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Temporal resolution deficits in the visual fields of MS patients

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Abstract

We assessed the relationship between temporal resolution and MS-induced neuropathy. A diagnostic strategy comprising assessments of temporal resolution at 16 points in the extra-foveal visual field up to 12° from the fovea was first compared with foveal temporal resolution and with a standard VEP procedure in the same MS patients. At the group level, foveal temporal resolution was less sensitive to demyelination than the 16-point diagnostic strategy, the detection rate of which was comparable to that of the VEP procedure. Cross-sensitivity of the VEP and the 16-point diagnostic procedure was low. Subsequently, the average severity of MS-induced temporal resolution deficits was studied at three retinal loci of the same size but different eccentricities. Foveal deficits were not significantly greater than more peripheral deficits within the central 12°. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Multiple sclerosis; Double flash; Fovea; Periphery; Eccentricity effect

1. Introduction

The primary objective of the present work was to study the efficacy of a diagnostic strategy based on multiple assessments of temporal resolution at different loci in the visual field in the detection of MS-induced neuropathy. Temporal resolution can be determined by means of a double-flash procedure, i.e. by measuring the time interval by which two brief flashes of light need to be separated in order to be seen as discrete events. In a double-flash procedure, as in other experimental procedures evaluating temporal resolution (such as critical-frequency procedures and perceptual-delay procedures), the luminance contrast between the flashes in on and off position is kept constant at a suprathreshold level, while the interval between the onset of successive flashes is manipulated. Examples of these procedures applied to MS patients can be found in the papers of Titcombe and Willison (1961), Heron, Regan and Milner (1974), Regan, Milner and Heron (1976) and Galvin, Heron and Regan (1977). The multiple diagnostic strategy presented in this paper represents a completely standardised method including a statistically calculated decision criterion and the results of this procedure are compared with the results of a VEP procedure conducted on the same patients. The detection rate of a similar, but non-standardised (Galvin et al., 1977) strategy reportedly compares well with that of the most favourable VEP results. The effect on the detection rate of restricting the temporal resolution strategy to only one (foveal) locus of assessment is demonstrated by comparing these results with those of the VEP results and the multiple diagnostic strategy. In a previous paper (Vleugels, van Nunen, Lafosse, Ketelaer & Vandenbussche, 1998) we have already suggested that foveal temporal resolution is relatively insensitive to MS-induced deficits.

It is a common finding that deficits of temporal resolution in MS patients can be restricted to small retinal sites (Miles, 1951; Galvin, Regan & Heron, 1976; Regan et al., 1976; Brussell, White, Bross, Mustillo & Borenstein, 1981/1982; Snelgar, Foster, Heron, Jones & Mason, 1985). In a study of impaired

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sensitivity to temporal modulation in the visual fields of patients with recovered optic neuritis (ON) (Edgar, Foster, Honan, Heron & Snelgar, 1990) it was found that these impairments were significantly milder outside the fovea. However, it has not yet been determined whether impairment of temporal resolution is dependent upon eccentricity in MS patients in the same way that sensitivity to temporal modulation is (Edgar et al., 1990). A second objective of this paper was to investigate this phenomenon, and to compare average severity of MS-induced deficits of temporal resolution in three localised retinal areas of the same size but different eccentricities. There is evidence that temporal resolution deficits in MS patients may not depend upon eccentricity, because measures of temporal resolution reflect processing capacity for stimuli with temporal frequencies at threshold level, while the eccentricity dependence of deficits of temporal modulation sensitivity in the experiment of Edgar et al. (1990) was more pronounced at the lowest temporal frequency (5 Hz) than at any higher (suprathreshold) temporal frequency.

2. Methods

2.1. Subjects

2.1.1. MS patients

Three experimental groups of MS patients were assembled. First, an effort was made to take a random sample of 111 in- and outpatients from the patient population of the Belgian National Multiple Sclerosis Centre. After the application of a series of exclusionary criteria, a group of 47 MS patients was selected. This group is designated group A. The criteria are listed in Table 1. Group A was also tested with a battery of neuropsychological tests (not reported here) and some of the exclusionary criteria were applied to facilitate interpretation of the neuropsychological test results.

