VISUAL FUNCTION IN OPTIC NEURITIS
IN RELATION TO
MULTIPLE SCLEROSIS

JOHANNA CATARINA VAN DER POEL

VISUAL FUNCTION IN OPTIC NEURITIS IN RELATION TO MULTIPLE SCLEROSIS

An electrophysiological and psychophysical study

OOGHEELKUNDIGE ASPECTEN VAN DE RELATIE TUSSEN NEURITIS OPTICA EN MULTIPLE SCLEROSE

Een electrophysiologische en psychophysische studie

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF.DR.M.W.VAN HOF
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 9 OKTOBER 1985 TE 15.45 UUR

DOOR

JOHANNA CATARINA VAN DER POEL

GEBOREN TE RIJSWIJK Z.H.

1985
Bosch & Keuning nv.
Baarn

Begeleidingscommissie

Promotor: Prof.Dr.G.H.M.van Lith
Overige leden: Prof.Dr.P.T.V.M.de Jong
                Prof.Dr.H.A.C.Kamphuisen
                Prof.Dr.M.de Vlieger

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*Those who try to interpret humankind through its eyes
are in for much strangeness, perplexity.*
Saul Bellow

CHAPTER I

INTRODUCTION

The short term prognosis of optic neuritis, the acute decrease in visual acuity without abnormalities in media or fundus, is excellent. Most patients recover within a few weeks to a month (Bradley & Whitty, 1967). Follow—up of these patients, however, may reveal signs and symptoms of demyelinating lesions outside the optic pathway. In 1884 Parinaud had already described a relation of optic neuritis and multiple sclerosis. Approximately 50% of the patients suffering from multiple sclerosis (MS) have a clinical episode of optic neuritis (ON) at some time during the course of the disease. Further, progression to MS has been observed in 8–85% of the patients who have suffered from ON (Cohen et al., 1979). As ON has a variety of causes, the variation in this percentage may be due to the criteria used as a basis for making the diagnosis of ON and MS, the patient selection, and/or the length of the follow—up. According to literature, the aetiology of an episode of optic neuritis may range from vascular and compressive lesions to toxic and psychogenetic origins. Among all the other causes of ON, MS is the one most frequently observed (1.5–69%; Bagley, 1952; Benedict, 1942). Further, in 1–56% of the patients presenting with an episode of optic neuritis the cause remains unknown (Benedict, 1942; Bagley, 1952). Several authors have tried to predict the progression to MS in these 'idiopathic' patients by analysing the epidemiological and clinical features at the time of the first attack. Risk factors in developing signs of demyelination outside the visual system include sex, age, a relapse of the ON, and seasonal influences (Cohen et al., 1979). Further, intrathecal IgG synthesis at the time of the attack (Stendhal––Brodin & Link, 1983) and an HLA–Dr2 antigen typing (Compston et al., 1978) may point to an increased risk of developing MS after an uncomplicated ON.

The purpose of the present study is to assess the predictive value of visual function in ON patients with regard to the development of MS. For this purpose, idiopathic optic neuritis patients were seen during the acute stage of the attack and after improvement of visual acuity. Visual function is assessed by standardized ophthalmological examination. Further, electrophysiological and psychophysical methods are used. The sensitivity of two methods of visual evoked responses (VER) used in the diagnosis of visual impairment is compared in both the acute stage and after recovery. In addition to Snellen charts, both electrophysiological and psychophysical methods are evaluated on their sensitivity in detecting visual loss after improvement of the optic neuritis.

In chapter II a literature review is given of the aetiology of optic neuritis. Further, the epidemiological and ophthalmological features in the acute stage are described. The short term and long term prognosis of optic neuritis is discussed. Risk factors which could point to the development of signs of MS in patients after ON are evaluated.

The history of the VER and its evolution into a clinically applicable method are described in chapter III. The results obtained with pattern presentation and pattern reversal evoked responses in both patients with optic neuritis and patients with multiple sclerosis are reviewed.

Psychophysical methods used in the diagnosis of optic neuritis and multiple sclerosis including colour vision tests, visual field analysis, contrast sensitivity function and pattern electroretinogram are discussed in chapter IV. The value of these methods in the detection of visual loss after optic neuritis is evaluated.

In chapters V and VI the methodology of the present study and the selection of patients are described. Chapter VII reports on the epidemiological and clinical features of 110 patients at the time of the first attack. Further, the short term prognosis with regard to visual acuity is described. In chapters VIII and IX a comparison of pattern presentation and pattern reversal evoked responses is made with regard to the diagnostic yield of each method in the diagnosis of optic neuritis in the acute stage, and after improvement of visual acuity.

Chapter X describes the results obtained using standardized ophthalmological methods and using psychophysical methods in relation to the prediction of the development of signs of MS and in relation to visual loss after an attack of optic neuritis. Visual function, assessed by means of electrophysiological and psychophysical methods is compared for patients with and without signs of MS and for patients with and without recovery of visual acuity.

In the final chapter, in 23 of the 53 reexamined patients signs of MS are described. The predictive value of the epidemiological and ophthalmological features in these patients is discussed.

I've seen a Dying Eye
Run round and round a Room
In search of Something—as it seemed
Then cloudier become—
And then—obscure with Fog—
And then—be soldered down
Without disclosing what it be
'Twere blessed to have seen

Emily Dickinson

CHAPTER II

OPTIC NEURITIS

Definition and aetiology

Optic neuritis is a broad definition, which may encompass all affections of the eye, without any abnormality of the media or fundus, in which a sudden decrease of visual acuity is experienced by the patient. Some of the most important causes of ON reported in literature are listed in table II.1. Infectious causes of ON include infections of the surrounding structures of the eye (nasal and dental sepsis, sinusitis, parotitis and periostitis), of the CNS (encephalitis, syphilis and meningeal infections) and general diseases (e.g. influenza). These causes can be excluded by means of general examination, blood tests and X–rays.

Tobacco, alcohol, anti–personnel gas, drugs, ethambutol and other chemical substances can lead to a toxic optical neuropathy. Careful history taking may reveal this aetiology, which is more likely when the affection is bilateral.

A diabetic neuropathy may be traced through a disturbed glucose tolerance test, urine and blood glucose levels.

Compressive lesions may give the impression of an attack of optic neuritis. These lesions include all tumours along the visual pathway. Peripheral visual field defects, e.g. bilateral hemianoptic visual field defects, a sign of chiasmatic compression, make the presence of a compressive lesion more likely as these defects are atypical of optic neuritis.

Vascular abnormalities are the most frequent cause of acute visual loss as in ON after the age of 60. They comprise arterial or venous occlusion of the optic vascular system. Signs of arteriosclerosis at other sites of the body and hypertension suggest a vascular origin of the ON. This may be confirmed by fluorescein angiography. Further, temporal arteritis may cause visual loss, a rise in blood sedimentation rate being an indication for arriving at this diagnosis.

Leber's optic atrophy is most frequently seen in young adult males. It is a more or less symmetric affection with an atypical presentation which makes it difficult to differentiate from other causes of ON especially from tobacco and alcoholic optic neuropathy. The family history is usually decisive.

Further, central serous retinopathy can simulate ON and cause diagnostic confusion. The similarities to idiopathic ON are sometimes striking. Central serous retinopathy mostly occurs in young adults, commonly under stress, has a seasonal predilection, is unilateral and produces visual blurring. On examination a central scotoma may be found. The diagnosis is more likely when a loss or change of the foveal reflex is present. Fluorescein angiography shows a macular leaking of dye. This affection usually improves spontaneously.

	Benedict 1942 N=225	Bagley 1952 N=133	Carroll 1952 N=240	Bradley Whitty 1967 N=123	Appen Allen 1974 N=56	Nikoske-lainen 1974 N=185	Cohen et al. 1979 N=325	Range %
MS	69 %	1.5 %	32 %	51 %	27 %	65 %	13 %	1.5–69
Toxic neuropathy	26	4	9		4	3	12	3–26
Infection	1	17	8		9	3		1–17
Compression		7					15	7–15
Vascular	1	1.5	13		9	2	10	1–13
Leber		3	8			5		3–8
Psychogenetic							6	6
Trauma		10						10
Error in diagnosis	2				9		22	2–22
Unknown	1	56	30	49	42	22	22	1–56

TABLE II.1 : CAUSES OF OPTIC NEURITIS ACCORDING TO VARIOUS AUTHORS. Considerable variability is found for all causes listed. In 1–56% of the patients with optic neuritis the cause remains unknown whilst, for multiple sclerosis the percentages range from 1.5–69%.

Author	N	Monocular	Aged 20–50	Female	Season April to July	Year
Bagley	39	46 %	56 %	51 %		1952
Hyllested et al.	52	79		62		1961
Kurland et al.	143	100	88	0		1966
Bradley & Whitty	78	71	82	62	44 %	1967
Nikoske lainen	185	82	81	58		1975
Kahana et al.	85	82	65	64		1976
Cohen et al.	60		83	70		1979
Range %		46–100	56–88	51–70	44	

TABLE II.2 : EPIDEMIOLOGY OF OPTIC NEURITIS ACCORDING TO VARIOUS AUTHORS. The majority of the patients are female and between 20 and 50 years of age. They usually suffer from unilateral ON in the months April to July.

Other causes listed in table II.1 include psychogenetic causes, trauma and error in diagnosis.

The incidence of the various causes varies greatly in literature (table II.1). This may be due to the patient selection and also partly due to the limited diagnostic means used in older studies. Moreover, criteria for making the diagnosis have changed over the years.

When all the above–mentioned causes are ruled out, MS remains the major cause of ON. Half of the number of patients with MS suffer from one or more episodes of ON during the course of the disease (McAlpine et al., 1965).

In a number of the patients who present themselves with an attack of ON the cause may remain unknown. This idiopathic form of ON has been subjected to much research over the past decades. A number of patients with idiopathic ON develop MS later on. There are still no clear parameters that may serve as a predicatives of the risk of developing MS. In the present study, the term ON is used to indicate this type of idiopathic ON.

Epidemiology and clinical features

ON is a more common disorder in females than in males (table II.2); the ratio being approximately 2:1 (Hyllested & Müller, 1961; Bradley & Whitty, 1967; Nikoskelainen, 1975; Kahana et al., 1976; Cohen et al, 1979). Kurland et al. (1966) studied only young male adults in military service. An attack of ON is seen more often in spring and at the beginning of summer (April to July) (Taub & Rucker, 1954; Bradley & Whitty, 1967; Hutchinson, 1976). This seasonal varia- tion in occurrence is one of the characteristics of ON. Eighty–one percent of the patients who suffer from ON are young or of middle age (Kurland et al., 1966; Nikoskelainen, 1975; Kahana et al., 1976; Cohen et al., 1979). Usually, in two–thirds or more of the patients the affection is unilateral.

Clinically, optic neuritis is usually described as the condition in which the patient experiences an alarming decrease in visual acuity together with a central scotoma. Sometimes, however, there is only a subjective reduction of bright- ness or some distortion of shapes (Duke Elder & Scott, 1971; Nikoskelainen, 1975; Gläser, 1979). In combination with visual symptoms the patient may suffer from painful eye movements and tenderness of the eyeball on palpation (table II.3). Carroll (1952) reports this in 39% of his patients, whereas Bradley & Whitty (1967) found pain in 70% of the patients studied.

Clinical examination

On ophthalmological examination (table II.3), abnormalities in fundo may be found in 15–70% of those examined. When present the abnormalities are

Author	Year	N	Decreased visual acuity	Painful eyes	(Para) central scotoma	Abnormal fundus	Duration impair— ment
Bagley	1952	39	97 %				< 6 mth 51 %
Carroll	1952	240		39 %			
Chamlin	1953	100			76 %		
Hyllested et al.	1961	52	85		88	15 %	< 1 mth 81%
Kurland et al.	1966	143	73		77	70	
Bradley & Whitty	1967	78	95	68		45	< 1 mth 50%
Nikoske— lainen	1975	185	83	62	73	54	< 1 mth 56%
Kahana et al.	1976	85		34	39	53	< 1 mth 35%
Cohen et al.	1979	60	78	70		48	
Range %			73–97	34–70	39–88	15–70	35–81

TABLE II.3 : OPHTHALMOLOGICAL FEATURES OF OPTIC NEURITIS PATIENTS ACCORDING TO VARIOUS AUTHOR. On examination painful eye movements, a central scotoma and funduscopic abnormalities may be found. Recovery is usually seen within 1 month after onset of the ON.

localized in or around the optic disc. Bradley & Whitty (1967) describe haemor-
rhages, papiledema and blurring or pallor in 45% of their ON patients, a percen-
tage confirmed by Nikoskelainen (1975). Visual acuity may decrease to as low as
0.02 or may be only slightly lower than in the unaffected fellow eye.
A characteristic feature in perimetry is a central scotoma (Nikoskelainen, 1975:
75%), a paracentral scotoma being less commonly found (Hyllested & Müller,
1961: 8%; Nikoskelainen, 1975: 8%).
The pupillary reaction to light in the affected eye is often delayed (Marcus Gunn
phenomenon; respectively 20% and 44% according to Kurland et al. and Nikos-
kelainen).
In the acute stage of ON, colour vision of the affected eye is reported to be
impaired (François & Verriest, 1957; Nikoskelainen, 1975; Wildberger et al.,
1976). As ON usually affects the papillomacular bundle and colour vision is
chiefly related to the macular area, the remaining colour perception in the acute
stage may be related to the peripheral retina (Grützner, 1966). The abnormality
most commonly found in the acute stage is a red–green deficit (Nikoskelainen,
1975; Wildberger et al., 1976).

Short term prognosis of idiopathic optic neuritis

Visual acuity gradually improves within a few weeks or a month in 50–81% of the
cases (Bagley, 1952; Bradley & Whitty, 1967; Nikoskelainen, 1975) (table II.3).
Hyllested & Müller (1961) report recovery of visual acuity up to 1.25 or more in
88% of their patients. Bradley & Whitty found a percentage of 75 after 6 months.
When the follow–up period is prolonged a recovery is reported in almost 100%
of the cases. Conversely, Nikoskelainen (1975) mentions a percentage of 25 in
whom the visual acuity as measured by Snellen charts remains poor.
Pain disappears in less than one week (Cohen et al., 1979). Permanent central or
paracentral defects occur in 62% of the patients Nikoskelainen studied in 1975,
whereas earlier Hyllested & Müller (1961), Bradley & Whitty (1967) and Ziegler
(1970) report smaller percentages ranging from 17 to 42. The higher abnormality
rate in·both visual acuity and visual fields observed by Nikoskelainen may be due
to the fact that in her study she also included patients suffering from Leber's
disease, vascular and infectious causes and polyneuropathy.
This may also explain the fact that pallor of the optic disc is found in 35% of the
patients described by Nikoskelainen (1975). This percentage increases when
there has been more than one attack in the same eye, indicating permanent
damage to the optic nerve due to degeneration of the nerve fibres (Uhthoff,
1889; Wikström et al., 1980).
According to literature, recurrences of ON in an eye that was initially affected
occur in 10–15% (Rucker, 1956) and 19% (Nikoskelainen, 1975).

Long term prognosis of optic neuritis

Long term prognosis of ON with regard to the development of MS varies. Figures on this subject range from 8% (Hierons & Lyle, 1959) to 85% (Lynn, 1959) of all patients with ON of unknown aetiology. Differences are due to the criteria used in patient selection and the length of the follow—up period.

Bradley & Whitty (1968) describe other symptoms of MS in 20% of their patients after a ten—year study of ON and conclude that in most cases developing MS the diagnosis can generally be made within four years.

Hutchinson (1976) however obtained a figure of 78% of the patients developing MS within ten years, using an actuarial analysis based on clinical observation alone. This is in agreement with the view of McAlpine et al. (1965) that the longer the follow—up period, the higher the proportion of patients developing MS. Compston et al. (1978) found an overall figure of 40% in 3.9 years and predict on this basis that in the following 8 years MS would be diagnosed in another 20%. A follow—up of his material has not been carried out so far. Other authors predict the development of MS within a period of 3.6 to 8 years (Adie, 1932; Yaskin et al., 1951; Leibowitz et al., 1966). A latency period of 47 years, however, has been described by Adie (1930).

From the available evidence it can be concluded that the percentage of ON patients developing signs of MS after their attack is highly dependant on the patient selection for the study and the length of the follow—up.

Conversely, retrospective history taking of MS patients reveals that in 14–38% of cases (table II.4) the ON constitutes the initial symptom of MS. Furthermore, 27–56% of the MS patients suffer from ON during the course of the disease. Gartner (1953) reports that histologically in almost all MS patients where a post—mortem examination was carried out involvement of the optic nerve is found, a finding confirmed by Lumsden (1970).

Author	Year	N	Initial symptom	During course
Adie	1930	92	38 %	50 %
Yaskin et al.	1950	100	27	56
Leibowitz et al.	1966	266	14	not investigated
Percy et al.	1972	54	15	27–37
Kahana et al.	1973	259	32	not investigated
Wikström et al.	1980	1271	17	..

TABLE II.4 : OPTIC NEURITIS IN MULTIPLE SCLEROSIS : OCCURRENCE AS INITIAL SYMPTOM AND DURING THE COURSE OF THE DISEASE.

There is still much debate regarding the severity of MS following ON after a certain period. Hyllested & Müller (1961) and Bradley & Whitty (1968) report that a mild form of MS occurs after ON; in the study of the latter 81% of the patients suffered only slight disability after 10 years of MS. Conversely, Nikoskelainen & Riekkinen (1974) found a percentage of 14 of chronically progressive disease after a ten–year follow–up. This percentage increased up to 30% after 20 years follow–up. After more than 20 years 50% of the patients had reached this stage. Wikström et al. (1980) found that patients with ON as the initial symptom had a milder form of MS during the first ten years of the disease compared with other patients. This difference disappeared after 10 years of MS. A country–wide survey of all MS patients by an Israeli research group reveals a higher level of disability in patients where the onset of illness was characterized by visual symptoms (Kahana et al., 1973).

Parameters influencing the risk in an ON patient of developing MS have been surveyed by many authors. Clinical features, bilateral involvement, recurrent ON attacks, seasonal influences and age have been studied. Further, sex differences and neurological abnormalities were included in their research.

In general, authors are convinced that neither visual acuity in the acute stage, nor final visual acuity is related to the development of MS. Bradley & Whitty (1968) report that painful eyeballs indicate an increased risk of developing neurological lesions. Bilateral involvement in ON, Hierons & Lyle (1959) conclude, does not indicate an increased risk. This finding, however, is contradicted by Hutchinson (1976) who observed that in patients with bilateral ON the risk was increased compared with the risk of patients with unilateral or non–recurrent ON.

Recurrent but homolateral ON increases the risk of developing MS (Bradley & Whitty, 1968; Rose, 1970; Cohen et al., 1979). Hutchinson (1976) again contradicts this by not finding an increased risk.

Compston et al. (1978) studied the significance of recurrent ON and found that in those patients who developed MS, recurrent attacks preceded histological proof of demyelination outside the visual system. In a recent report (Parkin et al., 1984), however, no difference in progression to MS was found in a group of patients suffering from sequential bilateral optic neuritis after a follow–up period ranging from 2 to 37 years. Taking this finding into consideration one cannot say that in clinical diagnosis recurrent attacks of ON should be seen as separate events and episodes of a more general demyelinating disease occurring in the CNS (Kurtzke, 1985). A correlation between the seasonal variation in ON and the development of MS, however, could not be established (Bradley & Whitty, 1967; Hutchinson, 1976; Compston et al., 1978). Compston obtained a significant correlation between cases of ON that began in winter and BT–101 tissue–typed patients.

Females are more often affected by ON than males. Windmöller (1910) had already found a female surplus in patients in whom MS started with ON. Cohen et al. (1979) report a significant difference in the frequency of progression to MS between female patients (45%) and male patients (11%). A more rapid progression to MS has not yet been observed.

Patients older than 20 years of age are reported to be at greater risk of developing MS than those under 20 years of age (Cohen et al., 1979), although other studies did not reveal such an age–specific risk (Collis, 1965; Bradley & Whitty, 1986; Hutchinson, 1976). Kahana et al. (1976) noted that the younger the patient, the higher the risk of developing signs of multiple sclerosis. The interval between 21 and 40 years of age is seen by some as the period in which the patient with ON is most prone to develop MS (Taub & Rucker, 1954; Percy et al., 1972; Appen & Allen, 1974; Cohen et al., 1979). According to Taub & Rucker (1954) and Collis (1965) this risk seems negligible after 44 years of age, although according to Bradley & Whitty (1968) not even old age provides protection against MS.

Neurological abnormalities at the time of the initial attack were studied by Hyllested & Müller (1961) and Nikoskelainen & Riekkinen (1974). Hyllested describes abnormalities in 13 (29%) of the patients at the time of the initial attack. Of these, 5 developed MS. Of the 31 patients without neurological signs at the initial attack, 15 patients subsequently developed MS. Nikoskelainen & Riekkinen (1974) report the presence of subjective neurological signs in patients even before the initial attack in 24% of the total patient group. Forty–five percent of the patients with uncomplicated ON (after neurological examination), however, had also a history of neurological symptoms. The mild character of these symptoms had kept the patients from consulting a doctor and when they did, these symptoms proved too slight to make a diagnosis. Exclusion of this group, however, did not materially change the risk rate of developing MS (more than half of the group). The most frequent neurological sign in these patients was dysaesthesia. Furthermore, eighteen percent reported numbness of the extremities. From the above it may be concluded that neurological symptoms at the time of the ON attack are not predictive of the later development of MS.

SUMMARY CHAPTER II

Optic neuritis, the acute decrease in visual acuity without abnormalities in the media or fundus, has been extensively studied in the past decades. Its differential diagnosis may range from infection in surrounding structures, and compressive and vascular lesions of the optic nerve to its most important cause: multiple sclerosis. In a number of the ON patients the cause of the optic neuritis remains obscure. The optic neuritis is then defined as 'idiopathic'.
Most optic neuritis patients are female, between 20 to 50 years of age, and usually suffer from an attack in the months April to July.
Clinical features of optic neuritis include a severe reduction of visual acuity, usually described by the patient as fogginess, painful eye movements and tenderness of the eyeball. On examination, a normal fundus, a central scotoma, a Marcus Gunn phenomenon, and colour vision deficits are usually present.
Although the short term prognosis of optic neuritis is good, the patients may, in the long run, develop symptoms and signs of multiple sclerosis. Percentages on this risk vary from 8–85%, depending on the length of the follow–up period and patient selection. Many attempts have been made to try to predict the development of multiple sclerosis after idiopathic optic neuritis by analysing the epidemiological and clinical features at the time of the first attack. Both bilateral and unilateral recurrent attacks have been reported to increase this risk. Female patients and patients of both sexes between 21 and 40 years of age are most prone to develop multiple sclerosis. Neurological signs at the initial attack do not indicate a higher risk factor in regard to the development of MS in these patients.

Delay
The radiance of that star that leans on me
Was shining years ago. The light that now
glitters up there my eye may never see,
and so the time lag teases me....

Elisabeth Jennings

CHAPTER III

THE VISUAL EVOKED RESPONSE

History

In 1875 Richard Caton had already published on electrical activity of the brain. He mentioned motor and sensory evoked responses. Further, he described responses evoked by light stimuli.

Caton noted the invariable presence of spontaneous electrical activity and the occurrence of negative waves at certain sites associated with localized function: 'When any part of the grey matter is in a state of functional activity, its electric current usually exhibits negative variation'. These currents were recorded by the use of a galvanometer.

About 60 years later, Adrian, apart from specific responses (1941), studied the reductions of the alpha activity of the brain by offering visual stimuli, proving that spontaneous electrical activity of the brain could be replaced or suppressed by specific sensory input, especially by visual stimuli (1944). Adrian points out that although alpha rhythm comes from neighbouring visual association areas rather than from the primary visual cortex itself, alpha rhythm and the specific input are in competition.

Dawson (1947) improved the detection rate of the specific 'visually evoked response' in the EEG noise level. First he used the superimposition method (1947) by superimposing a number of individual responses on an oscilloscope. Later he introduced a summation method (1951) by measuring the amplitudes and calculating the mean.

In these early days in the Netherlands basic research into the visual evoked response (VER) was carried out by Van Hof (1955), whilst clinical applicability was tested by Van Balen (1960).

The value of the VER as an aid to clinical diagnosis became obvious when averaging by means of amplifiers was introduced, though stimulus techniques had to be developed further.

Stimuli used in clinical application of the visual evoked response

Throughout the 1950's and 1960's a great deal of research was carried out on the application of visual stimuli to evoke specific responses of the visual cortex. Ciganek (1961), amongst others, describes its morphology. In those years, unstructured light stimuli, usually stroboscopic light flashes, were applied. There was a great intraindividual and interindividual variability of the responses. For this reason light flash responses are of limited value for clinical purposes (Spehlmann, 1965).

Clinical applicability substantially increased in the 1970's when structured stimuli came into use. Halliday's report on delayed responses in optic neuritis, multiple sclerosis, and compressive lesions (Halliday et al, 1972, 1973; Halliday et al., 1976) greatly contributed to an increased interest in the VERs. Structured stimuli or pattern stimuli consist of black and white stripes (gratings) or blocks (checkerboards). The former are more suitable for basic research as relatively small responses are obtained. Blocks generally elicit larger responses and therefore are more often used as a clinical diagnostic aid. Waveform, amplitude and latency of the VERs to structured stimuli are less variable compared with those obtained by unstructured light stimuli. Further, they are more sensitive as was clearly shown, amongst others, by Halliday et al. (1972) and Wilson et al. (1980).

As responses to pattern stimuli contain contrast and contour components rather than a luminance component they also represent a more refined technique, provided the mean luminance of the pattern remains constant (Spekreijse, 1980).

Checkerboard stimuli are commonly applied as a pattern presentation stimulus or as a pattern reversal stimulus. In a pattern presentation stimulus the pattern is superimposed on a blank field for a short time. Initially this was achieved by placing a translucent checkerboard in front of a flashing stroboscope. One of the disadvantages of this method is the large luminance contribution to the responses as the mean luminance increases considerably during the pattern presentations. A constant mean luminance level can be obtained by TV—techniques, which also have the advantage of versatility as to check size and to the contrast between the light and dark checks (Arden & Faulkner, 1977). By means of a TV, both pattern presentation and pattern reversal stimuli can be made. The disadvantages of using TV—equipment are the low contour sharpness of the picture and the frame frequency, which may interfere with the response (Van Lith et al., 1979).

Another technique, especially applied for pattern reversal stimuli, is that of Cobb et al. (1967). They use a projector system with a checkerboard slide. A moving mirror in front of the projector accomplishes the reversal movement of the checks. The projector technique provides a sharper image than the TV—system. Further, the disadvantage of the latency variability due to TV frame frequency is avoided. One of the disadvantages of the projector system is that check size and contrast cannot easily be changed.

The technique using polaroid plates (Behrmann et al., 1972) is hardly used anymore as as it is cumbersome to vary check size and contrast.

Another stimulus technique is that of presenting one check (45') on a blank field.

Namerow & Enns (1972) and Hennerici et al. (1977) report better discrimination using this technique in diagnosing optic nerve lesions compared with the results using pattern stimulation. Foveal stimulation comprises a luminance stimulus on the fovea, more often used in the late sixties and early seventies (Arden & Bankes, 1966; Van Lith & Henkes, 1970). One major problem connected with this type of stimulation is, that in order to obtain a response, a good fixation by the patient is indispensable. The lack of this may make the examination impossible, especially in patients with a low visual acuity. Fixation is less of a problem with pattern stimulation since the stimulus field may subtend a much larger visual angle making fixation less critical.

In literature, most papers reporting on VERs in ON or in MS deal with pattern reversal VERs. Halliday et al. (1972) also applied this type of stimuli elicited by means of a projector system. Later, advantages of pattern presentation stimuli in detecting demyelinating lesions were described (Riemslag et al., 1982). For this reason both methods have been used in the present study and are here compared. Unstructured light flash stimulation was not used. In general, it can be said that, since the introduction of structured stimuli for clinical purposes, light flash stimulation is only indicated when medial opacities prevent the forming of a proper image on the retina and consequently no response is obtained, or when due to other reasons no pattern response can be detected.

Parameters in structured stimuli

With regard to pattern stimuli there are three important influences on the response to be discussed, namely check size, contrast and luminance.
In most studies, the largest response is evoked by checks with a size of 10' (minutes). Using the same TV–equipment as that of the present study, Bartl et al. (1978) found a maximum response with 20' or 40' checks. The larger the checks and the higher the contrast, the more the response becomes a luminance response. VERs elicited with small checks (20' or less) are chiefly contrast specific (Sokol, 1972; Regan, 1972).
In studies on MS and ON patients, check size ranged from 15' to 60'. In the present study check sizes of 10', 20', 40' and 80' size are used in pattern presentation and of 60' and 30' in pattern reversal.

When using a high luminance in patterned stimuli, the chance of luminance contamination increases. This is especially so in pattern presentation stimulation, where a homogenous field is presented between the checkerboard stimuli. By keeping the mean luminance of the patterned field and the homogenous field

equal this effect can be avoided. In reversal stimulation the chance of luminance contamination is less, due to the constant presence of the checkerboard. However, even if the mean luminance is kept constant, luminance components of the response can be caused by individual checks in the case where they are large and the contrast between them is high. Luminance changes not only influence the amplitude of the response (Spekreyse et al., 1973), but also have an effect on the latency (Cant et al., 1978; Diener, 1982).

Stimulus frequency

Both in pattern presentation and pattern reversal stimulation transient responses and steady state responses can be discerned (Regan, 1972).
Transient responses are elicited by stimuli which are sufficiently spaced in time for the system to be regarded as returning to a state of rest between successive stimuli. Responses are directly linked with a particular stimulus presentation. Conversely, steady state stimulation can be obtained by presenting stimuli with a frequency of 4 Hz or more. Thus no separate wave complex is obtained but responses to stimuli are fused together and become more sinusoidal. Responses can no longer be associated with any particular stimulus. The analysis of these curves requires a complicated analytical method (Fourier analysis). For this reason, in the present study, transient stimulation has been preferred to steady state stimulation.

Retinal localisation and stimulus field

VERs mainly represent the macular part of the retina (Van Lith & Henkes, 1970). This is due to the fact that the macula has a large anatomical representation on the posterior part of the occipital lobes, whereas the peripheral representation is localized on the medial surfaces of the lobes.
Nevertheless, even when the macula is stimulated, luminance responses contain a substantial contribution from the peripheral retina, due to the scattering of light. This effect can be avoided by using pattern stimuli with constant luminance.

The smaller the checks, the more the central part of the retina contributes to the response. Amongst the first to demonstrate this were Harter & White (1971). They observed that checks subtending less than 20′ of arc will evoke large VER when placed in the central 3° of the retina. Responses decreased when small checks were placed outside the central 3°.

