

A quarter of all eyes, representing 25 (28%) of 89 eyes with abnormal visual fields, were categorized into group 2, in which SITA Fast showed a slightly larger visual field defect than GVF (Figure 22). It has been shown that automated perimetry is more sensitive than GVF in the detection of visual field defects in patients with glaucoma (15,17,19-20). Indeed, even in the hands of a skilled operator, GVF often underestimates the severity of the visual field defects, especially when the defects are located in the central part of the visual field (15,17,19-20). Another possible explanation is statokinetic dissociation, which has been reported in various pathological cases involving the optic nerves as well as the occipital lobes (117-118). Statokinetic dissociation is a physiologic phenomenon related to the easier perception of moving objects (as in Goldmann kinetic perimetry) than stable objects (as in static automated perimetry), giving rise to a greater visual field defect on automated perimetry compared with GVF (117-118). However, in 5 eyes with severe vision loss, GVF showed a slightly larger defect than SITA Fast (group 3).

In 9 (10%) of 89 eyes with abnormal visual fields, SITA Fast failed to show a visual field defect that was demonstrated by GVF (group 8). In 4 of these eyes, the visual field defects (or the residual island of vision) were localized at the border or outside of the central 24° of visual field evaluated by SITA Fast (Figure 24). Goldmann perimetry tests the entire visual field (180°) and is hence the obvious technique of choice in eyes with either residual eccentric islands of vision or with visual field defects not involving the central 24° of vision. The SITA software allows for the evaluation of the central 10°, 24°, or 30° of vision. We used the 24-2 instead of the 30-2 strategy to reduce the duration of the test, thereby limiting visual fatigue. However, it is unlikely that evaluation of the central 30° would have changed our results (116). The full-threshold Humphrey analyzer is able to test the central 60° of vision, but the length of the test (as long as 30 minutes per eye)
precludes easy usage. Development of a SITA strategy testing the central 60° of visual field could potentially solve this problem, with an acceptable minimal increase in test duration within the SITA Fast algorithm. However, it is also possible that certain lesions involving the retrochiasmal visual pathways may not be detected as well with automated perimetry as with GVF, even if the defects fall within the central visual field. For example, one of our patients with bilateral occipital infarctions had a GVF perimetry that exquisitely delineated bilateral homonymous defects—findings completely missed by SITA Fast perimetry, which was unreliable (Figure 38). Wong and Sharpe (22) evaluated 12 patients with occipital lobe infarctions using tangent screen, GVF, and the full-threshold Humphrey visual field, and correlated the findings with magnetic resonance imaging of the causative lesions. They observed that even though Humphrey automated perimetry was able to detect the visual field defects, it incorrectly localized the defects to the proximal portion of the retrochiasmal pathway in 2 patients, failed to detect sparing of the occipital pole in 4 patients, and overestimated the lesion size in 1 patient.

The duration of visual field testing was significantly shorter for SITA Fast than for GVF. Considering that SITA adjusts the time between stimuli based on the patient's answers, and that our experienced Goldmann perimetrist is faster than most, this difference is impressive. It helps explain why even patients with cognitive disorders and poor concentration were able to reliably perform a SITA Fast visual field test. Although the GVF was consistently performed first in all patients, the GVF and SITA Fast techniques are extremely different; it is therefore unlikely that a learning effect can explain the discrepancy between the 2 visual fields observed in some patients, or the shorter SITA Fast test duration.

Similar to previous studies (16-17), we found that nearly all our patients preferred GVF to SITA Fast perimetry. Our patients noted that it was difficult to maintain concentration without some communication with the examiner, and that the standard size III object was hard to see on the SITA Fast. The 6 patients who preferred SITA Fast were, in general, younger patients who seemed to enjoy the computerized method.

Our results suggest that SITA Fast perimetry could be ordered instead of GVF in most patients with optic neuropathies or lesions involving the intracranial visual pathways. Additionally, these findings may be applicable to younger children, in whom the realization
of a reliable visual field is often challenging (6). However, GVF may still be the test of choice in patients with occipital lesions, in those with peripheral visual field defects, and in those with large central defects of more than 30°. Furthermore, it is likely that GVF performed by a skilled operator is preferable to SITA Fast in patients with suspected nonorganic vision loss.