In group A, there were 34 female and 13 male patients whose age ranged from 31 to 73 years with a mean of 47 years and 7 months. A total of 29 of these patients had experienced one or more previous attacks of unilateral ON. Among patients having had such attacks, the interval between the last attack and testing ranged from 3 months to 35 years. Mean disease duration (i.e. time interval between diagnosis and testing) was 12 years (S.D. = 8.47; range 1–40 years). Type of MS was primary progressive in 24%, secondary progressive in 55% and relapsing remitting in 21% of the patients. Mean Kurtzke score was 5.92 (S.D. = 1.93; range 2.0–9.0). According to a large study (Gonsette, Lissoir, Theys, Ketelaer, Droissart & Demonty, 1994) on 1800 hospitalised definite (that is, definitively diagnosed: see Poser, Paty, Scheinberg, McDonald, Davis, Ebers et al., 1983) MS patients admitted at the Belgian National Centre for MS from 1970 to 1992, group A was representative of the population studied as to age and the most important disease variables. Nevertheless, group-A patients were homogeneous with respect to visual acuity and the absence of central scotomas (see exclusionary criteria), indicating that in cases where they had suffered from one or more ON attacks in the past, they no longer showed any major signs of the previous ON attacks at the time of testing. A second experimental group of MS patients was created by selecting ten patients meeting both the criteria for group A and showing neither central *nor* peripheral scotomas. This group is referred to as group B. To create a third experimental group (group C), ten patients were selected who met the criteria for group B *and* who exhibited an abnormal VEP in one eye only according to the VEP procedure described further in this section. To identify the subjects for group C more than 300 files had to be examined. The selection of subjects with an abnormal VEP on only one side secured a sufficiently high proportion of normal VEP eyes in a small sample and allowed a comparison between two groups of perfectly matched abnormal and normal VEP eyes. After the experimental procedure was completed, VEPs in group C were double-checked. In both groups B and C three of the ten subjects dropped out for reasons discussed in Section 3. Clinical and biographical details of the remaining subjects of

Table 1
List of exclusionary criteria applied to the initial sample of 111 randomly recruited MS patients

1.	Dazed or confused because of medication/alcohol or drug abuse/brain injuries, CNS diseases other than MS/major psychiatric conditions (not including adjustment disorders) ($n = 18$)[a]
2.	Not able/willing to cooperate ($n = 16$)
3.	Ophthalmological afflictions (such as: severe nystagmus, retinal anomalies and glaucoma) possibly interfering with temporal resolution tasks (Galvin et al., 1976) ($n = 14$)
4.	Mental deterioration (score below 24/30 on Mini Mental State Exam) ($n = 13$)
5.	Binocular Snellen acuity after optical correction less than 20/70 in both eyes (minimal visual acuity for neuropsychological testing proposed by Capruso, Hamsher & Benton, 1995 ($n = 11$)
6.	Diplopia while looking straight ahead ($n = 8$)
7.	Presence of either an absolute or a relative central scotoma according to Goldmann perimetry ($n = 8$)
8.	Signs of disease activity (relapse or obvious rapid evolution according to neurological examination) ($n = 8$)
9.	Recent VEP data (not older than 3 months) not available ($n = 2$)
10.	No definite MS according to Poser et al. (1983) ($n = 1$)
11.	Residing in a nursing home or other institutional setting ($n = 1$)

[a] Number of patients rejected because of the criterion. Several patients were eliminated because of more than one criterion.

group B ($n = 7$) and C ($n = 7$) are shown in Table 2. MS patients in all groups were checked and corrected for refractive errors.

2.1.2. Control subjects

A normal control (NC) group (control group 1) of 30 healthy volunteers was matched group-wise to MS group A on the basis of age. In control group 1, there were 19 females and 11 males, ranging in age from 27 to 73 years with a mean of 48 years and 10 months. Because of the neuropsychological part of the study, group 1 was also matched to group A as to education level. A second control group of ten normal individuals (control group 2, containing one male and nine females, ranging in age from 34 to 64 years with a mean age of 54 years) was also assembled and was matched well with group B on the basis of age. Because age distributions in groups B and C were comparable, group 2 served as a control group for group C as well. No NC subject exhibited any major ophthalmologic, neurological or psychiatric problems. Like the patients, NCs were checked and corrected for refractive errors.