The visual evoked response in optic neuritis

Most of the literature on VER in optic neuritis concerns pattern reversal responses. In the acute stage an attenuation of amplitude and an increase in latency are characteristic (table III.1). In a number of patients however the response may be completely absent. Halliday et al. (1972) report these abnormalities in 94% of their patients during the attack.

Although amplitude may be greatly reduced in the acute stage, a large interindividual and intraindividual variability makes it a less reliable parameter (Sharokki et al., 1978). Despite this variability, Halliday et al. (1972) and Milner et al. (1975) describe a correlation between amplitude and visual acuity.

As to latency, it may be prolonged in the acute stage and remain so after recovery of the visual acuity (Halliday et al., 1973; Bürki, 1981; Ladurner et al., 1983).

Author	Year	N	Abnormal
Halliday et al.	1972	18	94 %
Sharokhi et al.	1978	51	96
Wildberger et al.	1976	12	96
Wildberger et al.	1976	12	94

TABLE III.1 : PERCENTAGE OF ABNORMALITY IN PATTERN REVERSAL EVOKED RESPONSES IN PATIENTS WITH OPTIC NEURITIS. Characteristic changes include attenuation of amplitude and an increase in latency.

Little is known about the recovery of delayed responses in uncomplicated ON. Halliday et al. (1972) and Sharokhi et al. (1978) report respectively that latencies had returned to normal in 3% and 6% of the patients. Bynke et al. (1980) observed a normal latency in 12 out of 112 patients 2–8 years after the ON–attack. Matthews et al. (1977) found that latency had returned to normal within three months in six of the 28 eyes examined even in patients who suffered from an attack of ON during MS. Later, they report that a change in visual acuity was accompanied by an appropriate change in latency in 61% of the patients (Matthews & Small, 1979). Diener (1980) recorded the VER in the follow–up of MS patients with and without ON. He reports the greatest changes in possible MS patients with a history of ON. These changes included both improvement and impairment but improvement was the most common.

The visual evoked response in multiple sclerosis

The percentage of MS patients in whom the pattern reversal evoked responses are delayed varies greatly in the different studies. This is due both to the methods used and to the patient selection. Abnormalities due to demyelinational damage have been observed in a high percentage of patients who suffered from an attack of ON or experienced visual loss during the course of their disease (table III.2) ranging from 50–100%.

Author	Year	N	Definite MS	Probable MS	Possible MS	Total
Halliday et al.	1973	24	100 %	100 %	100 %	100 %
Asselman et al.	1975	15	100	100	100	100
Matthews et al.	1977	36	93	67	0	85
Zeese	1977	10	90			90
Sharokhi et al.	1978	62	90			90
Tackmann et al.	1979	31	95	50	100	92
Shibasaki & Kuroiwa	1982	27		93		93
Kjaer	1983	125	98	60	60	

TABLE III.2 : PERCENTAGE OF ABNORMAL PATTERN REVERSAL EVOKED RESPONSES IN PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS WITH A HISTORY OF VISUAL IMPAIRMENT. In those classified as definite MS patients the abnormality rate is highest.

In MS patients, whose visual acuity has not been affected by the disease so far, a delay may indicate subclinical affection of the optic nerve. Percentages in these patient groups range from 40–80%. Patients in whom the MS is diagnosed as definite have the highest rate of VER abnormalities (63–100%), whereas those in whom MS has been classified as probable show these abnormalities in 40–100% of the cases (table III.3).

Author	Year	N	Definite MS	Probable MS	Possible MS	Total
Halliday et al.	1973	27	94 %	100 %	83 %	93 %
Asselman et al.	1975	36	75	50	21	53
Lowitzsch et al.	1976	135	82	60	65	72
Hennerici et al.	1977	57	80	67	43	62
Zeese	1977	24	92			92
Sharokhi et al	1978	37	63	40	15	36
Tackmann	1979	29	100	40	30	52
Wilson & Keyser	1980	100	80			80

TABLE III.3 : PERCENTAGE OF ABNORMAL PATTERN REVERSAL EVOKED RESPONSES IN PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS WITHOUT A HISTORY OF VISUAL IMPAIRMENT. The abnormality rate increases as the disease progresses.

In conclusion it may be stated that responses obtained with pattern reversal stimuli tend to be abnormal in a higher percentage of the MS patients with clinical evidence of optic nerve involvement due to the disease. In patients without a history of visual impairment, the pattern reversal response is less often delayed, though this is not statistically significant. In the latter group, however, it may be a useful additional method for the confirmation of the diagnosis of multiple sclerosis.

In recent years attention has been turned towards the pattern presentation evoked response as a possible detector of VER changes in MS patients. Aminoff & Ochs (1981) compared pattern reversal and pattern presentation evoked responses in possible MS patients and report a higher detection rate in pattern presentation than in pattern reversal.

Riemslag et al. (1982) made the same comparison in a group of definite, probable, and possible MS patients and found a higher percentage of changes using the pattern presentation method, especially in the definite and probable group (table III.4).

Author	Year	N	Definite MS	Probable MS	Possible MS	Method
Aminoff & Ochs	1981	28			96% 75	presentation reversal
Riemslag et al.	1982	68 60	49% 63	60% 67	34 34	reversal presentation

TABLE III.4 : COMPARISON OF PATTERN PRESENTATION AND PATTERN REVERSAL IN LITERATURE IN PATIENTS WITH MULTIPLE SCLEROSIS. Both authors observed a higher diagnostic yield using the pattern presentation method.

Several authors have tried to asses other components of the pattern reversal VER in order to increase the diagnostic yield. Interocular differences in amplitude and latency, ratio of amplitude (affected eye divided by the fellow eye) and amplitude itself were used as means to detect abnormalities. Interocular difference in amplitude was used by Sharokhi et al. (1978) and Kupersmith et al. (1983). Sharokhi states that interocular difference in amplitude revealed pathology in only 1 out of 51 patients, whereas the latter found an abnormal amplitude in seven out of 24 patients (values ranging from 5 to 10 μV). Interocular difference in latency was applied by Asselman et al. (1975), Zeese (1977), Matthews et al. (1977), Hoeppner & Lolas (1978), Bürki (1981) and Kupersmith et al. (1983). The percentage of pathological responses thus obtained ranged from 14% (Asselman) to 67% (Kupersmith) using normal values ranging from 6 (Hoeppner & Lolas, 1981) to 10 ms (Bürki, 1981).

Interocular ratio (IOR) of amplitude was used by Tackmann et al. (1979), Bürki (1981) and Neima & Regan (1984), which revealed pathology in 8–27% of their patients (values ranging from 0.54 to 0.75; Bürki, 1981, Neima, 1984). Numerical changes in amplitude were used by Asselman et al. (1975), Matthews et al. (1977) and Wilson & Keyser (1980). They proved abnormal in 3–67%.

In conclusion one may say that a numerical delay in the response remains the most effective parameter for the assessment of a pathological response, together with an interocular difference in latency. Further, amplitude attenuation can be used.

The assessment of components other than latency requires statistical analysis of those of a control group in order to establish normal values as a basis for comparison with patient–group values.

Relation of the visual evoked response to other visual functions

Halliday et al. (1972) describe a correlation between amplitude and visual acuity in the recovery of ON patients, whereas Asselman et al. (1975) found no correlation. Diener (1980), however, could confirm Halliday's finding.

Several authors correlated visual acuity with latency and found significant correlations (Namerow & Enns, 1972; Regan et al., 1976). They, however, used different methods from those applied in this study (flash and steady state evoked responses, respectively).

VER and colour vision have been compared by Wildberger et al. (1976) in ON patients, both in the acute stage and in the recovery period. VER and colour vision were both disturbed in the acute stage but in the recovery stage the VER remained delayed whereas colour vision deficits disappeared. Rigolet et al. (1979) made the same comparison in MS patients and conclude that colour vision constitutes a good additional test for the detection of subclinical involvement of the optic nerve. Pinckers et al. (1982) confirm this finding by showing that the combination of VER and colour vision yields the highest percentage of abnormal results (80%). Results obtained with both tests (VER and colour vision) depend on the techniques used as these determine the sensitivity of the tests.

Differential diagnosis of delayed visual evoked responses

Delayed responses are by no means specific for ON and MS. They are also found in Leber's disease (Halliday et al., 1972) as well as in compressive lesions (Halliday et al., 1976; Van Lith et al., 1982). In these instances the final diagnosis has to be made by means of other clinical findings. Leber's disease is, as pointed out in chapter II, more common among young adults and is usually bilateral. Visual acuity remains low. When the history and clinical results do not show the typical findings of an attack of ON, such as an acute onset, a central scotoma and recovery within a few weeks to a month, delayed responses may point to a compressive lesion along the visual pathway. Visual field analysis and neurological examination may lead to the correct diagnosis.

Further, delayed responses are reported in glaucoma (Cappin & Nissim, 1975; Huber & Wagner, 1978), ischaemic neuropathy (Wilson, 1978; Brudet–Wickel & Van Lith, 1984) and diabetic neuropathy (Puvanendran et al., 1983). Special attention should be paid to the possible diagnosis of tilted disc syndrome (Wijngaarde & Van Lith, 1981).

Apart from ophthalmological purposes, the VER can serve in the diagnosis of neurological lesions. Prechiasmatic and chiasmatic processes (Halliday, 1976, Van Lith et al., 1982) can be detected by means of the VER. VER changes in this type of affection of the visual pathway are best revealed by half field pattern stimulation and placing electrodes 5 and 10 cm to the left and right of the midoccipital electrode. Characteristic abnormal responses include very low amplitude or absent transient VERs after stimulation of the affected hemifield. Furthermore, abnormal lateral and midoccipital ratios are reported.

There is still controversy on the detection of retrochiasmatic lesions with the VER (Blumhardt et al., 1977; Kuroiwa & Celesia, 1981; Van Lith et al., 1982).

Typical neurological diseases in which a change in VER has been reported include hemiparkinsonism, Charcot Marie Tooth disease and Friedreich's ataxia amongst others. In hemiparkinsonism (Mintz et al.,1981) the VER showed an increase of latency and reduced amplitudes on top of the physiological changes of old age. Study of the VER abnormality in Charcot–Marie–Tooth's disease (CMTD) and Friedreich's ataxia revealed an higher percentage of abnormal responses in patients with Friedreich's ataxia (Carroll et al., 1983; Nuwer et al., 1983; Ghezzi & Montanini, 1985). In CMTD, optic atrophy is a rare feature, so VER changes in CMTD represent additional evidence that central pathways may be involved in this principally peripheral nerve system disorder (Bird & Griep, 1981). VER changes have also been reported in Huntington's disease (Ellenberger et al., 1978), Creutzfeldt–Jakob's disease and epileptic disorders of the brain.

SUMMARY CHAPTER III

Since Caton published on electric activity of the brain in 1875, the visual evoked response has evolved into a clinically applicable method through the improvement of recording techniques (amplifiers, superimposition –Dawson– and, lastly, averagers) and stimulation methods.

The visual evoked response is the cortical potential produced in reaction to light stimuli on the eye. These stimuli may be unstructured or structured. Unstructured stimuli are less sensitive due to the great intraindividual and interindividual variability of the response obtained. Of the structured stimuli, checkerboard patterns are now widely used in clinical practice.

In the present study, the use of pattern presentation stimuli obtained by the use of a TV–equipment and pattern reversal by a mirror–projector system was preferred. The advantage gained over other methods by using the former lies in its great versatility, whilst the latter because of its short reversal movement excludes the problems encountered in TV.

During optic neuritis, changes in pattern reversal visual evoked responses include amplitude attenuation and delay in response. The former disappears as visual acuity recovers, the latter condition may persist. In multiple sclerosis patients, depending on the severity of the disease, the latency in pattern reversal evoked responses is abnormal in a large percentage. In those whose history of disease shows involvement of the visual system by the disease and those who are in the 'definite' stage, the highest percentage of delayed responses can be found.

Recently, pattern presentation evoked responses have been used in multiple sclerosis patients, showing a higher percentage of abnormal latencies.

Most authors used latency of the response as a measure of pathology. Changes in amplitude and interocular differences in amplitude and latency were also assessed. Assessment of latency proved most effective in detecting pathology. A relation between visual acuity and amplitude has been described.

A delay in the visual evoked response is also found in a large range of other ophthalmological and neurological affections for example Leber's disease, amblyopia, lesions of the optic chiasm, Parkinsonism, Charcot–Marie–Tooth's disease and Friedreich's ataxia.

It's light that makes the intervals
between the pyramides so large,
and shows them fair against the dark,
light that compels
the yellow bird to show its colour.
Light not as to me;
Let me change to blue,
Or throw a violet shadow where I will....

Dylan Thomas

CHAPTER IV

AUXILIARY METHODS IN THE DIAGNOSIS
OF VISUAL LOSS AFTER OPTIC NEURITIS

Introduction: hidden visual loss

It is a well-known feature of ON (whether its occurrence is isolated or appears during the course of MS) that although visual acuity, as measured by Snellen charts, may recover after the acute stage of the attack, the sight in the previously affected eye remains subjectively different from that in the unaffected fellow eye.

In clinical practice the determination of visual acuity, however, relies almost entirely on the use of Snellen charts or similar methods, in which the letters are in high contrast with their background and further, their sizes diminish from line to line so as to present a progressively smaller angle to the eye. Visual acuity as determined by means of these charts may be 1.0 (Snellen) or even higher either during or after the attack.

In order to detect subjective abnormalities reported by the patients after clinical recovery of visual acuity, regular psychophysical tests such as those for colour vision are available. Apart from these, new tests have been developed. The new tests include visual perceptive delay measurement, such as delay campimetry and critical flicker fusion frequency. In addition, a contrast sensitivity function test may reveal a relative insensitivity of the eye to objects of low contrast.

Hidden visual loss may be a symptom of permanent damage to the optic nerve and may therefore prove useful as an aid towards an early diagnosis of MS.

Colour vision and hidden visual loss

Burde & Gallin (1975) studied colour vision (CV) in recovered ON patients and observed colour vision deficits in one third of the patients, a percentage confirmed by Barber & Galloway (1977). In both studies the 100 Hue tests (as described by Farnsworth) were used. Barber also included in his study the results of VER and concludes that both methods are required to obtain a most accurate diagnosis. All ON patients had a visual acuity of 6/6 or more in the affected eye.

Apart from abnormalities of colour vision in ON, colour vision may also be impaired in MS patients (table IV.1). Rigolet et al. (1979) report a dyschromatopsia in 35% of 75 MS patients without a history of ON.

Author	Year	N	Colour test	Deficit	Nature
Burde & Gallin	1975	9 ON	Farnsworth 100 Hue	33 %	pro and/or deutan
Wildberger et al.	1976	20 ON (acute)	Farnsworth 100 Hue Panel D15	30 15	not mentioned ,,
Barber & Galloway	1977	30 ON	Farnsworth 100 Hue	20	,,
Griffin & Wray	1978	20 ON	Farnsworth 100 Hue Ishihara	100 61	,,
Rigolet et al.	1979	102 ON–MS	Farnsworth 100 Hue HRR	41 10	pro and deutan tritan/non–defined
Pinckers et al.	1983	210 MS (eyes)	Farnsworth 100 Hue	64	non–defined

TABLE IV.1 : COLOUR VISION DEFICITS IN PATIENTS AFTER OPTIC NEURITIS AND WITH MULTIPLE SCLEROSIS. Most studies used the Farnsworth 100 Hue test and pro/deutan deficits were most frequently obtained.

In a study of 226 subjects suffering from demyelinating disease, Pinckers & Verriest (1982) show that in MS a red–green colour vision deficit is frequent even when visual acuity is intact. In 1983 Pinckers et al. performed a study of colour vision in 109 patients with possible and probable demyelinating disease. Colour vision was abnormal in 64% of the cases. Combination of VER and colour vision yielded the highest number of abnormal results: 79%. The study of colour vision may therefore be useful in the study of anterior optic track lesions and reveal changes additional to those revealed by VER.

Visual perceptive delay measurement

One aspect of hidden visual loss is a delay in visual perception. This may be detected by delay campimetry as described by Regan et al. (1976). The method is based on the observation that a rise in the intensity of a light is not perceived by a subject until some time later. In practice, this is achieved by progressively shortening the interval between the setting on of two lamps. MS and ON patients can only detect a difference between the setting on of two lamps at a significantly longer interval than normal subjects (table IV.2).

Another method of detecting a visual perceptive delay is the critical flicker fusion frequency. In this method, the frequency of the flickering of a light is increased until the subject fails to perceive the consecutive light stimuli as separate. Galvin et al. (1976) reported this abnormality to be a persistent one, present for up to five years after visual acuity had returned to normal.

The neuronal basis for delay in perception has been sought in the observation that experimental demyelination in animals can reduce the maximum firing frequency of nerve axons (McDonald & Sears, 1970).

Author	Year	N	Isolated ON	ON–MS	MS	Method
Heron et al.	1974	12	100 %	100 %		delay campimetry
Galvin et al.	1976	14	100	83		CFF
			25	33		delay campimetry
Regan et al.	1976	33		100	63 %	delay campimetry
Salmi	1985	20	46		71	CFF

TABLE IV.2 : ABNORMAL DELAY CAMPIMETRY AND CRITICAL FLICKER FUSION IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS PATIENTS. Both methods are most effective in patients with a history of visual impairment.

Although both diagnostic methods used reveal a high incidence of abnormality in those who suffered from ON, either during MS or isolated from the disease, this is not true for MS patients without visual symptoms (Regan et al., 1976; Salmi, 1985). Comparison of the VER with CFF revealed that the VER is a more sensitive method for the detection of abnormalities in both patients suffering from ON and MS.

Contrast sensitivity function in optic neuritis and multiple sclerosis

Visual acuity, as measured by Snellen charts, is largely dependant on the degree of detail perception at high contrast levels (almost 100%). Contrast sensitivity function, however, measures the degree of detail perception in combination with the perception of contrast. The former is expressed as the spatial frequency (number of bright plus dark bars per cm on the screen or per degree of subtended visual angle). From physiological studies there is evidence that the visual system may contain channels for high, low and intermediate frequencies (Campbell & Maffei, 1970). This opens up the possibility that different channels may be affected in various disorders of the visual system.

In the course of the last decade several authors carried out studies on contrast sensitivity function. Most, however, based their studies on small groups, or made use of special scales, thereby making the description of frequency abnormalities more difficult. Sinewave gratings proved to be most accurate in clinical application (table IV.3).
In the acute stage of ON all frequencies may be depressed (Frisén & Sjostrand, 1978; Zimmern et al., 1979). In other studies intermediate frequencies appear to be most often affected (Regan et al., 1982).
Several authors compared VER and contrast sensitivity function. Arden & Gucukoglu (1978) conclude that the results obtained by both investigations are comparable, combination revealing the highest percentage of abnormalities in ON patients. Bürki (1981) reports an equal percentage of abnormality revealed when using both methods in both ON and MS patients. Neima & Regan (1984) show a relationship between VER and contrast sensitivity function. They observed that the loss of all spatial frequency functions was correlated with an attenuation of both large and small check VER. The disease that depressed contrast sensitivity function for high spatial frequencies was associated with depressed visual acuity and attenuated small check VER.

Electroretinogram in patients with multiple sclerosis and optic neuritis

In ON and MS patients, although not a psychophysical method for detecting hidden visual loss, an abnormal electroretinogram may be indicative of permanent neuronal loss on the retinal level.

Author	Year	N	Isolated ON	ON–MS	MS	Visual Symptoms	Method used	Frequency depressed
Regan et al.	1977	48			42 %	16 %	Sinewave	medium low medium&high
Frisén & Sjostrand	1978	9	100 %			100	Sinewave	all
Arden & Guçukoglu	1978	57	82	86 %			Arden scale	
Zimmern et al.	1979	8		100		–	Sinewave	all
Bürki	1981	34	63	73			Arden scale	
Regan et al.	1982	10			70	–	Sinewave	medium&low

TABLE IV.3 : PERCENTAGE OF CONTRAST SENSITIVITY ABNORMALITIES IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS ASSESSED WITH VARIOUS METHODS. Sinewave gratings revealing the highest percentage of abnormality in patients with visual complaints.

Author	Year	N	ON	Definite MS	Probable MS	Possible MS	MS without visual symptoms	Method used
Ellen—berger & Ziegler	1977	49			56 %		14 %	Static& Dynamic
Patterson & Heron	1980	54	92 %	100 %	91	81 %	75	Dynamic
Van Dalen & Greve	1981	74		86			73	Static
Meienberg et al.	1982	14		79			86	Static
D'Cruz & Ellenberger	1983	53	36–61					Dynamic

TABLE IV.4 : VISUAL FIELD DEFECTS IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS. Visual field defects are observed in 14–75% of the multiple sclerosis patients without visual symptoms whereas the number of abnormalities increase up to 100% in those with a history of visual impairment.

Halliday et al. (1972) observed that flash ERG in ON patients was not affected by the disease. This finding was confirmed by Fiorentini et al. (1981). Consequently, as the various components of the ERG originate in the receptor layer, the inner nuclear layer, and the pigment epithelium, these appear not to be affected by demyelinative disorders (Armington, 1974).

The pattern ERG (PERG), however, probably has a different origin. Experiments in cats have shown that integrity of the ganglion cells is necessary for the generation of pattern reversal and gratings ERG (Maffei & Fiorentini, 1981). Although the ganglion cells may not be the actual site of PERG generation, their normal function seems essential for its production. The amplitude in PERG may be attenuated by glaucoma, toxic and traumatic optic atrophy (Arden & Vaegan–Hogg, 1982) and macular abnormalities (Kirkham & Coupland, 1981). In a large group of glaucoma patients Van Lith et al.(1984) observed that the PERG was already disturbed in an early stage.

Bobak et al. (1983) and Kirkham & Coupland (1983) report that PERGs appear to be normal in both ON and MS patients. Bobak et al. (1983) suggest that PERG is more useful in evaluating glaucomatous (axonal) optic nerve disease than in diagnosing demyelination.

Visual field defects in patients with multiple sclerosis and optic neuritis

Several authors have studied visual field defects in MS patients with and without a history of visual disturbances (table IV.4). Several authors report that kinetic perimetry may not reveal defects (D'Cruz et al.1983) whereas with static perimetry small defects or a relative defect can frequently be detected (Ellenberger & Ziegler, 1977; Van Dalen & Greve, 1981; D'Cruz et al., 1983).

The highest abnormality rate is found in patients with definite MS (86–100%) and a history of visual symptoms. Yet even in those patients who did not have any visual complaints, 14–75% show defects in perimetry, depending on the method used. The defects most frequently encountered include patchy relative defects in the intermediate field (Van Dalen & Greve, 1981), absolute centrocoecal scotomas (D'Cruz et al., 1983), central and paracentral scotoma (Van Dalen & Greve, 1981)

Ellenberger & Ziegler (1977) compared flash evoked responses with static perimetry and concluded that evoked responses reveal a more accurate evidence of former affection of the eye or asymptomatic lesions in MS patients. A comparison of VER and visual field analysis showed a discrepancy between latency abnormality and defects in the visual field, which might be due to the other part of the visual field analysed (Van Dalen & Greve, 1981). This has also been observed by Meienberg et al. (1982).

SUMMARY CHAPTER IV

Hidden visual loss, i.e. loss of visual acuity not revealed by Snellen charts, can be detected by using a number of methods. Hidden visual loss may be a sign of permanent damage to the optic nerve. In literature several psychophysical methods have been applied to detect this damage.

Colour vision tests may reveal hidden visual loss in 64% of the patients, whereas in patients after ON up to 100% abnormality has been found. Contrast sensitivity function may be disturbed in 42% of the patients suffering from MS. When the test was used on patients after an attack of optic neuritis contrast sensitivity function (CSF) has been reported to be impaired in 63–100%. As CSF records the loss of contrast and detail perception in the eye, it is an extension of visual acuity as measured with Snellen or similar high contrasted charts. Visual field defects are reported in 14–75% of MS patients without a history of visual involvement. For the evaluation of impairment after ON, the method is useful in 61–92%.

The recording of pattern electroretinograms has been reported to be of no use in demyelinating disease.

CHAPTER V

METHODOLOGY OF THE PRESENT STUDY

Choice of method: visual evoked responses

For pattern reversal stimulation both the projector system and the TV set can be used. Technically, however, the projector system has certain advantages over the TV set. In the former system the latency is determined by the rotating speed of the mirror, this usually being 5 ms. The reversal movement of the TV screen, however, lasts 20 ms and is not carried out simultaneously, but is produced sequentially on the screen.

VERs, and especially those produced by pattern stimulation, are predominantly mediated by the central retinal cones and thus by a much smaller area than the psychophysical visual field. The combination of a limited visual field and a sequential reversal movement of 20 ms of the TV screen explains the large standard error of VER latencies in the TV pattern reversal (Van Lith et al., 1978). Consequently in this study pattern reversal stimulation by projector was preferred to pattern reversal by television.

In pattern presentation, the TV was used because of its greater versatility with respect to check size, contrast, and luminance.

Method of pattern presentation and pattern reversal evoked responses

For the pattern presentation examination the patient was seated 1.75 meters away from a TV set, subtending a visual angle of 16°. A checkerboard pattern with variable check size and modulation depth was presented during 39 ms with a frequency of 2 Hz, leaving a blank field with a luminance of 140 asb* The mean luminance during stimulation was held constant. Several combinations of check size and contrast were used. Responses were elicited by 80' checks at 80% contrast, 40' checks at 40% contrast, 20' checks at 20% contrast, 10' checks at 10% contrast and 10' checks at 5% contrast. The stimulus was locked to the frame frequency.

For the pattern reversal stimulation the patient was seated 1 meter away from a translucent screen subtending a visual angle of 30°. A slide with a black—and--white checkerboard pattern was projected on the screen. The fast reversal movement resulted from an electromagnetically actuated mirror (Cobb et al., 1967). The individual squares subtended 1° or 0.5°. The squares of 1° were presented at two mean luminance levels, 400 and 40 asb; the squares with the size of 0.5° were presented at a luminance level of 40 asb only. The modulation

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* 1 candela/m^2 = π asb

depth was approximately 80%. The stimulus frequency was 1 Hz (i.e. 2 reversals/s).

In both methods the patient was asked to look at a fixation spot in the centre of the stimulus field. The responses were led off from silver–silverchloride electrodes fixed to the scalp with collodium. According to Halliday's method two occipital electrodes were placed 2.5 cm and 5 cm above the inion (external occipital protuberance). A midfrontal electrode 12 cm above the nasion served as a reference electrode. This resulted in two derivations; the first of the electrode 2.5 cm above the inion to the one 12 cm above the nasion and the second of the electrode 5 cm above the inion to the one 12 cm above the nasion. The ground electrode was attached to the earlobe.
The band width of the amplifiers was 0.166 to 70 Hz. One hundred and twenty eight responses of both methods were usually averaged. The output was led simultaneously into an oscilloscope and a minicomputer with a sweep time of 500 ms and a sampling rate of 3.9 ms respectively. Using this technique, responses of 3 μV or less could not be discerned from the noise level. The VER thus obtained was recorded on a X–Y plotter.

PATTERN PRESENTATION

80' 80%

40' 40%

20' 20%

10' 10%

PATTERN REVERSAL

1° 400 asb en 1° 40 asb

0.5° 40 asb

Colour vision tests: American Optical Hardy Rand & Rittler and Panel D15 desaturated

In fig.V.1 the scoreform of the Hardy Rand and Rittler test (HRR) is presented. On the left of each row the screening pages are shown. Figures read correctly are indicated by a plus sign, figures not read by a minus sign. Results are coded according to François & Verriest (1957).

FIGURE V.1 : SCOREFORM OF THE HARDY RAND & RITTLER TEST.

The Panel D15 desaturated colour vision test consists of 15 coloured knobs and a reference knob. The patient has to select the knobs in a sequence starting with the reference knob.

Pattern electroretinogram

Pattern electroretinogram (PERG) was obtained by using a checkerboard pattern reversal consisting of 1° checks with a contrast of 80% according to the method described by Arden et al., 1977. The response is recorded using goldfoil electrodes folded over the lower eyelid directly under the pupil and taped to the skin, after instillation of 1 drop of Novesine (0.2%) into the eye. Both monocular and binocular stimulation were performed. After amplification with a bandwidth of 3.3–70 Hz a 100 responses were averaged and recorded on an X–Y plotter.
The morphology of the response is presented in figure V.2. Usually a positive peak can be discerned around 50 ms after the stimulus.
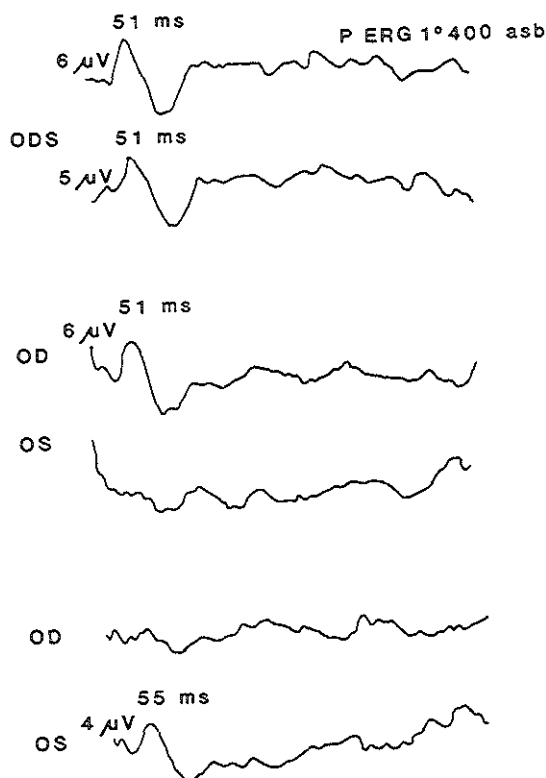
FIGURE V.2 : MORPHOLOGY OF THE RESPONSE OBTAINED WITH PATTERN ELECTRORETINOGRAM. At 45–55 ms a positive peak can be discerned.

Contrast sensitivity function

In order to obtain the contrast sensitivity function curve of each patient an automated system was used. A vertical sinusoidal grating was presented and the patient varied the contrast according to a modified Von Békésy tracking method (1947). By this method a threshold was determined for a range of spatial frequencies (0.1 to 25.6 cycles/degree) in each patient for optimal refraction. A detailed description is published by Keemink et al. (1979).