**STUDY B**

A critical, presently unresolved question concerns the plastic brain processes that are triggered by various ophthalmological and neurological diseases. The vast majority of these disorders cause a visual field loss that is responsible for disability of the patients and greatly impacts their activity of daily living. However, to be able to rehabilitate such individuals we needed to develop a method for the functional assessment of brain processes triggered by these diseases and also to assess the effect of different therapies. In Study B we used multiple stimuli to obtain retinotopic maps of the visual field quadrants (Figure 39), and described a novel technique developed by us for the mapping of perceptual and various neural visual field deficits provoked by neuro-ophthalmic disorders, so called fMRI-perimetry (Figure 39F). This technique allows us to assess neural plasticity processes underlying spontaneous and induced (by rehabilitation and or medication) recovery. Functional MRI-perimetry was designed to be useful and relatively easily applicable in everyday clinical practice. We found that cortical activity in low-order (V1, V2, V3 and V3a) and high-order visual systems is reliably mapped by fMRI-perimetry.

The performance on fMRI-perimetry closely corresponded to the performance indices (pattern deviation) obtained by automated perimetry (Figure 34).

The preliminary results of this pilot experiment seem to confirm our hypothesis that there is selective loss of signal intensity in the retinotopic regions corresponding to the visual field scotomas. However, when we compared the activation patterns of simulated and pathological scotomas (Figure 40) there were interesting findings. In case of artificial scotoma we found no significant BOLD activity in that part of V1 where the eliminated visual field is represented. Interestingly, on the inner border of the simulated deficit there is a stripe of elevated BOLD activity compared with the V1 activation more distal from the border of scotoma (Figure 40 A and B).
Figure 39. Visual stimuli used in the fMRI experiments and the corresponding activation maps and response patterns. Several kinds of stimuli were used to obtain retinotopic maps of the right superior quadrant of the visual world shown on the inflated left occipital cortex. Subjects fixated on a stationary target (red dot in the bottom left corner) while contrast reversing checkerboard patterns (100% contrast, 8 Hz flicker) were presented in the periphery.

In contrast, the pathological scotoma caused gradual decrease of activation in V1 with increasing eccentricity, and there was some remaining activity even in the part of V1 corresponding to the visual field defect. In addition, when we compared the decrease in the overall extent of retinotopic activity with the distance from the fovea there was close correspondence in the patient (Figure 40 C). This was also observed when we compared
the decrease in the summed retinotopic activity with the automated perimetry and fMRI-perimetry techniques.

We determined longitudinal changes in various visual functions such as fMRI BOLD activation, performance on fMRI-perimetry, performance indices of SITA Standard perimetry, pattern VEP and ERG, and OCT.

Figure 39. (Continued) Visual stimuli used in the fMRI experiments and corresponding activation maps and response patterns. **D)** Expanding rings continually expanded outward from the fixation point in each of the 12 cycles of 28.8 s. **E)** Scotoma mapping stimulus. A contrast reversing checkerboard pattern was presented in alternating ½ cycles of 36 s. **F)** fMRI-perimetry stimulus. 1.66° circular patches were presented in a pseudo-random manner overlaid on a continually expanding contrast reversing checkerboard pattern. Interstimulus interval (ISI) 2.4 s. **D, E** and **F** were presented either in the full quadrant (normal mode) or with the outer 40% of the stimulus masked with a patch having the same luminance as the background (simulated scotoma mode). On the left of each panel a frozen frame of the contrast reversing stimuli is presented, dotted red arrows represent direction of rotation/expansion, dashed blue line represent the border of the simulated scotoma, and dotted red circles represent the possible location of the target patches of the fMRI stimulus. On the right of each panel, BOLD activation maps of a single subject are presented, with V1 marked as a dotted white outline. On panels **D** and **E** activations for normal and scotoma mode stimulation are presented in a normal subject with the functional region of V1 located in the left hemisphere.
interest (ROI) corresponding to the inner and outer parts of the visual field quadrant marked as inner and outer, respectively. On panel F behavioral response of a patient with visual field defect is presented.