2.2. Stimuli, apparatus and procedures

2.2.1. Temporal resolution

Temporal resolution was evaluated with a procedure making use of double flashes (DF), a method known to be highly sensitive to MS-induced deficits (Galvin et al., 1976, 1997; Patterson, Foster, Heron & Mason, 1981). The DF-threshold (DFT) procedures used, were described in detail in an earlier paper (Vleugels et al., 1998). Testing was always monocular and each subject was tested in both eyes. DF stimuli were generated by red Light Emitting Diodes (LEDs) subtending a visual angle of 26′ of arc and having a luminance of 7 cd/m^2. Background luminance was approximately 0.4 cd/m^2. The luminance of the LEDs and the background luminance were measured with a photometer. The low background luminance level was expected to create a stimulus condition which had proven to be selectively sensitive to M-pathway lesions (Schiller, Logothetis & Charles, 1990) and to make DFTs less susceptible to the excessively variable luminance sensitivity MS patients can exhibit (Patterson, Foster & Heron, 1980). As in the study of Galvin et al. (1976), a temporal perimeter was used to present the DF stimuli. One meridian of the inner surface of a Plexiglass hemisphere was covered with a 1-cm array of LEDs. The subject's head was centered within the hemisphere by the use of a form-fitting device, thus keeping the viewing distance at 0.39 m for all stimuli. By rotating the hemisphere around its centre, it was possible to screen the entire visual field with the LEDs. In group A as well as in control group 1, only foveal DFTs were determined. For this purpose, only the central LED of the perimeter was required. In group B and group C, DFTs were measured at 17 testing points, i.e. at the fovea and at two eccentricities (i.e. at 6 and 12° from the fovea) in two directions along the principal meridians (horizontal, vertical, right oblique and left oblique) in the monocular visual field. The same was done for control group 2. To determine peripheral thresholds the subjects were asked to fixate a central target (a green spot) while a peripheral LED delivered the stimulus they had to judge. The apparatus employed did not allow a trial-wise interleaving of LED presentations at different retinal positions, which would have permitted a more effective control of voluntary eye movements. Instead, fixation was controlled indirectly by the presentation of catch trials between randomly chosen pairs of peripheral DFT procedures. In these catch trials stimuli were presented at the blind spot while the instructions remained unchanged, and the subjects were expected either not to respond at all, or to comment that they did not perceive a stimulus generated by a LED. When a subject reacted incorrectly during at least one catch trial, it was decided that she/he had not always maintained fixation on the peripheral target stimulus properly and that all of the subject's data had to be excluded from statistical analysis.

2.2.2. Evoked potentials

The VEP procedure employed for the purpose of this paper was based on the P100 response of a transient pattern-shift VEP procedure (PSVEP). The great sensitivity of this diagnostic procedure to conduction defects in the visual pathways of definite MS patients had already been reported by Halliday, McDonald and Mushin (1973). Full-field monocular stimulation was provided in a semi-darkened room. Stimulus pattern consisted of a checkerboard consisting of 98′ white-dark checks which were reversed in phase at 2 Hz. The dark and white checks had a luminance of 15 and 600 cd/m^2, respectively, giving a mean luminance of 307.5 cd/m^2 and a contrast of 97.5%. Stimulus field was a rectangle measuring $24.56 \times 18.92°$. The stimuli were generated on a Hitachi TV screen, the brightness and contrast of which were kept constant throughout the test. The spatial characteristics of the stimulus, its presentation mode and timing were under control of a Medelec V Sapphire Premiere microcomputer. Two readings were taken for each eye and averaged. Recordings were made using a four-channel averager modified to give a bandpass frequency response of 1–100 Hz. Averages of 128 sweeps were taken. Sweep duration was 300 ms. An active stainless steel subdermal needle electrode was placed at the occipital zone. The reference electrode was placed at the frontal zone and an electrode at the wrist acted as an earth. Impedances were maintained below 4 KΩ.