A normal modulation transfer curve (MTF) is obtained by point–by–point averaging of individual curves of 24 normal eyes. An abnormal contrast sensitivity function is defined as the normal contrast sensitivity function curve after subtracting twice the value of the standard deviation. In figure V.3 the normal curve is shown including the 2.5 SD curve for normal values.
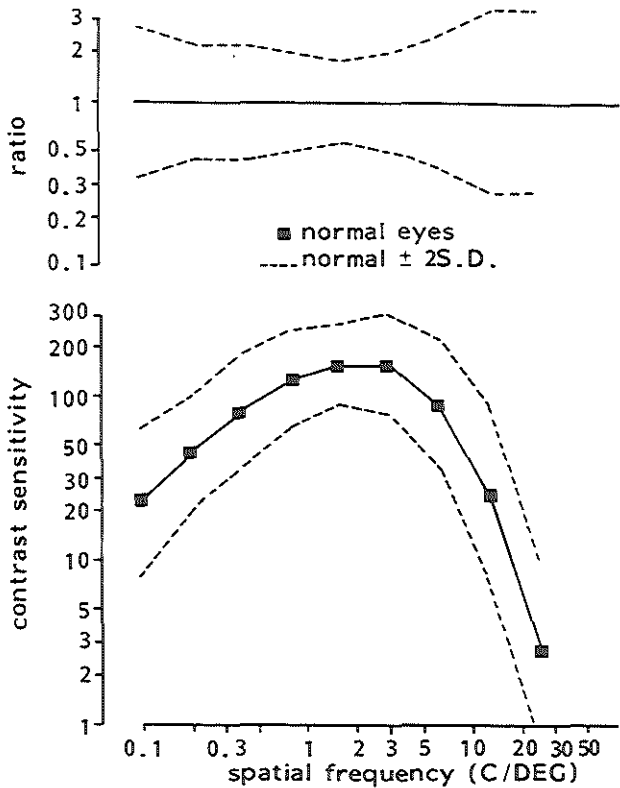
FIGURE V.3 : CURVE OF NORMAL CONTRAST SENSITIVITY FUNCTION. Note the low and high frequency cut–off. The high frequency cut–off is correlated with visual acuity as measured by Snellen.

Perimetry

Contrary to the kinetic method used in the acute stage (Goldmann perimeter), a static perimeter was used to detect any visual field defects in patients after an attack of optic neuritis. Static perimetry is a more accurate method of detecting relative and small paracentral or central scotomas. For this purpose a static computer perimeter 'OCTOPUS' was available.

A screening programme (no.3) was chosen which could distinguish between normal sensitivity, a relative scotoma or absolute scotoma by presenting light points at two levels of light intensity to the eye. In this way 130 points were screened, within 30° of the visual field.

Statistical methods

Correlations in $2 \times r$ tables at the first and second examination were assessed by X^2 tests. Non–parametric tests such as Spearman's, Kendall's and Kruskal–Wallis' tests were used for the correlation of clinical features versus age and visual acuity.

For the 2×2 tables Fisher's exact test was used.

CHAPTER VI

PATIENT SELECTION AND CONTROL GROUP

Patient selection for first examination

Two hundred and eighty two patients were selected from the referrals to the electrodiagnostic department of the Eye Hospital, Rotterdam. These patients, suspected of ON in one or both eyes, were referred by ophthalmologists. Abnormalities of media and fundus as the cause of acute visual loss in these patients had already been excluded by careful clinical examination. Further, other lesions of the conductive system as Leber's disease, compression and toxic neuropathy were excluded as far as could be ascertained by history taking and clinical examination. Thus 282 patients were selected.

In 28 patients the cause of the acute diminishment of visual acuity was found during electrophysiological examination and clinical follow—up (table VI.1).

Clinical and electrophysiological data on 46 patients were insufficient. Only one VER method had been used in the case of 30 others. For these reasons both groups were excluded from the present study. The diagnosis of ON remained uncertain in the case of a number of patients (28) and this group was also excluded. Forty—three patients in whom MS had already been diagnosed were also rejected.

Patients referred to the electrodiagnostic department, suspected of an optic neuritis in one or both eyes		282
Patients with clinical & electrophysiological unilateral optic neuritis		110
Patients with bilateral optic neuritis		5
Patients with already diagnosed MS before ON		43
Patients with other causes of lowered visual acuity		28
—Intoxication	3	
—Infection	3	
—Leber's disease	1	
—Vascular	5	
—Myelitis transversa	2	
—Tumor optic nerve	5	
—Refractive	4	
—Psychogenetic	5	
Patients with insufficient clinical & electrophysiological data		37
Patients on whom only one VER method was performed		30
Patients for whom the diagnosis ON remained uncertain		28
Patient who died shortly after the VER recording		1

TABLE VI.1 : PATIENT SELECTION FOR FIRST EXAMINATION

The patient group thus selected for this study consisted of 115 patients on whom tests were carried out using the two VER methods and of whom clinical data (Snellen visual acuity, funduscopy and Goldmann perimetry) of the acute stage of the ON were available. In 5 out of these 115 patients bilateral involvement had been found. For statistical reasons this group was not included in further analysis.

Patient selection for reexamination

For reexamination, 80 patients who had first been seen between 1980 and 1983, were contacted by phone or letter. Their general practitioner (GP) also received a letter asking his consent to further examination of his patient.
In the case of six of these patients (8%) the GP refused his consent. Thirteen patients (16%) were, for various reasons, not willing to participate (time, fear of results, absence of symptoms, occupation). Additionally, one patient had died (1%) and seven could not be traced (9%).
Thus, 53 (66%) were available for reexamination, which included repeating the VER. Visual function in these patients was assessed by means of psychophysical methods such as colour vision tests, perimetry and contrast sensitivity function tests. Visual acuity was measured using Landolt rings and Snellen charts. All patients were examined by a neurologist.

Control group

An age matched group of 47 normal subjects, healthy volunteers, was recruited from hospital staff. The volunteers were submitted to both pattern presentation and pattern reversal stimulus examination. As a visual acuity of 1.00 (measured by Snellen charts) was a criterion for selection, the visual acuity of all subjects was recorded. Both examinations were performed by a professional technician, under the same circumstances as for the patient group.

A process in the eye forewarns
The bones of blindness.....

Dylan Thomas

CHAPTER VII

CLINICAL FEATURES OF 110 PATIENTS
WITH UNILATERAL OPTIC NEURITIS

The epidemiological and ophthalmological features of 110 patients at the time of the first unilateral ON attack and after improvement were evaluated. In addition 17 of these patients, who afterwards suffered from a second attack, were reexamined. Only that data showing significant statistical differences from that obtained at the time of the first attack of ON will be described.

Epidemiology

All patients were seen 0–4 weeks after the onset of ON. At the first attack of ON, 76% percent of the patients were female, at the second attack this percentage was 88 (15 out of 17). In table VII.1 the age distribution of the patients at the first and the recurrent ON is shown. This distribution appeared to differ statistically significantly for the number of patients who suffered a second attack of ON between 41 and 50 years only (Fisher's exact test, P<0.03). The ages ranged from 12–66 years at the time of the first attack, the majority of patients being between 20 and 40 years of age (71 %). At the time of the second attack only 47% were of this age.

AGE	FIRST ATTACK N=110	SECOND ATTACK N=17
< 20	5 %	
20–30	38	35 %
31–40	35	12
41–50	14	41 P<0.03
> 50	8	12

TABLE VII.1 : AGE DISTRIBUTION AT FIRST AND SECOND ATTACK OF OPTIC NEURITIS. Most patients suffered from an attack between 20 and 40 years of age.

Male patients did not experience a first ON attack before the age of twenty contrary to 10% of the female patients. The difference in the age distribution between males and females, however, was not statistically significant (Wilcoxon test).

Onset of ON was most frequently seen in the months January, June and July (table VII.2; 42% of the patients). In respect to the second attack an increase in frequency was also seen in the month of January.

MONTH	FIRST ATTACK N=110	SECOND ATTACK N=17
January	16 %	29 %
February	5	
March	2	12
April	9	
May	8	6
June	11	12
July	15	
August	7	12
September	8	
October	6	29
November	7	
December	6	

TABLE VII.2 : MONTH OF ONSET OF FIRST AND SECOND ATTACK OF OPTIC NEURITIS. The onset of the first attack was most frequently seen in January, June and July. In respect to the second attack an increase in frequency was also seen in the month of January.

A single recurrence of ON was seen in 13 patients, two patients suffered from ON three times, another two four times. In 10 patients ON recurred in the homolateral eye, whereas in seven it recurred in the contralateral eye. The majority of the patients experienced a second attack within 10 years after the first attack of ON.

Ophthalmological features

Seventy–eight percent of the patients complained of blurred vision at the time of the first attack. Other complaints included patches (8%) or lines (4%) in the visual field. These data were not evaluated for the second attack. Painful eye movements were reported by 55% of the patients at the first ON attack.

On examination, visual acuity was less than 1/60 in 36%, visual acuity of 1 or more was found in only 3% of the affected eyes (table VII.3).

Funduscopy (table VII.4) revealed among other findings a normal optic disc in 55%, disc edema was noted in 19%. Pallor of the disc, denoting atrophy of the optic nerve, and usually seen after recurrent visual damage in MS, had already been found in 12%. In recurrent ON patients, it was seen considerably more often (7 out 17, Fisher's exact test, P<0.02).

SNELLEN	FIRST ATTACK N=110	SECOND ATTACK N=17
<0.02	36 %	5 % P<0.02
0.02–0.06	12	4
0.07–0.10	10	4
0.11–0.25	18	47 P<0.03
0.26–0.50	11	41 P<0.01
0.51–0.99	9	
> 1.00	3	

TABLE VII . 3 : VISUAL ACUITY IN THE AFFECTED EYE IN FIRST AND SECOND ATTACK OF OPTIC NEURITIS. Visual acuity of 0.1 or less was found in 58%. At the time of the second attack, 88% of the patients had visual acuity between 0.1 and 0.5.

FUNDUSCOPY	FIRST ATTACK N=110	SECOND ATTACK N=17
Normal disc	55 %	41 %
Blurred disc	30	18
Pallor	12	41 P<0.02
Unknown	3	

TABLE VII.4 : FUNDUSCOPY IN FIRST AND SECOND OPTIC NEURITIS. Note the high percentage of patients in whom disc pallor was observed at the time of the second attack.

A Marcus Gunn phenomenon could be elicited in 55% of the patients, yet it was not listed in 30% of the patient group at the time of the first ON attack. Visual field defects, studied by Goldmann perimetry, revealed a central scotoma in 66% (table VII.5). Another 14% had an enlarged blind spot or quadrant anopsia. In only 4% of the patients could no field defects be found. The defects observed during the first and the second attack of optic neuritis appeared not to be different.

VISUAL FIELD DEFECT	FIRST ATTACK N=110	SECOND ATTACK N=17
Central scotoma	66 %	53 %
Non–typical defect	14	12
Normal	4	12
Unknown	16	23

TABLE VII.5 : VISUAL FIELD ANALYSIS IN OPTIC NEURITIS. A central scotoma was found in the majority of the patients in both attacks.

Short—term prognosis of optic neuritis

Visual acuity after the first attack of ON improved to 1.00 (Snellen) in 55% of the patients (table VII.6). It remained lower than 0.1 in 4%, and less than 0.5 in only 14%. After the second attack, visual acuity recovered completely (Snellen 1.00 or more) in only 23% (Fisher's exact test, P<0.03).

SNELLEN	FIRST ATTACK N=110	SECOND ATTACK N=17
< 0.10	4 %	
0.11–0.40	10	18 %
0.50–0.90	24	47
> 1.00	55	23 P<0.03
Unknown	7	12

TABLE VII.6 : VISUAL ACUITY AFTER MAXIMAL IMPROVEMENT AFTER FIRST AND SECOND ATTACK OF OPTIC NEURITIS. In 55% of the patients visual acuity recovered to 1.00 or more after the first attack, compared with 23% after the second attack.

Improvement to a certain level usually occurred within 4 weeks after the patient was first seen (47%), table VII.7. After the second attack, visual acuity usually improved within a few days (47%; Fisher's exact test, P<0.001).

DURATION OF IMPROVEMENT	FIRST ATTACK N=110	SECOND ATTACK N=17
Within a few days	7 %	47 % P<0.001
1– 4 weeks	40	23
1– 3 months	18	12
4–12 months	15	
> 1 year	12	
No data	8	18

TABLE VII.7 : DURATION OF VISUAL IMPROVEMENT AFTER OPTIC NEURITIS. Note that symptoms usually subsided within a few days after the second attack, whereas in the first attack 47% subjectively improved within a month.

Statistical analysis

No statistically significant correlation could be found between the clinical parameters such as visual acuity, painful eye movements, visual field defects, funduscopy and Marcus Gunn phenomenon. Clinical parameters and visual acuity were not related (non—parametric tests: Spearman, Kendall, Kruskal–Wallis test).

During the acute stage of ON no relation could be found between the degree of visual loss on the one hand and age or sex on the other. After the acute attack, improvement of visual acuity was seen less in men to a statistically significant degree (X^2 9.15; 1 df, P<0.001). Further, pain experienced during the attack was more often mentioned by female patients (not statistically significant).

There was a statistical correlation between visual acuity in the acute stage of the first attack of ON and visual acuity after improvement (R 0.21, P<0.05). This means that a low visual acuity at the start of an ON attack is a bad prognostical sign for its eventual outcome. Another statistically significant relation was found between visual acuity at the time of the first attack and that at the time of the second attack (Spearman correlation R 0.60, P<0.03).

Figure VII.1 shows a number of characteristic features of ON which were common to a number of patients.

Central Scotoma	77					T = 77 (66%)
Fundus Normal	42	18				T = 60 (55%)
M Gunn	21	19	9	12		T = 61 (55%)
Pain	17	14	6	7	17	T = 61 (55%)

T = total
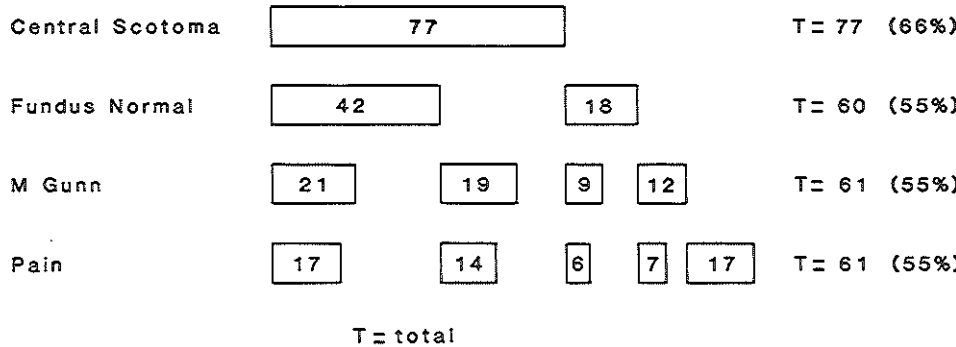
FIGURE VII.1 : CHARACTERISTICS OF 110 PATIENTS WITH OPTIC NEURITIS. Note that in only 17 (15%) all characteristics of an optic neuritis (central scotoma, normal optic disc, M.Gunn phenomenon and painful eye movements) were found.

SUMMARY CHAPTER VII

Seventy–six percent of the group of 110 idiopathic ON patients seen at the time of the first attack were female. Almost 90% of them suffered from their first attack when they were between 20 and 50 years of age. In the months January, June and July a relatively high percentage of the patients had suffered from an ON attack. Recurrence of the attack was seen in 16% and had generally occurred within 10 years.

Of the patients studied 78% complained of blurred vision and 60% reported painful eye movements. In 88% of the patients visual acuity was 0.5 (Snellen) or less, whilst in 58% it was even less than 0.1. Funduscopy revealed no abnormalities in 55%; disc edema or disc pallor was observed in 33% and 12%, respectively. Disc pallor was found more at recurrence of the ON. Field defects consisted of a central scotoma in 66%, whereas a non–typical defect was found in 14%. This finding was confirmed on examination at the time of the second attack.

The good short–term prognosis was confirmed by reported subjective improvement of visual acuity in 47% within a month and recovery of visual acuity to 1.00 or more in 55% of the patients.

Statistical analysis showed that a low visual acuity during the acute stage of the first attack is a bad prognostical sign as to its eventual outcome and the severity of visual loss on a second attack.

CHAPTER VIII

COMPARISON OF PATTERN PRESENTATION AND PATTERN REVERSAL EVOKED RESPONSES IN THE DIAGNOSIS OF OPTIC NEURITIS

Introduction

Both pattern presentation and pattern reversal evoked responses of all patients were recorded during the acute stage of the ON attack. In the pattern presentation (PP) method amplitude and latency were measured of responses obtained with four different combinations of check size and contrast. Pattern reversal evoked responses (PR) were recorded for 1° and 0.5° check size and for the one degree checks at two luminance levels.

Morphology of the pattern evoked response in normals

A response, obtained by pattern presentation stimuli, consists of a waveform in which one or two peaks can be discerned. The first peak, denoted PP100, appears around 100 ms after the stimulus; the major PP160 peak is seen about 160–180 ms after onset of the stimulus. Both have a positive deflection.
Pattern reversal evoked responses contain a major positive peak at about 100 ms, usually denoted PR100 (figure VIII.1).
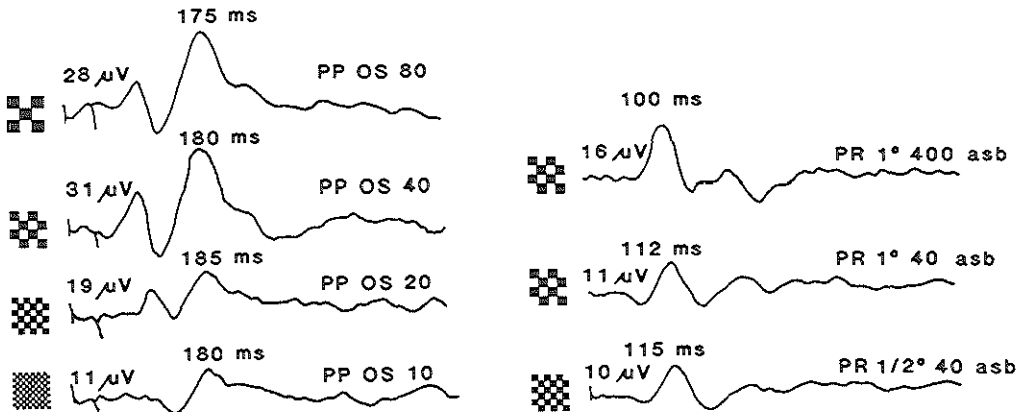
FIGURE VIII.1 : PATTERN PRESENTATION AND PATTERN REVERSAL EVOKED RESPONSES IN NORMALS. Pattern presentation responses may show a positive deflection at 90–100 ms after the stimulus, denoted PP100, and at 160–180 ms after the stimulus, denoted PP160, which is maximal with 40' checks. In pattern reversal responses, only one deflection can be discerned, referred to as PR100.

Results with pattern presentation evoked responses in a control group

The PP100 peak was absent in a high percentage of the normal subjects (table VIII.1), ranging from 50–100% absence, depending on the check size used. On the strength of these results it was concluded that PP100 can not be regarded as a reliable measure of pathological changes in PP responses and has therefore been excluded from further analysis. The PP160 responses, however, were present in 95–100%, except for those elicited by checks of 10′ 5% contrast (table VIII.1). Responses obtained through the latter stimulus have therefore not been used in further analysis.

PATTERN PRESENTATION ABSENT RESPONSES

STIMULUS	N	PP100 OD–OS	PP160 OD–OS
80′80%	47	50–64 %	5–5 %
40′40%	47	64–68	0–4
20′20%	47	66–79	0–2
10′10%	47	92–100	4–4
10′ 5%	47	100–100	34–45

TABLE VIII.1 : PATTERN PRESENTATION; RESPONSE ABSENCE PERCENTAGE FOR PP100 & PP160 IN 47 NORMAL SUBJECTS. Note the high frequency of absence of PP100 and the small check–low contrast PP160 responses.

Amplitudes appear to vary greatly. This is expressed by a large standard deviation (up to almost 50% of the mean). Another feature of amplitudes is that the maximum value is not obtained by using the largest checks (80′), but by check size 40′, 40% contrast. Lower limits of normal for amplitude were computed by logarithmic transformation of the numerical value, which showed a log normal distribution. Further, the interocular ratio (IOR) was chosen for statistical reasons.

The range of latencies of PP160 (table VIII.2) is smaller than amplitudes and therefore a relatively small standard deviation (SD) was found, i.e. within the range of 10–15% of the average. For latency, mean value plus 2.5 SD was chosen as the upper limit of normal. In addition, the interocular difference in delay (IOD) was chosen. The mean and SD of the IOR and the IOD did not differ from zero to a statistically significant degree (Student's t–test).

Mean values for both amplitude and latency are shown in table VIII.2.

PATTERN PRESENTATION

STIMULUS	N	AMPLITUDE MEAN AND SD (μV)		IOR	LOWER LIMIT (μV)
80'80%	45	16.8	7.9	0.50	4
40'40%	47	24.4	11.3	0.59	7
20'20%	47	16.1	7.8	0.58	3
10'10%	45	10.8	5.2	0.34	2
		LATENCY MEAN AND SD (ms)		IOD (ms)	UPPER LIMIT (ms)
80'80%	45	161.8	15.2	20	206
40'40%	47	170.5	12.4	14	205
20'20%	47	180.6	20.6	28	237
10'10%	45	162.4	17.8	26	204

TABLE VIII.2 : MEAN, STANDARD DEVIATION, INTEROCULAR RATIO (IOR), INTEROCULAR DIFFERENCE (IOD) FOR AMPLITUDE AND LATENCY IN A CONTROL GROUP OF 47 NORMAL SUBJECTS. Using the 40'40% checks, maximum amplitudes were obtained, whereas using 10'10% checks, latency was shortest. The IOR was lowest using 10'10% checks, whereas using 40'40% checks the IOD of latency was smallest.

Results with pattern reversal evoked responses in a control group

Of all stimulations performed , both latency and amplitude of PR100 were recorded. Amplitudes are rarely absent in PR (table VIII.3).

PATTERN REVERSAL

STIMULUS	N	PR100 OD–OS
1° 400 asb	47	0–0
1° 40 asb	47	4–4
0.5° 40 asb	47	2–2

TABLE VIII.3 : PATTERN REVERSAL : RESPONSE ABSENCE PERCENTAGE FOR PR100 IN A CONTROL GROUP.

Amplitudes, just as in pattern presentation responses, varied greatly. The standard deviation, however, did not amount to more than 33% of the average, compared with 50% in pattern presentation (table VIII.4).

Latency of the PR100, as defined in the introduction and as obtained by this stimulation showed very little variation; the SD being 5% or less of the average response. A survey given in table VIII.4 reveals that both amplitude and latency in PP showed a greater variance than in PR. This indicates that the use of the lower limit for amplitudes of PP responses in the patient group may prove less useful.

	AMPLITUDE	LATENCY
PATTERN PRESENTATION	47–48 %	7–11 %
PATTERN REVERSAL	29–33	5

TABLE VIII.4 : VARIANCE OF NORMAL RESPONSES IN PERCENTAGE OF THE MEAN IN PATTERN PRESENTATION AND REVERSAL FOR AMPLITUDE AND LATENCY. In both methods amplitude varied more than latency. In PP, the difference in variance between amplitude and latency was greater than in PR responses.

The lower limit of normal for amplitude was calculated by logarithmic transformation as in PP. The upper limit of latency was computed by taking the mean plus 2.5 SD. The mean and standard deviation of the interocular ratio (IOR) for amplitude and of the interocular difference (IOD) for latency again did not differ significantly from zero (Student's t–test). This suggests it may be a good measure of pathology in unilaterally affected patients. Mean, standard deviation, IOR and IOD of amplitude and latency are presented in table VIII.5.

PATTERN REVERSAL

STIMULUS	N	AMPLITUDE MEAN AND SD (μV)		IOR	LOWER LIMIT (μV)
1° 400 asb	47	12.6	3.7	0.62	5
1° 40 asb	45	11.1	3.4	0.55	4
0.5° 40 asb	46	10.4	3.4	0.55	4
		LATENCY MEAN AND SD (ms)		IOD (ms)	UPPER LIMIT (ms)
1° 400 asb	47	101.4	4.9	7	114
1° 40 asb	45	112.3	5.7	10	126
0.5° 40 asb	46	111.2	5.4	9	126

TABLE VIII.5 : MEAN, STANDARD DEVIATION, INTEROCULAR RATIO (IOR) AND INTEROCULAR DIFFERENCE (IOD) FOR AMPLITUDE AND LATENCY IN PATTERN REVERSAL RESPONSES OF A CONTROL GROUP. Note there is no maximal response as in PP with any of the check sizes, whereas latency upper limits are lowest with 1° 400 asb stimuli.

The correlation between latency changes and age was 0.4, suggesting a relatively small age contribution to latency changes in the patient group (age ranging from 17–62 years). In normal subjects visual acuity and amplitude were not correlated.

Criteria for pathology

Based on the results obtained from the control group, three criteria for pathology were introduced for both PP and PR.
1. Absence of response (no amplitude measurable–table VIII.1–control group).
2. Interocular ratio (affected eye divided by fellow eye) for amplitude or the interocular difference for latency outside the normal range (table VIII.2 & 5).
3. A response numerically outside the normal range (table VIII.2 & 5).
For latency, only criteria 2 and 3 were used, as it is impossible to assess whether or not delay is present when responses are absent.
The total percentage of abnormal responses for each stimulus of PP and the 1° 40 asb stimulus in PR were thus obtained for both amplitude and latency. Apart from this, amplitude in PP was denoted as pathological when response to any of the four stimuli was abnormal. The same was done for amplitude in PR and latency in both methods. Next, to compare both methods, any abnormality, either in amplitude or in latency, was assessed in PP and PR.

Results with pattern presentation evoked responses in the patient group

In 54–91% of the affected eyes, depending on the stimulus used, no response could be recognized (table VIII.8). Comparative percentages in the control group ranged from 1–5%, in the fellow eyes from 1–16% (table VIII.1, table VIII.15).
The mean and standard deviation (SD) of affected and fellow eyes are shown in table VIII.6. There was a statistically significant difference between the mean of amplitudes in the affected eye and that of the control group for all stimuli (Student's t–test, $P=0.000$). For latency, mean and SD of 80', 40' and 10' stimuli differed to a statistically significant degree (Student's t–test, $P=0.000$), whereas for 20' checks this difference could not be found. This is probably due to the fact that in the control group the mean at 20' stimuli is relatively large. For the fellow eye, only in 80' check responses was a statistically significant difference found for latency (Student's t–test, $P<0.05$).
Both amplitude and latency varied greatly, which is revealed by a relatively large SD (in percentages of the mean–table VIII.7).

PATTERN PRESENTATION

STIMULUS	N	AFFECTED EYE AMPLITUDE MEAN AND SD (μV)		N*	FELLOW EYE AMPLITUDE MEAN AND SD (μV)	
80'80%	51	9.7	5.5	66	21.1	12.1
40'40%	33	9.3	6.1	97	26.7	12.9
20'20%	20	5.6	2.7	105	15.6	8.9
10'10%	10	5.3	2.5	91	12.6	7.2
		LATENCY MEAN AND SD (ms)			LATENCY MEAN AND SD (ms)	
80'80%	51	200.5	39.4	66	169.9	24.6
40'40%	33	205.4	37.9	97	175.9	22.6
20'20%	20	196.1	39.8	105	175.9	27.1
10'10%	10	186.7	40.0	91	167.8	21.1

TABLE VIII.6 : MEAN AND STANDARD DEVIATION OF AMPLITUDE AND LATENCY IN PATTERN PRESENTATION (PATIENTS). Again a great variance in amplitude is observed. Maximum of amplitude was now found with 80'80% checks in the affected eye, whereas in the fellow eye maximal response was found with 40'40% checks as in the control group.

	AFFECTED EYES	FELLOW EYES	CONTROL GROUP
AMPLITUDE	47–66 %	48–57 %	47–48 %
LATENCY	19–22	13–15	4–11

TABLE VIII.7 : VARIANCE OF AMPLITUDE AND LATENCY IN PATTERN PRESENTATION IN PERCENTAGE OF THE MEAN. Latency in the fellow eye revealed a greater variance than latency in the control group, which may indicate subclinical damage to the clinically unaffected eye.

In respect to the amplitude in PP, both a response outside the normal range and the pathological interocular ratio gave a good indication of abnormality, the latter revealing a higher percentage of abnormality (table VIII.8). Using both these criteria in addition to absence of response, another 14–20% of pathology was found in responses obtained by check sizes 80', 40', and 20'. At check size 10', however, the practical usefulness of criteria 2 and 3 was very limited as absent responses greatly outnumbered the measurable ones.

Further, table VIII.8 reveals that the interocular ratio of amplitude by itself can be sufficient to indicate abnormality, as all patients whose amplitude is numerically outside the normal range also have an abnormal interocular ratio.

* Due to the retrospective nature of the present study, a number of responses were not available because the responses to all check sizes were not recorded for all fellow eyes at the time of the attack.

The total percentage of pathological amplitudes varied from 68% (80' checks) to 96% (20' checks). The lesser degree of pathology revealed by the use of eighty–minutes checks as compared with the degree of pathology revealed when using other check sizes is statistically significant (McNemar's test, P<0.01). As to latency, after the exclusion of those in whom no response could be elicited, the percentages of total abnormality for each stimulus were lower than those found for amplitude. This difference was statistically significant for check sizes of 40' and 20' checks (Fisher's exact test, P=0.0000), but not for 80' and 10' stimuli.
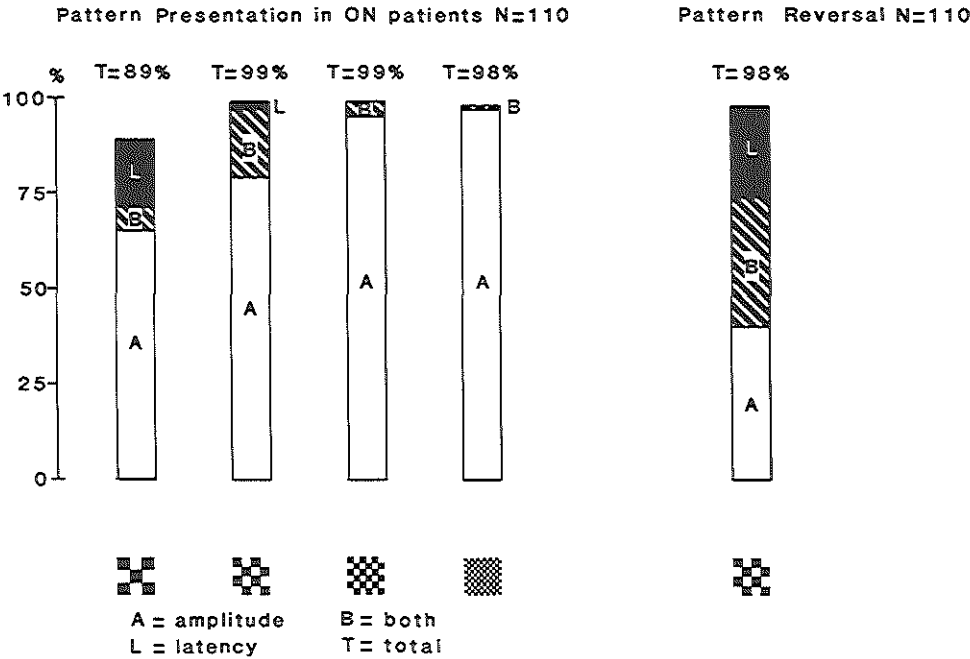
FIGURE VIII.2 : GRAPHIC PRESENTATION OF ABNORMAL RESPONSES IN PATTERN PRESEN-TATION AND PATTERN REVERSAL(responses using 1° 40 asb checks). Note the increase in abnormal amplitudes with decreasing check sizes. Using small checks pathology is for the greater part ascertained by amplitude abnormality. With PR, however, pathology is indicated for 60% by latency.