Our pilot patient showed decreased activation in the corresponding retinotopic areas as predicted by his SITA Standard automated visual fields. The retinotopic pattern in the chronic phase of optic neuritis corresponds to the findings of other authors. However, we did not find compensatory cortical activation in other cortical areas like Werring et al (88). They described extra-occipital activation in seven patients who had recovered from a single episode of unilateral optic neuritis and found activity involving the insula-claustrum, lateral temporal and posterior parietal cortices and thalamus. The volume of extra-occipital activation in patients was strongly correlated with VEP latency. In contrast, stimulation of healthy control eyes activated only the occipital visual cortex, and stimulation of the unaffected eye activated visual cortex and right insula-claustrum only. The reason for this discrepancy may be that we placed our coil under the occipital pole. Thus, areas further away may have not been readily detectable.

Although the mechanism of visual recovery in optic neuritis remains unclear the activation shifted from the unaffected hemisphere to the affected hemisphere may cause some of the visual recovery.

There is great need to investigate other forms of optic neuropathies with fMRI-perimetry as there may be differences in the activation patterns of patients with different forms of optic neuropathy. These alterations may represent distinct patterns in cortical adaptation and hypothetically be responsible for spontaneously recovered versus permanently damaged disease states. Further studies on larger patient populations need to be performed to confirm the above findings. The knowledge obtained through the use of fMRI-perimetry may serve as a basis for the development of a customizable visual restoration program with hopefully great impact on patients’ activity of daily living.
Figure 40. Extent of BOLD activation during the fMRI-perimetry task in the primary visual cortex (V1). The extent of significant BOLD activation is compared between a normal visual field (blue on all panels) and a visual field either with simulated scotoma (A and B on the same eye) or with optic neuritis induced visual field defect (C on the contralateral eye). There is a marked difference at the borders of the scotoma between the healthy volunteers and the investigated patient: in the volunteers the highest simulated eccentricity has a widened representation in V1 (green ellipses). Moreover, the artificial scotoma diminishes the activation in V1, while there is some residual activity observable in the patient. Asterisks represent p<0.05 significance with Student’s t test, error bars are SEM.

Furthermore, by designing various stimuli and applying them either mono- or binocularly we will be able to see if there is selective injury to a pathway such as parvo-magno-kineocellular. In addition, as an analogy to multifocal fMRI (mfMRI) (119) which applies the same stimulus as the multifocal visual-evoked potential (mfVEP) (Figure 41), it may be clinically useful to develop mfMRI-perimetry for direct comparison of these techniques.

In conclusion, the first part of this study suggests that the SITA Fast strategy of automated perimetry may be useful in the evaluation of central visual field defects associated with neuro-ophthalmic disorders. The development of additional SITA software that could test out to 60° might allow even better use of SITA strategies in neuro-ophthalmic practice. Our results suggest that for the general ophthalmologist or neurologist, visual field testing with SITA Fast perimetry might even be preferable to GVF.
(especially if the GVF is performed by a marginally trained technician) even in patients with severely decreased vision or who are neurologically disabled.

In addition, the second part provides further evidence for the adaptive capacity of neuronal systems and brain plasticity during the recovered stage of optic neuritis. We found fMRI-perimetry a clinically useful novel test for use in everyday patient care. However, we need to further validate this method on larger patient population. When done so, this refined fMRI protocol may be incorporated in future clinical trials as a more sensitive outcome measure to assess drug effects and correlate it with clinical functional status and disability. We hope that fMRI-perimetry will enable us to further our knowledge in the understanding of brain plasticity processes. Thus, it may be another step towards the development of successful visual field restoration therapies (122, 123).
VII. SUMMARY

In summary, we conducted two complementary clinical studies in which we investigated the neuro-ophthalmological applicability of recently developed perimetry techniques.

In our prospective study (Study A), we tested a new algorithm: Swedish Interactive Thresholding Algorithm (SITA) Fast against the gold standard perimetry: Goldmann visual field (GVF) in 64 consecutive patients with either severely decreased vision (20/200 or worse) (n=50 eyes) or neurological impairment (n=50 eyes). The recent development of the SITA family of perimetry has allowed for shorter testing time in normal subjects and in glaucoma patients. However, its usefulness for detecting visual field defects in patients with poor vision or neurological disease has not been evaluated. We categorized the results into 1 of 9 groups based on similarities and reliabilities. Overall, GVF and SITA Fast were equally reliable in 77% of eyes and showed similar visual field results in 75% of all eyes (70% of eyes of patients with severe neurologic deficits and 80% of eyes with poor vision). The mean +/- SD duration per eye was 7.97 +/- 3.2 minutes for GVF and 5.43 +/- 1.41 minutes for SITA Fast (P<.001). Thus, our results suggest that for the general ophthalmologist and neurologist, visual field testing with SITA Fast perimetry might even be preferable to GVF, especially if performed by a marginally trained technician, even in patients with severely decreased vision or who are neurologically disabled.