Table 2
Clinical and biographical details of the experimental groups B and C

Subjects		Age (years)	Sex (Female/Male)	Type Of MS[a]	EDSS (Kurtzke, 1983)	History of ON[b]		Time interval between last ON attack and testing	PSVEP abnormal (+) or normal (−)		Disease duration in years
Number	Initials					R	L		R	L	
Group B											
1	LDG	39	F	SP	6.5	+	−	14 years	+	+	14
2	ADR	57	F	SP	6.5	−	−	−	+	+	18
3	AK	40	F	PP	8.0	−	−	–	−	−	12
4	ML	58	F	SP	6.0	−	−	–	+	+	14
5	G	65	F	SP	7.0	+	−	3 years	+	+	27
6	MV	48	F	SP	6.5	+	+	20 years	+	+	20
7	JC	55	F	RR	5.5	−	−	–	+	+	21
Group C											
8	RS	39	M	PP	6.5	+	−	6 months	+	−	12
9	MVD	44	F	RR	3.0	+	−	4 years	+	−	4
10	NC	64	F	SP	7.5	+	−	34 years	+	−	34
11	SVB	63	F	SP	6.5	−	−	−	+	−	11
12	VM	54	F	SP	6.5	−	−	–	−	+	30
13	MP	57	F	SP	7.0	+	−	29 years	−	+	29
14	JC	47	F	SP	6.0	−	+	8 years	−	+	27

[a] PP, primary progressive type; SP, secondary progressive type; RR, relapsing remitting type.
[b] −, no attack; +, at least one attack in file.

2.3. Data analysis

Statistical analyses were performed with the Statistical Analysis System software package (SAS Institute Inc., 1991) and individual eyes were considered independently. In group A, the occurrence of foveal temporal resolution deficits was compared to that of abnormal PSVEPs. The closest approximation of the 95th percentile of the NC-eye scores of control group 1 ($n = 30$ subjects, 60 eyes) was used as the cut-off for determining the foveal DFT value which was considered to reflect a foveal temporal resolution deficit for the MS patients. In each of the MS eyes in group B and in group C, the occurrence of a foveal temporal resolution deficit was compared to PSVEP abnormality *and* with the results of a simultaneous evaluation of 16 DFTs. These DFTs were determined at all testing points except for the foveal testing point. The 16-point diagnostic strategy was considered as abnormal if at least three (= the closest approximation of the 95th percentile of the NC subjects of control group 2) of the 16 peripheral thresholds were found to be abnormal. An abnormal DFT for a given eccentricity was defined as a DFT value exceeding the closest approximation of the 95th percentile of the NC-eye scores of group 2 ($n = 10$ subjects, 20 eyes). Results of group B ($n =$ seven subjects, 14 eyes) and of group C ($n =$ seven subjects, 14 eyes) were considered separately. PSVEP responses in MS eyes were assessed by considering P100 latencies. The PSVEP procedure had been conducted on neither control group 1 nor 2. For this reason, the 95th percentile of scores of the normal eyes in a large normative study of Chiappa (1989) was used as cut-off. A PSVEP response was considered as abnormal when its P100 latency exceeded 111.9 ms.