PATTERN PRESENTATION (AMPLITUDE)

STIMULUS	N	ABSENT RESPONSES	OUTSIDE NORMAL RANGE	ABNORMAL IOR	BOTH	TOTAL
80'80%	110	54 %	6 %	13 %	5 %	68 %
40'40%	110	70	14	23	12	95
20'20%	110	82	4	14	4	96
10'10%	110	91	0	0	0	91

TABLE VIII.8a : PATTERN PRESENTATION; ABSENCE OF RESPONSE, RESPONSE OUTSIDE NORMAL RANGE AND ABNORMAL INTEROCU-LAR RATIO (IOR) IN AMPLITUDE. For the assessment of pathology, absence of responses proved to be most useful. Further, IOR revealed abnormalities in 0–23% of the responses, whereas the use of lower limits did not give additional information in more than 1–2%.

PATTERN PRESENTATION (LATENCY)

| STIMULUS	N	OUTSIDE NORMAL RANGE	ABNORMAL IOD	BOTH	TOTAL
80'80%	51	37 %	31 %	10 %	58 %
40'40%	33	48	55	36	67
20'20%	20	10	15	5	20
10'10%	10	10	10	10	10

TABLE VIII.8b : PATTERN PRESENTATION; RESPONSE OUTSIDE NORMAL RANGE AND ABNORMAL INTEROCULAR DIFFERENCE (IOD) IN LATENCY. The use of the upper limit of normal revealed pathology in PP responses in 10–48%, whereas the IOD detected abnormality in 10–55%.

Table VIII.9 presents the number of patients in whom either amplitude, latency, or both, in response to any stimulus were abnormal. Figure VIII.3 is a graphic presentation in percentages of the whole patient group (N=110). A 'B' denotes patients in whom both amplitude and latency were pathological for any of the 4 stimuli used. Figure VIII.3 shows that most information is obtained by the assessing of amplitudes (69%). Increased latency may be found but as a single pathological feature (i.e. without amplitude changes) this has not been observed in the patient group.

Separate analysis of each check size shows the same: latency alone contributes very little, or nothing, to the percentage of abnormality (18% in 80' checks to 0% in 20' and 10' checks).

	AMPLITUDE PATHOLOGY (N)	LATENCY PATHOLOGY (N)	BOTH ABNORMAL (N)	TOTAL (N)
PP	109	33	33	109 (99%)
PR	90	69	53	106 (96%)
	P<0.01	P<0.01		

TABLE VIII.9 : COMPARISON OF AMPLITUDE AND LATENCY ABNORMALITIES IN PATTERN PRESENTATION AND PATTERN REVERSAL EVOKED RESPONSES. In both PP and PR amplitudes appeared to be affected most. In PP latency changes could not be assessed due to absence of responses. PP responses are therefore less useful in the detection of these changes.
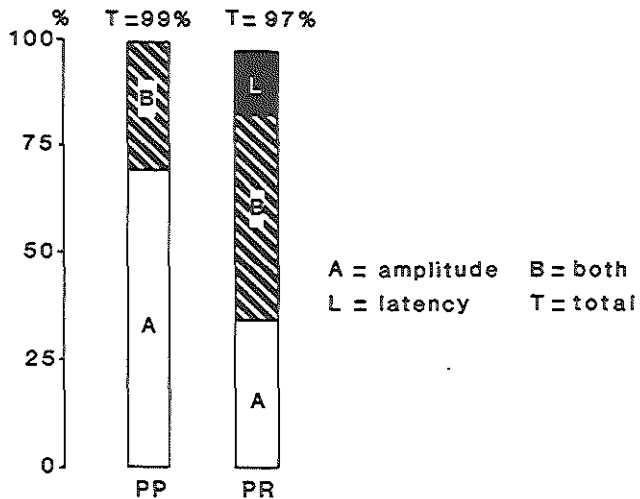
FIGURE VIII.3 : GRAPHIC PRESENTATION OF TABLE VIII.9. In PP no pathology was revealed by latency alone, whereas in PR in 15% of the patients only latency was abnormal

The difference in amplitude pathology between PP and PR is statistically significant (McNemar's test, P<0.01) and so is the difference between these methods in regard to the percentage of abnormal latencies..

Results with pattern reversal evoked responses in the patient group

Using pattern reversal, 27–48% of the responses were absent (table VIII.12a). The mean and SD of the affected and fellow eye are shown in table VIII.10. As in PP, the SD was relatively large, ranging from 48–91% for amplitude and from 18–21% for latency (table VIII.11) in the affected eye. There is a statistically significant difference in the mean and SD of amplitude and latency in the affected (eye) group, as compared with the control group, for all stimuli (Student's t–test, P=0.0000). In the fellow eye, the mean and SD of 1° 400 asb responses were different from the responses of the control group to a statistically significant degree (Student's t–test, P<0.002).

PATTERN REVERSAL

STIMULUS	N	AFFECTED EYE		N	FELLOW EYE	
		AMPLITUDE MEAN AND SD (μV)			AMPLITUDE MEAN AND SD (μV)	
1° 400 asb	49	5.9	4.9	48	13.6	6.2
1° 40 asb	68	6.9	6.3	106	11.6	5.7
0.5° 40 asb	37	6.2	3.0	77	10.5	5.4
		LATENCY MEAN AND SD (ms)			LATENCY MEAN AND SD (ms)	
1° 400 asb	49	155.5	32.1	48	111.2	19.6
1° 40 asb	68	157.4	32.4	106	116.3	16.0
0.5° 40 asb	37	149.8	27.5	77	114.0	10.8

TABLE VIII.10 : MEAN AND STANDARD DEVIATION OF AMPLITUDE AND LATENCY IN PATTERN REVERSAL. Note the relatively high SD of the pattern reversal responses with regard to amplitude, especially in the affected eye.

	AFFECTED EYES	FELLOW EYES	CONTROL GROUP
AMPLITUDE	48–91 %	46–51 %	29–33 %
LATENCY	18–21	9–18	5

TABLE VIII.11 : VARIANCE OF AMPLITUDE AND LATENCY IN PATTERN REVERSAL. Note that in the fellow eyes the variance in amplitude and latency is higher than that of the control group.

Criteria for pathology were applied to the responses obtained. It appeared that the IOR and IOD provide less information in addition to upper and lower limits of normalcy when applied than in the PP method. This was especially so for latency (interocular difference—criterion 2); in only 2–8% was a pathological difference the only abnormality.

The results obtained by PR for both the amplitude and latency of each stimulus type are shown in table VIII.12. Total percentages of abnormality for each stimulus of amplitude and latency do, as in PP, differ significantly (Fisher's exact test, P<0.05). The total number of responses found in PR is less than that in PP as not all stimuli were recorded for each patient.

AMPLITUDE

STIMULUS	N	ABSENT RESPONSES	OUTSIDE NORMAL RANGE	ABNORMAL IOR	BOTH	TOTAL
1° 400 asb	69	27 %	37 %	37 %	22 %	79 %
1° 40 asb	109	38	28	30	24	72
0.5° 40 asb	71	48	14	21	10	73

TABLE VIII.12a : PATTERN REVERSAL; ABSENCE OF RESPONSE, RESPONSE OUTSIDE NORMAL RANGE AND ABNORMAL INTEROCULAR RATIO (IOR) OF AMPLITUDE. Both the lower limits of normal and the IOR proved equally effective, contrary to findings in PP where the IOR was more useful.

LATENCY

STIMULUS	N		OUTSIDE NORMAL RANGE	ABNORMAL IOD	BOTH	TOTAL
1° 400 asb	49		94 %	63 %	63 %	94 %
1° 40 asb	68		88	82	79	91
0.5° 40 asb	37		84	89	81	92

TABLE VIII.12b : PATTERN REVERSAL; RESPONSE OUTSIDE THE NORMAL RANGE AND ABNORMAL INTEROCULAR DIFFERENCE OF LATENCY. The IOD appeared to detect little abnormality in addition to the upper limit of normal.

The abnormality rate of amplitude and latency showed a statistically significant difference for all stimuli (Fisher's exact test, P<0.05).

Table VIII.9 presents the number of patients in whom either amplitude, latency or both were abnormal using any stimulus. As amplitudes could cover pathology in most cases (82%) additional information by using latency alone could be obtained in only 15% (figure VIII.3).

Comparison of pattern presentation and pattern reversal evoked responses in 110 patients with unilateral optic neuritis

The first parameter to be compared for both methods is the absence of response. This occurred 2.5–3 times more often using PP than using PR. This finding has great impact on the evaluation of the measurable responses and the definition of pathology in both methods.

The variance in amplitude was relatively large in PR (50–100%) compared with PP (40–50%). This is contrary to findings in the control group where a greater variance of amplitude was observed using PP (table VIII.4). When comparing amplitude pathology using any stimulus, 81% of the patients appeared to have an abnormality as measured by both methods (table VIII.13). In practical terms this implies that in a given patient an abnormal amplitude, obtained in PP, will probably be matched by a pathological one in PR. However, the main difference is that in PP this is due to a complete loss of response whereas in PR it is only an attenuation of the response (compare table VIII.8a and table VIII.12a).

The rate of latency abnormality using both methods is presented in figure VIII.4 and table VIII.13. In a given patient, a delay in PR does not necessarily signify a pathological latency in PP. In about 40% of the patients latency could be denoted as abnormal in PR, whereas in PP latency could not be measured (due to absence of response) or was within the normal range.

However, by using latency as a measure of pathology, 36% of the patients could be dismissed as healthy, whereas with amplitudes an abnormality could be found in all patients. Yet in a large percentage of the patients no latency measurement could be performed due to absence of response, which may account for this difference. For both methods the difference in amplitude and latency abnormality rate is statistically significant (McNemar's test, $P<0.01$).

	N	PP	PR	BOTH PP and PR	TOTAL
AMP.PATH	110	99 %	82 %	81 %	100 %
LAT.PATH.	110	30	63	28	65

TABLE VIII.13 : COMPARISON OF PATTERN PRESENTATION AND PATTERN REVERSAL EVOKED RESPONSES WITH REGARD TO AMPLITUDE AND LATENCY. PP increased the diagnostic yield of amplitude with 18%, whereas PR did so for latency with 35%.

Finally, the total percentage of abnormality, i.e. a pathology of response in amplitude, latency or both, was compared for PP and PR. Results are presented in table VIII.14.
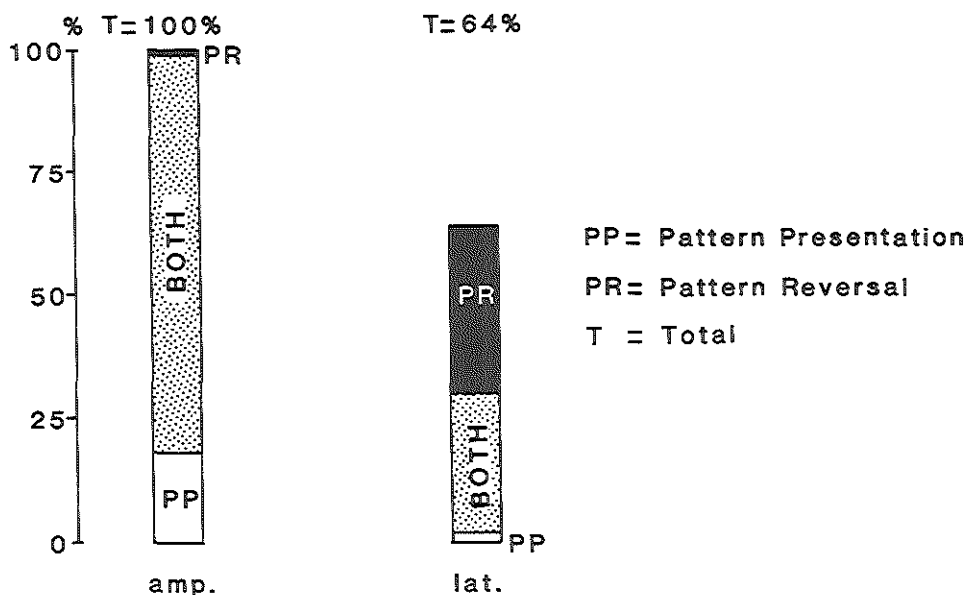
FIGURE VIII.4 : GRAPHIC PRESENTATION OF TABLE VIII.13. Note that an abnormal amplitude was found in 100% of the patients using both methods, whereas a delay was seen in 64% using both PP and PR.

	N	PP	PR	BOTH PP and PR	TOTAL
ABNORMAL	110	99 %	96 %	95 %	100 %
NO ABNORMALITY	110	1	4	0	5

TABLE VIII.14 : COMPARISON OF TOTAL PATHOLOGY (EITHER IN AMPLITUDE OR IN LATENCY) IN PATTERN PRESENTATION AND PATTERN REVERSAL EVOKED RESPONSES

In 105 patients, both PP and PR were abnormal. In four patients, using PR, and in one patient, using PP, no pathological responses could be detected.

Clinical features and electrophysiology

No correlation could be found between visual acuity and amplitude of both PP and PR. However, when combining visual acuity and latency a correlation, though low, could be found between visual acuity and latency of the first stimulus of PP (checks 80', 80%; R=0.4, P<0.05).

Fellow eyes in pattern presentation and pattern reversal evoked responses

Although a clinical abnormality may not be present in the fellow eye, it may be present subclinically (which may be the first sign of systemic demyelinating disease). To see whether, in the subjects of our study, in the fellow eyes minor symptoms of demyelination could already be detected the criteria introduced for the affected eyes were applied to the 110 fellow eyes. Further, the use of an interocular ratio or difference as a pathological notion has to be justified, as this rests on the presumption that one eye is affected (clinically ON), whereas the other is healthy within the limits based on the control group findings.

In PP, the percentage of abnormalities fell within the 5% interval chosen for both amplitude and latency of the responses to 80', 40', and 20' checks. The 10' checks elicited an abnormal response in 16%, which is however statistically not significantly different from the rate in the control group (4%, table VIII.15). This goes for amplitude only. For latency there was also a higher frequency of abnormality compared with the control group, though not statistically significant. In those patients in whom a pathological ratio or difference was found, the fellow eye was healthy, i.e. had a response within normal limits, so the difference or ratio is a true measure of pathology.

For PR amplitudes the same goes as for amplitudes in PP. Interocular ratios revealed the same percentage of abnormality as did application of a normal range as a criterion for pathology. The small checks in PR, however, did not show a significant difference in pathological responses when compared with the control group, as did the 10' checks in PP.
Conversely, the percentage of delayed responses in PR of the fellow eyes is striking (29%, table VIII.15). This was especially so in responses evoked by the large (1°) checks at the highest luminance level (400 asb). However, this did not have any implication with regard to the affected eye. When the interocular difference appeared too large, the latency of the response was usually also outside the normal range.
However, in 29% the abnormal latencies obtained using 1° 400 asb stimuli serve as a warning, especially when the other responses are within the normal range (Fisher's exact test, $P < 0.002$).

VER ABNORMALITIES IN THE FELLOW EYE *

PATTERN PRESENTATION
AMPLITUDE

STIMULUS	N	ABSENT RESPONSE	OUTSIDE NORMAL RANGE	TOTAL ABNORMALITY
80'80%	67	1 %	0 %	1 %
40'40%	98	1	2	3
20'20%	107	2	1	3
10'10%	105	16	0	16

LATENCY

STIMULUS	N			
80'80%	66		2 %	2 %
40'40%	97		2	2
20'20%	109		1	1
10'10%	88		7	7

PATTERN REVERSAL
AMPLITUDE

STIMULUS	N			
1° 400 asb	49	2 %	4 %	6 %
1° 40 asb	109	3	4	7
0.5° 40 asb	78	1	5	6

LATENCY

STIMULUS	N			
1° 400 asb	48		29 %	29 %
1° 40 asb	106		13	13
0.5° 40 asb	77		9	9

TABLE VIII.15 : RESPONSE ABNORMALITIES OBTAINED IN THE FELLOW EYES; ABSENCE OF RESPONSE AND RESPONSE OUTSIDE THE NORMAL RANGE. Note that in 16% of the fellow eyes, no response could be observed using stimuli of 10' 10% contrast in PP amplitude, whereas using 1° 400 asb stimuli in PR (latency), 29% of the fellow eyes were found to have a delay compared with normal eyes. In four fellow eyes, both amplitude in PP and latency in PP were found to be abnormal.

* Due to the retrospective nature of the present study, a number of responses were not available as not all responses to all check sizes were recorded for all fellow eyes at the time of the attack.

Check size and stimulus response in affected and fellow eyes

Apart from group characteristics (such as number of absent responses, mean and SD of all stimuli) for each patient the smallest check size which could still elicit a response was recorded. This was done regardless of the numerical value of the response (table VIII.16). For the affected eye no response to any of the four checks used in PP constitutes the most prominent feature. In only one of the patients could a response be recognized when using 10' checks.

Significant differences between the fellow eye of the patient group and the control group are noted also in table VIII.16. In the fellow eyes, the number of responses evoked by PP stimuli is always larger than in the affected eye. However, there are some differences between the patient group fellow eyes and those of the control group. As has been discussed already, a relatively large percentage of the patients did not have a response with the 10' checks. This finding may imply that although the fellow eye may seem clinically unaffected, when using sufficiently small checks subclinical damage may be detected. Furthermore, responses obtained using all four stimuli in PP were less frequently found in the fellow eyes to a statistically significant degree (Fisher's exact test, $P < 0.03$).

PATTERN PRESENTATION	AFFECTED EYES (N=110)	FELLOW EYES (N=110)	CONTROL GROUP(N=47)
NO RESPONSE	54 %	0 %	0 %
RESPONSE 80' ONLY	16	1	0
RESPONSE 80' & 40'	12	1	2
RESPONSE 80',40',20'	9	16	2
RESPONSE 80',40',20',10'	8	82	96 ($P < 0.03$)

TABLE VIII.16 : NUMBER OF RESPONSES OBTAINED FOR EACH EYE BY PATTERN PRESENTATION. In 16% of the fellow eyes, no response could be obtained with 10'10% checks.

In pattern reversal, the number of absent responses in the affected eyes is lower than in pattern presentation to a statistically significant degree (Fisher's exact test, $P < 0.05$). Further, compared with PP a significantly higher percentage of patients responsed to all 3 stimuli. Also in the fellow eye there was a statistically significant lesser degree of absence of response than seen in the affected eye (Fisher's exact test, $P < 0.0001$). The same was found for responses to all three PR stimuli (Fisher's exact test, $P < 0.0001$).

PATTERN REVERSAL	AFFECTED EYES (N=110)	FELLOW EYES (N=110)
NO RESPONSE	33 %	0 % P<0.0001
RESPONSE 1° 400 asb ONLY	5	0
RESPONSE 1° 400 & 40 asb	28	30
RESPONSE 1° 400 & 40 asb, 0.5° 40 asb	34	70 P<0.0001

TABLE VIII.17 : NUMBER OF RESPONSES OBTAINED FROM EACH EYE BY PATTERN REVERSAL EVOKED RESPONSES.

The pathological findings in PP and PR may be a sign of subclinical damage to the optic nerve.

SUMMARY CHAPTER VIII

Based on the observations obtained from a control group of 47 normal subjects, criteria for pathology were calculated. Amplitude and latency changes of all subjects were assessed.

Comparison of both parameters in pattern presentation responses led to the conclusion that amplitude attenuation in the affected eye is the outstanding feature of optic neuritis in the acute stage. Amplitude abnormality was expressed by an absence of responses in 54 to 91% of the patients (no amplitude recognizable). This makes an assessment of a delay impossible. Yet of those responses in which an amplitude could be measured, 53–66% showed a delay. As the only pathological feature, however, it is rarely present.

Comparison of amplitude and latency in pattern reversal shows less difference between abnormal responses obtained by either. This was mainly due to the fact, that amplitudes are less often absent in PR than in PP. Abnormality assessed by latency with pattern reversal (91–94%) was higher than that by amplitude (72–79%), which is contrary to findings in pattern presentation.

Comparison of pattern presentation and pattern reversal led to the conclusion, that in the acute stage in PP the amplitude absence and in PR the amplitude attenuation, is a prominent feature. Pattern presentation proved the most sensitive method for detecting amplitude pathology. For latency change, however, pattern reversal proved to be the most sensitive method, which may have consequenses for the long term prognosis of optic neuritis.

Apart from the conclusive notions on the affected eye, no amplitude could be recognized in responses obtained with small check, low contrast pattern presentation stimuli in the fellow eye. Large check pattern reversal stimuli showed a delay in 30% of these clinically unaffected eyes. These observations may be a sign of subclinical damage and/or forebode the development of multiple sclerosis in these patients.

CHAPTER IX

VISUAL EVOKED RESPONSES IN PATIENTS AFTER UNILATERAL OPTIC NEURITIS

Of the 110 patients seen in the acute stage 53 could be reexamined using the same methods. The time lapse between the first and second examinations, which is denoted as follow—up, ranged from 8 weeks to 4 years (average 2 years). On history taking and neurological examination, 23 (44%) had developed symptoms and signs of MS. The neurological characteristics of these patients will be discussed in more detail in chapter XI. On reexamination, visual acuity remained lower than 1.00 (Landolt rings) in 25 (47%) of the patients, nine (36%) of them having signs of MS.

PP and PR components (amplitude and latency) were compared in patients with and without signs of MS. This was done for both the initially affected and the unaffected (fellow) eye.

Further, after improvement of visual acuity, the patients were classified in two groups: those with a visual acuity of 1.00 or higher in the initially affected eye (recovered eyes), and those with a visual acuity of less than 1.00 (non—recovered eyes). For these groups amplitude and latency changes using both methods have also been compared.

Pattern presentation evoked responses in patients with and without signs of multiple sclerosis

In both groups, amplitude attenuation and delay were assessed. In addition, the percentage of complete normalization for amplitude as well as latency was compared in those with and without signs of MS.

Figure IX.1 presents the abnormalities found with use of each stimulus of pattern presentation. For amplitudes, no significant difference between those with and without signs of MS could be found. In both groups, the percentage of abnormal amplitudes increased with decreasing check size; the interocular ratio of amplitude revealing most of the pathology.

Also in latency, no difference in the percentage of abnormality was found between the groups. Contrary to the findings obtained using amplitudes, the percentage of abnormality in latency decreased with decreasing check size. This result is probably due to the increasing number of absent responses when using smaller check sizes. The maximum rate of abnormality in patients without signs of MS was found using 40′ checks.

Comparison of amplitude and latency in each stimulus showed that amplitude reveals a higher percentage of abnormality.
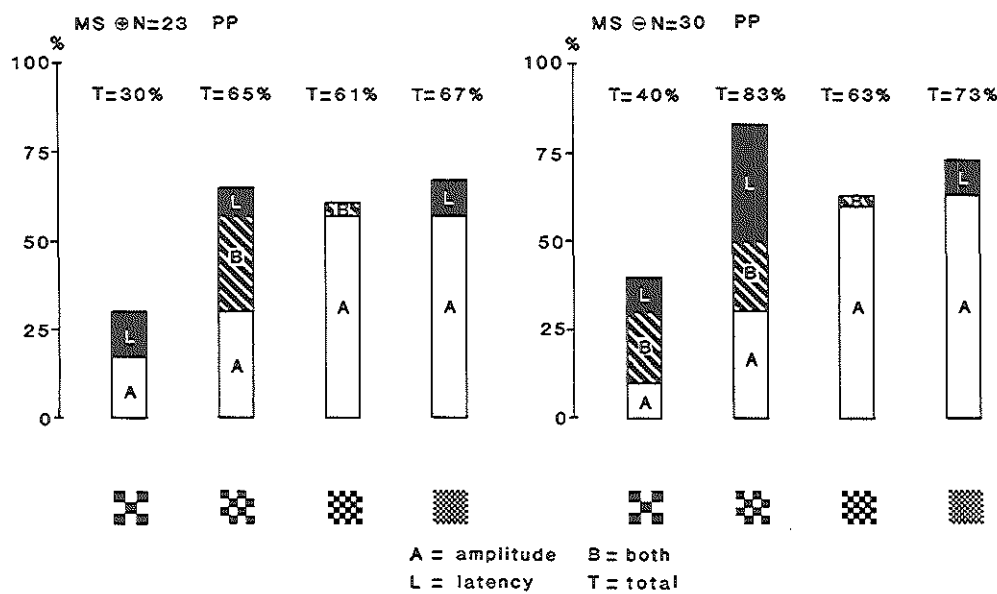
FIGURE IX.1 : COMPARISON OF AMPLITUDE AND LATENCY IN EACH STIMULUS OF PATTERN PRESENTATION. In those without signs of MS the highest percentage of abnormality was found using 40' checks. Using smaller check sizes amplitude changes were found more frequently than latency changes. Further, the percentage abnormality in the group without signs of MS was higher due to a higher percentage of latency abnormality using 40' checks.

When the results of all PP stimuli were collectively studied no difference in total abnormality rate (i.e. either in amplitude, latency, or both, for any of the stimuli) could be observed between the groups, the total percentage being 96% and 93% respectively for patients with and without signs of MS (table IX.1). Latency contributed 70% to this percentage in patients without signs of MS, whereas in those with signs of MS a delay was found in 44% (not statistically significant, P=0.1).

PATTERN PRESENTATION

	N	AMPLITUDE PATHOLOGY	LATENCY PATHOLOGY	BOTH AMP & LAT	TOTAL
MS+	23	83 %	44 %	30 %	97 %
MS−	30	73	70	50	93
			P=0.1		

TABLE IX.1 : COMPARISON OF TOTAL ABNORMALITY RATE IN PATTERN PRESENTATION FOR PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. A delay was observed more frequently in patients without signs of MS.

Further, changes in amplitude and latency abnormalities were evaluated by making a comparison of the PP responses in both groups at the first and the second examination. In six patients of the MS group amplitudes of all stimuli returned to normal, compared with eight of the non−MS group.

Most interesting was the percentage of latency increase in both groups both during the acute attack and at reexamination. In 14 of the patients without signs of MS, it seemed as if a delay had developed during the follow−up period, whereas in the MS group this had happened in only four of the patients. This difference is of statistical significance (Fisher's exact test, $P<0.05$).

PATTERN PRESENTATION
LATENCY

	N	FIRST PP examination	SECOND PP examination	BOTH FIRST & SECOND	NORMAL
MS+	23	26 %	44 %	17 %	56 %
MS−	30	27	70	23	30

TABLE IX.2 : PERCENTAGE OF LATENCY INCREASE IN PATTERN PRESENTATION IN PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. In four patients with signs of MS an increase in latency was found, whereas in 14 of those without signs of MS a delay could be observed.

Complete recovery, i.e. normal for both amplitude and latency in all stimuli was found in only three of the patients with and in two of the patients without signs of MS.

Further, in PP, 43% of the patients in both groups regained responses to all four stimuli in the initially affected eye; in PR (three responses) these percentages were also equal in both groups (80%).

In the fellow eye, in 82% of the patients responses were obtained using all stimuli, whereas using PR recognizable responses could be observed in 83% of the patients when using all three stimuli.

Pattern reversal evoked responses in patients with and without signs of multiple sclerosis

Contrary to the findings in pattern presentation, latency abnormality was more frequently found than amplitude abnormality for all pattern reversal stimuli. This difference between both components of the responses was of statistical significance for 1° 400 asb responses in patients with signs of MS (Fisher's exact test, P<0.05) and for 1° 400 & 40 asb responses in those without signs of MS (Fisher's exact test, P<0.05). Again, however, no difference in the pathology rate between MS and non–MS patients was observed for any of the three stimuli (figure IX.2). Compared with PP, latency changes accounted for a higher percentage of abnormalities found than amplitude.

Even when the results of responses to all stimuli were collectively examined no difference between these two groups as to latency changes could be detected.
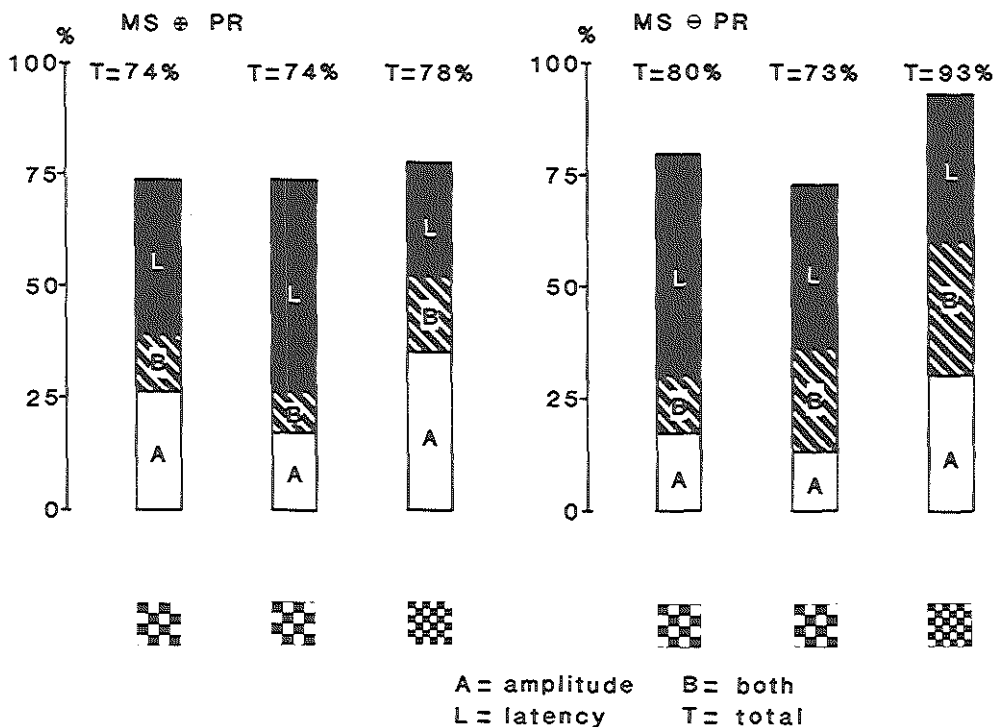
The total percentage of abnormality in PR (either in amplitude or in latency or in both) was 87% in patients with and 88% in patients without signs of MS. As pointed out before these percentages were, in both groups, mainly due to latency changes.