In our pilot study (Study B), we tested a novel technique: functional MRI-perimetry (fMRI-perimetry) on a neuro-ophthalmological patient against healthy controls. We performed three functional MRI experiments on this pilot patient in addition to SITA Standard perimetry, electrophysiological testings, optical coherence tomography (OCT) and contrast sensitivity. We describe the findings of these visual functional and structural tests. We found that performance on fMRI perimetry closely correlates with pattern deviation (PD) performance as assessed by static automated perimetry.

In conclusion, both Study A and Study B provide important results that have relevance in everyday clinical practice of ophthalmic, neurologic and neuro-ophthalmic patients with disease processes affecting any parts of the afferent visual system.
ÖSSZEFOGLALÁS

A két egymást kiegészítő klinikai tanulmányunkban új perimetria vizsgálatok neuroophthalmológiai felhasználhatóságát vizsgáltuk.

Elődleges vizsgálatunk során (Tanulmány A) egy néhány éve kifejlesztett perimetria algoritmust (Swedish Interactive Thresholding Algorithm: SITA Fast) prospektív módon hasonlitottunk össze az arany standarddal (Goldmann látótér: GVF). Hatvannégy bejegyzett vizsgáltunk akiknek vagy súlyos látásvesztése (visus: 0,1 vagy rosszabb) (50 szem) vagy súlyos ideggyógyászati fogyatékossága (50 szem) volt. Korábbi vizsgálatok során a SITA perimetria családdal rövidebb vizsgálati időt tudak elérni ép látótérrel rendelkező és glaucomás betegeken. Viszont ezen módszert még nem tanulmányozták súlyos látás- és ideggyógyászatilag sérült betegeken. A látóterek hasonlósága és megbízhatósága alapján vizsgálataink eredményét 9 csoportba soroltuk. Összesítve, GVF és SITA Fast közé egyenlő megbízhatóságot (77%) és hasonlóságot (75%) mutattott (70%-ban a súlyos ideggyógyászatilag sérült és 80%-ban a súlyos látásvesztett szemek esetében). Az átlag +/- SD vizsgálati időtartam szemenként GVF-el 7.97 +/- 3.2 perc, míg SITA Fast-al 5.43 +/- 1.41 perc volt (P<.001). Tehát eredményeink azt jelzik, hogy az általános szemész és neurológus számára a SITA Fast perimetria kedvezőbb lehet mint a GVF, különösen nem képzett asszisztens kezében, még azon betegek esetében is akiknek súlyos látásvesztésük és neurológiai sérülésük van.

Pilot tanulmányunkban (Tanulmány B) a kutatócsoportunk által kifejlesztett retinótiási protokollal vizsgáltunk egy neuroophthalmológiai beteget. Ezt a funkcionális vizsgálati módszert funkcionális mágneses rezonancia perimetriának neveztünk el (fMRI-perimetria). A tanulmány második részében részletezzük a betegen végzett funkcionális (alacsony kontraszt érzékenység, SITA Standard, VEP) és struktúrális (OCT) vizsgálatok eredményeit, melyek legfontosabbika, hogy a fMRI-perimetria teljesítmény igen jól korrelál a statikus automata perimetria minta deviációs teljesítményével.

Tanulmány A és B eredményei jelentőséggel bírnak a mindennapi szemészeti, ideggyógyászati és neuroophthalmológiai klinikai praxisban és az efféren látórendszer sérüléseit legkorábban jelezhetik.
VIII. REFERENCES

1. Listed in the diploma work


2. Literature by the author pertinent to the diploma work


3. Other Literature by the author

4. Lectures and presentations by the author pertinent to the dissertation


IX. ACKNOWLEDGMENT

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