The results of experimental group B ($n = 14$ eyes) and of control group 2 ($n = 20$ eyes) were used to calculate average DFTs for MS patients and NCs at three eccentricities (foveally and at 6 and 12°). To study normal DFTs as a function of eccentricity, a randomised-block RB-3 experimental design (one within-factor with three levels corresponding to three degrees of eccentricity: 0, 6, and 12°; Kirk, 1968) was used. To examine whether the size of DF deficits varied significantly with retinal eccentricity the significance of the interaction between the NC-MS contrast and eccentricity was tested using a split-plot SPF-2.3 experimental design (one between-factor with two levels, referring to the MS and NC experimental groups, respectively; one within-factor with three levels, corresponding to the 0, 6, and 12° conditions, respectively; Kirk, 1968). Both the SPF-2.3 and the RB-3 model have the advantage of permitting a statistical dependence between the observations (Kirk, 1968) at the three eccentricities. ANOVAs were carried out on the original data set provided by the subjects of groups B and 2, that is, DFTs at a given eccentricity were not averaged (over meridians) per subject before an ANOVA was performed. Because of this, the number of observations was not equal among eccentricity conditions and statistical dependence of observations was also expected *within* each eccentricity condition, i.e. among the observations originating from the same subject. The significance of this subject factor effect was tested separately for NC-subject data and for the MS-subject data, respectively. The problem of unequal numbers of observations in different eccentricity conditions was taken into account by a maximum likelihood procedure (SAS Institute Inc., 1992).

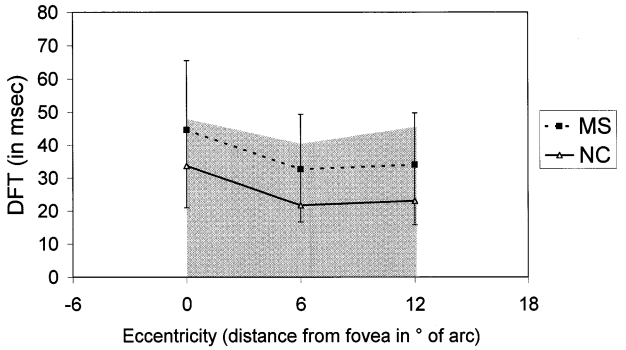

Fig. 1. Double-flash thresholds (DFTs) as a function of eccentricity. The solid line connects the means for the NC group ($n =$ ten subjects, 20 eyes). The hatched area is the area below the 95th percentile of NC scores. The dotted line connects the means for the MS group (= group A; $n =$ seven subjects, 14 eyes). Vertical lines indicate 1 S.D. of MS scores. The NC results were based on 20 (0° condition), 160 (6° condition) and 160 (12° condition) observations. The MS results were based on 14, 80 and 80 observations, respectively.

3. Results

3.1. Control data

All NC subjects of group 2 reacted 100% correctly to the random catch trials of the blind-spot test. In Fig. 1 mean values (solid line) and 95th percentiles of normal DFTs are shown as a function of eccentricity in the visual field. Data from 340 measurements (control group 2, $n = 20$ eyes, ten NC subjects) are presented. Since the NCs exhibited no differences between temporal and nasal DFTs on retinal sites at the same eccentricity ($F_{(1, 36)} = 1.30$; $P = 0.26$ at 6° and $F_{(1, 36)} = 1.38$; $P = 0.24$ at 12°) no distinction between temporal and nasal fields was made in Fig. 1. Similarly, since no differences were found in the NCs between upper-quadrant and lower-quadrant DFTs at the same eccentricity ($F_{(1, 36)} = 1$; $P = 0.32$ at 6° and $F_{(1, 36)} = 0.22$; $P = 0.64$ at 12°), neither was this distinction made in Fig. 1. Mean DFT at 0° was significantly higher than at 6 or 12° eccentricity ($F_{(2, 18)} = 9.35$; $P = 0.001$). Within NCs, the subject factor did not interact significantly with this

eccentricity effect ($Z = 0.87$; $P = 0.386$), suggesting that the eccentricity effect consistently emerges in every subject.

3.2. MS patients

In group B as well as in group C three of ten subjects either declined further participation before the testing was completed or failed to react 100% correctly to the random catch trials of the blind-spot procedure and were excluded from statistical analysis.

3.2.1. Comparison of foveal temporal resolution and PSVEP

In group A ($n = 94$ eyes), the frequency of foveal temporal resolution deficits was 0.35 while the proportion of abnormal PSVEP was 0.83. Frequencies and proportions given in Table 3 provide a detailed picture of the relation between the occurrence of foveal temporal resolution deficits and abnormal PSVEP responses. The PSVEP procedure identified most (i.e. 82%) of the abnormal DFTs and detected abnormality in many (i.e. in 51) cases that were normal according to the foveal DFT procedure. The opposite was not true. The φ correlation was as low as -0.026. A test for association proved to be negative (Fisher Exact P-value (two-tailed) $= 0.78$).