Further, changes in amplitude and latency abnormality in pattern reversal were evaluated as in PP by making a comparison of the responses obtained in the acute stage and those at reexamination. As opposed to PP, the frequency of amplitude and latency changes was the same for both groups.

It should be noted, however, that in only three patients in both groups the PR recovered completely.

Comparison of pattern presentation and pattern reversal evoked responses in the follow–up of optic neuritis

For amplitude, no significant difference in abnormality rate was found between PP and PR (table IX.3). Amplitude tended to be pathological in a higher percentage of the patients when using PP responses. The total percentage of abnormality was 83% and 80% respectively for patients with and without signs of MS, as obtained using both methods combined.

FIGURE IX.2 : COMPARISON OF AMPLITUDE AND LATENCY IN EACH STIMULUS OF PATTERN REVERSAL.

AMPLITUDE	N	PP	PR	BOTH PP and PR	TOTAL
MS+	23	74 %	61 %	52 %	83 %
MS−	30	73	67	60	80

TABLE IX.3 : PERCENTAGE OF ABNORMALITY IN AMPLITUDE AT REEXAMINATION IN PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. PP responses proved more effective in the detection of abnormal amplitudes, though this finding is not statistically significant.

As to latency, in patients with signs of MS PR revealed a significantly higher percentage of pathology compared with PP (Fisher's exact test, P<0.05; table IX.4). For patients without signs of MS, both methods were equally effective (70% in PP and 77% in PR).

LATENCY	N	PP	PR	BOTH PP and PR	TOTAL
MS+	23	43 %	74 % P<0.05	39 %	78 %
MS−	30	70	77	63	84

TABLE IX.4 : PERCENTAGE OF ABNORMALITY IN LATENCY AT REEXAMINATION IN PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. Comparison of both methods reveals that PR is more sensitive with regard to the detection of latency abnormality than PP, especially in MS patients.

Comparison of total abnormality (in amplitude, latency, or both) did not show a difference in percentages found per method or observed per patient group (table IX.5). In only one patient, were both methods unable to reveal an abnormality.

TOTAL ABNORMALITY	N	PP	PR	BOTH PP and PR	TOTAL
MS+	23	87 %	87 %	78 %	96 %
MS−	30	93	89	87	95

TABLE IX.5 : COMPARISON OF TOTAL ABNORMALITY RATE USING BOTH METHODS. No significant differences were observed in total abnormality (in amplitude, latency, or both).

Fellow eyes in patients with and without signs of multiple sclerosis

In regard to the fellow eye, the greatest difference in amplitude abnormality was observed in PP responses during the acute attack. For latency, a difference was observed in PR responses at reexamination. Although the differences were considerable, they are not statistically significant (Fisher's exact test, P<0.44 and P<0.07; table IX.6 and IX.7). This difference may, however, imply that in a patient a pathological amplitude in the fellow eye at the time of the acute attack may be a sign of subclinical involvement in the same process causing the visual loss in the other eye. Furthermore, at reexamination, a delay in the initially unaffected fellow eye may indicate progressive demyelinating disease outside the visual system. In the acute stage of the attack of ON, PP is a more sensitive means of detecting amplitude changes in the fellow eye, whereas after recovery latency changes in this eye are revealed by PR.

PP responses in the acute stage	N	AMPLITUDE PATHOLOGY	LATENCY PATHOLOGY	BOTH PP and PR	TOTAL
MS+	23	26 %	4 %	4 %	26 %
MS−	30	10	3	0	13
		P=0.44			

TABLE IX.6 : DIFFERENCES IN PERCENTAGE OF ABNORMALITY IN THE FELLOW EYE OF PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS IN PATTERN PRESENTATION EVOKED RESPONSES AT FIRST EXAMINATION (due to amplitude pathology).

PR responses at reexamination	N	AMPLITUDE PATHOLOGY	LATENCY PATHOLOGY	BOTH AMP & LAT	TOTAL
MS+	23	13 %	43 %	9 %	47 %
MS−	30	13	17	3	27
			P=0.07		

TABLE IX.7 : DIFFERENCE IN PERCENTAGE OF ABNORMALITY IN THE FELLOW EYE OF PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS IN PATTERN REVERSAL EVOKED RESPONSES AT REEXAMINATION (due to latency pathology).
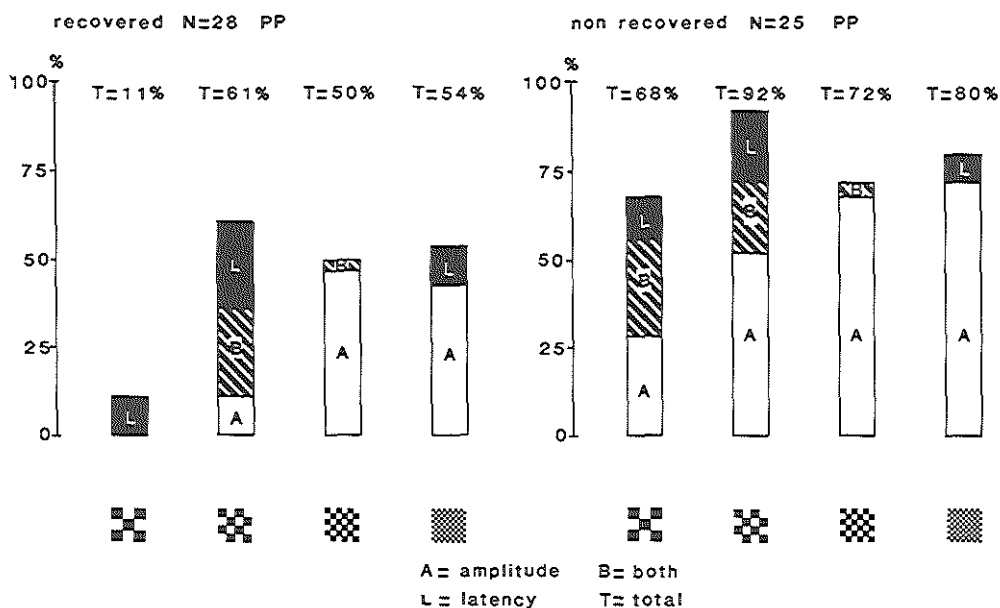

Visual acuity and changes in pattern presentation evoked responses

In 25 of the reexamined patients, the visual acuity remained lower than 1.00 (Landolt rings; 'non–recovered' eyes) after the attack of ON; in the other 28 normal visual acuity was regained ('recovered' eyes). PP and PR components have been compared for both groups.

Figure IX.3 presents the abnormalities per stimulus of pattern presentation for both amplitude and latency in both groups. Amplitude appeared to be more disturbed in PP than latency for both groups. There was a statistically significant difference between the amplitude abnormality rate in the non–recovered eyes and that of the recovered eyes (Fisher's exact test, P<0.01, for 80', 40' and 10' checks).

There was a statistically significant difference in latency for stimuli obtained by 80' checks (48% abnormality in non–recovered and 11% in recovered eyes; Fisher's exact test, P<0.01).

Table IX.8 presents the percentage of amplitude and latency abnormalities obtained by grouping responses to all stimuli. This shows no difference between the groups. The total percentage of pathological responses is lower in those with recovery of visual acuity though this is not statistically significant.

recovered N=28 PP · non recovered N=25 PP

A= amplitude   B= both
L= latency   T= total

FIGURE IX.3 : GRAPHIC PRESENTATION OF AMPLITUDE AND/OR LATENCY ABNORMALITY OBTAINED BY PATTERN PRESENTATION STIMULI IN EYES WITH AND WITHOUT A RECOVERY OF VISUAL ACUITY AFTER AN ATTACK OF OPTIC NEURITIS. Note that the total percentage of abnormality is higher for all stimuli in non—recovered eyes, amplitude being its most important detector.

PATTERN PRESENTATION	N	AMPLITUDE PATHOLOGY	LATENCY PATHOLOGY	BOTH AMP & LAT	TOTAL
RECOVERED	28	64 %	57 %	36 %	85 %
NON—RECOVERED	25	84 P=0.2	60	48	96

TABLE IX.8 : PERCENTAGE OF AMPLITUDE AND LATENCY ABNORMALITY IN RECOVERED AND AND NON—RECOVERED EYES. Note the higher percentage of abnormal amplitudes in non—recovered eyes, whereas latency tests could not distinguish between those with recovery of visual acuity and those without.

Comparison of the first and second PP recording for patients with and for patients without recovery of a visual acuity of 1.00 revealed that amplitude fully recovered in 10 (36%) of those with a visual acuity of 1.00 or more, whereas it did so in only four (16%) of the non-recovered eyes. This difference could not be found for latency (table IX.9).

AMPLITUDE	N	FIRST PP examination	SECOND PP examination	BOTH examinations	NORMAL
RECOVERED	28	100 %	64 %	64 %	36 %
NON-RECOVERED	25	100	84	84	16

TABLE IX.9 : PERCENTAGE OF ABNORMAL AMPLITUDES IN PATTERN PRESENTATION. The difference between recovered and non-recovered eyes at reexamination is not statistically significant.

The responses obtained in PP were completely normal in four patients with recovery of visual acuity compared with one only in the other group.

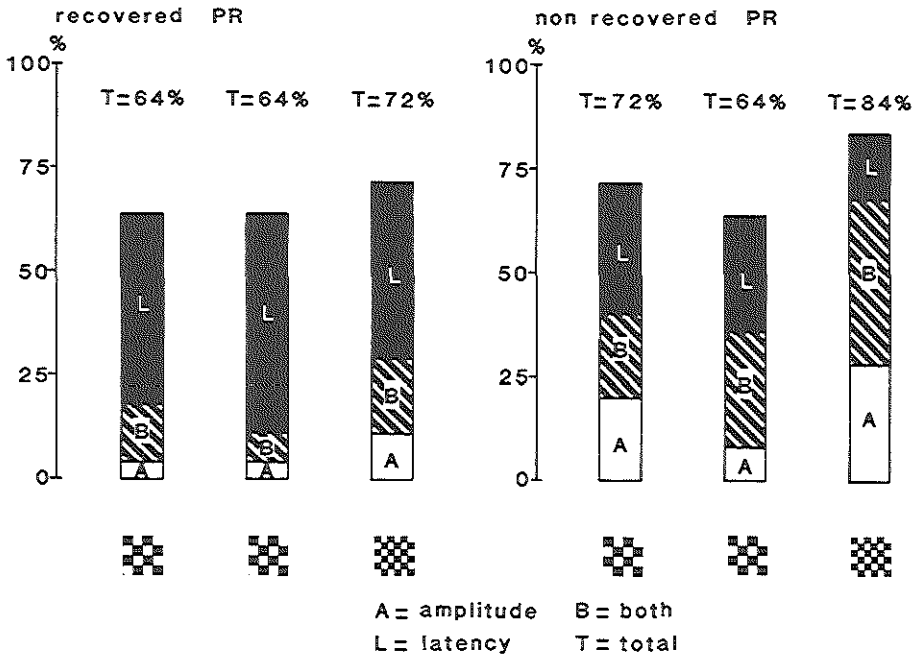*Visual acuity and changes in pattern reversal evoked responses*
Again, amplitude was less affected in those with recovery of visual acuity (significantly so for all check sizes; Fisher's exact test, P<0.02) compared with those without recovery of visual acuity.

The pathology rate for all three stimuli in PR is shown in table IX.10; the table shows a great difference in amplitude, latency and total abnormality rate (47% vs. 96%), which is statistically significant (Fisher's exact test, P<0.01). For amplitude the difference is also statistically significant (Fisher's exact test, P<0.001).

PATTERN REVERSAL	N	AMPLITUDE PATHOLOGY	LATENCY PATHOLOGY	BOTH AMP & LAT	TOTAL
RECOVERED	28	43 %	43 %	39 %	47 %
NON-RECOVERED	25	88	72	64	96
		P<0.001			P<0.01

TABLE IX.10 : PERCENTAGE OF AMPLITUDE AND LATENCY ABNORMALITY IN PATTERN REVERSAL EVOKED RESPONSES AND FOR BOTH GROUPS. The total percentage of abnormality in the recovered group was lower to a statistically significant degree than in the non-recovered group and so was the amplitude percentage.

Figure IX.4 presents the abnormalities observed for amplitude, latency or both in pattern reversal responses for recovered and non–recovered eyes.

A = amplitude   B = both
L = latency   T = total

FIGURE IX.4 : GRAPHIC PRESENTATION OF ABNORMALITY IN AMPLITUDE, LATENCY OR BOTH IN PATTERN REVERSAL STIMULI FOR EYES WITH AND WITHOUT A RECOVERY OF VISUAL ACUITY. The percentage of total abnormality found was equal for all check sizes. Pathological changes in the non–recovered eyes, however, were more often due to amplitude changes, whereas in the recovered eyes latency was more often found to be abnormal.

Further, changes of amplitude in both groups were studied by making a comparison of the results obtained using PR stimuli at the times of the first and second examinations. In the recovered eyes, amplitudes became normal in 14 patients, whereas in those in whom the visual acuity remained less than 1.00, only two regained a normal amplitude. Responses to all three stimuli were seen in 96% and 64% respectively of the recovered and the non–recovered eyes. Comparative percentages in PP (four or more responses) were 61% and 24% (statistically significant for PP (Fisher's exact test, $P<0.02$) and PR (Fisher's exact test, $P<0.01$)). A significant correlation between amplitude and visual acuity could be found in connection with responses to all PP stimuli and with 1° 40 asb stimuli in PR ($R=0.4$, $P<0.01$).

Latency abnormalities disappeared in six and seven of the patients respectively with and without recovery of visual acuity.

Complete recovery for both amplitude and latency was observed in three of the recovered patients only and in one of the non–recovered group.

Comparison of pattern presentation and pattern reversal evoked responses in recovered and non–recovered eyes

Twenty–eight percent of the patients with a visual acuity of 1.00 or more had an abnormal amplitude in PP only, whereas in PR only 7% of the patients with a recovery of visual acuity had a pathological amplitude as a single sign. This indicates that PP is a more sensitive method in detecting amplitude abnormality in recovered patients. This difference was not observed in non–recovered patients.

The total abnormality rate with regard to amplitude as obtained by the use of both PP and PR was higher to a statistically significant degree in those without recovery of visual acuity (Fisher's exact test, $P<0.05$; table IX.11). For latency this difference was not found.

	N	AMPLITUDE IN PP	AMPLITUDE IN PR	BOTH PP & PR	TOTAL
RECOVERED	28	64 %	43 %	36 %	71 %
NON–RECOVERED	25	84	88	76	96
		$P=0.2$	$P<0.001$		$P<0.05$

TABLE IX.11 : COMPARISON OF PERCENTAGE OF AMPLITUDE ABNORMALITY IN BOTH METHODS FOR RECOVERED AND NON–RECOVERED PATIENTS. In non–recovered patients, both methods were equally effective. In recovered patients, however, use of PP detected more amplitude changes, possibly indicating 'hidden visual loss'.

Despite the difference in the percentage of pathological amplitudes between the PP and PR methods, the total abnormality rate (i.e. for amplitude, latency or both) did not differ (96% in non–recovered eyes, figure IX.5).

Pattern electroretinogram in optic neuritis

The lower limit of normal as obtained in the control group described in chapter VIII of amplitude was 2.8 μV. For latency the upper limit was 56 ms.

Of 12 patients the PERG was recorded in the acute stage of the ON, revealing no abnormality either in amplitude or in latency.

After recovery from ON, in only three patients a latency just outside the normal range (56 ms) was observed. Two of these patients had signs of MS.
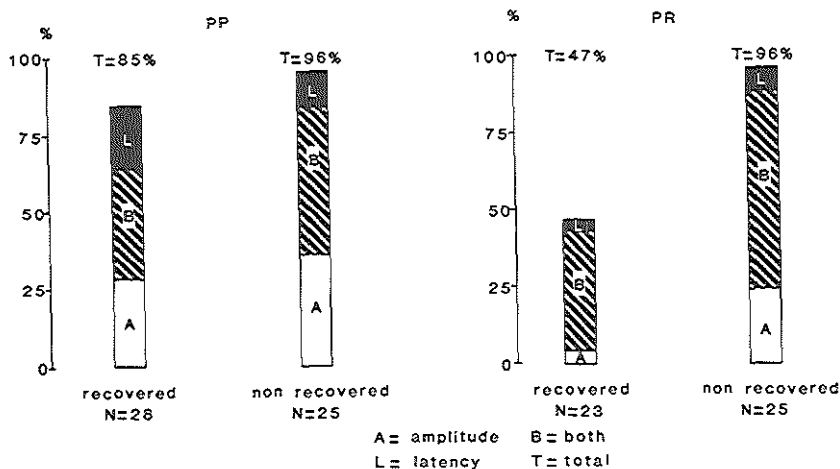
FIGURE IX.5 : COMPARISON OF TOTAL ABNORMALITY IN BOTH METHODS FOR AMPLITUDE AND LATENCY.With PP stimuli, an abnormality could be detected in 85% of the recovered eyes. This indicates that PP is a sensitive method for the evaluation of visual loss after optic neuritis.

SUMMARY CHAPTER IX

At follow–up, in 23 of the 53 patients after an attack of optic neuritis (44%) signs of multiple sclerosis were found on neurological examination. A second record-ing of both PP and PR responses could not distinguish between the groups, neither in amplitude nor in latency. Using PP, amplitude changes were the most frequent finding; using PR, latency changes were more often observed. There was however no statistical difference between both methods with regard to the detection of amplitude and latency changes. PR appeared to be more sensitive than PP in the detection of latency changes in patients with signs of MS.

In the fellow eye of the initially affected eye there was a significant difference between patients with and patients without signs of MS for latency changes in the pattern reversal recording at reexamination.

In eyes in which the visual acuity remained less than 1.00 after recovery from the optic neuritis, using pattern presentation the results showed that amplitudes were affected in the majority of the patients. Using pattern reversal the results showed that both amplitude and latency changes were found more often in non–recovered eyes.

In the recovered eyes (visual acuity of 1.00 or more), pattern presentation stimulation detected an abnormality of amplitude in 64%, which may indicate subclinical visual loss. Using pattern reversal, in only 43% of these patients was an abnormal amplitude observed. Latency changes appeared to have no relation to visual acuity.

CHAPTER X

OPHTHALMOLOGICAL FEATURES IN 53 PATIENTS
AFTER UNILATERAL OPTIC NEURITIS

Three additional psychophysical tests were performed on the 53 reexamined patients. These included colour vision assessment (HRR and Panel D15), visual field analysis (Octopus) and contrast sensitivity function. The visual acuity (Landolt rings), funduscopy and visual complaints of all patients were also recorded.

Again, as stated in chapter IX, the patient group was split up into two groups: those with neurological signs and those without these signs and those with a recovery of visual acuity to 1.00 or more and those without. Visual acuity in the affected eyes of the patients with signs of MS showed no significant difference from that in the patients without these signs (40% and 33% respectively). In the fellow eyes, however, visual acuity was lower than 1.00 in 31% of patients with signs of MS, compared with 10% in those without these signs (Fisher's exact test, P=0.13).

Colour vision deficits in 53 patients after optic neuritis

The majority of the colour vision deficits were found in patients without signs of MS. For these patients both tests proved to be equally useful. The HRR test, however, detected more circumscribed deficits (pro– and deutan deficits) whereas the Panel D15 test could not be performed in 8 (27%) of the patients without signs of MS (table X.1). In those with signs of MS, slightly more abnormalities were found using the Panel D15 test (30 vs. 22% in HRR). However, the total percentage of colour vision abnormalities in this group was significantly lower for both tests (table X.1).

The fellow eye showed a significantly higher percentage of abnormality in MS patients using the HRR test, though not statistically so. The reverse was found using the Panel D15 test (table X.2).

Contrary to findings in patients with and patients without signs of MS, a statistically significant difference between the percentage of patients with colour vision disturbances in the recovered group (i.e.with regard to visual acuity) was observed, compared with those with a non–recovered visual acuity (Fisher's exact test, P<0.001 and P<0.01 for HRR and Panel test, respectively).

This difference was most impressive in regard to the HRR test, but was significant statistically for both tests. For both tests, in a high percentage of patients, no examination could be performed due the low visual acuity (HRR: 28%; PANEL D15: 44%).

In the fellow eye no difference was observed.

HRR	N	PRO DEUTAN	TRITAN	NOT POSSIBLE	VARYING	MILD	MEDIUM	STRONG	TOTAL
MS+	23	13 %		9 %		9 %	4 %	9 %	22%
MS−	30	27	3 %	13		23	7	13	43
PANEL									
MS+	23	4		22	4 %				30
MS−	30	3		27	13				43

TABLE X.1 : COLOUR VISION DEFICITS IN PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. Although a higher abnormality rate was observed in those without signs of MS this difference was not statistically significant.

HRR	N	PRO DEUTAN	TRITAN	NOT POSSIBLE	VARYING	MILD	MEDIUM	STRONG	TOTAL
MS+	23	9 %		9 %		9 %		9 %	18 %
MS−	30	3				3			3
PANEL									
MS+	23			4 %					4
MS−	30		3 %	10	3 %				16

TABLE X.2 : COLOUR VISION DEFICITS IN THE FELLOW EYE OF PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. Using the HRR test, more abnormalities were found in patients with signs of MS, with the Panel the reverse was observed. Further, the Panel test could not be performed in a higher percentage of the patients.

HRR	N	PRO DEUTAN	TRITAN	NOT POSSIBLE	VARYING	MILD	MEDIUM	STRONG	TOTAL
RECOVERED	28	11 %				11 %			11%
NON–RECOVERED	25	32	4 %	28 %		24	12 %	28 %	64 % $P<0.001$
PANEL									
RECOVERED	28	7		7	7 %				21
NON–RECOVERED	25	8		44	12				64 $P<0.01$

TABLE X.3 : COLOUR VISION DEFICITS IN PATIENTS WITH AND WITHOUT RECOVERED VISUAL ACUITY. Using both tests, deficits were more frequently observed in those without recovery of visual acuity.

Funduscopy and visual field defects

No difference could be found between funduscopic pictures obtained in patients with other symptoms of MS and those seen in patients without other symptoms of MS. In the fellow eye, however, normal optic discs were significantly more frequently seen in patients without signs of MS (table X.4). Visual acuity appeared to have no relation to funduscopic abnormalities.

FUNDUSCOPY

AFFECTED EYE	N	NORMAL	TEMPORAL PALLOR	TOTAL PALLOR	TOTAL ABNORMALITY
MS+	23	13 %	17 %	70 %	87 %
MS−	30	20	13	67	80
FELLOW EYE					
MS+	23	54 %	10 %	33 %	43 %
MS−	30	77	4	20	24
		P=0.2080			

TABLE X.4 : FUNDUSCOPY IN PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS. No difference could be observed between those with and those without signs of multiple sclerosis with regard to the affected eye. In the fellow eye, however, disc pallor was found in a higher percentage in those with signs of MS.

Visual field defects were found less frequently in the initially affected eyes of patients with signs of MS (39% vs. 47% in those without). In the fellow eyes of these patients, a field defect was found in 17% and 10% respectively of the patients with and without signs of MS.
In patients, however, whose visual acuity did not recover, visual field defects were detected in 72% (compared with 16% in the recovered group), which is statistically significant (Fisher's exact test, P<0.0002).

VISUAL FIELD DEFECTS

AFFECTED EYES	N	CENTRAL	PARA CENTRAL	BOTH	TOTAL ABNORMAL
RECOVERED	28	10 %	17 %	10 %	17 %
NON−RECOVERED	25	62	57	47	72
					P<0.0002

TABLE X.5 : VISUAL FIELD DEFECTS IN PATIENTS WITH AND WITHOUT RECOVERY OF VISUAL ACUITY. In the non−recovered eye, a higher percentage of abnormalities was found compared with the recovered eye which is statistically significant.

Subjective visual complaints

All patients were asked about subjective complaints such as fogginess of vision, changes of visual acuity on exertion, and subjective colour vision changes. Fogginess of vision was found more in the non–MS group, this difference not being statistically significant (MS+: 44%; MS–: 64%). Further, 10 (19%) of the patients complained of visual blurring on exertion (Uhthoff phenomenon).

Contrast sensitivity function in patients after optic neuritis

Table X.6 presents the results obtained by contrast sensitivity function tests (CSF) in patients with and patients without signs of MS. The most frequently encountered abnormality was a decreased CSF for all spatial frequency ranges. There was no significant difference between the groups, neither for the affected nor for the fellow eye.

CSF AFFECTED FREQUENCY	AFFECTED EYE		FELLOW EYE	
	MS+ (N=23)	MS– (N=30)	MS+ (N=23)	MS– (N=30)
LOW FREQUENCY	4 %		9 %	3 %
LOW & MEDIUM	4	3 %		
LOW & HIGH	4		9	
MEDIUM & HIGH	4	3		
MEDIUM FREQUENCY		3		
HIGH FREQUENCY	9	10	13	10
ALL FREQUENCIES	31	43	9	13
TOTAL	56	62	40	26
UNKNOWN		9		9
NORMAL	44	29	60	65

TABLE X.6 : CONTRAST SENSITIVITY ABNORMALITIES IN 53 PATIENTS WITH AND WITHOUT SIGNS OF MULTIPLE SCLEROSIS AFTER OPTIC NEURITIS. In the patients with signs of MS slightly fewer abnormalities were found in the initially affected eye.

CSF proved a good measure of visual function in both recovered and non–recovered eyes (table X.7). There was a statistically significant difference between abnormalities found in the recovered and those found in the non–recovered eye (Fisher's exact test, P<0.002). Again the most frequently encountered dysfunction was a totally decreased curve.

CSF

AFFECTED FREQUENCY	RECOVERED EYES (N=28)	NON–RECOVERED EYES (N=25)
LOW FREQUENCY	4 %	
LOW & MEDIUM	4	4 %
LOW & HIGH		4
MEDIUM & HIGH	4	4
MEDIUM FREQUENCY	11	4
HIGH FREQUENCY		8
ALL FREQUENCIES	18	60
TOTAL	41	84 % P<0.002
UNKNOWN	4	

TABLE X.7 : CONTRAST SENSITIVITY ABNORMALITIES IN RECOVERED AND NON–RECO-VERED EYES. Abnormalities were most frequently found in non–recovered eyes, a depression of all frequencies being most common.

Relation between contrast sensitivity function and other psychophysical tests in eyes after optic neuritis

Analysis including all eyes investigated (N=106) revealed statistically significant correlation between visual acuity and each of the three frequency ranges: the correlation coefficient for low, medium and high frequency being 0.59, 0.65, and 0.71, respectively.
Contingency tables (table X.8 a & b) demonstrate a statistically significant association between colour vision deficits (HRR and/or Panel), visual field defects and CSF. This association was present for all types of visual field defects (central or paracentral, absolute or relative).
Colour vision deficits were only just significantly associated with visual field defects (P = 0.05, not shown in tables). Subjective complaints, e.g. fogginess, silhouettes or a degraded ability to see fine details were associated with CSF, while these complaints were not associated with colour vision deficits or visual field defects.

CSF
LOW FREQUENCY VS.COLOUR VISION

(P<0.001)	N	COLOUR DEFICIT	NORMAL	TOTAL
DECREASED LF	32	19 %	11 %	30 %
NORMAL	74	12	59	70
TOTAL		31	70	100

MEDIUM FREQUENCY VS.COLOUR VISION

(P<0.001)	N	COLOUR DEFICIT	NORMAL	TOTAL
DECREASED MF	32	19 %	11 %	30 %
NORMAL	74	11	59	70
TOTAL		30	70	100

HIGH FREQUENCY VS.COLOUR VISION

(P<0.01)	N	COLOUR DEFICIT	NORMAL	TOTAL
DECREASED HF	32	19 %	11 %	30 %
NORMAL	74	22	48	70
TOTAL		41	59	100

TABLE X.8 a : CONTINGENCY TABLE OF CONTRAST SENSITIVITY ABNORMALITY AND COL-OUR VISION ABNORMALITY IN 106 EYES (EYES OF ALL REEXAMINED PATIENTS)

CSF

LOW FREQUENCY VS. VISUAL FIELD

(P<0.001)	N	VISUAL FIELD DEFECT	NORMAL	TOTAL
DECREASED.LF	32	19 %	11 %	30 %
NORMAL	74	15	55	70
TOTAL		34	66	100

MEDIUM FREQUENCY VS. VISUAL FIELD

(P<0.001)	N	VISUAL FIELD DEFECT	NORMAL	TOTAL
DECREASED MF	32	21 %	9 %	30 %
NORMAL	74	9	61	70
TOTAL		30	70	100

HIGH FREQUENCY VS. VISUAL FIELD

(P<0.001)	N	VISUAL FIELD DEFECT	NORMAL	TOTAL
DECREASED HF	32	21 %	9 %	30 %
NORMAL	74	20	50	70
TOTAL		41	59	100

TABLE X.8 b : CONTINGENCY TABLE OF CONTRAST SENSITIVITY ABNORMALITIES AND VISUAL FIELD DEFECTS IN 106 EYES (ALL REEXAMINED PATIENTS). Visual field abnormalities appeared to occur at all frequencies.

Comparison of visual evoked responses and psychophysical tests in eyes after optic neuritis

When all 106 eyes were considered, the amplitudes of the VERs appeared to be correlated with contrast sensitivity function for all frequencies (correlation coefficient ranging from 0.4 to 0.6, these values are highly significant from $R=0$: $P<0.001$), while there was no association between latency and CSF. These results were found for both VER recordings (pattern presentation as well as pattern reversal).

Amplitudes in VER showed a highly significant association with colour vision deficits, visual field defects and complaints of fogginess (R between 0.5 and 0.6). No relation was found between VER latencies and these clinical parameters.

Hidden visual loss in patients after optic neuritis

Table X.9 presents the incidence of abnormality in all tests performed in 53 recovered ON patients.

TEST	VISUAL ACUITY RECOVERED N=28	VISUAL ACUITY NON–RECOVERED N=25	STATISTICS (Fisher's exact)
PATTERN PRESENTATION	85 %	96 %	NS
AMPLITUDE	64	84	NS
LATENCY	57	60	NS
PATTERN REVERSAL	47	96	P<0.01
AMPLITUDE	43	88	P<0.001
LATENCY	43	72	NS
CONTRAST SENSITIVITY	41	84	P<0.002
COLOUR VISION	19	68	P<0.001
VISUAL FIELD	17	72	P<0.0002

TABLE X.9 : INCIDENCE OF ABNORMALITY OBSERVED USING VARIOUS OPHTHALMOLOGICAL AND ELECTROPHYSIOLOGICAL TESTS AFTER OPTIC NEURITIS AND THEIR RELATION TO VISUAL ACUITY. In non–recovered eyes, both electrophysiologal and psychophysical testing were effective. In the recovered eyes abnormalities were most often found using the more sensitive pattern presentation stimuli.

In non–recovered eyes the VER proved the most worthwhile test, the percentage of abnormality found being 96%. Other tests revealed an abnormality in 68–84%; CSF being the most sensitive test. In the eyes with a visual acuity of 1.00 or more, however, pattern presentation evoked responses outshone all other visual tests; colour vision and perimetry revealing an abnormality in only 16–19%. This implies that in 64% of the patients who recovered after suffering from an attack of ON, the amplitude of PP (associated with subjective visual loss) may be objective evidence of permanent damage to the optic nerve.

Hidden visual loss in patients with and patients without signs of multiple sclerosis

All psychophysical tests were compared with the electrophysiological findings in patients with and patients without signs and symptoms of MS after recovery of visual acuity to 1.00 or more. Results of this comparison are shown in table X.10.

TEST	RECOVERED EYES in MS PATIENTS (N=14)	RECOVERED EYES in NON–MS PATIENTS (N=14)
PATTERN PRESENTATION, amplitude	64 %	64 %
PATTERN REVERSAL, amplitude	50	36
CONTRAST SENSITIVITY	36	36
COLOUR DEFICITS	21	28
VISUAL FIELD DEFECTS	21	7

TABLE X.10 : PERCENTAGE OF ABNORMALITY OBSERVED USING ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL TESTS IN RECOVERED EYES OF PATIENTS WITH AND PATIENTS WITHOUT SIGNS OF MULTIPLE SCLEROSIS. Both PP and PR responses were most often abnormal. Further, a hidden visual loss detected when using perimetry was most often found in patients with signs of MS.

As is presented in this table, both PP and PR testing revealed abnormalities in 71–86% of the patients in both groups. In patients with signs of MS, PR proved slightly more sensitive, though the differences were not statistically significant.
Visual field defects were observed in 21% of those with signs of MS and in only 7% of the patients without signs of MS (not statistically significant, Fisher's exact test, P=0.6). Neither contrast sensitivity function, nor colour vision abnormality tests could distinguish the eyes of patients with signs of MS from those without signs.

Comparison of visual evoked responses and psychophysical tests in fellow eyes

Fellow eyes of patients with and patients without signs of MS were compared with regard to abnormalities found in PP, PR, contrast sensitivity function, colour vision, visual field and funduscopy.

There was a significant difference between both groups with regard to abnormalities found using PR. This difference was both quantitative and qualitative because in the MS group, abnormalities were due to a delay. In the non–MS group, however, amplitudes were abnormal. In PP responses, abnormalities in both groups were due to latency changes.

Further, in the fellow eyes of patients with signs of MS a pallor of the optic disc was more often observed than in those without these signs. These findings may indicate demyelinative damage to the fellow eye due to progression of the disease.

TEST	FELLOW EYE in MS PATIENTS N=23	FELLOW EYE in NON–MS PATIENTS N=30
PATTERN PRESENTATION	22 %	20 %
PATTERN REVERSAL	52	23 P=0.06
CONTRAST SENSITIVITY	40	26
COLOUR VISION	9	13
VISUAL FIELD DEFECTS	18	10
FUNDUS	44	23 P=0.2

TABLE X.11 : EVOKED RESPONSES AND PSYCHOPHYSICAL TESTS IN FELLOW EYE OF PATIENTS WITH AND PATIENTS WITHOUT SIGNS OF MULTIPLE SCLEROSIS. A delay in PR responses and disc pallor was found more frequently in those with signs of MS.

SUMMARY CHAPTER X

The results of tests, using psychophysical methods including colour vision tests, visual field analysis and contrast sensitivity function tests, were recorded for 53 patients after an attack of unilateral optic neuritis. The results obtained from these tests were compared with amplitude and latency changes in pattern presentation and pattern reversal evoked responses.

Colour vision tests revealed no differences in visual function between patients with and patients without signs of multiple sclerosis, either in the initially affected eye or its fellow eye. Between eyes with a visual acuity of 1.00 and those with a visual acuity lower than 1.00, a statistically significant difference was found in the occurrence of colour vision deficits.

Funduscopy of the initially affected eye showed no difference between patients with and those without signs of multiple sclerosis. In the fellow eye of those with signs of multiple sclerosis an abnormality was found significantly more often.

Visual fields parallelled visual acuity; defects occurred more often in non–recovered eyes.

Contrast sensitivity function tests could not distinguish patients with signs of MS from those without, but was a good measure of visual function in eyes both with and without a recovery of visual acuity. A totally decreased curve was the most frequently encountered dysfunction.

A correlation could be found between amplitude in visual evoked responses, contrast sensitivity function, colour vision, visual fields and visual acuity, suggesting a common origin. No correlation with latency could be assessed.

For the detection of hidden visual loss in eyes with a visual acuity of 1.00 or more, pattern presentation amplitudes proved to be most useful. In patients with signs of MS, hidden visual loss was not encountered more often than in those without signs of MS.

In the fellow eye of patients with signs of MS, pattern reversal latency changes and fundus abnormalities were found significantly more often than in patients without these signs.

Conclusively, electrophysiological tests proved most sensitive in the evaluation of visual loss after unilateral optic neuritis both in the initially affected eye and its fellow eye.

'Until we know the etiology, I believe we must continue with the pragmatic definition of multiple sclerosis as a clinical entity whose signs and symptoms indicate lesions 'scattered in time and space' in the central nervous system white matter.
Two optic nerves are not discrete enough to be multiple in my view.'

Kurtzke, 1985

CHAPTER XI

NEUROLOGICAL ABNORMALITIES IN 53 PATIENTS AFTER OPTIC NEURITIS

Fifty–three patients of the 110 patients, seen in the acute stage of ON, were reexamined by a neurologist. Twenty three of these patients were assessed as showing signs of MS on the basis of either the case history or physical examination. Table XI.1 presents the signs of MS found in 23 patients after optic neuritis.

SIGNS OF MULTIPLE SCLEROSIS

Sensory impairment	61 %
Diplopia	43
Paresis upper extremities	17
Paresis lower extremities	22
Absent abdominal reflexes	4
Speech difficulties	4
Chronic fatigue	23
Intrathecal IgG synthesis	9

TABLE XI.1 : SIGNS OF MULTIPLE SCLEROSIS IN 23 REEXAMINED PATIENTS AFTER OPTIC NEURITIS

All other possible symptoms indicative of MS in all patients who were reexamined using VER recording and psychophysical tests were retrospectively examined. Sensory disturbances in upper and lower extremities could be assessed in 32% of the patients.

	SYMPTOMS (N=53)	
	paraesthesia	numbness
BEFORE ON	9 %	4 %
DURING ON	13	4

TABLE XI.2 : SYMPTOMS OF MS BEFORE AND DURING ON IN 53 PATIENTS

Of the patients who were already showing slight symptoms of MS before or during the ON attack (N=17), 11 (65%) later developed objective signs of MS, whereas of those who had not reported these subjective symptoms (N=36), 12 (33%) later showed objective signs of MS (not statistically significant, Fisher's exact test P=0.06).

Epidemiology and ophthalmological features of 23 reexamined patients

Of the reexamined patients (40 females, 13 males) 23 had developed signs of MS, 20 of whom were female and 3 male. This implies that in 50% of the women and in only 30% of the men other signs of MS were found. This difference is not statistically significant. the ratio of female to male patients in the present population of patients with signs of MS is 7 : 1, whereas in literature a ratio of 1.5–2 : 1 is reported.
Of those between 20 and 40 years of age, 47% developed signs of MS, whereas in those under 20 and over 40, this risk was 31%.
No relation could be assessed between pain, severity of visual impairment and duration of recovery. There was a clear difference between both groups, however, in the number of patients in whom visual acuity recovered after the optic neuritis, though the difference is not statistically significant (20% and 44% respectively in patients with and those without signs of MS). Further, a visual acuity of less than 1.00 in the acute stage in the fellow eye was more often found in those who later developed signs of MS to a statistically significant degree (Fisher's exact test, $P<0.03$).
A recurrence of the ON was not more frequently found in patients with signs of MS.

Electrophysiology of the affected eye in the acute stage of ON offered no predictive indication with regard to the development of MS, neither in amplitude nor in latency. In the fellow eye of the patients, contrary to findings at the second VER, no difference in amplitude or latency abnormality could be observed.

SUMMARY CHAPTER XI

In 23 of the 53 reexamined patients, signs of multiple sclerosis were found. Subjective signs in all 53 patients were recorded retrospectively. Subjective signs were reported more frequently by those who developed other signs later. Female patients developed a higher percentage of these signs than male patients. Neither clinical nor ophthalmological findings in the acute stage were predictive with regard to the development of MS.

CHAPTER XII

DISCUSSION AND CONCLUSIONS

Most patients suffering from multiple sclerosis experience an impairment of visual function in the course of the disease, indicating an involvement of the optic pathway in the demyelinative process. This involvement may present itself as an attack of acute optic neuritis or as a chronically progressive visual loss. Conversely, a case of idiopathic optic neuritis, for which no cause can be discerned at the time of the attack, may indicate a higher risk of developing multiple sclerosis.

In the present study, visual function in idiopathic optic neuritis has been analysed by electrophysiological and psychophysical tests with the aim of assessing the predictive value of these tests with regard to the development of signs of MS. Additionally, the sensitivity of various parameters of the VER and psychophysical tests have been evaluated as for their usefulness in the detection of visual loss after ON.

Patient selection and clinical features

In order to obtain a group of patients with idiopathic optic neuritis, careful selection and follow–up is required to exclude patients with other causes of acute visual loss. According to other studies the incidence of these causes varies greatly. This may be due to the criteria used in patient selection and the diagnostic tools available to the clinician. Of all causes of optic neuritis multiple sclerosis is the most frequently observed. Nevertheless, percentages ranging from 1.5–69% have been reported, which variance is probably due to the above–mentioned variables (Bagley, 1952; Benedict, 1942). For the same reason, the cause of the attack of ON may remain unknown in 1–56% of the patients (Benedict, 1942; Bagley, 1952). Variation in the risk rate of idiopathic optic neuritis patients to develop multiple sclerosis is due to differences in follow–up and patient selection and range from 8–85% (Cohen et al., 1979; Kurtzke, 1985). In the patient selection of the present study, 15% of the patients referred to the Eye Hospital suspected of an attack of optic neuritis were already suffering from MS. In 10% of the patients another cause of optic neuritis was found, either in the acute stage or after follow–up. A vascular cause or a compressive lesion was most frequently observed (17% for both). Due to the retrospective nature of this study, a large percentage of the patients had to be discarded because of insufficient data, either clinical or electrophysiological. Thus, by retrospective selection and electrophysiological examination a homogenous group of idiopathic patients was obtained.

Some of the patients selected had already experienced slight, subjective symptoms of neurological involvement outside the visual system. Some authors excluded these patients from follow–up, which may have influenced the conclusions reached in relation to the risk rate of later development of objective signs (Hutchinson, 1976; Kahana et al., 1976).

A relatively large percentage of the idiopathic optic neuritis patients were female (76%) and between 20 and 50 years of age (87%) compared with other studies in which patients with other causes of ON were also included (51–70% females; Bagley, 1952; Cohen et al., 1979; age 20–50: 56–88%; Bagley, 1952; Kurland et al., 1966). No difference was found in the present study between the ophthalmological features of patients suffering from idiopathic optic neuritis and of those with ON of other origin.

Comparison of pattern presentation and pattern reversal tests in the diagnosis of optic unilateral neuritis

Electrophysiological examination using pattern presentation stimuli of a patient suffering from an attack of unilateral, idiopathic optic neuritis results in attenuation of the responses obtained using large check (80' and 40') or in absence of responses found using small check stimuli (20' and 10'). For the detection of abnormalities 40' checks are the most sensitive.

Although in most studies on evoked responses only latency changes were assessed, in the present study quantitative criteria for pathology such as a diminished interocular ratio (IOR) for amplitude and an increase in interocular difference (IOD) for latency were used in addition to the lower limits and upper limits of normal. The reason for this was that visual function in optic neuritis is primarily related to amplitude (Halliday et al., 1972; Diener, 1980), whereas in demyelinative disease abnormality is mainly due to changes in latency. Normal values for the quantitative criteria were assessed by the statistical analysis of data on a control group consisting of 47 normal subjects. Numerical values of amplitudes in this group revealed a logarithmic distribution of amplitude. By logarithmic transformation, the assessment of lower limits of normal for amplitude was made possible. Further, sustained by the Student's t–test normal values for IOR and IOD could be calculated.

For the assessment of amplitude abnormality in PP, absence of response proved most useful (54–91% abnormality). Further, the IOR revealed more pathology than the lower limit of normal for amplitudes. As to latency, both IOD and upper limits were equally effective. However, as frequently no response could be recognized after pattern presentation stimulation, amplitude remains the most important parameter. Comparison with literature was not possible as there are

no data on pattern presentation evoked responses in optic neuritis. Both Aminoff & Ochs (1981) and Riemslag et al. (1982) reported on pattern presentation in MS patients.

In pattern reversal evoked responses no difference in results using the various check sizes and luminance levels could be observed. Responses were less frequently absent (27–48%) compared with results with pattern presentation stimuli. Halliday et al. (1972) and Sharokhi et al. (1978) report an absence of response in 6 and 60% of their patients, respectively. IOR in pattern reversal responses could reveal only slightly more abnormality (21–37%) than the lower limit of normal (14–37%). Sharokhi et al. (1978) observed this in only 2% of his patients.

In studies on ON patients, the latency of pattern reversal responses has been most frequently assessed. In the present study, percentages of abnormality ranged from 91–94%. This is in agreement with literature; abnormality ranging from 76%–100% (Sharokhi et al., 1978; Halliday et al., 1972). Further, Sharokhi et al. (1978) report an abnormal IOD in 8% compared with 63–89% in this group. In the present study, IOD did, however, not reveal more abnormality in addition to the upper limit of normal criterion.

Conclusively, in PP the IOR is useful in assessing amplitude changes, whereas for latency the IOD in PP and PR may not reveal pathology in addition to that found by using the upper limit of normal.

Responses in the fellow eye may appear normal, stimulation using large check pattern presentation stimuli revealing no abnormality. Variance of amplitude and latency in responses of fellow eyes is however larger than in the control group. Moreover, when using small checks (10') an abnormality could be traced in the clinically unaffected eye for amplitude in 16% (due to absence of response). In pattern reversal responses, large checks detected abnormal latencies in 30% of the clinically unaffected fellow eyes. This suggests a systemic process extending itself to the fellow eye already taking place at the time of the first clinical presentation of the idiopathic optic neuritis patient. In literature, little is said on the fellow eye during the acute stage of ON. Halliday et al. (1972) observed an abnormal latency in 2 (11%) of the 19 fellow eyes at the time of the first attack. Wildberger et al.(1976) found a pathological amplitude in 7 out of the 15 fellow eyes (47%).

To conclude, pattern presentation responses in the acute stage of an optic neuritis are more sensitive to amplitude changes. In the acute stage, use of PP increased the diagnostic yield of PR with regard to amplitude by 18%. Con-

versely, pattern reversal responses may give more information on latency abnormalities because the absence of response is less frequently found when using this method of stimulation. In the present study the use of PR increased the diagnostic yield of PP by 35% for latency. This difference in sensitivity was also found in the fellow eye of all patients.

Comparison of pattern presentation and pattern reversal evoked responses in the follow–up of optic neuritis

At follow–up, there was again a difference in the number of absent responses between PP (8–57%) and PR (9–17%), depending on the check size used. Further, the IOR of amplitudes proved more useful than the criterion of lower limits of normal in PP, which difference was not found in PR. As to latency, taking the IOD revealed most pathology in PP (4–47%), whereas in PR the upper limit of normal for latency was more effective (47–53%).

Others have observed pathological responses in 8–27% with the use of IOR in pattern reversal responses (Tackmann et al., 1979; Bürki, 1981; Neima & Regan, 1984). Further, numerical changes in amplitude were reported in 67% of the patients studied by Asselman et al. (1975), a finding which could not be confirmed by the present study. In PR the IOD of amplitude revealed an abnormal response in 14–67% according to Asselman et al. (1975) and Kupersmith et al. (1983).

No studies are available on these changes in PP. Finally, in PP IOR and IOD may increase the diagnostic yield, whereas in PR a numerical change in latency may be most effective diagnostically.

Electrophysiological follow–up of patients with responses obtained from the affected eye could not distinguish between those who, in the course of the follow–up, developed signs of MS and those who did not develop these signs.

Complete recovery of amplitude or latency in PP for all stimuli was found in 14 (26%) and three (6%) of the patients, respectively. Recovery of latency or the development of a delay bore no relation to the development of signs of MS, nor did amplitude changes. In patients without signs of MS, an increase in latency was observed even more frequently than in those with signs of MS in PP. Due to the fact that responses in the acute stage were absent in a large percentage of the patients, assessment of delay was also impossible, which makes changes in delay difficult to assess.

Amplitude recovery in relation to all four stimuli was less frequently observed in those with a visual acuity of less than 1.00. This is in agreement with the correlation between amplitude and visual acuity described by Halliday (1972) and Diener (1980).

In the pattern reversal responses, amplitude returned to normal for all stimuli in 17 of the patients (32%), whereas for latency this occurred in only four (8%). Changes in amplitude and latency, either becoming pathological or normal, could not be said to be predictive of the development of MS. Recovery of latency has been reported by Bynke et al. (1980) in 17% of his patients 2–8 years after the attack. As the follow–up period in the present study ranged from 8 weeks to 4 years, a higher percentage of patients with normal latency than has been now observed might be found after increasing the length of the follow–up. Matthews et al. (1977) and Diener et al. (1980), however, observed a normalization of latency in 21 and 45% respectively, of the patients with signs of MS who had previously suffered from an attack of ON. This suggest there may be no relationship between latency and the presence of a demyelinating lesion outside the visual system as far as the initially affected eye is concerned.

Comparison of the diagnostic yield of the two methods revealed that pattern presentation may increase the detection rate of abnormal amplitudes (ranging from 8–28%, depending on the check size used). The responses obtained using pattern reversal increase the diagnostic yield by 9–35% for latency (depending on the check size used) as pattern reversal responses are more sensitive indicators of latency changes. This was especially so for patients with signs of MS and the fellow eye in these patients. This finding is contrary to studies by Aminoff & Ochs (1981) and Riemslag et al (1982) who report a greater sensitivity of the pattern presentation evoked responses in MS patients. However, as they used checks of 50' and 20' & 55' respectively, their methods gave less information compared with the more versatile method used in the present study. Further, Riemslag et al. used a TV equipment for stimulation in both methods, so that the difference may be attributed to the technique used.
In the non–recovered eye (i.e. with a visual acuity of 1.00 or less) amplitude in PP was affected most. In the recovered eyes, PP also detected an abnormality for amplitude which may indicate 'hidden visual loss'. In pattern reversal, mostly latency changes which were in general not correlated with visual acuity were found in this group. These findings again confirm the difference in sensitivity between the methods (PP and PR) which was also observed in the acute stage of ON. In the initially unaffected fellow eye, latency changes, detected by pattern reversal stimuli, were more frequently encountered in those with signs of MS (43%) compared with those without signs of MS (17%). The percentage found in patients with signs of MS is in agreement with the percentages reported by others on possible and probable MS patients who did not suffer from visual impairment during the course of their disease (15%–83%, Sharokhi et al., 1978; Halliday et al., 1973).

From the above it may be concluded that the use of IOR and IOD in PP at follow–up are useful indicators in the assessment of pathology. In pattern reversal responses, both IOR and lower limits of normal for amplitude together with the upper limit of normal for latency may be effective indicators. Complete recovery of visual evoked responses after ON was seen in only four patients using PP and seven using PR. Changes found using pattern presentation or pattern reversal cannot be said to predict the development of MS. However, in the fellow eye, latency changes detected by pattern reversal may indicate demyelinative damage. Further, amplitude changes in the acute stage detected using PP stimuli may indicate subclinical visual loss related to affection by the disease. Pattern presentation responses increase the diagnostic yield for amplitude, whereas pattern reversal does so for latency. This difference in sensitivity has also been observed in patients with and patients without recovery of visual acuity. PP responses were also more sensitive indicators with regard to the detection of subclinical loss because of amplitude changes in those with a visual acuity of 1.00 or more.

Visual function in the follow–up of 53 patients after optic neuritis

Comparison of the visual evoked response with psychophysical tests revealed that amplitude was associated with colour vision deficits, visual field defects and contrast sensitivity function. This finding suggests a common origin of the function expressed by these tests. In the acute stage of optic neuritis, amplitude may be attenuated due to a blockage of optic nerve fibres. After recovery of the acute symptomatology, patchy or diffuse loss of fibres may lead to permanent visual impairment reflected in amplitude attenuation and psychophysical defects. A retinal cause of these changes in visual function is unlikely, as pattern electroretinograms, probably generated by ganglion cells, show no abnormality either in the acute or in the recovery stage of optic neuritis (Bobak et al., 1983; Kirkham & Coupland, 1983). The results of the latter were confirmed by the present study. Contrary to findings in glaucoma patients, in whom the PERG may be disturbed in an early stage of the disease (Van Lith et al., 1984), in ON patients this method could not reveal any damage at the retinal level.

Several authors compared the VER with psychophysical tests. Wildberger et al.(1976) conclude that colour vision returns to normal after ON, whereas latency may remain prolonged. Arden & Gucukoglu (1978) report that when using contrast sensitivity function and VER in ON patients, an equal percentage of abnormality is revealed. The diagnostic yield of each method depends greatly on its sensitivity, this makes it difficult to compare various psychophysical tests with the VER in the present study. Neima & Regan (1984) observed a relation

between amplitudes in VER and contrast sensitivity function. They report a qualitative correlation between responses elicited using various check sizes and the characteristic changes in contrast sensitivity function.

In the present study no relation could be detected between latency and visual function (as expressed by visual acuity, colour vision tests, contrast sensitivity function and visual field defects). Van Dalen & Greve (1981) also observed a discrepancy between findings on perimetry and latency in the VER, a finding confirmed by Meienberg et al. (1982). As latency reflects the conduction velocity in the optic nerve, visual function may not be affected by changes in conduction velocity. According to Ulrich & Groebke (1983) an extensive amount of demyelination found at post mortem examination may still be compatible with a well-preserved visual acuity.

Finally, one may say that the varying sensitivity of tests makes comparison difficult. However, amplitudes in VER appear to have a direct relation to visual function such as tested by psychophysical tests and Snellen visual acuity. Latency changes reflect changes in conduction velocity and have no relation to visual function. Changes in velocity may however finally lead to complete loss of axonal conduction reflecting itself in amplitude loss (detected by amplitude changes in PP). This decrease in the number of axons conducting the response to optic stimuli may also explain the subjective complaints of patients, as the loss of nerve fibres may be too slight to produce a decrease of Snellen visual acuity. Furthermore, the increase of subjective complaints on exertion reported by 19% of the patients may be related to changes in conduction velocity passing a critical value and thus causing a blockage in a proportion of the nerve fibres. McDonald & Sears (1977) report a decrease in conduction velocity with temperature changes in vitro.

Latency and disc pallor appeared to be associated with the development of MS when found in the initially unaffected fellow eye. Demyelinative changes may therefore be associated with changes in latency and more indirectly to a loss of visual function.

Psychophysical tests and visual function in 53 patients after optic neuritis

Psychophysical tests in the initially affected eye could not distinguish between those with and without signs of MS. Colour vision deficits were observed in 11–64% (recovered and non–recovered eyes) of the initially affected eyes. Comparative figures in other studies range from 10–100% (Rigolet et al., 1979; Griffin & Wray, 1978). In most studies, however, the more sensitive Farnsworth 100 Hue tests was used. In the present study the HRR and Panel D15 were preferred because of the complementary part of the visual field they cover

(Pinckers, personal communication). In the initially unaffected fellow eye, no difference in colour deficit rate could be observed between patients with and without signs of MS (9 and 13%, respectively). In 64% of the MS patients studied, Pinckers et al. (1983) report a colour vision deficit, using the 100 Hue.

Contrast sensitivity function was disturbed in 60% of all initially affected eyes. A totally decreased curve was most frequently found. Frisén & Sjostrand (1978) observed this abnormality in all patients studied in the acute stage of ON. After recovery, however, depression of low and medium frequencies was more commonly found (Regan et al., 1977, 1982). The percentage of abnormality observed in the present study is relatively low compared with that reported by others (70–100%; Regan et al., 1982; Zimmern et al., 1979). In the fellow eye, no difference in CSF abnormality rate between those with and those without signs of MS could be observed.

Visual field defects were detected in 40% of the patients studied (central in 36%, paracentral in 39%). This percentage is relatively low compared with literature in which a defect is reported in 36–92% of the recovered ON eyes (Patterson & Heron, 1980; D'Cruz & Ellenberger, 1983). In 81% of the possible MS patients a defect has been reported (Patterson & Heron, 1980). Visual field defects were found in 18% of the fellow eyes in patients with signs of MS compared with 14–75% in literature (Ellenberger & Ziegler, 1977; Patterson & Heron, 1980).

Finally, psychophysical tests were unable to differentiate between those with and those without signs of MS both in the initially affected and the unaffected fellow eye. Further, the percentage of abnormalities detected by each test was relatively low compared with those reported by others. This may be due to the methods used and the severity of the demyelinating disease in patients studied by other authors. Only the funduscopic findings in fellow eye were more often abnormal in patients with signs of MS (43%, compared with 24% in those without other signs of demyelinating disease).

Hidden visual loss in patients after optic neuritis

Hidden visual loss in the previously affected eye was revealed best by amplitude changes in pattern presentation responses (64%). Again this percentage was relatively low compared with other results (60–100%; Kjaer, 1983; Halliday et al., 1973) reporting on MS patients without a history of visual impairment. The difference in pathology rate may be due to the severity of the disease in the patients studied and the length of the follow–up. Further, in most studies latency of the responses was used in the assessment of pathology in the VER.

Hidden visual loss was not a factor on which one could discriminate between those with and those without signs of multiple sclerosis as far as the initially affected eye was concerned. Psychophysical methods were less sensitive than visual evoked responses, CSF revealing abnormality in only 36% (in literature 42–100%; Regan et al., 1977; Zimmern et al., 1979). Of all psychophysical methods used, CSF proved most sensitive. Moreover, it appeared to be associated with subjective complaints, contrary to colour vision deficits and visual field defects.

Neurological abnormalities in patients after optic neuritis

In 23 of the 53 reexamined ON patients (44%), signs of MS were found after a follow–up period ranging from eight weeks to 4 years (average 0.8 years). This percentage is relatively large compared with findings by others, reporting MS in 25–35% of the ON patients (Cohen et al., 1979). Several factors influence the risk factor in this and other studies. First of all, patient selection in the present study was done using electrophysiological examination. Further, the retrospective nature of the study made it possible to exclude other causes of ON. This, however, also influenced the selection criteria, as not all patients seen in the acute stage of the ON were examined neurologically at the time of the attack. Thus, patients with subjective signs of MS preceding or accompanying the attack of ON were also included. Hyllested & Müller (1961), Carroll (1952), Rose (1970), Nikoskelainen & Riekkinen (1974), who also included patients with slight neurological symptoms before or during the attack, report a risk ranging from 45–55%. Moreover, most authors classified their patients as 'definite' (Schumacher criteria, 1965), whereas in the present study patients were classified as probable and possible.

In the present study, clinical symptoms in the affected eye at the time of the first ON attack appeared to have no predictive value with regard to the development of signs and symptoms of MS. In literature, there is still considerable controversy on this. In the fellow eye, however, a visual acuity of 1.00 or less at the time of the attack was found more often in those developing signs of MS at a later date. Furthermore, female patients developed signs of MS in 50% of the cases, whereas male patients did so in only 30%. This implies that female patients have a higher risk of progression to MS after ON. This risk factor has also been reported by Windmöller (1910) and Cohen et al. (1979). The female/male sex ratio in 10 incidence studies of multiple sclerosis is 1.9:1 (Acheson, 1972), whereas in the present study it is 7:1. A similar preponderance of MS in female patients after optic neuritis has been reported in other surveys of optic neuritis

(Bradley & Whitty, 1967; Leibowitz et al., 1966; Percy et al., 1972). Wikström et al. (1980), however, did not observe this sex difference in a group of MS patients whose disease started with ON. Recently, Parkin et al. (1984) reported that even in patients with bilateral ON attacks, no increased risk of MS could be observed after a follow—up ranging from 5–30 years. In the present study also, no increased risk of progression to MS in patients with recurrent ON could be observed.

CONCLUSIONS

1. Selection of patients with idiopathic optic neuritis requires ophthalmological and electrophysiological examination and follow–up to exclude patients with other causes of an acute visual loss.
2. Selection criteria such as electrophysiological abnormalities, the presence of signs of demyelination outside the visual system, advanced neurological examination (lumbal puncture, NMR–scan) may influence the risk rate of the development of multiple sclerosis in idiopathic optic neuritis patients.
3. The epidemiology of patients with idiopathic optic neuritis reflects that found in patients suffering from multiple sclerosis, for both age and sex.
4. The ophthalmological features of the idiopathic optic neuritis patient are conform to those seen in patients with optic neuritis due to a defined cause.
5. Statistical analysis of electrophysiological responses in a control group may reveal other criteria for the assessment of pathology in a patient group. In pattern presentation, the interocular ratio for amplitude and the interocular difference for latency increase the diagnostic yield. For pattern reversal responses, the upper limit of normal for latency remains the most effective criterion for pathology.
6. Electrophysiology of the affected eye in the acute stage of an idiopathic optic neuritis is characterized by amplitude attenuation or absence of the response in pattern presentation and pattern reversal. Latency changes play a minor role in the detection of pathology.
7. In the acute stage, amplitude changes in the clinically unaffected 'fellow eye' may be a sign of a more systemic affection; latency changes in pattern reversal after optic neuritis confirm this suspicion.
8. Only by changes in the initially unaffected 'fellow eye', the VER can distinguish between patients with and those without signs of multiple sclerosis.
9. In the patients after optic neuritis the amplitude of evoked responses is associated with visual acuity, colour vision deficits, visual field defects and contrast sensitivity function, suggesting a common origin of these visual functions.
10. Latency changes and optic disc pallor in the 'fellow eye' after optic neuritis may be due to subclinical affection by a systemic demyelinative process.
11. 'Hidden visual loss' is a common feature in patients after optic neuritis; amplitude in pattern presentation and pattern reversal evoked responses being its most sensitive detector. It is, however, not found more often in combination with signs of multiple sclerosis outside the visual system.