3.2.2. Comparison of PSVEP and the 16-point strategy

Table 4A compares abnormal PSVEP latencies, foveal temporal resolution deficits and other abnormalities detected by the 16-point strategy for each of the 14 eyes of the group B-subjects. In Table 4B the same comparisons were made for the 14 eyes of the subjects of group C. In group B and in group C the PSVEP procedure and the 16-point strategy showed abnormalities about equally often. Both the PSVEP and the 16-point strategy were more frequently abnormal than foveal temporal resolution. This contrast was very clear in both groups. The foveal DFT proved to be more sensitive to MS than the PSVEP in only a single instance (Table 4A, left eye of subject AK), and in one other isolated case (Table 4B, left eye of subject MP) the foveal DFT proved more sensitive than the 16-point strategy. Table 4A and B also testify to the poor correlation between PSVEP and the 16-point strategy. Only 57% of the eyes were similarly classified by the PSVEP and the 16-point strategy. In group B and group C the cross-sensitivity of the foveal temporal resolution procedure and the 16-point diagnostic strategy was also very low: only 15/28 eyes were classified alike by the latter two diagnostic procedures.

3.2.3. Double-flash abnormality as a function of eccentricity

Means (dotted line) and S.D. (vertical lines) of DFTs in MS patients are shown as a function of eccentricity in Fig. 1. Data shown are from 174 measurements (group B, $n = 14$ eyes, seven subjects). Overall, DFTs of MS patients were significantly greater than those of NCs (main effect of groups (MS, NC) was significant ($F_{(1, 15)} = 9.69$; $P = 0.007$)). The interaction between experimental groups (MS, NC) and eccentricity (0, 6 and 12°) was not significant ($F_{(2, 30)} = 0.15$; $P = 0.83$), implying that MS-NC contrasts did not differ significantly as a function of eccentricity, thus indicating that MS patients exhibit no greater DFT deficit at the fovea than at the more peripheral sites.

3.2.4. The problem of dependent observations

The subject factor (main) effect was not significant in either of the two sets of data compared in Fig. 1: neither in control group 2 ($Z = 1.61$; $P = 0.10$), nor in the MS subjects of experimental group B ($Z = 1.63$; $P = 0.10$). It was therefore concluded that the statistical dependence among the observations coming from the

Table 3
Contingency table of abnormal PSVEP responses and foveal temporal resolution deficits in group A ($n = 94$ eyes, 47 MS patients)[a]

	PSVEP responses (P100 latencies)		
	P100 latency ≤ 111.9 ms: normal PSVEP response	P100 latency > 111.9 ms or inexistent: abnormal PSVEP response	Marginal frequencies of rows
Foveal temporal resolution			
Foveal DFT ≤ the 95th NC percentile: normal foveal temporal resolution	10 (10.6%)	51 (54.3%)	61 (64.9%)
Foveal DFT > the 95th NC percentile: abnormal foveal temporal resolution	6 (6.4%)	27 (28.7%)	33 (35.1%)
Marginal frequencies of columns	16 (17%)	78 (83%)	Total of observations 94 (100%)

[a] The observed frequencies and proportions resulted from a two-way classification of the eyes of group A. Whether or not an abnormal foveal DFT was exhibited was the determinant for the row, while its PSVEP (P100 latency) response determined the column position.

Table 4
Comparisons of the foveal temporal resolution procedures, the 16-point diagnostic strategies and the PSVEP procedures in the 14 eyes of group B and Comparisons of the foveal temporal resolution procedures, the 16-point diagnostic strategies and the PSVEP procedures in the 14 eyes of group C.