SUMMARY

In 1884 the relation between optic neuritis and multiple sclerosis had already been described by Parinaud. After recovering from the acute visual loss, the patient suffering from optic neuritis may develop signs and symptoms of demyelinating disease outside the optic pathway.

In 1–56% of the patients examined with an acute visual loss and without abnormalities in media or fundus, it is possible to diagnose multiple sclerosis. Further, the risk rate of developing multiple sclerosis in patients with uncomplicated optic neuritis varies from 8–85%. The range in the percentages is due to variation in the diagnosis of optic neuritis and multiple sclerosis.
Predictive factors in literature with regard to the development of multiple sclerosis after optic neuritis include age, sex and recurrent attacks of optic neuritis. Apart from this, intrathecal IgG synthesis and HLA–Dr2 typing may increase the risk of MS.
In the present study, the short term and long term prognosis of visual function in idiopathic optic neuritis has been assessed by means of standardized ophthalmological, psychophysical and electrophysiological examination. Further, the predictive value of visual function with regard to the development of multiple sclerosis was evaluated.
Since, in 1972, Halliday reported on delayed pattern reversal evoked responses in a high percentage of patients suffering from an attack of optic neuritis this method has become widely used in clinical practice. In ON patients, the characteristic changes during the acute attack include an attenuation or absence of amplitude and a delay. Apart from ON patients, the pattern reversal visual evoked response has also found a clinical application in MS patients with and MS patients without a history of visual impairment. In definite MS patients and those who suffered from an attack of optic neuritis during the course of the disease, a delay is observed in up to 100%. In those without symptoms of involvement of the visual system by the disease, a delay may prove the presence of subclinical damage, thus providing additional evidence for the presence of a systemic process in those for whom the diagnosis based on the clinical presentation remains uncertain.
Apart from pattern reversal evoked responses, pattern presentation evoked responses have been reported to be of use in the detection of a delay in MS patients. In the present study, both methods have been used in the acute stage of optic neuritis and after follow–up and the results compared.

In addition to evoked responses, a wide range of psychophysical tests are used in literature for the detection of visual loss after optic neuritis (either isolated or during the course of MS). In the present study, contrast sensitivity function, colour vision tests and visual field analysis have been evaluated.

Patients were selected on the basis of electrophysiological changes. Of the 282 patients referred to the Eye Hospital in the period from 1977–1983 110 fulfilled these criteria. Epidemiology of these patients and symptomatology in the acute stage of the first attack in these patients did not differ from that reported in literature. The majority of the patients were female and had suffered from an attack between their 20th and 50th years. Further, they had experienced severe visual loss and complained of painful eye movements. On ophthalmological examination, a central scotoma and a normal optic disc were frequently observed. A comparison of pattern presentation (PP) and pattern reversal (PR) evoked responses in 110 patients suffering from a unilateral optic neuritis was made in the acute stage to determine the differences in sensitivity of both methods. PP responses showed a disappearance of responses in a high percentage of the patients, which makes assessment of a delay impossible. As pattern reversal evoked responses were absent in a lower percentage of the patients than pattern presentation evoked responses, the first method appeared to be more sensitive for the detection of a delay. However, with both stimulation methods, amplitude changes were most frequently observed. Of the additional criteria for pathology, based on observations in an age–matched control group, only the interocular rate of amplitude increased the diagnostic yield of pathology.

The good short term prognosis of ON was confirmed by the subjective improvement of visual acuity in the affected eye within a month and recovery to 1.00 in half of the patients. At follow–up after eight weeks to 4 years, 23 (44%) of 53 reexamined patients had developed objective signs of multiple sclerosis. Sensory impairment and diplopia were most frequently found. The percentage of patients in this study observed developing signs of MS after ON is relatively high compared with other studies.

Patients with signs of MS and patients without these signs could not be distinguished on the basis of either PP or PR responses in the initially affected eye. The difference in sensitivity of the methods was again observed in the affected eye after optic neuritis. PR proved more sensitive with regard to the detection of latency changes in patients with signs of MS compared with those without these signs. PP responses detected amplitude abnormality in a high percentage of eyes with a visual acuity of 1.00 or more, which may indicate hidden visual loss.

When comparing the results of the first examination with the results of the second for both methods, changes in amplitude or latency were found to be not associated with the development of MS. The PP responses had returned to

normal in only four patients and in only seven had the PR responses returned to normal for both parameters. This is in agreement with literature. For both methods, amplitudes of all stimuli were correlated with visual acuity and with subjective loss in visual function reported by the patient.

In the initially unaffected fellow eyes, PR evoked responses detected changes in latency in a higher percentage of those with signs of MS compared with those without these signs. Further, in these eyes a response in the acute stage was more often absent compared with the control group. These findings may indicate subclinical affection of the fellow eye by the same process affecting the other eye.

Results of psychophysical tests showed relatively low abnormality compared with literature, which may be due to the relatively insensitive tests used.

The presence of hidden visual loss (i.e. subjective loss of visual acuity in the presence of a Snellen 1.00 or more) is detected best with amplitude changes in pattern presentation responses. Further, a decreased contrast sensitivity function (all frequencies) was observed in these patients. The presence of 'hidden visual loss' is, however, not predictive for the presence of neurological symptoms outside the visual system.

A comparison of visual evoked responses with psychophysical tests revealed a relation of amplitude to colour vision deficits, visual field defects and CSF changes. This finding suggests a common origin of the function expressed by these tests.

Latency changes reflecting changes in conduction velocity have no relation to visual function. Both latency and optic disc pallor may be associated with the development of signs of MS outside the optic pathway when found in the initially unaffected eye.

Finally, the short term and long term prognosis of visual function in patients suffering from unilateral optic neuritis are not predictive of multiple sclerosis. In those with subclinical affection of the optic nerve in the fellow eye, however, the risk of developing signs of MS outside the visual system after ON may be increased.

SAMENVATTING

De relatie tussen neuritis optica (NO) en multiple sclerose (MS) werd reeds in 1884 door Parinaud beschreven. Na herstel van het acute visusverlies kunnen in de neuritis optica patiënt symptomen van demyelinisatie buiten het visuele systeem ontstaan. In 1–56% van de NO patiënten kan de diagnose MS reeds ten tijde van de neuritis gesteld worden. Voorts varieert het risico op het ontwikkelen van MS na een ongecompliceerde neuritis optica van 8–85 %. Deze uiteenlopende percentages kunnen worden verklaard door verschillen in de diagnose van NO en MS. Voorspellende factoren met betrekking tot het ontwikkelen van MS na NO zoals genoemd in de literatuur omvatten leeftijd, sexe, en recidiverende aanvallen van neuritis optica. Verder blijken IgG synthese in de liquor ten tijde van de NO en HLA–Dr2 antigeen typering een verhoogd risico op te leveren.

In de huidige studie zijn de oogheelkundige aspecten van de relatie tussen NO en MS nagegaan. De prognose van de visus op korte en lange termijn werd bepaald met behulp van gestandaardiseerde oogheelkundige, psychophysische en electrophysiologische methoden. De voorspellende waarde van de resultaten ten aanzien van het ontwikkelen van MS werd nader geëvalueerd.

Sinds Halliday in 1972 afwijkende responsies met patroon omkerings 'visual evoked responses' (VER) in een hoog percentage van de NO patiënten beschreef is het klinische gebruik van deze methode toegenomen. Karakteristieke veranderingen van de responsie bestaan uit een verlaging van de amplitude en een verlenging van de latentie–tijd ('delay').

Behalve in neuritis optica patiënten bleek ook in een hoog percentage van de patiënten met MS een 'delay' aanwezig, zowel in patiënten met visus verlies tengevolge van de ziekte als in degenen die geen neuritis optica in het beloop van hun ziekte doormaakten. Bij 'definite' MS patiënten en bij degenen die een aanval van neuritis optica doormaakten, kan een 'delay' in bijna 100% van de gevallen worden waargenomen.

Het is gebleken dat naast de PO methode de patroon presentatie methode (PP) een plaats verdient bij de detectie van een 'delay' in MS patiënten. In deze studie zijn beide methoden gebruikt in het acute stadium van NO en in de follow–up. Het verschil in gevoeligheid van beide methoden is nader geanalyseerd.

Visus verlies na een neuritis optica, hetzij klinisch manifest, hetzij subklinisch, kan voorts worden opgespoord door een groot aantal psychophysische methoden.

In deze studie zijn de contrast gevoeligheids methode (CSF), kleurenzien testen en perimetrie gebruikt.

Patiënten werden geselecteerd op basis van electrofysiologische criteria. Van de 282 patiënten die in de periode 1977–1983 voor electrodiagnostisch onderzoek naar het Oogziekenhuis Rotterdam werden verwezen voldeden 110 aan deze criteria. Bij deze patiënten was de oorzaak van de neuritis optica onbekend gebleven. Epidemiologie en symptomatologie van deze patiënten in het acute stadium verschilden niet van de in de literatuur beschreven frequenties. De meerderheid van de patiënten was van het vrouwelijk geslacht en in de leeftijd van 20–50 jaar. De visus was sterk verlaagd en velen klaagden over pijnlijke oogbewegingen. Bij oogheelkundig onderzoek werden frequent een centraal scotoom en een normale papil gevonden.

Om het verschil in gevoeligheid tussen de PO en de PP methode te bepalen werden de resultaten van beide methoden verkregen in de 110 NO patiënten vergeleken. Bij een groot deel van de patiënten kon met de PP methode geen responsie worden verkregen, hetgeen het vaststellen van een 'delay' onmogelijk maakt. Daar de PO responsies bij een veel kleiner deel van de patiënten afwezig waren, is deze laatste methode veel gevoeliger voor het detecteren van een 'delay'. Ondanks het verschil in gevoeligheid waren amplitude veranderingen, hetzij verlaging of afwezigheid, het meest opvallend in beide methoden. Van de criteria voor pathologie, gebaseerd op de resultaten verkregen met beide stimu-latiemethoden in een controle groep, bleek, naast de normaal waarde voor latenties, alleen het interoculaire verschil in amplitude de diagnostische gevoelig-heid van beide methoden te verhogen.

De goede prognose op korte termijn werd bevestigd door herstel van de visus tot 1.00 of meer in de helft van het aantal patiënten. Ten tijde van de follow–up (na 8 weken tot 4 jaar) werden bij 23 (44%) van de 53 opnieuw onderzochte patiënten tekenen van MS waargenomen. Achter– en zijstreng stoornissen werden het meest frequent aangetroffen. Het percentage patiënten met tekenen van MS is relatief hoog ten opzichte van andere studies.

De VER herstelde zich bij de patiënten met symptomen van MS niet anders dan bij degenen die deze symptomen niet vertoonden. Het verschil in gevoeligheid van beide methoden (PO en PP) werd ook tijdens de follow–up duidelijk. Met name bij patiënten met tekenen van MS bleek de PO methode gevoeliger voor veranderingen in de latentie van de responsie dan de PP methode. Bij patiënten met een herstel van de visus tot 1.00 of meer werden in 64% van de gevallen met de PP methode afwijkende amplitudes ontdekt, hetgeen kan duiden op subklinische schade.

Volledig herstel van de PO responsies trad bij zeven patiënten op, terwijl de PP responsies slechts bij vier patiënten volledig normaliseerden. In beide methoden bleek de amplitude gecorreleerd te zijn met de visus en met subjectief visusver-lies.

In het niet–aangedane 'fellow eye' bleek ten tijde van de NO aanval met de PO methode vaker een 'delay' aantoonbaar bij patiënten met symptomen van MS dan bij patiënten zonder deze symptomen. Verder kon bij patiënten met symptomen van MS vaker geen responsie worden herkend met de kleinste stimuli van de PP methode dan bij degenen zonder symptomen van demyelinisatie buiten het visuele systeem. Deze bevindingen zouden kunnen duiden op een subklinische beschadiging van het klinisch niet aangedane oog. Psychophysische methoden leverden vergeleken met de literatuur weinig afwijkende resultaten op, hetgeen verklaard kan worden door de relatief ongevoelige methoden die in deze studie zijn gebruikt. Voor de detectie van 'hidden visual loss', d.w.z. visusverlies bij een Snellen visus van 1.00 of meer, bleken amplitudes in PP het meest gevoelig. Verder waren de resultaten van contrast gevoeligheids methoden gecorreleerd met subjectief visusverlies. De aanwezigheid van 'hidden visual loss' was echter niet voorspellend voor de aanwezigheid van symptomen van MS buiten het visuele systeem. De correlatie tussen amplitude veranderingen in de VER enerzijds en kleurenzien stoornissen, gezichtsvelddefecten en veranderingen in de contrast gevoeligheid anderzijds suggereert een gemeenschappelijke oorsprong van de functies die door deze tests worden uitgedrukt. Veranderingen in latentie van responsies verkregen in het aangedane oog hebben geen duidelijke relatie met het ontstaan van symptomen van MS.

Tenslotte blijkt de prognose op korte en lange termijn van een patiënt met een unilaterale NO niet voorspellend voor het ontwikkelen van MS. Subklinische afwijkingen in het niet aangedane 'fellow eye' kunnen echter wel gerelateerd zijn met het ontwikkelen van symptomen van MS buiten het visuele systeem.

ABBREVIATIONS

ASB :   APPOSTILB

CNS :   CENTRAL NERVOUS SYSTEM

CMTD :   CHARCOT–MARIE–TOOTH'S DISEASE

CSF :   CONTRAST SENSITIVITY FUNCTION

CV :   COLOUR VISION

GP :   GENERAL PRACTITIONER

HF :   HIGH FREQUENCY

HRR :   HARDY RAND RITTLER

LF :   LOW FREQUENCY

MF :   MEDIUM FREQUENCY

MS :   MULTIPLE SCLEROSIS

MTF :   MODULATION TRANSFER CURVE

ON :   OPTIC NEURITIS

PERG :   PATTERN ELECTRORETINOGRAM

PP :   PATTERN PRESENTATION EVOKED RESPONSES

PR :   PATTERN REVERSAL EVOKED RESPONSES

SD :   STANDARD DEVIATION

VA :   VISUAL ACUITY

VER :   VISUAL EVOKED RESPONSE

VF :   VISUAL FIELD

A darkness in the weather of the eye
Is half its light.....

Dylan Thomas

APPENDIX I

PATHOPHYSIOLOGICAL HYPOTHESES CONCERNING VISUAL LOSS
IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS

	TEST	AUTHOR
1. Reduced conduction velocity.	Visual evoked response—latency	Halliday & McDonald, 1977
2. Axonal loss.	Visual evoked response—amplitude	Feinsod & Hoyt, 1975
3. Affection of channels for various spatial frequencies.	Contrast sensitivity function	Campbell & Maffei, 1970
4. Affection of channels for various temporal frequencies.	Temporal CSF	Medjbeur & Tulunay–Keesey, 1985
5. Retinal loss of ganglion cells.	(Pattern) electroretinogram	Not confirmed
6. Desynchronization of impulse conduction.	VER; shape of curve	Ghezzi & Montanini, 1985

APPENDIX II

CASES

CASE I ♀, 33 yrs.

Seen January 1982 in outpatient clinic. Blurred vision and painful eye movements of right eye. Normal optic disc. Central scotoma.
VA: OD 2/60; OS 1.60
Optic neuritis right eye. Recovery within 4 weeks

Follow–up period: 1 yr., 6 months.
VA : OD 1.25; OS 0.80
Neurological examination :   paraesthesia in left arm
                                  sensory impairment in lower extremities
                                  nightly cramps in lower extremities

Psychophysical examination :   CSF : OD decrease of HF; OS decrease of HF
                               CV :   no abnormalities
                               VF :   no abnormalities

No subjective visual loss.

Electrophysiology :
On the left side of the figure the VER recording at the time of first examination in the affected eye is shown. Due to the low visual acuity, there were no recognizable responses to large–check PP stimuli. After recovery, responses to all check sizes were found in PP. Note, however, that the recorded responses are relatively low and of irregular shape despite recovery of visual acuity. This 'visual loss' is also reflected in the decrease of high frequency CSF in the affected eye.
Furthermore, a visual acuity of less than 1.00 is present in the 'fellow eye'.

CASE I: AFFECTED EYE IN ACUTE STAGE AND AFTER RECOVERY OF VISUAL ACUITY
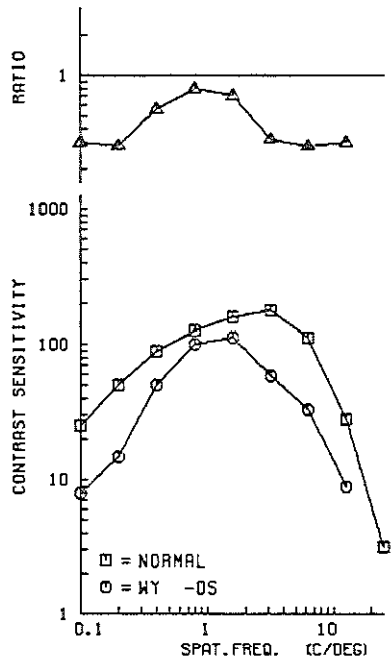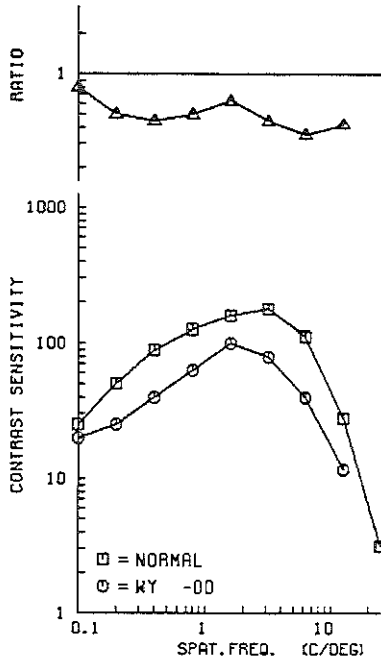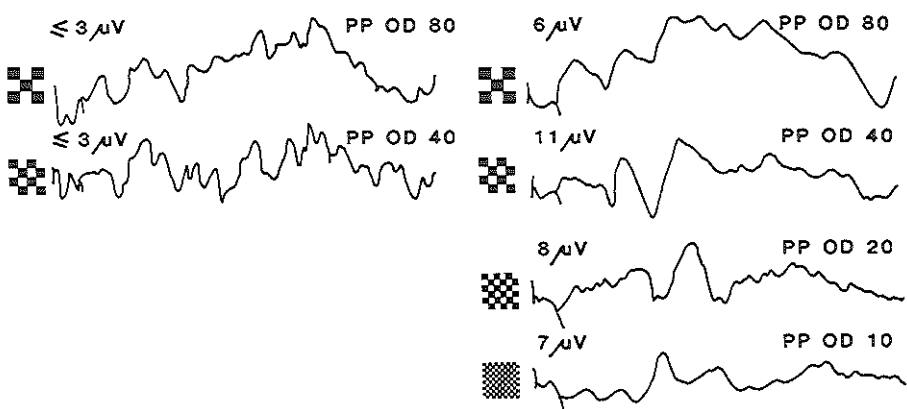
CASE II ♂, 36 yrs.

Seen April 1982 in outpatient clinic. Patches and blots in the visual field and painful eye movements in left eye. M.Gunn phenomenon positive. Normal optic disc. Central scotoma.
VA: OD 1.00; OS 1/60
Optic neuritis left eye. No recovery.

Follow–up period: 1 yr., 6 months.
VA: OD 2.00; OS 1/60
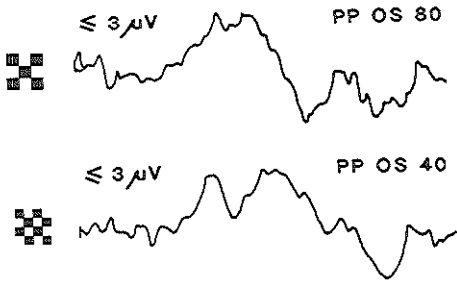Neurological examination :   bilateral nystagmus
                                  cerebellar ataxia left arm

Psychophysical examination :   CSF :   OD decrease of HF; OS totally decreased
                                    CV :   OS both tests not possible
                                    VF :   OS paracentral and central scotoma

Electrophysiology :
No response could be obtained to either of the stimuli either in the acute stage or at follow–up.

CASE II: AFFECTED EYE IN THE ACUTE STAGE AND AT FOLLOW UP; NO RECOVERY OF VISUAL ACUITY
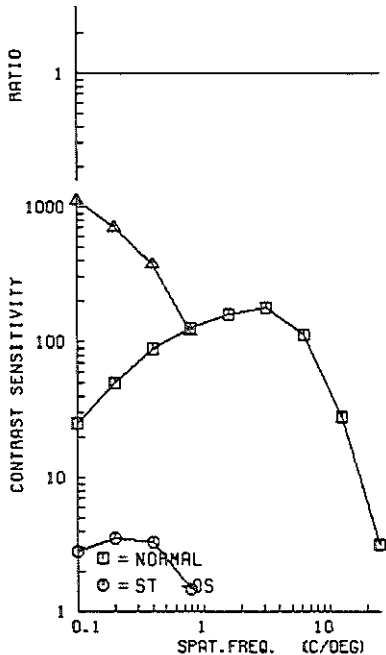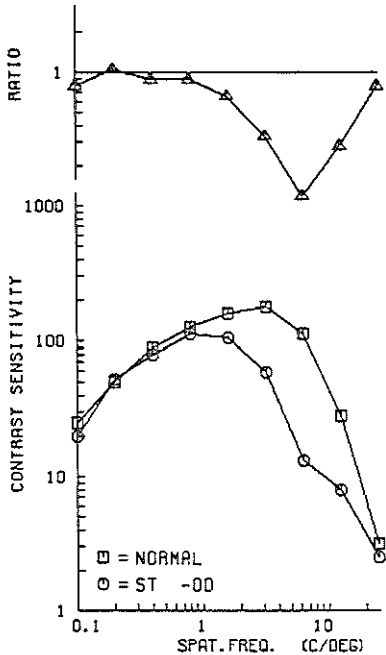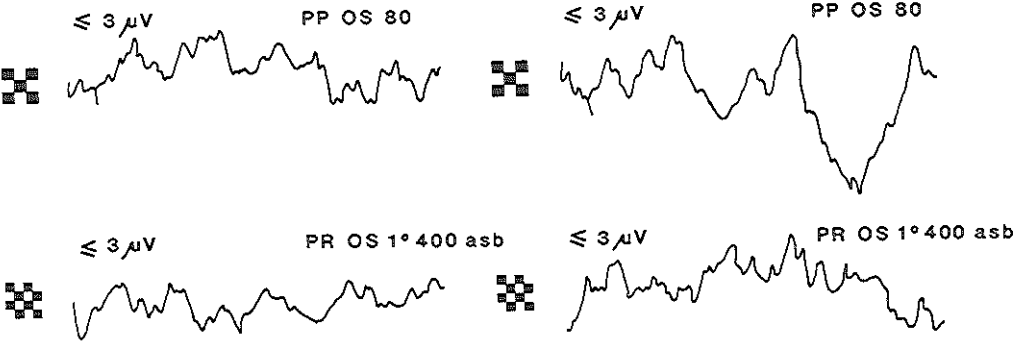
CASE III ♂, 34 yrs.

Seen September 1981, referred by ophthalmologist. Blurred vision in left eye. Pallor of optic disc.
Central scotoma.
VA: OD 1.00; OS 2/60
Optic neuritis left eye. No recovery.

Follow–up period: 2 yrs., 1 month.
VA: OD 1.25; OS 0.4
Neurological examination :   no abnormalities
                                  intrathecal IgG synthesis

Psychophysical examination :   CSF : OS totally decreased curve
                               CV :   OS not possible
                               VF :   OS central and paracentral scotoma

Electrophysiology:
In the acute stage, no response could be obtained using large check PP stimuli in the affected eye. At
follow–up, no recognizable response in the affected eye was assessed. In the 'fellow eye', a delay of
the responses was found using both PP and PR.

CASE III: AFFECTED EYE IN ACUTE STAGE

AFFECTED EYE AT REEXAMINATION
AND FELLOW EYE AT REEXAMINATION

≤ 3 μV   PP OS 80

≤ 3 μV   PP OS 40

≤ 3 μV   PP OS 80

220 ms
PP OD 80

222 ms
PP OD 40

240 ms
PP OD 20

RATIO

1

1000

100

10

1

CONTRAST SENSITIVITY

☐ = NORMAL
⊙ = GR -OD

0.1   1   10
SPAT. FREQ.   (C/DEG)

RATIO

1

1000

100

10

1

CONTRAST SENSITIVITY

☐ = NORMAL
⊙ = GR -OS

0.1   1   10
SPAT. FREQ.   (C/DEG)
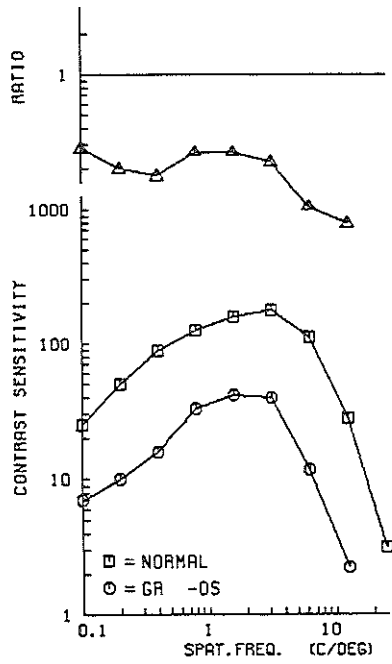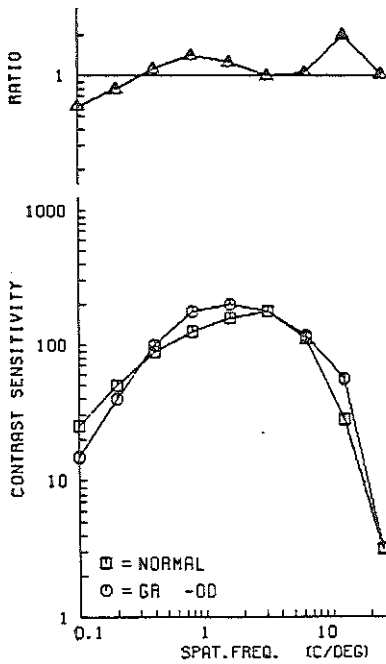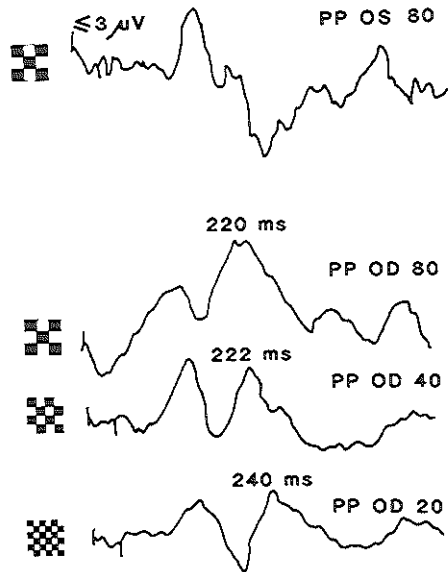
CASE IV ♂; 37 yrs.

Seen January 1982 in outpatient clinic. Blurred vision and painful eye movements of right eye. M.Gunn phenomenon positive. Papiledema. Central scotoma.
VA: OD 0.5; OS 1.00
Optic neuritis right eye. Recovery within 6 months.

Follow–up period: 1 yr.
VA: OD 1.00; OS 1.25
Neurological examination :   cerebellar ataxia left arm
                                    hyperreflexia lower extremities

Psychophysical examination :   CSF :   OS decrease of HF
                                    CV :   OS no abnormalities
                                    VF :   OS no abnormalities

Visual complaints : darker images and grey patches in visual field.

Electrophysiology:
In the acute stage, PP responses could only be obtained using 80' and 40' checks. After recovery a response could also be recognized using 20' checks. The curves are, however, shaped irregularly. Furthermore, in PR a delay persisted despite complete recovery of visual acuity.
The incomplete recovery of amplitudes in PP and the HF decrease in CSF may explain the visual complaints reported by the patient.

134
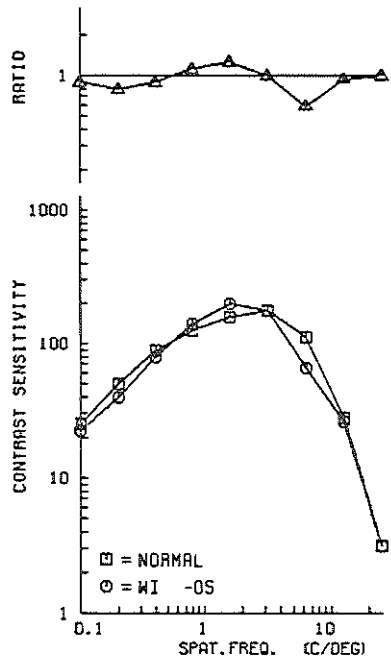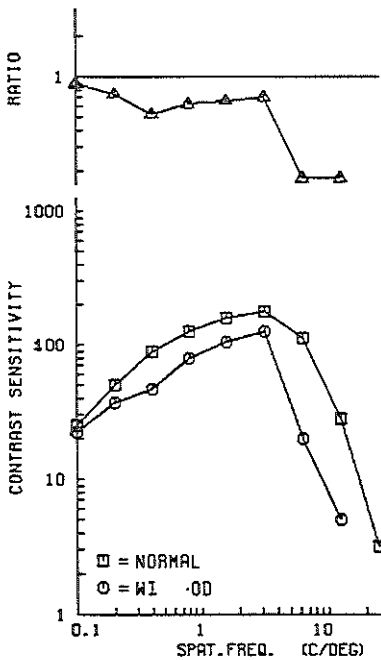
CASE IV: AFFECTED EYE IN THE ACUTE STAGE AND AT REEXAMINATION (PP)
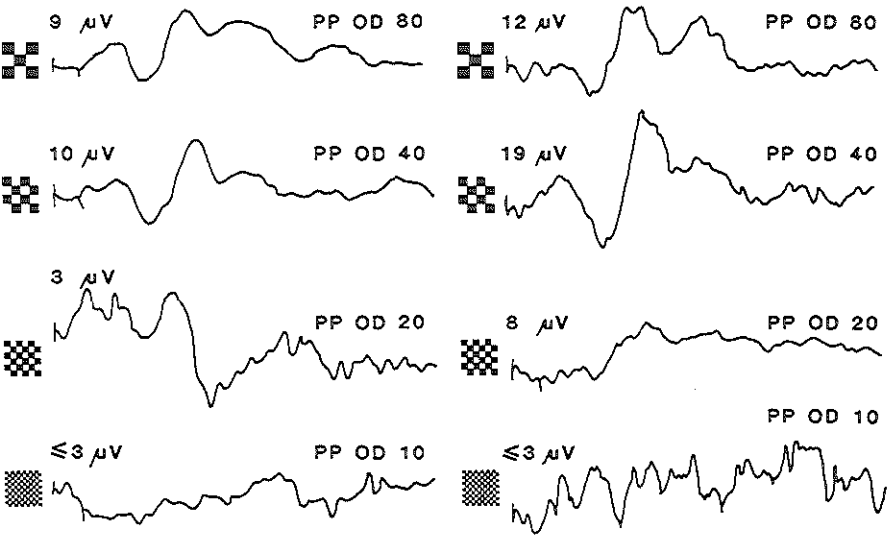
AFFECTED EYE IN THE ACUTE STAGE AND AT REEXAMINATION (PR)
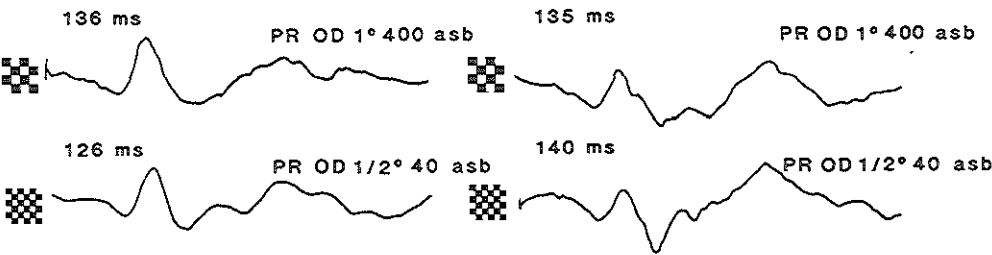
CASE V ♀, 45 yrs.

Referred in January 1980 by ophthalmologist. Blurred vision in left eye. Normal optic disc. Central scotoma.
VA: OD 1.00; OS 0.03
Optic neuritis left eye. Recovery within 3 months.

Follow—up period: 3 yrs., 11 months.
VA: OD 0.8; OS 0.4
Neurological examination: ataxia lower extremities
                                   chronic fatigue

Psychophysical examination: CSF : OD totally decreased curve
                                         OS totally decreased curve
                                 CV : OS mild protan and medium tritan deficit
                                 VF : OS : paracentral defect

Electrophysiology:
In the fellow eye, no response could be obtained at the time of the first attack using 10' checks. After improvement of visual acuity in the affected eye, fellow eye responses could be recognized with all check sizes. Note that visual acuity in the 'fellow eye' is less than 1.00 in this patient who also suffered from other symptoms of demyelinating disease.

CASE V: FELLOW EYE IN THE ACUTE STAGE AND AT FOLLOW UP
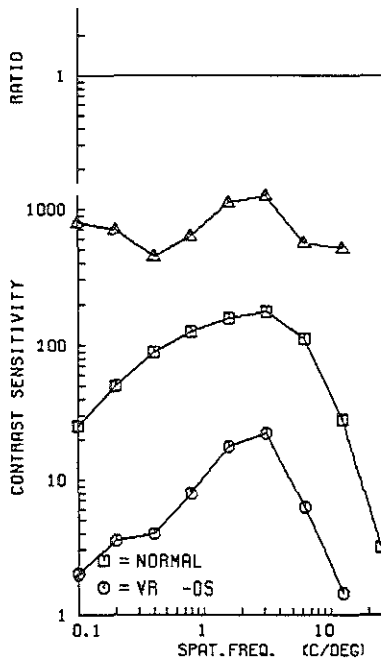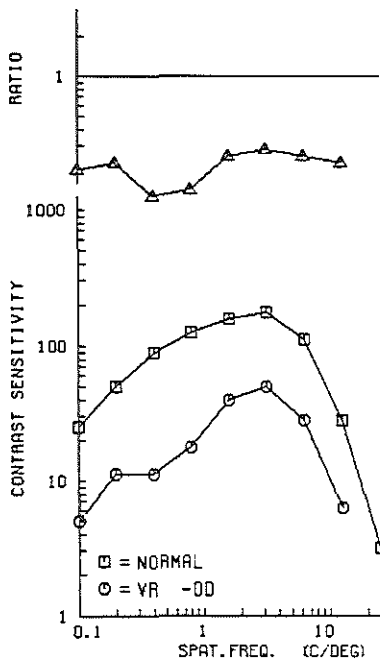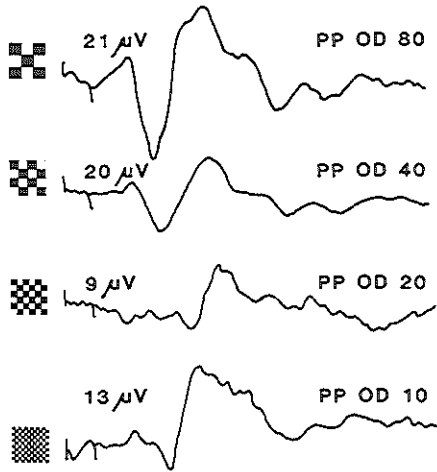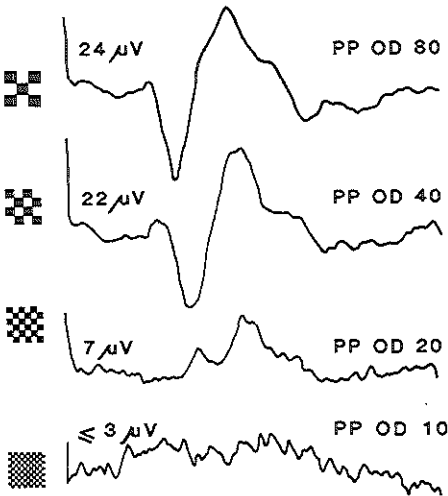
CASE VI ♀, 18 yrs.

January 1982 referred by ophthalmologist. Blurred vision and painful eye movements in right eye. Pallor of optic disc. Central scotoma.
VA: OD 1/60; OS 1.20
Optic neuritis right eye. Complete recovery within 4 weeks.

Follow—up period: 1 yr., 11 months.
VA: OD 1.25; OS 1.50

| Neurological examination: | sensory impairment and paraesthesia in left side of body |
| | intrathecal IgG synthesis |

Psychophysical examination:	CSF :	no abnormalities
	CV :	no abnormalities
	VF :	no abnormalities

No subjective loss of visual function

Electrophysiology:
Complete recovery of all responses in PP. The IOR of amplitude is, however, decreased in responses using 40′ and 20′ checks. In PR a decrease of the delay was seen with all check sizes; latency returning to high normal values.
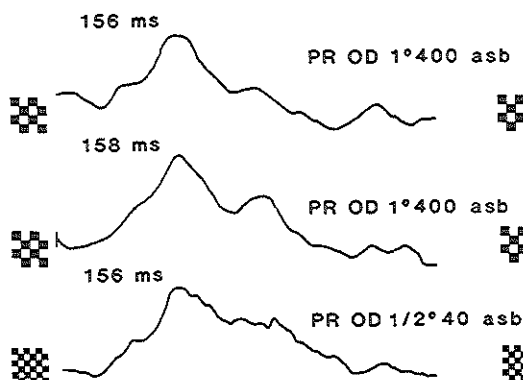Recovery of visual function in this patient did not exclude the presence of demyelinative damage outside the visual system.

CASE VI: AFFECTED EYE IN THE ACUTE STAGE
AND AFTER RECOVERY (PP)

FELLOW EYE AT REEXAMINATION (PP)

≤ 3 μV   PP OD 80

12 μV   PP OD 80

21 μV   PP OD 40

18 μV   PP OD 20

17 μV   PP OD 10

16 μV   PP OS 80

45 μV   PP OS 40

39 μV   PP OS 20

19 μV   PP OS 10

AFFECTED EYE IN THE ACUTE STAGE AND AT FOLLOW UP (PR)

156 ms   PR OD 1°400 asb

158 ms   PR OD 1°400 asb

156 ms   PR OD 1/2°40 asb

127 ms   PR OD 1° 400 asb

126 ms   PR OD 1° 400 asb

122 ms   PR OD 1/2°40 asb
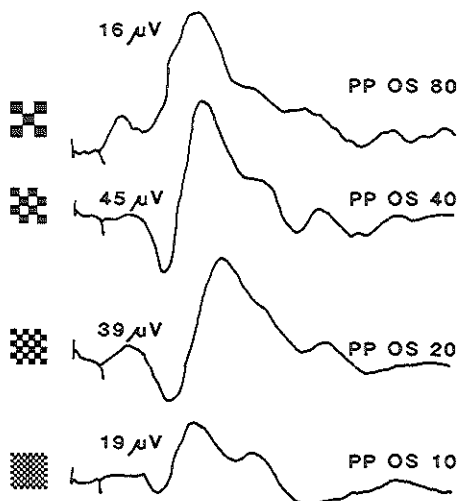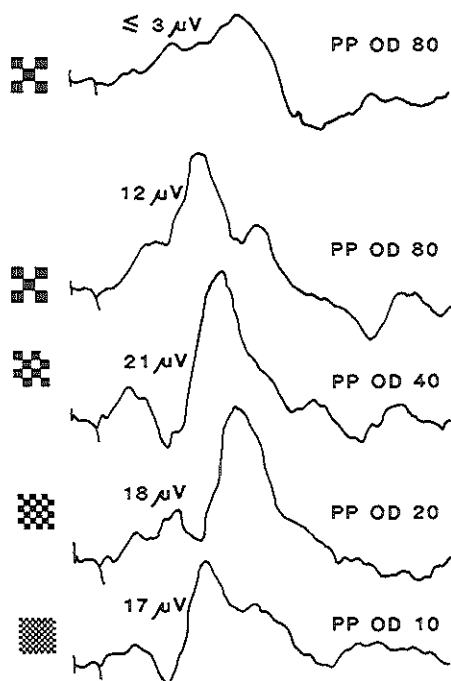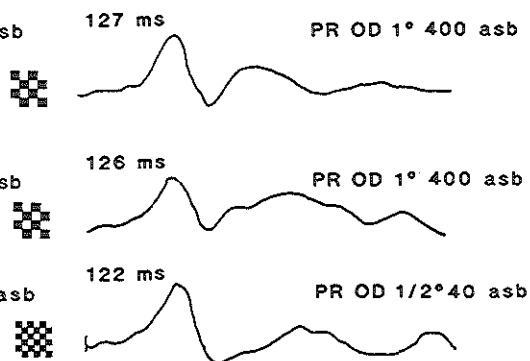
CASE VII ♀, 30 yrs.

Seen in outpatient clinic in January 1983. Distortion of images and painful eye movements in right eye. M.Gunn phenomenon positive. Normal optic disc. Central scotoma.
VA: OD 0.5; OS 1.25
Optic neuritis right eye. Recovery within 6 months.

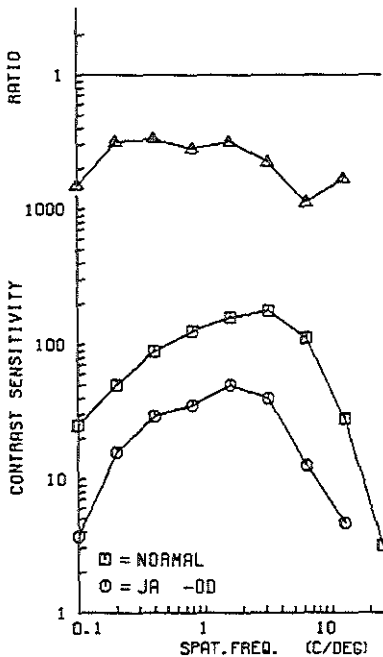Follow–up period of 11 months.
VA: OD 1.0; OS 1.25

| Neurological examination: | paraesthesia in left leg and arm |
| | paresis right leg |

Psychophysical examination:	CSF :	both eyes totally decreased curve
	CV :	no abnormalities
	VF :	no abnormalities

Subjective visual complaints: on exertion: fogginess of vision and lines within the visual field (Uhthoff phenomenon)
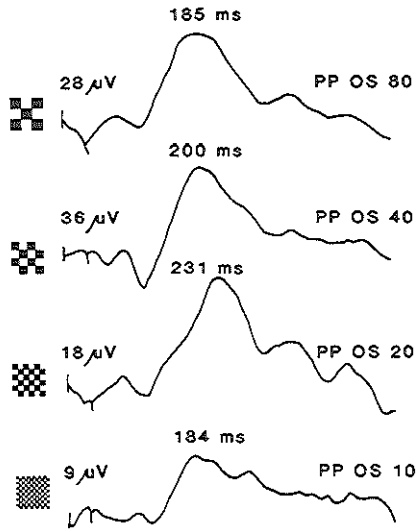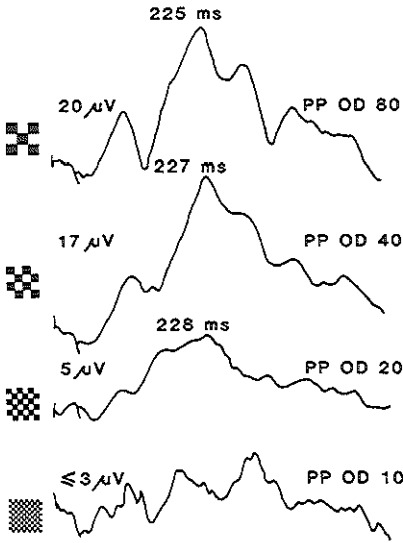
Electrophysiology:
In the initially affected eye, responses at reexamination could be obtained using 3 check sizes. The visual complaints reported by the patient may be due to loss of responses found using 10' checks. Furthermore, there was still a decrease of interocular ratio of amplitude especially using 40' and 20' checks.
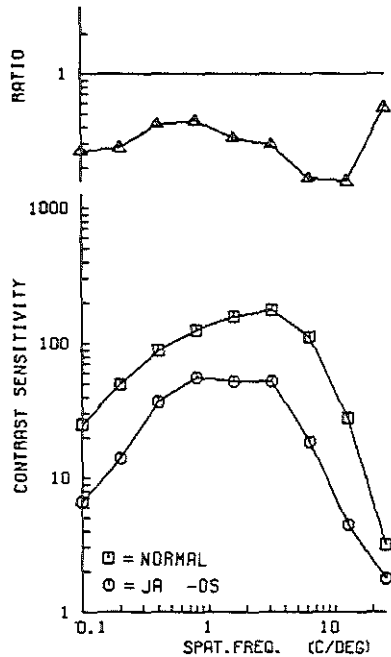
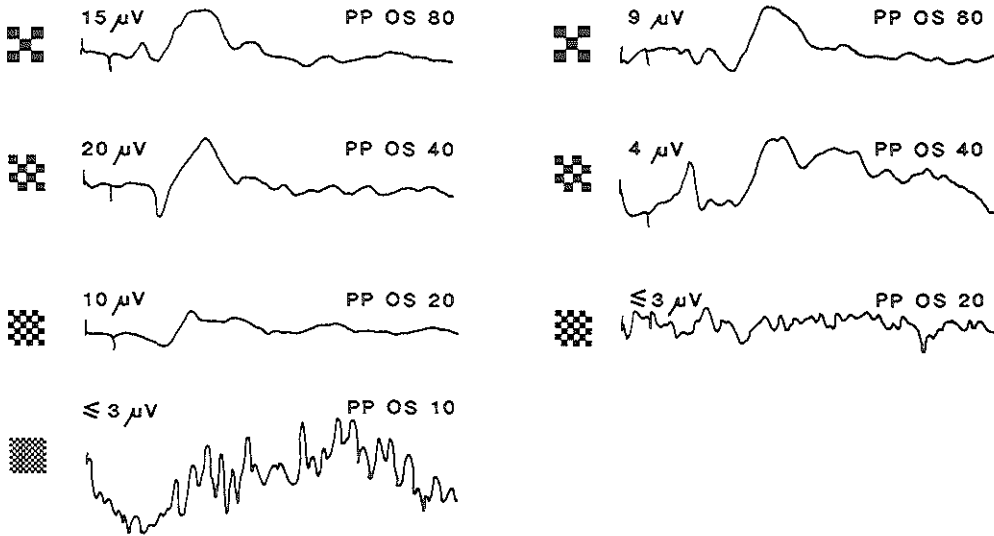**CASE VII**: AFFECTED EYE AND FELLOW EYE; ACUTE STAGE

241 ms

12 μV   PP OD 80

181 ms

25 μV   PP OS 80

179 ms

10 μV   PP OS 40

249 ms

5 μV   PP OD 40

198 ms

10 μV   PP OS 20

179 ms

9 μV   PP OS 10

AFFECTED EYE AND FELLOW EYE AT REEXAMINATION

225 ms

20 μV   PP OD 80

185 ms

28 μV   PP OS 80

227 ms

17 μV   PP OD 40

200 ms

36 μV   PP OS 40

228 ms

5 μV   PP OD 20

231 ms

18 μV   PP OS 20

≤ 3 μV   PP OD 10

184 ms

9 μV   PP OS 10

CASE VIII ♀, 24 yrs.

October 1983. Fogginess of vision and painful eye movements in right eye. M.Gunn phenomenon positive. Normal optic disc. Non–typical visual field defect.
VA: OD 0.25; OS 0.70
Optic neuritis right eye. No recovery.

Follow–up period: 8 weeks.
VA: OD 0.02; OS 0.25
Neurological examination: bilateral pyramidal tract involvement
ataxia lower extremities

Psychophysical examination: CSF : both eyes all frequencies depressed
                                  CV : not possible in both eyes
                                  VF : not performed

Electrophysiology:
As this patient suffered from chronically progressive visual loss in both eyes, the VER also deteriorated. This was expressed by a loss in the number of responses obtained using PP, whereas in PR a delay was observed in both eyes. A delay could not be found in PP, which finding is due to the difference in sensitivity of both methods.

CASE VIII: FELLOW EYE IN ACUTE STAGE AND AT FOLLOW UP (PP)

15 μV   PP OS 80

9 μV   PP OS 80

20 μV   PP OS 40

4 μV   PP OS 40

10 μV   PP OS 20

$\leqslant$ 3 μV   PP OS 20

$\leqslant$ 3 μV   PP OS 10

INITIALLY AFFECTED EYE AND FELLOW EYE AT REEXAMINATION (PR)

140 ms   PR OD 1° 400 asb

128 ms   PR OS 1° 400 asb

125 ms   PR OS 1° 40 asb

148 ms   PR OD 1° 40 asb

153 ms   PR OD 1° 40 asb

146 ms   PR OS 1° 40 asb

143
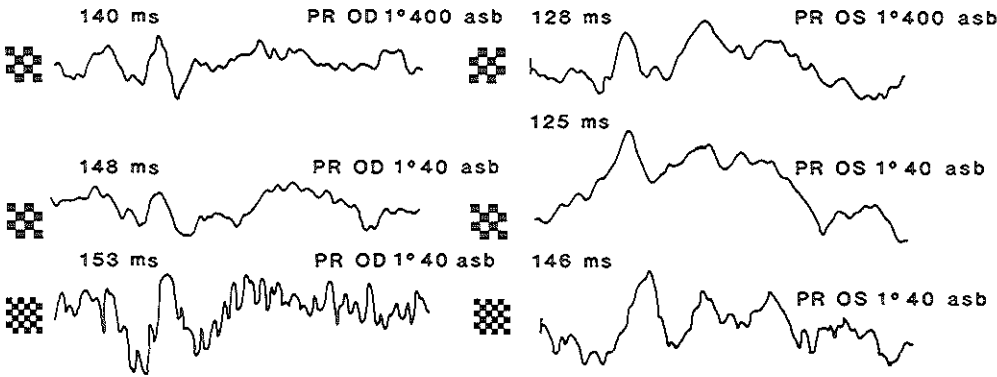
CASE IX ♀, 23 yrs.

Seen October 1982 in outpatient clinic. Blurred vision and painful eye movements in right eye.
M.Gunn positive. Non–typical field defect.
VA: OD 1/60; OS 1.00
Optic neuritis right eye. Recovery within 4 weeks.

Follow–up period: 1 yr., 2 months.
VA: OD 1.25; OS: 1.25
Neurological examination: no abnormalities

Psychophysical examination: CSF :   no abnormalities
                               CV :   no abnormalities
                               VF :   no abnormalities

Electrophysiology:
Complete recovery of PP responses with regard to amplitude. In responses with 80' and 40' checks,
however, a delay was observed, which in this patient did not influence visual function. In the 'fellow
eye', no response with 10' could be recognized in the acute stage. After recovery of the initially
affected eye, high normal latencies were also found in this eye in PP responses.

CASE IX: AFFECTED EYE; ACUTE STAGE
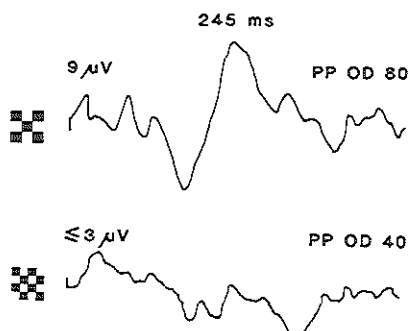
245 ms
9 μV   PP OD 80

≤3 μV   PP OD 40

AFFECTED EYE; AT REEXAMINATION

228 ms
13 μV   PP OD 80

234 ms
12 μV   PP OD 40

222 ms
12 μV   PP OD 20

160 ms
10 μV   PP OD 10

FELLOW EYE; ACUTE STAGE

220 ms
15 μV   PP OS 80

240 ms
10 μV   PP OS 40

225 ms
5 μV   PP OS 20

≤3 μV   PP OS 10

FELLOW EYE; AT REEXAMINATION

235 ms
15 μV   PP OS 80

200 ms
14 μV   PP OS 40

225 ms
11 μV   PP OS 20

175 ms
9 μV   PP OS 10

145
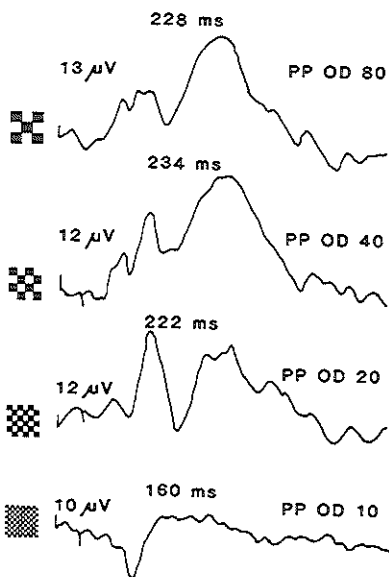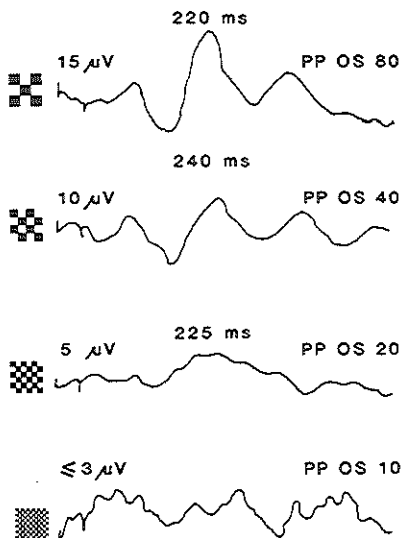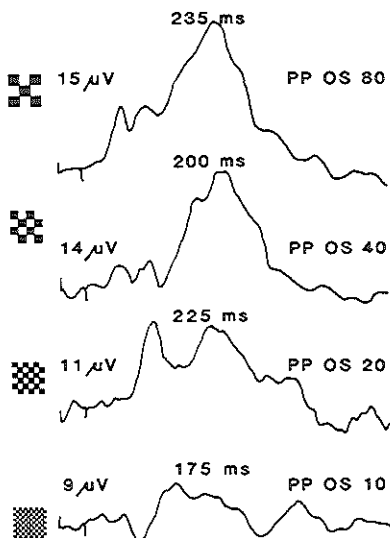
CASE X ♀. 25 yrs.

Seen in September 1980 in outpatient clinic. Blurred vision and painful eye movements in left eye.
M.Gunn positive. Normal optic disc. Central scotoma.
VA: OD 1.00; OS 0.03
Optic neuritis left eye. Recovery within 4 weeks.

Follow–up period: 3 yrs., 2 months.
VA: OD 1.00; OS 0.50
Neurological examination: no abnormalities

Psychophysical examination: CSF :   OS totally decreased curve
                               CV :   OS Panel varying deficits
                                       OS HRR protan/deutan
                               VF :   central scotoma

Subjective visual function: fogginess of vision

Electrophysiology:
The IOR of amplitude was decreased both in PP and PR. Furthermore, latency in PR was still
prolonged. In PP no delay was observed. Curves were however, irregularly shaped and no response
could be recognized to 10' stimuli.
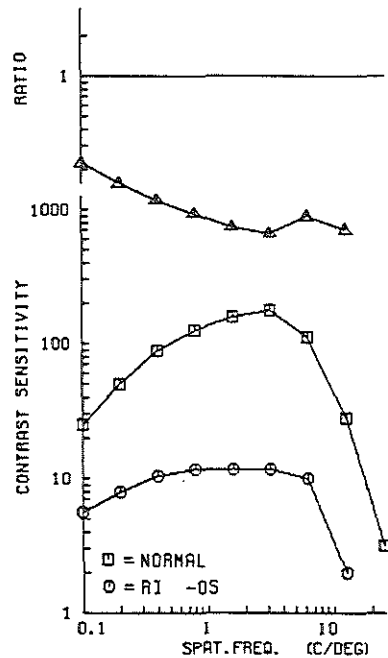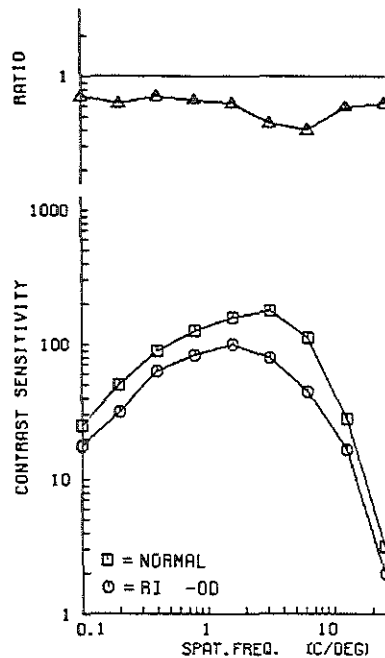
CASE X: INITIALLY AFFECTED EYE AND FELLOW EYE AT REEXAMINATION (PP)

8 µV   PP OS 80

38 µV   PP OD 80

9 µV   PP OS 40

46 µV   PP OD 40

4 µV   PP OS 20

31 µV   PP OD 20

≤3 µV   PP OS 10

19 µV   PP OD 10

INITIALLY AFFECTED EYE AND FELLOW EYE AT REEXAMINATION (PR)

129 ms   16 uV   PR OS 1° 400 asb

107 ms   22 uV   PR OD 1° 400 asb

8 uV   153 ms   PR OS 1° 40 asb

123 ms   22 uV   PR OD 1° 40 asb

7 uV   157 ms   PR OS 1° 40 asb

121 ms   18 uV   PR OD 1° 40 asb

147
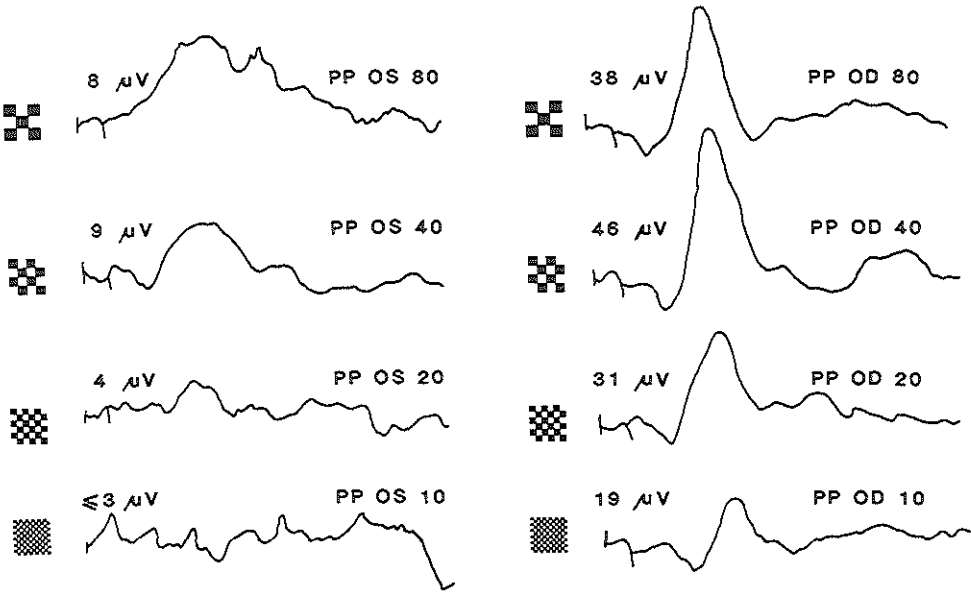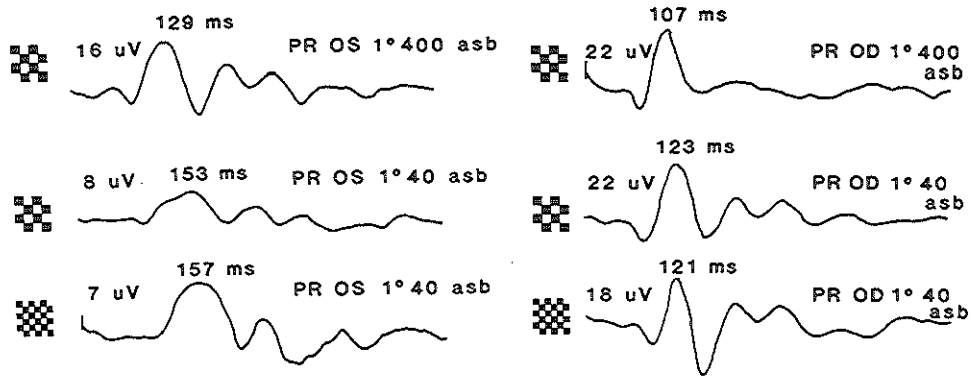
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ACKNOWLEDGEMENTS

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 10 juni 1960 te Rijswijk Z–H.
In 1978 begon zij, na het eindexamen Atheneum B aan het Visser 't Hooft lyceum te Leiden, met de studie Geneeskunde aan de Rijksuniversiteit te Leiden.
In de periode van april 1983 tot februari 1984 werkte zij als student–assistent op de afdeling Electrodiagnostiek van het Oogziekenhuis te Rotterdam (Hoofd: Prof.Dr.G.H.M.van Lith).
Dit onderzoek werd geëntameerd vanuit de afdeling Neurologie van het Academisch Ziekenhuis te Leiden (Hoofd: Prof.Dr.G.W. Bruyn).
Het artsexamen wordt op 18 oktober 1985 afgelegd.