Subject	Eye[a]	Diagnostic procedures		
		Foveal temporal resolution	16-point diagnostic strategy	PSVEP
(*A*) *Group B*				
ML	L	–[b]	–	+
ML	R	–	–	+
MV	L	–	+	+
MV	R	–	+	+
AK	L	+	+	–
AK	R	–	+	–
ADR	L	+	+	+
ADR	R	+	+	+
JV	L	+	+	+
JV	R	+	+	+
LDG	L	+	+	+
LDG	R	+	+	+
GG	L	–	–	+
GG	R	–	+	+
Proportions of abnormal procedures		0.5	0.78	0.86
(*B*) *Group C*				
RS	L[c]	–	+	–
RS	R[d]	–	+	+
NC	L[c]	–	–	–
NC	R[d]	–	–	+
JC	L[d]	–	+	+
JC	R[c]	–	+	–
MVD	L[c]	–	+	–
MVD	R[d]	–	+	+
SVB	L[c]	–	+	–
SVB	R[d]	–	+	+
VM	L[c]	–	–	–
VM	R[d]	–	–	+
MP	L[d]	+	–	+
MP	R[c]	–	–	–
Proportions of abnormal procedures		0.08	0.57	0.50

[a] L, left eye; R, right eye.
[b] –, procedure yielding a normal result; +, procedure yielding an abnormal result.
[c] Eye classified in the PSVEP normal subgroup.
[d] Eye classified in the PSVEP abnormal subgroup.

same subject was inconsequential and had no bearing on the interpretation of the eccentricity effects discussed in this study.

4. Discussion

In the NC group foveal DFTs (Fig. 1) were significantly higher compared to more peripheral DFTs. The normal control data further suggest that significant differences exist neither between nasal and temporal DFTs, nor between upper- and lower-hemifield DFTs at equal distances from the fovea. Comparisons of the present data with the literature discloses conflicting evidence, both concerning the presence of an eccentricity effect in normal DFTs (Galvin et al., 1976; Patterson et al., 1981; Yasuma, Miyakawa & Yamazaki, 1986), and with regard to the retinal distribution of DFT values in healthy subjects (Skandries, 1985). Since the stimuli used to elicit DFTs in these experiments differed in several aspects from our own, notably background lumination and field size, inconsistencies between previous work and ours probably point to the importance of the specific conditions under which DFTs are determined. On the other hand, the eccentricity effect we find in man is consistent with the physiological reports of Cleland and Levick (1974) on cats and with physiological (f.i. de Monasterio & Gouras 1975; de Monasterio, 1978; Merigan & Eskin, 1986; Merigan & Maunsell, 1990; Schiller et al., 1990) and anatomical data on non-human primates (Jonas, Müller-Bergh, Schlötzer-Schrehardt & Naumann, 1990; Silveira & Perry, 1991).

While the peripheral DFT procedure used here has been reported (Galvin et al., 1976) capable of placing peripheral stimulus presentations with a high degree of precision in normal controls, the same may not hold for patients showing central or peripheral scotomas. Because of this, only patients with intact visual fields were selected for this paper. The results of the blind-spot test suggest that both the NC and the MS experimental groups fixated the target stimulus as instructed. Nevertheless it must be acknowledged that this test provides only indirect evidence for proper fixation.

The primary objective of the present work was to investigate the detection rate of a 16-point diagnostic strategy for MS-induced neuropathy, which was found to be comparable to that of a standard PSVEP procedure (see Table 4A and B). This is in accordance with the conclusion of Galvin et al. (1977). In contrast with Galvin's procedure, our diagnostic strategy was completely standardised, and consequently permitted an unequivocal conclusion concerning the existence of abnormal temporal resolution in every case examined. At the group level, foveal DFTs were less sensitive to demyelination than either the PSVEPs or the 16-point diagnostic strategies (see Tables 3, 4 A and B). Because of this, and on the basis of the data presented in Fig. 1, we conclude that the clinical evaluation of visual temporal resolution should not be restricted to a single measurement at any given retinal site, since this would make the evaluation less sensitive to MS than the standard PSVEP procedure in most cases. Fig. 1 demonstrates that a single extra-foveal DFT is not more sensitive to demyelination than a single foveal DFT, suggesting that the higher sensitivity of the 16-point diagnostic strategy as compared to the foveal temporal resolution procedure must be due to the higher number of assessments in the former, and can not be explained by the more peripheral localisations of the sites of these assessments. Because our largest MS experimental group (group A) can be considered as a representative sample of the population of the Belgian National Centre for MS with regard to the most important disease variables, the abnormality rates of foveal DFTs (35%) and of PSVEPs (83%) found in group A were expected to provide acceptable estimations of the sensitivities of these diagnostic procedures to MS in patients from similar populations showing no major evidence of previous ON attacks. The PSVEP abnormality rate is in accordance with several previous reports on definite MS patients (see a.o. Ruessmann & Beneicke, 1993).

From the poor correlation between the PSVEP procedure and the 16-point diagnostic strategy, we conclude that the PSVEP procedure is probably inadequate for detecting patchy patterns of impaired temporal resolution occurring outside the fovea but within the central 12° of the visual field. Obviously, a great number of differences between the nature of the PSVEP procedure and the 16-point diagnostic procedure concerning both stimulus characteristics (Weinstein, Odom & Cavender, 1991; Andersson & Sidén, 1994) and response characteristics, may account for this result. Since generally VEP-responses represent activity recorded in the visual cortex, where the peripheral retina is less well represented than the fovea (f.i. Weinstein et al., 1991), the PSVEP-procedure may have predominantly revealed visual damage within the central 5° part of the retina (see Table 3), whereas its sensitivity to defects of temporal resolution outside the fovea may have been relatively low (f.i. Hennerici & Wist, 1982).

A second objective of this work was to assess the severity of temporal resolution deficits as a function of eccentricity. On average, a temporal resolution deficit was not significantly greater foveally than at an eccentricity of 6 or 12°. This finding is in accordance with experimental data of Plant and Hess (1987) demonstrating an absence of eccentricity-dependent losses of contrast sensitivity in ON patients to 8 Hz modulated low-spatial-frequency stimuli, but it is not in agreement with other data from the same authors reporting significantly reduced impairment of visual acuity to 8 Hz modulated stimuli at larger eccentricities (Plant & Hess, 1987). It is also in contradiction to the report of Edgar et al. (1990) showing significantly milder impairments of temporal modulation sensitivity outside the fovea in patients with recovered ON. We are aware that the considerably higher levels of background illumination and the higher brightness level of the test stimuli employed in the experiments of Plant and Hess (1987) and of Edgar et al. (1990) may complicate a comparison of these experiments with the present data. Nonetheless we believe that important factors contributing to the failure to find any eccentricity-dependent deficit with our procedures might have been the low spatial frequency and the high temporal frequency of the test stimuli used. Both the evidence of Edgar et al. (1990) discussed in Section 1 and the paper of Plant and Hess (1987) seem reconcilable with this view. According to Edgar et al. (1990), the absence of eccentricity-dependent losses at lower spatial frequencies in the experiment of Plant and Hess (1987) might have to be ascribed to the temporal frequency of stimulus modulation, which could have been too high to observe the effect for medium-to-low spatial frequencies. Hess and Plant (1985) have suggested the existence of an independent psychophysical channel tuned for low-spatial-frequency, high-temporal-frequency stimuli. Because lesion experiments have demonstrated that disturbed information processing in this channel necessarily implies a compromised magnocellular system (for a review see a.o. Lennie, 1993), our data suggest that the function of foveal magnocellular fibres responsible for tem-

poral resolution capacity is not more vulnerable to MS-induced damage than the function of magnocellular fibres subserving a more peripheral retinal locus of a comparable size and being responsible for temporal resolution capacity at that retinal locus.

In conclusion, this paper presents a completely standardised 16-point diagnostic strategy capable of detecting MS-induced neuropathy with a sensitivity comparable to that of the most commonly used PSVEP diagnostic procedure. While the placements of the assessment sites did not seem to be of great importance for the sensitivity of this diagnostic strategy, the number of the assessments conducted did. Finally, evidence was presented that the information provided by a diagnostic strategy based on multiple assessments of temporal resolution at different loci in the visual field can be complementary to a standard PSVEP diagnostic procedure.

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